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**Article** · January 2016

DOI: 10.7754/Clin.Lab.2016.151128

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## ORIGINAL ARTICLE

# Analysis of the Association between MDM4 rs4245739 Single Nucleotide Polymorphism and Breast Cancer Susceptibility

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## SUMMARY

***Background:*** **MDM4 is a negative regulator of the p53 tumor suppression pathway. Recent studies have revealed that the rs4245739 A>C polymorphism of MDM4 in the 3′-untranslated region makes it a miR-191 target site which leads to lower MDM4 expression. This study is aimed to detect if rs4245739 single nucleotide polymorphism (SNP) of the MDM4 gene influences the breast cancer development in Iranian-Azeri women.**
***Methods:*** **Blood samples were taken from 260 healthy controls and 220 breast cancer women with ethnicity of Iranian-Azeri. Genotyping was done using Tetra-ARMS PCR.**
***Results:*** **Alleles of MDM4 rs4245739 SNP had no significant different frequency between patients and controls ($p > 0.05$). Additionally, genotypes of MDM4 rs4245739 SNP did not increase or decrease breast cancer risk in patients when compared to healthy women. Also, there was no significant association between the alleles of MDM4 rs4245739 SNP and clinicopathological factors ($p > 0.05$).**
***Conclusions:*** **Considering the lack of association between MDM4 rs4245739 polymorphism and breast cancer, rs4245739 polymorphism of this gene seems to have no significant role in the pathophysiology of the disease. (Clin. Lab. 2016;62:1303-1308. DOI: 10.7754/Clin.Lab.2016.151128)**

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Manuscript accepted January 2, 2016

**KEY WORDS**

breast cancer, MDM4, polymorphism, ARMS PCR

## INTRODUCTION

Breast cancer is a heterogeneous group of malignancies and classified into certain subtypes according to various clinical manifestations. The heterogeneity of breast cancer has been linked to individuals and genetic variability [1]. Breast cancer is the main cause of cancer-associated mortality and the most common malignancy of women worldwide [2]. The incidence of breast cancer is rising, and this increase is high in the developing countries of Africa, Southeast Asia, and South America [3]. The etiology of breast cancer is unclear and multifactorial, the result of the interactions between genetic, environment-

al, and lifestyle-related risk factors [4]. In respect of gene role, several mutations especially in *BRCA1* and *BRCA2* as well *P53* and DNA repair-related genes such as *ATM*, *ATM1*, and *PALB2* have been detected to be associated with breast cancer [5]. It has been shown that the incidence difference of breast cancer is associated with geographical variation which can be linked to exposure towards various risk factors which implies a role of environment in breast cancer. Among the major environmental factors are no breast feeding, early menarche, late menopause, late first full-term pregnancy, nulliparity, and family history of breast cancer in two or more first-degree relatives [6,7].

On the other side are the genome-wide association studies (GWAS) with emphasis on the direct genetic association of single nucleotide polymorphisms (SNPs) with breast cancer risk [8]. However, almost all breast cancer-related SNPs have failed to disclose the role of genetic factors in the development and progression of breast cancer [9]. As a result, follow-up studies to novel potential SNPs, pertaining to breast cancer risk, seem to be a worthwhile approach to investigate the genetic role in breast cancer.

Mouse double minute 2 homolog (MDM2), a major negative regulator of tumor suppression pathway of p53, acts through direct binding to p53 which leads to ubiquitination and then degradation of p53 [10]. Mdm4 p53 binding protein homolog (MDM4) which structurally has homology with MDM2, can collaborate with MDM2 to inhibit p53 activity when cells respond to DNA damage [11]. Furthermore, MDM4 can interact with MDM2 protein and inhibit degradation of MDM2 [12]. MDM4 becomes phosphorylated in response to DNA damage, which results in a shift from the degradation of p53 to the degradation of MDM4. The consequence is stabilization of p53 and cell cycle suppression [13]. It has been shown that transgenetic mice overexpressing MDM4 develop spontaneous carcinogenesis which makes it more clear that MDM4 may act as an oncogene *in vivo* interacting with p53 [14].

The SNP, rs4245739 A>C, in the 3′-untranslated region (3′-UTR) of MDM4 has been shown as a putative target site for miR-191 [15]. It has been shown that miR-191 can selectively bind to the C allele contained in MDM4 mRNA but not the A allele contained in MDM4 mRNA. Therefore, this results in a lower level expression of the C allele contained in MDM4 mRNA. This phenomenon perhaps explains the significantly increased expression of MDM4 mRNA and protein in MDM4 rs4245739 A allele carriers in malignancies [16]. P53 pathway malfunctions have pivotal roles in mammary tumorogenesis. Furthermore, MDM4 has been shown to be overexpressed in almost 19% of breast cancer cases [17]. Considering the role of the p53-MDM4 pathway in preventing tumor development, we hypothesized that rs4245739 A>C polymorphism of MDM4 might be involved in breast cancer.

## MATERIALS AND METHODS

### Subjects

In this study, genetic analysis was performed on a total of 480 individuals which comprised 220 unrelated breast cancer patients and 260 healthy women with no history of cancer. Patients with histologically confirmed breast cancer were chosen from Imam Reza Hospital, Tabriz, Iran. Clinical status of the cases was collected through 2013 until 2014 according to documentary files of patients diagnosed by physicians and pathologists. All study patients were native of Azerbaijan to elicit valid results of race-related associations. Also, healthy women had the same race as the patients. As a rational point, patients and healthy controls were age-matched. All of the participants have given informed written consent, and the study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (TUMS), which was in compliance with the Helsinki Declaration. Five milliliters of venous blood was taken from each patient and control in EDTA-anticoagulated venoject tubes. Afterwards, genomic DNA was extracted from peripheral blood using a salting-out approach.

### Genetic analysis

We designed the T-ARMS-PCR assay for allele and genotype detection. The primers were designed using Primer3Plus (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi) and were blasted in the NCBI website: http://www.ncbi.nlm.nih.gov/tools/primer-blast/ (Table 1). The allele-specific (inner) primer was designed in opposed directions and, in combination with the common primers, can simultaneously amplify both the mutant allele and wild type alleles in a single-tube PCR. PCR-amplified DNA samples were electrophoresed through agarose gel (2%). After that, a number of amplicons were examined randomly by DNA sequencing in order to confirm if the results determined by T-ARMS-PCR were in concordance with those determined by sequencing.

Genotyping was performed by T-ARMS PCR using the Taq-PCR Master Mix (Cat. No. 5200350-0050, Lot. No. 13C18, amplicon, Denmark) and the thermocycler PCR System (SensoQuest, Germany). Each reaction mixture contained a total volume of 26.4 µL (master mix 10 µL, forward and reverse inner primer 1 µL each, forward and reverse outer primer 0.2 µL each, and $H_2O$ 12 µL). The thermocycler conditions were: 95°C for 5 minutes, then 35 cycles of 95°C for 30 seconds 56°C for 30 seconds, and 72°C 40 seconds and final extension of 72°C for 10 minutes.

### Statistical analysis

Genotype and allelic distribution between case and control groups were implemented by Fisher's exact test. Pearson's $\chi 2$ tests were applied to test for significant differences of both genotype and allele frequencies between two groups. Universally, $\alpha = 0.025$ was regarded as the significant level. Moreover, the odds ratio (OR)

and 95% confidence interval (CI) were calculated. The genotype distributions of chosen SNPs were tested for deviation from Hardy-Weinberg equilibrium in case and control. The Bonferroni correction test was used in multiple statistical testing (i.e., p-value was set to < 0.01) to recognize statistically significant results, adjusting the multiple comparison, and controlling the false discovery rate (FDR) [18]. Also, several statistical analyses were performed using the SPSS for Windows (version 22.0, IBM SPSS Inc., USA). Additionally, the SHEsis online software was used for analyzing the haplotype and genotype, and also Hardy-Weinberg equilibrium for gene-gene interactions [19].

## RESULTS

Specifications of the study subjects according to genotype distribution are listed in Table 2. Most of the patients (72.3%) were detected at the age of more than 40 and the rest 27.7 percent were less than 40 years old. Breast cancer women had the mean age of 46.9 ± 10.47 and healthy women were 44.8 ± 9.74. There was no significant difference in age distributions between the two groups (p > 0.05). Furthermore, there was no significant difference in the age of patients with genotypes of MDM4 rs4245739. The side of the involved breast was equally distributed between the patients. Also there was no significant difference between genotypes of MDM4 rs4245739 and the side of involved breast in women. Tumor types of women mainly were found to be IDC (90%). Other types, ILC and DCIS, had frequencies of approximately 10% collectively. However, genotypes of MDM4 rs4245739 had no significant association with tumor type in women. Using TNM classification criteria [20], approximately 20% of the women were detected to be at stage I, and 68.5% of them were at stage II. But 11.5% of the cases were at stage III. Size of tumor in the patients with AA, AC, and CC genotype was 3.94 cm ± 2.2 cm, 3.94 cm ± 2.6 cm, and 3.8 cm ± 1.4 cm, respectively. About 80% of patients had 0 - 10 lymph nodes involved, but 20% of women collectively had 10 - 20 and 20 - 30 lymph nodes involved . However, the amount of involved lymph nodes was not associated with the genotypes of MDM4 rs4245739 (A/C) polymorphism.

The rs4245739 (A/C) polymorphism was analyzed in 220 breast cancer patients and 260 healthy subjects. Distributions of the rs3129882 (A/G) polymorphism in both breast cancer and healthy groups disclosed no evidence of deviation from Hardy-Weinberg's equilibrium. The A allele of MDM4 rs4245739 (A/C) polymorphism was detected in 75.2% of the patients and 77.4% of the healthy individuals. Furthermore, the C allele showed equal distribution between patients and controls (24.8% vs. 22.6%, respectively). Hence, there was no significant difference in the A and C allele frequencies of rs4245739 SNP between the patient and the control groups (p = 0.46, OR = 1.90, 95% CI: 0.66 - 1.21 vs. p = 0.48, OR = 1.109, 95% CI: 0.82 - 1.49, respectively).

The AA genotype was disclosed to be the most common genotype, which was represented in 55.4% of the patients and 60.3% of the controls (p = 0.09, OR = 0.73, 95% CI: 0.50 - 1.05). The frequency of the AC genotype in the patients was higher than in the control group, albeit this difference was not significant (39.8% vs. 34.2%, respectively; p = 0.07, OR = 1.44, 95% CI: 0.99 - 2.10). Finally, there was no significant difference with respect to the CC genotype between the patient and the control groups (4.8% vs. 5.5%, respectively; p = 0.17, OR = 0.83, 95% CI: 0.36 - 1.92).

## DISCUSSION

Breast cancer has been regarded as a major cause of morbidity and mortality for women all over the world. Genetic alterations have been associated with the development of the disease [21]. Several studies in past two years have pointed on the pivotal importance of MDM4 in human cancers. It has been shown that MDM4 is conceivably amplified or overexpressed in roughly 10 - 20% of over 800 different tumors such as lung, colon, stomach, and breast cancers [22]. Association studies, mainly GWAS, have been used in an attempt to identify common genetic variations that carry an increased risk for developing the disease. Among the candidates for being the functionally relevant gene mapped by GWAS hits, is the MDM4 rs4245739 polymorphism [23]. In this study, in order to make the results more reliable, standard confirmed safeguards were employed to decrease possible biases. All breast cancer and healthy women were selected from a population native of the same geographic region (Iranian-Azeri women). In this case-control study, we contemplated a hypothesis to examine if there is potential association between MDM4 rs4245739 polymorphism and the breast cancer risk. To our best knowledge, this is the first gene association study in Iranian-Azeri women to survey the association between the MDM4 rs4245739 polymorphism and breast cancer risk.

It has been shown that the p53 pathway is inactivated in almost all human cancers [24]. About half of human malignancies have been estimated to carry mutations in the TP53 gene itself whereas the remaining tumors with wild type TP53 have genetic alterations in other key regulatory genes in the p53 pathway [25,26]. Among others, genetic amplification of the MDM2 or MDM4 genes can result in aberrant protein expression and suppression of the p53 response over the course of tumor development [11,27]. Furthermore, data suggests that polymorphisms at the MDM2 or MDM4 loci may contribute to increased basal expression of these important p53 antagonists and increase cancer susceptibility [28-30]. The MDM4 rs4245739 polymorphism in the 3'-untranslated region (3'-UTR) creates a potential target site for micro RNA-191 [15]. The miR-191 can selectively

**Table 1. Primers used in T-ARMS PCR, the amplicon size, and melting temperature (°C) of each reaction.**

| SNP | | Sequence | Amplicon Size | Tm (°C) |
|---|---|---|---|---|
| MDM4 A/C | Forward inner primer (A allele) | 5′GTAGTACGAACATAAAAATGCATTTATCCA3′ | 232 | 56 |
| | Reverse inner primer (C allele) | 5′ATTTTCAAATAATGTGGTAAGTGAGCG3′ | 275 | 56 |
| | Forward outer primer | 5′ACAGAGAACAGATACAGAAAACATGGAG3′ | 450 | 56 |
| | Reverse outer primer | 5′ACCTAACTATGTACCTGACTGCTGCATA3′ | 452 | 56 |

**Table 2. Correlation of several clinical statuses of patients with genotypes of MDM4 and p53.**

| Clinical properties | Total Count | MDM4 | | | p-value |
|---|---|---|---|---|---|
| | | AA | AC | CC | |
| **Age** | | | | | |
| < 40 | 60 (27.3%) | 37 (17%) | 20 (9%) | 3 (1.3%) | 0.502 |
| ≥ 40 | 160 (72.7%) | 85 (38.3%) | 67 (30.5%) | 8 (3.3%) | |
| **Involved-Breast Side** | | | | | |
| Right | 109 (49.5%) | 64 (29%) | 40 (18%) | 5 (1.9%) | 0.567 |
| Left | 111 (50.5%) | 58 (26.2%) | 47 (21.3%) | 6 (2.9%) | |
| **Tumor Type** | | | | | |
| IDC | 197 (89.5%) | 113 (51.4%) | 75 (34%) | 9 (3.8%) | 0.396 |
| ILC | 13 (5%) | 4 (1.5%) | 8 (3.3%) | 1 (0.5%) | |
| DCIS | 10 (4.5%) | 5 (2.4%) | 4 (2%) | 1 (0.5%) | |
| **Grade of Tumor** | | | | | |
| I | 42 (19%) | 26 (11.65%) | 14 (6.8%) | 2 (0.9%) | 0.223 |
| II | 151 (68.6%) | 83 (37.8%) | 60 (27.1%) | 8 (3.3%) | |
| III | 27 (12.2%) | 13 (5.8%) | 13 (5.8%) | 1 (0.5%) | |
| Size of Tumor (cm) | 220 | 3.94 ± 2.2 | 3.94 ± 2.6 | 3.8 ± 1.4 | 0.982 |
| **Count of Involved Lymph Nodes** | | | | | |
| 0 - 10 | 175 (79.5%) | 96 (43.6%) | 67 (30.5%) | 12 (4.9%) | 0.474 |
| 10 - 20 | 37 (16.8%) | 21 (9.9%) | 16 (7.2%) | 0 (0%) | |
| 20 - 30 | 8 (3.6%) | 4 (2%) | 4 (2%) | 0 (0%) | |
| **Stage of Cancer** | | | | | |
| S0 | 9 (4%) | 4 (2%) | 4 (2%) | 1 (0.5%) | 0.421 |
| IA | 24 (109%) | 8 (3.9%) | 16 (7.2%) | 0 (0%) | |
| IIA | 40 (18.1%) | 25 (11.6%) | 13 (5.9%) | 2 (1%) | |
| IIIA | 45 (20.4%) | 27 (12.2%) | 16 (7.2%) | 2 (1%) | |
| IB/IIA | 8 (3.6%) | 4 (2%) | 3 (1.5%) | 1 (0.5%) | |
| IB | 1 (0.5%) | 0 (0%) | 1 (0.5%) | 0 (0%) | |
| IIB | 25 (11.3%) | 15 (6.8%) | 7 (3.4%) | 3 (1.5%) | |
| IIIB | 27 (12.3%) | 18 (8.2%) | 9 (4%) | 1 (0.5%) | |
| IC | 1 (0.5%) | 0 (0%) | 1 (0.5%) | 0 (0%) | |
| IIC | 1 (0.5%) | 1 (0.5%) | 0 (0%) | 0 (0%) | |
| IIIC | 39 (17.7%) | 21 (9.5%) | 18 (8.1%) | 0 (0%) | |

**Table 3. Allele and genotype distribution of MDM4 and p53 in breast cancer cases and healthy controls.**

| dbSNP | Alleles/ Genotypes | Case (n = 220) n (%) | Control (n = 260) n (%) | p | Adj. p [a] | OR (95% CI) |
|---|---|---|---|---|---|---|
| MDM4 | C | 109 (24.8%) | 119 (22.6%) | 0.486 | 0.45 | 1.109 (0.8238 - 1.4947) |
| | A | 331 (75.2%) | 401 (77.4%) | 0.468 | 0.45 | 0.9012 (0.6690 - 1.2138) |
| | CC | 10 (4.8%) | 14 (5.5%) | 0.176 | 0.15 | 0.8367 (0.3641 - 1.9230) |
| | AC | 87 (39.8%) | 81 (34.2%) | 0.078 | 0.09 | 1.4456 (0.9918 - 2.1069) |
| | AA | 123 (55.4%) | 165 (60.3%) | 0.092 | 0.12 | 0.7301 (0.5059 - 1.0536) |
| HWE | | 0.325957 | 0.738510 | | | |

[a] - Adjusted p-value for multiple testing using Benjamini-Hochberg method, OR - odds ratio, CI - confidence interval.

bind to the MDM4-C allele mRNA but not MDM4-A allele mRNA, and therefore may result in a decreased expression of MDM4-C allele mRNA. This may explain the observation of a significantly increased expression of MDM4 mRNA and protein in MDM4 rs4245739 A allele carriers of ovarian cancer and retinoblastoma [15,16].

An ascertainment looking at the consequence of gene-gene interplay was done by Jibing Liu et al., and they reported that functional MDM4 rs4245739 SNP, alone and in combination with p53 Arg72Pro genetic variant, was associated with a significantly decreased risk of breast cancer in Chinese women. Meanwhile, they postulated that perhaps genetic variants modifying microRNA-mediated gene regulation could be regarded as an important genetic regulation approach in breast cancer risk and mark the potential role of genes in the p53 tumor suppressor pathway in the initial steps of affecting as well during breast cancer development [31]. In our investigation, in contrast to the findings of Jibing Liu in Chinese population, the alleles and genotypes of MDM4 rs4245739 SNP were not significantly more frequent in patients in comparison to controls. Therefore, none of the alleles could affect the risk of breast cancer in our population. Genetic heterogeneity or sample size differences among various studies may be the cause of such discrepancies. Technical differences in the genotyping assay can be another potential reason for such incongruity.

The potential risk for breast cancer underlies several clinical characteristics which supposedly can affect contracting cancer, disease level, or being healthy. Regarding the research proven clinical manifestation of breast cancer, we attempted to correlate age of onset, involved-breast side, tumor type, grade of tumor, size of tumor, number of involved lymph nodes, and stage of cancer with various genotypes in MDM4 rs4245739 SNP towards breast cancer risk. It was observed that none of the clinical characteristics were associated with various genotypes of MDM4 rs4245739 SNP. We found no statistically significant association between genotype distribution and specific prognostic predictors and clinical features for breast cancer outcome. Therefore, at least according to our data, MDM4 rs4245739 A>C SNP did not interfere with the clinical features of breast cancer. It seems that long time follow-up of the patient's clinical changes will facilitate to elicit a more definitive conclusion pertaining to the influence of this polymorphism on breast cancer manifestation. It has been proven that the more distinct biological property of breast cancer is described by an enduring natural period and delayed development of metastases; therefore, more than 10 year follow-up periods are commonly a requisite factor in order to efficiently and accurately evaluate prognostic factors in breast cancer [32].

## CONCLUSION

This is the first study designed to assess the role of the MDM4 rs4245739 gene variants in a replicated case-control of Iranian-Azeri women with breast cancer. We could not identify a significant difference in either allelic and genotype frequency in the breast cancer group compared with the control group. Last but not least, these results suggest the MDM4 rs4245739 (A/C) polymorphism may not be a risk factor for breast cancer in Iranian-Azeri population. However, further studies are still needed to validate these data in other populations.

**Acknowledgement:**
We are thankful of the cordial collaboration of conscientious personnel of the Department of Medical Genet-

ics of Tabriz University of Medical Sciences and Nour-Nejat Hospital of Tabriz, Iran.

**Declaration of Interest:**
There is no conflict of interest.

## References:


1. Poller D, Barth A, Slamon D, et al. Prognostic classification of breast ductal carcinoma-in-situ. Lancet 1995;345(8958):1154-7.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin 2008;58(2):71-96.
3. Agarwal G, Ramakant P, Forgach ERS, et al. Breast cancer care in developing countries. World J Surg 2009;33(10):2069-76.
4. Byrne C, Brinton LA, Haile RW, Schairer C. Heterogeneity of the effect of family history on breast cancer risk. Epidemiology 1991;2(4):276-284.
5. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007, 447(7148):1087-93.
6. Pakseresht S, Ingle G, Bahadur A, et al. Risk factors with breast cancer among women in Delhi. Indian J Cancer 2009;46(2):132.
7. Porter PL. Global trends in breast cancer incidence and mortality. Salud Publica Mex 2009;51:s141-6.
8. Cavallaro S, Paratore S, de Snoo F, et al. Genomic analysis: toward a new approach in breast cancer management. Crit Rev Oncol Hematol 2012;81(3):207-23.
9. Eichler EE, Flint J, Gibson G, et al. Missing heritability and strategies for finding the underlying causes of complex disease. Nat Rev Genet 2010;11(6):446-50.
10. Landers JE, Cassel SL, George DL. Translational enhancement of mdm2 oncogene expression in human tumor cells containing a stabilized wild-type p53 protein. Cancer Res 1997;57(16):3562-8.
11. Wade M, Wang YV, Wahl GM. The p53 orchestra: Mdm2 and Mdmx set the tone. Trends Cell Biol 2010;20(5):299-309.
12. Linares LK, Hengstermann A, Ciechanover A, Müller S, Scheffner M. HdmX stimulates Hdm2-mediated ubiquitination and degradation of p53. Proc Natl Acad Sci USA 2003;100(21):12009-14.
13. Wang YV, Wade M, Wong E, Li Y-C, Rodewald LW, Wahl GM. Quantitative analyses reveal the importance of regulated Hdmx degradation for p53 activation. Proc Natl Acad Sci USA 2007;104(30):12365-70.
14. Xiong S, Pant V, Suh Y-A, et al. Spontaneous tumorigenesis in mice overexpressing the p53-negative regulator Mdm4. Cancer Res 2010;70(18):7148-54.
15. Wynendaele J, Böhnke A, Leucci E, et al. An illegitimate microRNA target site within the 3′ UTR of MDM4 affects ovarian cancer progression and chemosensitivity. Cancer Res 2010;70(23):9641-9.
16. McEvoy J, Ulyanov A, Brennan R, et al. Analysis of MDM2 and MDM4 single nucleotide polymorphisms, mRNA splicing and protein expression in retinoblastoma. PloS One 2012;7(8):e42739.
17. Danovi D, Meulmeester E, Pasini D, et al. Amplification of Mdmx (or Mdm4) directly contributes to tumor formation by inhibiting p53 tumor suppressor activity. Mol Cell Biol 2004;24(13):5835-43.
18. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Statist Soc B 1995:289-300. https://www.jstor.org/stable/2346101?seq=1#page_scan_tab_contents
19. Yong Y, Lin H. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res 2005;15(2):97-8.
20. Sobin LH, Fleming ID. TNM classification of malignant tumors, (1997). Cancer 1997;80(9):1803-4.
21. Van de Vijver MJ. Genetic alterations in breast cancer. Current Diagnostic Pathology 2000, 6(4):271-81. Doi: 10.1054/cdip.2000.0043
22. Eischen CM, Lozano G. The Mdm network and its regulation of p53 activities: a rheostat of cancer risk. Hum Mutat 2014;35(6):728-37.
23. Fachal L, Dunning AM. From candidate gene studies to GWAS and post-GWAS analyses in breast cancer. Curr Opin Genet Dev 2015;30:32-41.
24. Vousden KH, Lane DP. p53 in health and disease. Nat Rev Mol Cell Biol 2007;8(4):275-83.
25. Horn H, Vousden K. Coping with stress: multiple ways to activate p53. Oncogene 2007;26(9):1306-16.
26. Marine JC, Jochemsen AG. Mdmx and Mdm2: brothers in arms? Cell Cycle 2004;3(7):900-4.
27. Marine JC, Francoz S, Maetens M, Wahl G, Toledo F, Lozano G. Keeping p53 in check: essential and synergistic functions of Mdm2 and Mdm4. Cell Death Differ 2006;13(6):927-34.
28. Bond GL, Hu W, Bond EE, et al. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell 2004;119(5):591-602.
29. Kulkarni DA, Vazquez A, Haffty BG, et al. A polymorphic variant in human MDM4 associates with accelerated age of onset of estrogen receptor negative breast cancer. Carcinogenesis 2009;30(11):1910-5.
30. Atwal GS, Kirchhoff T, Bond EE, et al. Altered tumor formation and evolutionary selection of genetic variants in the human MDM4 oncogene. Proc Natl Acad Sci USA 2009;106(25):10236-41.
31. Liu J, Tang X, Li M, et al. Functional MDM4 rs4245739 genetic variant, alone and in combination with P53 Arg72Pro polymorphism, contributes to breast cancer susceptibility. Breast Cancer Res Treat 2013;140(1):151-7.
32. Heimann R, Hellman S. Clinical progression of breast cancer malignant behavior: what to expect and when to expect it. J Clin Oncol 2000;18(3):591-9.