Investigation of the significance of *TP53* gene polymorphism in *BRCA1/2* negative hereditary breast and ovarian cancer

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1. Introduction

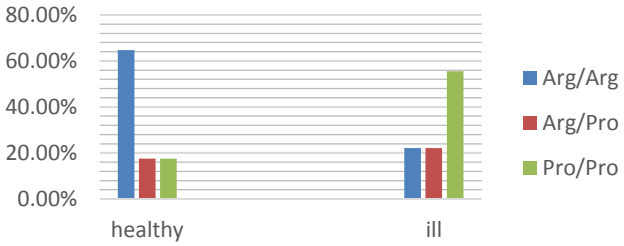
Breast cancer is the most common malignant disease among women, representing as much as 23% of all cancers. Among the most frequent risk factors for developing this cancer are: age, high density of breast tissue, overweight, high radiation dose and genetic predisposition [1]. *BRCA1* and *BRCA2* are the most commonly mutated genes in hereditary breast and ovarian cancer, responsible for 20% - 40% of cases. They belong to highly penetrant genes, whose mutations are rarely seen in the population, but, on the other hand, they highly increase the risk for cancer. Although they contribute with high risk for the illness, mutations in the *BRCA1/2* genes can not explain the entire corpus of hereditary cancer, and today it is known that other genes also influence the occurence of hereditary predisposition [2]. *TP53* is a tumor suppressor gene, one of the most commonly mutated gene in human cancers. Its main role is to remove damaged cells and inhibit their proliferation, and it also induces the formation of proapoptotic proteins [3]. Arg72Pro is a gene polymorphism where guanine is changed to cytosine in codon 72 of exon 4. CCC enccodes for proline and CGC for arginine [4]. The aim of this research is to determine the significance of Arg72Pro polymorphism in the *TP53* gene among *BRCA1/2* negative patients with multiple primary carcinoma, originated from families with accumulation of breast and ovarian carcinoma.

2. Materials and Methodes

The total number of participiants was 35 and they were all female. 18 of them had multiple primary carcinoma, and 17 healthy women made up a control group. All patients originate from families with acuumulated breast and ovarian carcinoma and they were all negative for mutations in *BRCA1/2* genes. For the isolation of DNA from lymphocytes, BlodPrepTM Chemistry Kit was used, which isolates DNA from fresh or frozen blood and cell cultures. Shimadzu BioSpec-nano UV/Vis spectrophotometer was used, in order to measure the concentration and purity of the DNA. PCR multiplied 296 base pairs of the exon 4 *TP53* gene. Amplification products of PCR were analyzed on 2% agarose gel. After second measument of the concentration of the DNA, the samples were incubated with restriction enzyme *Bsh1236I*. By the presence of the enzyme, Arg allele disassembles and produces 126 and 170 base pairs, while Pro allel remains unharmed with 296 base pairs. The results were read on Agilent BioAnalyzer microchip.

3. Results

Of the total of 18 patients who had previously been identified with cancer, 55.60% had Pro/Pro genotype, and only 22.20% both per Arg/Pro and Arg/Arg. In the control group, the situation was reversed, Arg/Arg genotype was observed in 64.70% of samples, and only 17.60% were representatives of Pro/Pro and Arg/Pro. The overall occurence of Pro allele in patients with multiple primary carcinoma was 66.70%, and in healthy representatives, it was found in only 26.50% of them. These results show a significant statistical difference between this group with the factor $p < 0.001$ ($p = 0.000759$)



Picture 1. Graphic of representation of both genotypes among healthy and ill people

4. Conclusion

The results of this study showed that in the *TP53* gene, codon 72, gene for proline was statistically significantly more represented than the gene for arginine in *BRCA1/2* negative individuals with multiple primary carcinoma, while in the contol group the situation was opposite. Preliminary results on a selected group of rare cases of multiple primary carcinoma suggest that Pro allel of Arg72Pro polymorphic variants of the *TP53* gene represents a higher risk and may be a potential additional marker for the selection of high risk patients. Since multiple primary carcinoma within the hereditary breast and ovarian cancer syndrome is very rare, for further research it is necessary to expand the investigated group to confirm these preliminary results.

5. References

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