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DNA Repair Genes in Ovarian Cancer According to Inheritance Pattern

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Abstract

Objective: Ovarian Cancer (OC) is the most lethal gynecological malignancy. This tumor has been proven to be influenced by alteration in some DNA repair genes. Most of these alterations are changes in a unique nucleotide in the genome, Single-Nucleotide Polymorphisms (SNPs). Therefore, the aim of this study was to analyze whether different SNPs on genes of DNA repair pathways (base excision repair, nucleotide excision repair or homologous recombination repair) modified the risk of developing OC.

Methods: An association study of SNPs rs1799782, rs25487, rs1130409, rs13181, rs11615, rs1799794 and rs861539 of *XRCC1*, *APEX1*, *ERCC2*, *ERCC1* and *XRCC3* genes was performed in the germinal DNA of 185 OC patients and 129 healthy controls.

Results: The A allele of *XRCC1* polymorphism rs1799782 was associated with increased susceptibility to OC (p-value <0.001; OR: 2.187 (95% IC: 1.448-3.302)). The T allele of *APEX1* polymorphism rs1130409 was associated with hereditary OC (p-value =0.009; OR: 1.298 (95% IC: 1.073-1.571)). In relation to *XRCC3* gene (rs1799794), the TT genotype was associated with an increase of susceptibility to familial OC (p-value <0.001; OR=1.744 (95% IC: 1.199-2.535)).

Conclusion: Our study suggests that DNA repair genes different from *BRCA1/2* like *APEX1*, *XRCC1* or *XRCC3* could modify the risk of developing OC.

Keywords: DNA repair genes; Ovarian cancer; Single-nucleotide polymorphism; Genotyping

Introduction

Ovarian Cancer (OC) includes a collection of malignant tumors that affects the ovaries, the peritoneum, and the fallopian tubes [1]. These tumors can be originated from three different types of cells: Epithelial cells, stromal cells, and germ cells. In developed countries, 90% of ovarian cancers have an epithelial origin. Within this group we can distinguish five types of tumors based on histopathological and molecular features: High Grade Serous Carcinoma (HGSC), Low Grade Serous Carcinoma (LGSC), Endometrioid Carcinoma (EC), Clear Cell Carcinoma (CCC) and Mucinous Carcinoma (MC) [1-4].

OC is the eighth most common female cancer and represents the eighth cause of cancer death in this population. The incidence of OC is bigger in developed countries, especially in Europe and North America [5]. In Europe, OC is the eight most common female cancers and has the highest incidence of the world [5]. Moreover, OC has the highest mortality rate between gynecologic malignancies mainly due to a diagnosis in advances stages, a relapse of the disease and the appearance of resistances to standard chemotherapeutic treatments [4,6].

There are diverse genetics factors associated with an increased risk in developing OC. Between 20% and 25% of OC are hereditary and these cases are due to mutations of genes involved in DNA repair, mainly in Homologous Recombination Repair (HRR) [4,7-9]. The most common hereditary OC syndrome is associated with germinal mutations in the *BRCA1* or *BRCA2* genes. Mutations in other DNA repair genes (*BARD1*, *BRIP1*, *MRE11A*, *ATM*, *CHEK2*, *MSH6*, *MLH1*,

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PMS2, *MSH2*, *PALB2*, *RAD50*, *RAD51C*, *RAD51D*, *TP53*) are also related with hereditary OC but these mutations appear with a lower frequency [3,8,10-13]. In these cases, a damaged copy of the gene is inherited, but the other copy needs to mutate throughout the life of the individual for tumor developing, which is known as Knudson's two-hit hypothesis [8,10]. The rest of OC cases are the result of somatic mutations in different genes like *TP53* (96% of the cases), NF1, *BRCA1*, *BRCA2*, *RB1* and *CDK12* [4,12]. Those OC patients that harbor mutations in HRR genes, especially in *BRCA1/2* are candidates for PARP inhibitors treatment. In these cases, the inhibition of PARP leads to an accumulation of single strand-breaks in the DNA. Cells with mutations in those genes are unable to repair this damage by HRR and that generates a synthetic lethality resulting in cell death [13,14].

Therefore, the most common altered DNA repair pathway involved in OC is homologous recombination repair. HRR is mainly implicated in the repair of DNA double-strand breaks and DNA inter-strand crosslink's. During this process, this damage is repaired using as a template the homologous sequence of the sister chromatid. First, DNA damage is recognized by MRN complex and this complex together with other proteins, like exonuclease 1, resect this damage, generating single-strand DNA at the end of double strand break (mediated by *BRCA1*). After that, Rad51 protein attaches to this single-strand DNA and recruits several proteins including *RPA*, *XRCC3* and *BRCA2*. These proteins search a homology area within the sister chromatid and invades the homologous sequence, forming a loop. Then, DNA polymerases read the complementary area and synthesize the new nucleotides. Finally, the junction is resolved, nicks are sealed and the ends are ligated by DNA ligase I [15-19].

Nevertheless, there are other DNA repair pathways such as Base Excision Repair (BER) and Nucleotide Excision Repair (NER) involved in the repair of DNA damage that have been related to OC carcinogenesis and risk [16,20]. BER is involved in the repair of single-strand DNA damage and is also responsible for removing small base lesions from DNA that do not significantly alter the structure of the DNA [16,20]. During this process, different specific glycosylases recognize altered bases and cleave it from it sugar moiety in the DNA. After that, AP-Endonuclease (APE1) cleaves the phosphodiester backbone 5' to the Apurinic/Apyrimidic (AP) site, generating a single-strand break in the DNA. Several polymerases (POLB, POLD or POLE) adds then a nucleotide that are finally ligated by a DNA ligase (*LIG3* or *LIG1*). During this process, *XRCC1* acts as a scavenger, stabilizing the damaged area, opening the DNA helix and attracting other proteins needed for the repair [18-21]. On the other hand, NER acts when bulky and single strand DNA lesions, such as adducts or intra-strand crosslink's, distortion the helical conformation of the DNA [16-18]. This pathway required from different sequential steps to repair the DNA. Firstly, DNA damaged site is detected by two complexes of proteins. Secondly, TFIIH complex, which includes XPB and *XPD* helicases, opens and stabilizes the DNA; after that, two endonucleases (XPG and XPF) acts with *ERCC1* cleave the abnormal strand near the area of the defect, removing some nucleotides around this defect. Then, DNA polymerases (δ or ε) synthesize new nucleotides, using as a template the complementary strand. Finally, these nucleotides are ligated by the activity of DNA ligase 3, PCNA and replication factor C to repair the gap [16,18].

In the last few years, Genome-Wide Association Studies (GWAS) have been performed to determine common genetic variants that presented a strong association with the risk of developing ovarian cancer [12]. Most of these genetic variants are changes in a unique nucleotide in the genome, Single-Nucleotide Polymorphisms (SNPs). Those SNPs are located in various genomic regions and affect several pathways including DNA repair, steroid hormone pathways, cell metabolism, cell cycle control or cellular transport systems [13,22,23].

Therefore, the aim of this study was to analyze whether different SNPs on genes of DNA repair pathways HRR (*XRCC3*), NER (*XPD*, *ERCC1*) and BER (*XRCC1*, *APEX1*), which have not been previously identified in a GWAS study, could increase the risk of developing OC. Our results showed that polymorphisms in HRR, BER and NER pathways could modify the risk of developing this disease in our cohort of patients.

Materials and Methods

Study population

In this study, 185 OC patients were selected randomly from the Department of Gynecology and the Genetic Counseling Unit of the Department of Oncology of University Hospital of Salamanca. Those patients were selected from different provinces of the region of Castile and León (León, Zamora, Ávila and Salamanca) from January 2012 to June 2018. The diagnosis of OC was established by a gynecologist, based on the medical history, physical examination and analysis of complementary imaging tests and anatomic pathology tests. The study did not include patients whose results from the anatomic pathology tests did not confirm malignancy or those whose primary tumor did not belong to the group of malignant tumors originated in ovaries, fallopian tubes or peritoneum. In addition, a data collection protocol was designed for all the patients included. The data used in this study and the variables analyzed in it were obtained from the medical history files of the patients. In this study, hereditary OC was considered when there were mutations in the *BRCA1/2* genes. Familial OC was established when the patient had a first and/or second-degree family member with OC or breast cancer without a mutation in the *BRCA* genes. Finally, sporadic OC was established when the patient did not have a family history of OC or breast cancer. The study also included 129 healthy donors who were women without OC from Salamanca in whom the polymorphisms of the genes used in this study had previously been analyzed and whose anonymized data were included in the files of the Unit of Molecular Medicine of the University of Salamanca-IBSAL. All the patients and controls signed an informed consent prior to the sample collection.

DNA isolation and genotyping

DNA was obtained from leukocytes of peripheral blood by phenol-chloroform method. It was stored in Eppendorf® tubes at -20°C for preventing the progressive degradation of DNA and its potential contamination. All the SNPs were analyzed with real-time polymerase chain reaction (RT-qPCR). Genotyping was performed using the TaqMan® Allelic Discrimination Assay (Applied Biosystems, Foster, CA) in those SNPs included in Table 1. For that analysis, 40 ng of DNA sample were added to 5 μL of TaqMan® Universal PCR Master Mix and it was combined with the specific forward and reverse primers, and VIC (allele 1) and FAM (allele 2) allele specific labeled probes. The assay was performed in a 96 well plate and the detection was carried out in the StepOnePlus™ Real-Time PCR system thermocycler (Applied Biosystems).

Statistical analysis

Before comparing the data, the normality of the populations was

verified with the Shapiro-Wilk test. In the case of a normal distribution, the Chi-squared test was used to observe the differences in the genotypic and allelic distribution of the categorical variables between the different groups. Values of p<0.05 were considered statistically significant. The statistical analysis was carried out with the SPSS v.23 software (IBM-SPSS Inc, Chicago, IL). In the descriptive statistics, the mean value and standard deviation were measured for continuous variables and the total frequency of appearance and percentage were measured for categorical variables, as well as their 95% confidence interval whenever necessary. To assess the association between the different categorical variables, the odds ratios and 95% confidence intervals were measured.

Results

We studied a total of 185 DNA samples from women with OC and 129 healthy female donors. We included in the study polymorphisms of DNA repair genes related to HRR, NER and BER pathways. The SNPs were evaluated according to the genotypic distribution in the population, to their haplotypes and their epidemiology (hereditary, familial and sporadic OC). Patient's characteristics are indicated in Supplementary Table 1.

XRCC1 rs1799782 polymorphism is associated with higher risk of developing OC

First, we studied whether the genotypic distribution of the polymorphisms of the *XRCC1* (rs1799782 and rs25487) and *APEX1* (rs1130409) genes, related to the BER pathway, *XPD* (rs13181) and *ERCC1* (rs11615) genes, related to NER pathway, and *XRCC3* (rs1799794 and rs861539) gene, related to HRR, confer a higher risk of developing OC. We observed that the rs1799782 polymorphism of the *XRCC1* gene, in a dominant model, showed a statistically significant difference in their distribution between cases and controls. The association between the GA genotype of the *XRCC1* gene (rs1799782) and the risk of developing OC is highly significant (p-value <0.001; OR: 3.668 (95% CI: 2.053-6.554)) (Table 2). In our population cohort, and according to the results of the statistical analysis, GG and AA genotypes are protective factors against OC. The A allele of *XRCC1* rs1799782 polymorphism was related to a higher risk of developing ovarian cancer (p-value <0.001; OR: 2.187 (95% IC: 1.448-3.302)) (Table 2). The rest of the studied polymorphisms did not show any significant differences in their genotype distributions between the two groups analyzed (Supplementary Table 2).

APEX1 (rs1130409) and *XRCC1* (rs1799782) polymorphisms increase the risk of developing hereditary OC

Next, we analyzed whether these polymorphisms confer an increased risk of developing hereditary OC. We divided our cases series according to their family cancer history and their mutational status of *BRCA1/2* genes. The allele A of *XRCC1* rs179982 (p-value <0.001; OR: 1.419 (95% IC: 1.077-1.868)) and the allele T of *APEX1* rs1130409 (p-value =0.009; OR: 1.298 (95% IC: 1.073-1.571)) were associated with higher risk of developing hereditary OC (Table 3). The rest of the polymorphisms did not appear to be associated with the risk of developing hereditary OC (Supplementary Table 3).

XRCC3 (rs1799794) and *XRCC1* (rs1799782) polymorphisms increase the risk of developing familial OC

After that, we decided to study whether these polymorphisms were involved in a higher risk in developing familial OC. According to the analysis, the allele T of the *XRCC3* rs1799794 (p-value =0.029; OR=1.821 (95% IC: 1.057-3.136)) and the allele A of *XRCC1* rs1799782 (p-value <0.001; OR=1.650 (95% IC: 1.164-2.339)) were related to a higher risk of developing familial OC (Table 4). The rest of the SNPs seemed not to be related with familial OC risk (Supplementary Table 4).

XRCC1 (rs1799782) polymorphism increases the risk of developing sporadic OC

We next decided to study whether SNPs were involved in a higher

Table 1: SNPs included in this work.

Gene	DNA Repair pathway	SNP ID	Change of amino acid	Change of base	Cr.	ASSAY ID	HWE
XRCC1	BER	rs1799782	Arg194Trp	c.580C>T	19	C_11463404_10	>0.05
XRCC1		rs25487	Gln399Arg	c.1196A>G	19	C_622564_10	>0.05
APEX1		rs1130409	Asp148Glu	c.444T>G	14	C_8921503_10	>0.05
XPD (ERCC2)	NER	rs13181	Lys751Gln	c.2251A>C	19	C_3145033_10	>0.05
ERCC1		rs11615	Asn118Asn	c.354T>C	19	C_2532959_ 10	>0.05
XRCC3	HRR	rs1799794	N/A	c.-316A>G	14	C_2983904_10	>0.05
XRCC3		rs861539	Thr241Met	c.722C>T	14	C_8901525_10	>0.05

SNP ID: Single-Nucleotide Polymorphism Identification; Cr: Chromosome; HWE: Hardy-Weinberg Equilibrium Test

Table 2: SNP in *XRCC1* gene showing statistical differences between patients with OC and controls.

SNP	Genotype	Controls	OC	P-value	OR (95% CI)
XRCC1 (rs1799782)	GG	111 (86.0%)	116 (62.7%)	<0.001	3.231 (1.492-10.351)
	GA	17 (13.2%)	64 (34.6%)		
	AA	1 (0.8%)	5 (2.7%)		
	GG+GA	128 (99.2%)	180 (97.3%)	0.22	
	AA	1 (0.8%)	5 (2.7%)		
	GG	111 (86.0%)	116 (62.7%)	<0.001	3.668 (2.053-6.554)
	AA+GA	18 (14.0%)	69 (37.3%)		
	G	239 (92.6%)	296 (80%)	<0.001	2.187 (1.448-3.302)
	A	19 (13.2%)	74 (24.6%)		

Table 3: SNPs in BER genes showing statistical differences between hereditary OC patients and controls.

SNP	Genotype	Controls	Hereditary OC	P-value	OR (95% CI)
APEX1 (rs1130409)	GG	24 (18.5%)	1 (5.3%)	0.075	
	GT	68 (53.1%)	8 (42.1%)		
	TT	37 (28.5%)	10 (52.6%)		
	GG+GT	92 (71.5%)	9 (47.4%)	0.034	3.358 (1.135-4.952)
	TT	37 (28.5%)	10 (52.6%)		
	GG	24 (18.5%)	1 (5.3%)	0.15	
	TT+GT	105 (81.5%)	18 (94.7%)		
	G	116 (45%)	10 (26.3%)	0.009	1.298 (1.073-1.571)
	T	142 (55.0%)	28 (73.7%)		
XRCC1 (rs1799782)	GG	111 (86.2%)	9 (47.4%)	<0.001	5.538 (0.224- 21.771)
	GA	17 (13.1%)	9 (47.4%)		
	AA	1 (0.8%)	1 (5.3%)		
	GG+GA	128 (99.2%)	18 (94.7%)	0.112	
	AA	1 (0.8%)	1 (5.3%)		
	GG	111 (86.2%)	9 (47.4%)	<0.001	6.914 (2.471-19.345)
	AA+GA	18 (13.8%)	10 (52.6%)		
	G	239 (92.6%)	27 (71.1%)	<0.001	1.419 (1.077-1.868)
	A	19 (7.4%)	11 (28.9%)		

Table 4: SNPs in HRR and BER genes showing statistical differences between patients with familial OC and controls.

SNP	Genotype	Controls	Familial OC	P-value	OR (95% CI)
XRCC3 (rs1799794)	TT	69 (53.5%)	44 (68.3%)	0.05	0.651 (0.417-1.017)
	TC	53 (41.1%)	21 (31.7%)		
	CC	7 (5.4%)	0 (0%)		
	TT+CT	122 (94.6%)	65 (100%)	0.06	
	CC	7 (5.4%)	0 (0%)		
	TT	69 (53.5%)	44 (68.3%)	0.05	0.535 (0.284-1.008)
	CC+TC	60 (46.5%)	21 (31.7%)		
	T	191 (74%)	109 (83.8%)	0.029	1.821 (1.057-3.136)
	C	67 (26%)	21 (16.2%)		
XRCC1 (rs1799782)	GG	111 (86%)	40 (61.5 %)		2.430 (1.49-9.85)
	GA	17 (13.2%)	24 (36.9%)	0.001	
	AA	1 (0.8%)	1 (1.5%)		
	GG+GA	128 (99.2%)	64 (98.5%)	0.619	
	AA	1 (0.8%)	1 (1.5%)		
	GG	111 (86%)	40 (61.5 %)	<0.001	3.854 (1.903-7.804)
	AA+GA	18 (14%)	25 (38.5%)		
	G	239 (92.6%)	104 (80.0%)	<0.001	1.650 (1.164-2.339)
	A	19 (7.4%)	26 (20.0%)		

risk of developing sporadic OC. In this case, the genotype GT of the *XPD* rs13181 seemed to be related to a decreased risk of developing sporadic OC (p-value =0.031; OR=0.697 (95% IC: 0.475-1.023)) (Table 5S). The allele A of *XRCC1* was associated with a higher risk of developing sporadic OC (p-value <0.001; OR=1.744 (95% IC: 1.199-2.535)) (Table 5). The rest of the polymorphisms did not show any differences in genotype distributions between the two groups analyzed (Supplementary Table 5).

The haplotypes of *XRCC1* gene (rs1799782 and rs25487) modulate the risk of developing OC

Finally, we studied the haplotype distribution of the patients and controls of rs1799782 and rs25487 polymorphism of the *XRCC1* gene. In this analysis, we have studied the combined genotype of rs1799782 (GG, GA and AA) together with the genotype of rs25487 (CC, CT and TT). In total, there were 9 haplotypes in our population of study (Supplementary Table 6). Statistically significant differences

Table 5: SNPs in BER genes showing statistical differences between patients with sporadic OC and controls.

SNP	Genotype	Controls	Sporadic OC	P-value	OR (95% CI)
XRCC1 (rs1799782)	GG	111 (86%)	67 (66%)	0.001	2.632 (1.49-5.852)
	GA	17 (13.2%)	31 (31%)		
	AA	1 (0.8%)	3 (3%)		
	GG+GA	128 (99.2%)	98 (97%)	0.202	
	AA	1 (0.8%)	3 (3%)		
	GG	111 (86%)	67 (66%)	<0.001	3.177(1.663-6.070)
	AA+GA	18 (14%)	34 (34%)		
	G	239 (92.6%)	165 (81.7%)	<0.001	1.744 (1.199-2.535)
	A	19 (7.4%)	37 (18.3%)		

Table 6: Haplotypes in *XRCC1* gene showing statistical differences between patients with OC and controls.

SNP	Haplotypes	Controls	OC	P-value	OR (95% CI)
XRCC1 (rs1799782) (rs25487)	AGCC	72 (27.9%)	133 (36%)	0.034	1.451 (1.027-2.050)
	AA+GG+CT+TT	186 (72.1%)	237 (64%)		
	Total	258 (100%)	370 (100%)		
	GGCT	165 (64%)	203 (54.8%)	0.022	0.682 (0.492-0.946)
	AA+AG+TT+CC	93 (36%)	167 (45.2%)		
	Total	258 (100%)	370 (100%)		
	AGCT	71 (27.5%)	150 (40.6%)	0.001	1.800 (1.277-2.528)
	AA+GG+TT+CC	187 (72.5%)	220 (59.4%)		
	Total	258 (100%)	370 (100%)		
	AGTT	37 (14.3%)	94 (25.3%)	0.001	2.270 (1.332-3.086)
	AA+GG+CC+CT	221 (85.7%)	276 (74.7%)		
	Total	258 (100%)	370 (100%)		
	GGCC	166 (64.3%)	185 (50.1%)	<0.001	0.557 (0.402-0.773)
	AA+AG+TT+CT	92 (35.7%)	185 (49.9%)		
	Total	258 (100%)	370 (100%)		
	GGTT	131 (50.8%)	146 (39.5%)	0.005	0.633 (0.459-0.873)
	AA+AG+CC+CT	127 (49.2%)	224 (60.5%)		
	Total	258 (100%)	370 (100%)		

were observed in the distribution of 6 haplotypes among patients and controls. On the one hand, the risk of developing OC was higher for patients with the AGTT (p-value =0.001), AGCC (p-value =0.034) and AGCT (p-value =0.001) haplotypes (Table 6). On the other hand, GGTT (p-value =0.005), GGCC (p-value <0.001) and GGCT (p-value =0.022) haplotypes confer a lower risk of developing OC (Table 6). The haplotypes with non-statistical differences are showed in supplementary results (Supplementary Table 7).

Discussion

DNA repair capacity is clearly related to cancer origin and development. Indeed, defects of the proteins involved in this process and their control are associated with an increased susceptibility to carcinogenesis. Polymorphisms of the DNA repair genes may alter cell repair capacity leading to an accumulation of DNA damage that influence the generation of a tumor malignancy [23,24]. Therefore, we have studied seven SNPs related to several DNA repair pathways (BER, NER and HRR) and analyzed their association with the risk of developing OC. Our study revealed a significant association between polymorphisms in *XRCC1*, *APEX1* and *XRCC3* genes and an OC risk in our cohort of patients. In the case of *XRCC1* polymorphisms, the allele A of rs1799782 polymorphism was associated with a higher risk of developing sporadic, familial or hereditary OC and the presence of different haplotypes of these gene polymorphisms could modulated this risk. For *APEX1* gene, we found that the allele T of rs1130409 polymorphism was associated with a higher risk of developing hereditary OC. Lastly; we observed a significant association between the allele T of *XRCC3* rs1799794 polymorphism and the risk of developing familial OC. This is the first time that the association of this SNPs and OC developing has been described according to the disease inheritance. In this sense, not only the *BRCA1/2* status but also the SNPs of *XRCC1*, *APEX1* and *XRCC3* could be relevant for the prevention, diagnosis, treatment and prognosis of hereditary and familial OC.

During the repair of single-strand DNA damage and the removal of small base lesions by BER, *APE1* and *XRCC1* proteins have an important role [16,20]. *APE1* generates single-strand break in the DNA close to the apurinic/apyrimidic site while *XRCC1* stabilizes the damage area and attracts other repair proteins to this zone [18-21]. Several studies have studied the relationship between SNPs in *APEX1 and XRCC1* genes and cancer risk and prognosis [25,26].

The rs1799782 (p.Arg194Trp) and rs25487 (p.Arg399Gln) SNPs of *XRCC1* gene have been extensively studied in different types of tumors. In this work, we have found an association between the A allele of the rs1799782 polymorphism of the *XRCC1* gene and the susceptibility to develop OC in Spanish population, independently of the *BRCA1/2* mutational status. However, there are several studies that do not find this association [26,27], so the genetic background derived from ethnicity or the population sample size seems to be an important factors. Besides, we have found an increase in recurrences in patients carrying the GA (Arg/Trp) genotype of *XRCC1* gene (rs1799782) after receiving a platinum-based treatment (data not shown). Although resistance to platinum-based chemotherapy has been documented in patients carrying the AA (Arg/Arg) genotype [28], our results suggest that this type of therapy should be reconsidered in patients with the *XRCC1* polymorphism. In addition, we have identified for the first time the association between the AGCC, GGCT, AGCT, AGTT, GGCC, and GGTT haplotypes of the *XRCC1* gene (rs1799782 and rs25487) and their susceptibility to the development of OC. Thus, it seems of vital importance to consider the heritability of these haplotypes independently of the presence or absence of *XRCC1* polymorphisms for the prevention, diagnosis or treatment of OC. Biologically, a deficiency in *XRCC1* protein function results in defects in the DNA damage repair through base excision repair pathway, where *XRCC1* is the first protein to participate as it facilitates the access of other DNA repair proteins such as DNA ligase IIIa, DNA Polymerase β (POLβ) and poly (ADP-ribose) polymerase [29]. The presence of these polymorphisms is associated with a deficient functioning of this protein complex and, therefore, with an accumulation of non-repaired DNA damage that facilitates carcinogenesis. Moreover, there is an association between *XRCC1* Arg/Arg and the number of chromosomal breaks [30,31]. This fact highlights the importance of the rs179982 SNP of the *XRCC1* gene because of its localization since it is located at the N-terminal end of the protein, where the POLβ binding domain is sited. *XRCC1* and POLβ are involved in the maintenance of chromosomal stability, so a malfunction of both proteins impairs DNA damage repair and would facilitate the development of OC [32]. In this sense, the rs179982 polymorphism of *XRCC1* has already been related to susceptibility to different solid tumors such as lung, colorectal, gastric, prostate, thyroid or breast cancer [28]. The SNP rs1130409 of *APEX1* gene is one of the most frequent polymorphism studied in this gene because it results in an amino acid substitution (p.Asp148Glu). This substitution could generate a structural destabilizing effect since it causes an alteration of the protein structure. Besides, it could alter APE1 binding efficacy to its substrate [33]. In previous studies, it has been described that this polymorphism was associated with lung, ovarian, breast or renal clear cell carcinomas [25,33-35]. Regarding OC, the allele G of this polymorphism has been associated with less risk of developing OC in a Chinese population, mainly in the subgroup of OC patients with more than 50 years [25]. In our study, we found that the T allele was associated with a higher risk of developing OC in older patients (p-value =0.025, data not shown). However, we did not observe a significant association between the G allele and a reduction in the risk of developing this tumor type which might be explained by the Caucasian ethnicity of our patients. Moreover, we described a correlation between the allele T of this SNP and a risk of developing hereditary OC. Within the patient group, there were a higher proportion of patients with GT and TT genotype (18 out of 19 patients with hereditary OC), being TT genotype the most common genotype. In another studies, an association between the T allele and the risk of developing lung and breast cancer has been described [33,34].

The most common altered DNA repair pathway involved in OC is HRR [16]. *XRCC3* is a relevant protein involved in HRR, the repair of double-strand breaks and the maintenance of genome integrity. Polymorphisms of *XRCC3* genes may result in a reduction in the DNA repair efficacy [36]. The SNPs rs1799794 (c.-316A>G) and rs861539 (p.Thr241Met) of this gene have been extensively studied and are related to a reduction of DNA repair capacity [37]. The Thr241Met is the most frequent polymorphism of *XRCC3* gene and it has been suggested that this SNP could play a role in the development of several tumors such as glioma, hepatocellular, head and neck or lung cancer [38]. However, the role of XRCC3 Thr241Met in ovarian cancer is controversial differing between different researchers [36-40]. To solve this controversy, Yang et al. [38], performed a meta-analysis and concluded that this SNP was not associated with a risk of developing OC in Caucasian ethnicity which concords with our results [38]. The c.-316A>G polymorphism is located in 5' UTR of *XRCC3* gene, so it does not generate a change in the amino acid sequence. It has been described a weak association between the allele G and a decreased risk of developing OC [39,41]. In our study population, the protective role of the G allele was only found in familial ovarian cancer. This may be due to the effect of the differential genetic background between populations and to the fact that the sample size of our work is smaller than Yuan et al. study [41].

Conclusion

In conclusion, our research reveals a significant association between the A allele of *XRCC1* polymorphism rs1799782 and OC risk in our cohort of patients. Moreover, the T allele of rs1130409 polymorphism of *APEX1* and T allele of rs1799794 polymorphism of *XRCC3* were associated with a higher risk of developing hereditary or familial OC, respectively. The fact that these SNPs appear in the germ line makes it possible to hypothesized that these polymorphisms are associated with a worse DNA repair capacity, and that these patients can therefore be treated with PARP inhibitors, regardless of their *BRCA1/2* status. Given the importance of these data in future research on the prevention, treatment and prognosis of patients with OC, it is essential to analyze whether these results are confirmed in a larger study of our population.

Synopsis

Genetic variants in DNA repair genes have been related to ovarian cancer risk and predisposition. Depending on the disease inheritance, the single-nucleotide polymorphisms that are associated with ovarian cancer risk may vary, which could be important in the prevention, treatment and prognosis of these patients.

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Authors Contribution

Conceptualization, R.G.-S and MJ.D.S; Methodology, M.G.F, M.O.-S and A.M.-M; Validation, R.G.-S; Formal analysis and investigation, M.G.F, M.O.-S and A.M.-M; Writing - original draft preparation, M.O.-S and A.M.-M, Writing - review and editing, M.O.-S, A.M.-M and R.G.-S; Funding acquisition, R.G.-S; Resources, M.G.F, EM. S.-T, T.M.G, MJ.D.S and R.G.-S and Supervision, MJ.D.S and R.G.-S. All authors have read and agreed to the published version of the manuscript.

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