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LETTER TO THE EDITOR

XRCC1 Arg399Gln and RAD51 5′UTR G135C polymorphisms and their outcome in tumor aggressiveness and survival of Portuguese breast cancer patients

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Breast cancer (BC) is the most common type of cancer in female, including Portugal, where this disease presents the highest incidence and mortality rates [1]. BC risk factors, like prolonged exposure to estrogen and/or ionizing radiation, *BRCA1, BRCA2, TP53, ATM* and *CHEK2* mutations [2, 3], are related with an increased chance of DNA damage, acting as initiators of cellular alterations. DNA repair pathways are critical processes in order to maintain genome integrity. Therefore, genetic polymorphisms in DNA repair genes are common events [4]. We previously showed correlations of some of these genetic variations, as *XRCC1 Arg399Gln, RAD51 5'UTR G135C* and *XRCC3 Thr241Met*, with changeable BC susceptibility [5].

In the present study, we aimed to investigate the possible correlations between DNA repair polymorphisms with BC clinico-pathological phenotypes, identifying subgroups of patients according to their genetic background.

We analysed DNA from 165 BC patients, including 33 unrelated family history (FH) and 132 sporadic BC cases from Surgical Departments of S. João Hospital and the Oncology Portuguese Institute, at Porto. All participants provided informed consent. Patients presented a mean age of 51.01 years (standard deviation (SD) ± 12.68).

We determined *XRCC1 Arg399Gln, RAD51 5″UTR G135C* and *XRCC3 Thr241Met* genotypes by PCR-RFLP technique, as previously described [5]. Chi-square (χ^2 test) analysis was used to compare different variables. Logistic regression analysis was applied to calculate the adjusted p value for age and FH in identification of subgroups of patients according to genotypes. The Kaplan-Meier method was used to estimate overall survival (OS). OS was defined as minimal 60 months follow-up, from clinical diagnosis until death or censorship (were alive at the end of the follow-up time period). Differences on OS were obtained by Log Rank test.

The correlation of the analysed DNA repair polymorphisms with some clinical-pathological features is presented in Table 1. According to our results, *XRCC1 Gln/Gln* genotype seems to be associated with less aggressive tumors, since this genotype was correlated with well differentiated tumors ($p = 0.022$ adjusted for age and BC FH, using logistic regression analysis). Deficient efficiency of the XRCC1 protein has been described in *XRCC1 Gln399* variant [6, 7]. Furthermore, repair of more complex base lesions [8, 9, 10] by base excision repair (BER) pathway can potentially convert

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Table 1 Correlation between DNA repair polymorphisms and clinical pathological parameters in Portuguese breast cancer patients

Parameters	*XRCC1 Arg399Gln*		*RAD51 G135C*		*XRCC3 Thr241Met*	
	Gln/Gln	Others	*GC* or *CC*	*GG*	*Met/Met*	*Others*
Histological Type						
Invasive ductal	23 (92.0)	115 (86.5)	32 (91.4)	113 (86.9)	23 (88.5)	120 (88.2)
Invasive lobular	0 (0.0)	3 (2.3)	0 (0.0)	3 (2.3)	1 (3.8)	2 (1.5)
Others	2 (8.0)	15 (11.3)	3 (8.6)	14 (2.3)	2 (7.7)	14 (10.3)
P value	0.654		0.606		0.665	
Histological Grade						
I	5 (23.8)	8 (7.1)	6 (18.2)	9 (8.3)	1 (4.0)	14 (12.4)
II	6 (28.6)	61 (54.0)	21 (63.6)	51 (47.2)	11 (44.0)	57 (50.4)
III	10 (47.6)	44 (38.9)	6 (18.2)	48 (44.4)	13 (52.0)	42 (37.2)
P value	0.021[a]		0.017[b]		0.269	
Axillary lymph node status						
Negative	10 (41.7)	52 (40.0)	12 (40.0)	54 (41.5)	8 (32.0)	57 (43.5)
Positive	14 (58.3)	78 (60.0)	18 (60.0)	76 (58.5)	17 (68.0)	74 (56.5)
P value	0.878		0.877		0.285	
Oestrogen receptor status						
Negative	1 (33.3)	9 (31.0)	2 (28.6)	7 (25.9)	1 (33.3)	8 (27.6)
Positive	2 (66.7)	20 (69.0)	5 (71.4)	20 (74.1)	2 (66.7)	21 (72.4)
P value	0.935		0.888		0.833	
Survival status at last follow-up						
Death	3 (15.0)	13 (12.5)	2 (8.3)	15 (14.0)	1 (4.0)	16 (15.4)
Alive	17 (85.0)	91 (87.5)	22 (91.7)	92 (86.0)	24 (96.0)	88 (84.6)
P value	0.760		0.454		0.131	
Recurrence at last follow-up						
No	14 (77.8)	74 (82.2)	19 (86.4)	74 (80.4)	20 (87.0)	72 (80.0)
Yes	4 (22.2)	16 (17.8)	3 (13.6)	18 (19.6)	3 (13.0)	18 (20.0)
P value	0.658		0.519		0.444	

[a] p value = 0.022, adjusted for age and history family of breast cancer to compare the influence of different genotypes in histological grade (I vs II/III grade), using logistic regression analysis

[b] p value = 0.011, adjusted for age and history family of breast cancer to compare the influence of different genotypes in histological grade (I/II vs III grade), using logistic regression analysis

non-lethal lesion into lethal double strand breaks [11, 12]. Thus, deficiency in BER, by low efficiency of XRCC1, may actually reflect a well differentiated nature of the tumor cells in less aggressive tumors, since less lethal lesions are produced.

We also observed that *RAD51 C135* genotypes show a relationship with more aggressive tumors and also with a poorer OS, since we found a significant association of *RAD51 C135* genotypes with moderate to poor differentiated grade ($p = 0.011$, adjusted for age and BC FH, using logistic regression analysis). Additionally, assessment of OS demonstrated that patients with *RAD51 C135* genotypes (102.87 months mean OS) presented a poorer survival compared with other genotype (136.36 months mean OS) (Fig. 1). These results can be explained by the location of this polymorphism in the untranslated region, may be affecting mRNA stability and/or translation efficiency, leading to altered RAD51 protein levels [13]. Thus, RAD51, the key factor of homologous recombination process, can disturb the activity of the multi protein DNA repair complex, including BRCA1, BRCA2 and XRCC3, contributing to high levels of genetic instability [14], and as a result, being correlated with more aggressive breast tumors and poor survival.

We had previously showed *XRCC1 Arg399Gln* and *RAD51 5′UTR G135C* as important polymorphism to predict breast cancer risk [5]. According to the present results, we clearly underlie the role of these same polymorphisms in the prediction of breast tumor aggressiveness and patients' survival.

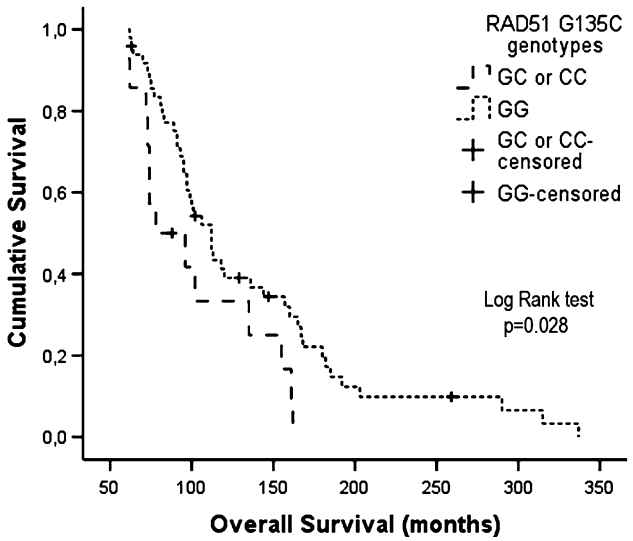

Fig. 1 Kaplan-Meier overall survival curve in breast cancer patients relating with *RAD51 G135C* polymorphism. Log-rank test for statistical analysis

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