RESEARCH ARTICLE

The GADD45A (1506T>C) Polymorphism Is Associated with Ovarian Cancer Susceptibility and Prognosis

Cunzhong Yuan1,2, Xiaoyan Liu1,2, Xiaolin Liu1,2, Ning Yang1,2, Zhenping Liu1,2, Shi Yan1,2, Keng Shen3*, Beihua Kong1,2*

1 Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University, Jinan, Shandong, P.R. China, 2 Gynecologic Oncology Key Laboratory of Shandong Province, Qilu Hospital of Shandong University, Jinan, Shandong, P.R. China, 3 Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, P.R. China

Citation: Yuan C, Liu X, Liu X, Yang N, Liu Z, Yan S, et al. (2015) The GADD45A (1506T>C) Polymorphism Is Associated with Ovarian Cancer Susceptibility and Prognosis. PLoS ONE 10(9): e0138692. doi:10.1371/journal.pone.0138692

Abstract

GADD45A (growth arrest and DNA damage 45 A) is the first stress-inducible gene identified to be a target of p53. However, no studies to date have assessed variants of the GADD45 gene and their potential relationship to tumor susceptibility. We investigated the association of the GADD45A (1506T>C) polymorphism with ovarian cancer development in 258 ovarian cancer patients and 332 age-matched healthy women as controls using sequence analysis. We found a statistically significant difference in the GADD45A (1506T>C) genotype distributions between the case and control groups (TT vs. TC vs. CC, P = 0.0021) and found that variant 1506T>C was significantly associated with an increased risk of ovarian cancer (P < 0.001, OR = 1.71, 95% CI [1.28–2.29]). We observed a statistically significant effect between tumor histology (P = 0.032) and CA125 status (P = 0.021). Carrying the C allele (TC+CC) was associated with an increased risk of positive CA125 (OR = 3.20, 95% CI [1.15–8.71]). Carrying the T allele (TT+TC) showed a significant correlation with both higher GADD45A mRNA expression and longer ovarian cancer RFS (relapse-free survival) and OS (overall survival). We are the first group to demonstrate that the GADD45A (1506T>C) polymorphism is associated with ovarian cancer susceptibility and prognosis. These data suggest that GADD45A (1506T>C) is a new tumor susceptibility gene and could be a useful molecular marker for assessing ovarian cancer risk and for predicting ovarian cancer patient prognosis.

Introduction

Ovarian cancer is the deadliest cancer of the female reproductive system, with over 21,980 new cases and over 14,270 deaths in the United States in 2014 [1]. Similar to other malignancies, ovarian cancer occurs as a result of interactions between the environment and genetic factors.
An accumulation of genetic variants in many genes may be involved in the process of ovarian carcinogenesis [2]; for example, BRCA1, BRCA2, RAD51C, RAD51D, MLH1, MSH2, RB1, CASP8, LIN28B, SMAD6, ERCC4 and PRG have been implicated in this process [3–12]. Recently, genome-wide association studies (GWAS) have found several common susceptibility alleles in four loci with strong associations [13–15]. Braem et al. reviewed 147 candidate genes and 3 GWAS published from 1990 to October 2010, including approximately 1100 genetic variants in more than 200 candidate genes and 20 intergenic regions [8]. However, only a few genetic variants exhibited strong evidence of an association with ovarian cancer, and the identification of genes associated with a predisposition to ovarian cancer requires further investigation [8].

The growth arrest and DNA damage 45 (GADD45) family consists of three members, GADD45A, -B, and -G. The human GADD45A gene is located on chromosome 1 (1p31.2–31.1), contains 4 exons and 3 introns, encodes a 165 amino acid acidic protein (18.4 kDa), and is highly conserved in all species [16]. As a confirmed target of p53 [17, 18], GADD45A can be regulated by both p53-dependent (ionizing radiation) and p53-independent (non-ionizing radiation) pathways [19] and plays important roles in the G2/M checkpoint and in genome stability [18]. Multiple transcription factors, such as BRCA1, WT1, Oct-1, NF-YA, ATF4, AP-1, c-myc, ZBRK1, and Jun D, can regulate GADD45A expression by binding to the intronic or promoter region at the transcriptional level [16, 18, 20, 21].

Previous studies have shown that downregulation of GADD45A and GADD45G enables tumor cells to escape programmed cell death in multiple tumor types [22]. GADD45 expression is frequently decreased in non-small cell lung cancer [23], hepatocellular carcinoma [22], and glioblastoma [24]. The downregulation of GADD45 expression confers poor tumor prognosis and is correlated with the differentiation status. Abnormal methylation of the GADD45A gene promoter region has been found in multiple breast cancer cell lines and breast cancer samples, but not in lymph nodes or normal mammary epithelium [25]. GADD45A overexpression is associated with a favorable prognosis, which suggests that the abnormal methylation of GADD45 may contribute to breast cancer risk [25]. However, no GADD45A polymorphism associated with tumor susceptibility has been reported. A variant GADD45A (1506T>C) located at intronic regions was found in our study. Thus, we hypothesized that this variant might disrupt transcription factor binding sites, thereby altering GADD45A expression and affecting tumor genesis. Thus, we investigated the GADD45A (1506T>C) polymorphism, GADD45A expression, and ovarian cancer risk and prognosis.

Materials and Methods

Patients and Samples

This study included 258 patients diagnosed with ovarian cancer (mean age of 52.1± 13.9 years, from 21 to 81 years old) in Qilu Hospital (Shandong, China) between September 2008 and September 2012. Clinical characteristics, including age at diagnosis, degree of differentiation, FIGO stage, histological type, lymph node metastasis, CA125 status, and tumor size, were obtained from the patients’ medical records. In addition, 332 age-matched healthy women (mean age of 50.2 ± 13.4 years, from 21 to 82 years old) were recruited as controls from among patients undergoing a physical examination in our hospital. We calculated the GADD45A genotype with respect to relapse-free survival (RFS) and overall survival (OS) in 151 ovarian patients based on our ability to contact the patients. Most of the subjects were of Han Chinese background and resided in Shandong Province, China. All of the participants provided written informed consent to participate in this study. The Ethical Committee of Shandong University approved this research (IRB number: KYLL-
All participants (patients and controls) donated 2 ml of peripheral blood, which was stored at -80°C in our laboratory.

DNA was extracted using a TIANamp Genomic DNA Kit (Tiangen, Beijing, China) according to the manufacturer’s protocol. The DNA concentration and purity were measured using an ultraviolet spectrophotometer (GE Healthcare, USA). The DNA samples were routinely stored at -80°C.

Genotyping Analysis of GADD45A (1506T>C)

Genotyping of the GADD45A (1506T>C) polymorphism was performed using PCR and sequencing. The sequence of the GADD45A gene was obtained from NCBI (Gene ID: 1647, GenBank sequence, AY135686.1, GI: 22122007). Primers were designed using Primer Premier 5 according to the sequence of GADD45A as follows: forward primer 5'-AGTTTGCAACAGGCAACTCC-3' and reverse primer 5'-CCTGCTAAAGGAATTAGTCACG-3'. The PCR product size was 1255 bp. PCR amplification was performed in a final volume of 50 μL, containing 1 μL of genomic DNA (100 ng/μL), 4 μL of 2.5 mM dNTPs, 5 μL of buffer, 2 μL of each primer and 1 U of high fidelity Taq Polymerase (TransStart FastPfu Fly DNA Polymerase, Transgen, Beijing, China). The PCR amplification conditions were as follows: 94°C for 5 min, followed by 35 cycles of 94°C for 30 seconds, 61°C for 30 seconds, and 72°C for 2 min, and a final extension step of 72°C for 10 min. All sequencing was performed by BioSune Biotechnology Co., Ltd. (Shanghai, China), and the sequence data were analyzed using Chromas 2.31 and MegAlign 7.0 software.

RNA Isolation, Reverse Transcription PCR, and Quantitative Real-Time PCR (QRT-PCR)

Total RNA was extracted from cancer tissues using TRIzol reagent (Invitrogen) based on the suggested protocol. Reverse transcription PCR was performed using a PrimeScript RT-PCR kit (TaKaRa, Dalian, China). QRT-PCR was performed using the Applied Biosystems 7900HT Real-time PCR System. The mRNA sequence of the GADD45A gene was obtained from NCBI (NM_001924.3 GI: 315075321). The following primers were used to amplify the GADD45A gene: 5'-GAAAAGGATGGATAAGGTGGG-3' and reverse primer 5'-CCTGGATCAGGGTGAAGTGGA-3'. GAPDH (forward primer 5'-GGGCTGCTTTTAACTCTGGTAAAG-3' and reverse primer 5'-CCATGGGTGGAATCATATTGG-3') was used as the internal control. The experiments were repeated three times to confirm the findings.

Statistical Analysis

Statistical analyses were performed as previously described [26]. Hardy-Weinberg equilibrium was tested for all of the SNPs using a public web-based statistical tool (http://www.ogee.org/software/hwe-mr-calc.shtml), and the threshold for disequilibrium was P <0.05. The allele and genotype distributions in the ovarian cancer group and the control group were compared using chi-square tests, and Fisher’s exact test was used when the one cell count was <5. The risk of ovarian cancer development was estimated as an odds ratio (OR) with a 95% confidence interval (CI) using unconditional logistic regression analysis. The patient survival rates were estimated using the Kaplan-Meier method. Multivariate analysis of prognostic factors was performed using Cox regression analysis. All p-values were calculated as two-sided, and the threshold for significance was P <0.05. The data were analyzed using SPSS (Statistical Package for the Social Sciences) 17.0 (SPSS, Chicago, Illinois, USA).
Results
Relationship between the GADD45A (1506T>C) Polymorphism and Ovarian Cancer Risk

SNP GADD45A (1506T>C) is a novel, previously unidentified variant. Sequencing chromatograms from randomly selected cases were used to illustrate variants of GADD45A (Fig 1).

The participants in the ovarian cancer and control groups were all from Mainland China; there were no significant clinical differences (i.e., median age, body mass index [BMI], menstrual history or other related parameters) between the 2 groups. Hardy-Weinberg equilibrium was tested. The chi-square values of the case group and control group were 0.51 and 0.47, respectively. As shown in Table 1, the GADD45A (1506T>C) genotypes and allele distributions exhibited a statistically significant difference between the case and control groups. Strong associations with ovarian cancer risk were found for SNP 1506T>C in the log-additive genetic model (TT vs. TC vs. CC, P = 0.0021), dominant genetic model (TT + TC vs. CC, P = 0.0017, OR = 1.95, 95% CI [1.28–2.95]), and recessive genetic model (TT vs. TC+CC, P = 0.0093, OR = 2.05, 95% CI [1.19–3.53]). We observed a greater prevalence of C alleles (P<0.001, OR = 1.71, 95% CI [1.28–2.29]) in ovarian cancer patients compared to the controls.

In summary, variant 1506T>C is correlated with an increase in ovarian cancer risk.

Relationship between the GADD45A (1506T>C) Polymorphism and Clinicopathological Variables

As shown in Table 2, there is an association of the TT and TC+CC genotypes with the clinicopathological characteristics, including age at diagnosis, degree of tumor differentiation, clinical stage, lymph node metastasis, CA125 expression, tumor size and tumor histology. We observed a statistically significance effect between tumor histology (P = 0.032) and CA125 status (P = 0.021). Carrying the C allele (TC+CC) was associated with an increased risk of positive CA125 (OR = 3.20, 95% CI [1.15–8.71]).
Relationship between the GADD45A (1506T>C) Polymorphism and GADD45A Expression Levels

We further tested the potential relationship between the GADD45A (1506T>C) polymorphism and GADD45A mRNA expression levels in vivo. As shown in Fig 2A, the levels of GADD45A

| Genotype | Ovarian Cancer n(%)† | Controls n(%)† | P-value | OR 95%CI |
|----------|----------------------|---------------|---------|----------|
| TT       | 33(12.8)             | 77(23.1)      | 0.0021  | 1 (reference) |
| TC       | 110(42.4)            | 158(47.5)     | 1.61 (0.90–2.89) |
| CC       | 115(44.8)            | 97(29.4)      | 2.75 (1.51–5.00) |
| TT+TC    | 143(55.2)            | 235(70.6)     | 0.0017  | 1 (reference) |
| CC       | 115(44.8)            | 97(29.4)      | 1.95 (1.28–2.95) |
| TT       | 33(12.8)             | 77(23.1)      | 0.0093  | 1 (reference) |
| CC       | 115(44.8)            | 97(29.4)      | 1.95 (1.28–2.95) |
| TT       | 33(12.8)             | 77(23.1)      | 0.0093  | 1 (reference) |
| CC       | 115(44.8)            | 97(29.4)      | 2.75 (1.51–5.00) |

† The X² for Hardy-Weinberg equilibrium test results of the ovarian cancer group and the control group are 0.51 and 0.47, respectively (both P > 0.05).

doi:10.1371/journal.pone.0138692.t001

| Clinical data information | All (%) | Genotype | P-value | OR 95%CI |
|---------------------------|---------|----------|---------|----------|
| Age                       |         |          |         |          |
| <50                       | 88(34.3)| 15(5.8)  | 73(28.5)| 0.238    | 1.00 (reference) |
| >50                       | 170(65.7)| 18(7.0)  | 152(58.7)| 0.582(0.235–1.440) |
| Degree of Differentiation |         |          |         |          |
| Low                       | 185(84.8)| 23(10.3) | 162(74.5)| 0.677    | 1.00 (reference) |
| Middle & High             | 33(15.2)| 3(1.4)   | 30(13.8)| 0.720(0.153–3.394) |
| Unknown                   | 40      |          |         |          |
| Clinical stage            |         |          |         |          |
| I & II                    | 69(28.9)| 12(5.0)  | 57(23.9)| 0.177    | 1.00 (reference) |
| III & IV                  | 170(71.1)| 17(6.9)  | 153(64.2)| 0.512(0.191–1.370) |
| Unknown                   | 19      |          |         |          |
| Positive lymph node       |         |          |         |          |
| Negative                  | 74(66.2)| 12(10.8) | 62(55.4)| 0.540    | 1.00 (reference) |
| Positive                  | 38(33.8)| 3(2.70)  | 35(31.1)| 0.594(0.111–3.188) |
| Unknown                   | 146     |          |         |          |
| CA125                     |         |          |         |          |
| >65(U/ml)                 | 212(84.0)| 29(8.64) | 183(75.3)| 0.021    | 1.00 (reference) |
| ≤65(U/ml)                 | 39(16.0)| 11(4.32) | 28(11.7)| 3.20(1.15–8.71) |
| Unknown                   | 7       |          |         |          |
| Size of tumor             |         |          |         |          |
| <10 cm                    | 145(60.2)| 16(6.8)  | 129(53.4)| 0.608    | 1.00 (reference) |
| ≥10 cm                    | 96(39.8)| 14(5.6)  | 82(34.2)| 1.279(0.498–3.287) |
| Unknown                   | 17      |          |         |          |
| Tumor histology           |         |          |         |          |
| Serous                    | 174(76.3)| 15(6.6)  | 159(69.7)| 0.032    | 1.00 (reference) |
| Other                     | 54(23.7)| 16(7.0)  | 38(16.7)| 2.688(1.063–6.803) |
| Unknown                   | 30      |          |         |          |

doi:10.1371/journal.pone.0138692.t002
mRNA in 22 ovarian cancer tissues were significantly lower than the levels observed in 15 normal tissues (P < 0.001). As shown in Fig 2B, the GADD45A mRNA expression was higher in patients with TT or TC genotypes compared to patients with the CC genotype (P < 0.001). As shown in Fig 2C, the GADD45A mRNA expression was higher in controls with TT or TC genotypes than with the CC genotype, (P < 0.001). These findings suggest that the SNP 1506T>C may significantly affect the expression of the GADD45A gene.

**Relationship between GADD45A (1506T>C) Polymorphism and Ovarian Cancer Prognosis**

To test the prognostic power of the GADD45A polymorphism in ovarian cancer, we calculated the GADD45A genotype with respect to ovarian relapse-free survival (RFS) and overall survival (OS). As shown in Fig 3, the TT+TC genotype showed significant correlation with both longer ovarian cancer RFS and OS in 151 patients (P = 0.018, P = 0.0093, respectively).
A large number of genetic variants in the candidate genes involved in the process of ovarian carcinogenesis have been reported [8]. Three GWAS with overlapping sets of study participants for ovarian cancer have been performed [13–15]. A total of 18 SNPs in 5 regions were found to be associated with ovarian cancer in 3 GWAS studies. However, there was no overlap between the genetic variants identified through the GWAS studies and the variants identified using a candidate gene search [8]. We believe that the evidence of an association with ovarian cancer is insufficient and that it is necessary to further investigate candidate genes associated with ovarian cancer.

GADD45 expression is frequently decreased in some cancers [22–24]. Abnormal GADD45 expression has been associated with tumor prognosis [25], and abnormal GADD45 methylation may contribute to cancer risk [25]. A study showed that 1,25-dihydroxyvitamin D3 causes cell cycle arrest at the G2/M transition through p53-independent induction of GADD45 in ovarian cancer cells [27]. The induction of GADD45A expression might play a role in mediating the apoptotic response of ovarian cancer cells to the synthetic retinoid CD437 [28]. The association of GADD45A polymorphisms with tumor susceptibility and prognosis has never been reported.

In this study, the GADD45A (1506T>C) polymorphism was found to be associated with the ovarian cancer risk, clinicopathological characteristics, GADD45A expression levels and ovarian cancer prognosis. To the best of our knowledge, GADD45A is a novel ovarian cancer susceptibility gene and this study is the first to report an association between germline mutations in GADD45A and tumor risk and prognosis. We expect GADD45A to be a useful molecular marker for assessing ovarian cancer risk and prognosis.

The SNP 1506T>C is located in introns and thus cannot alter the sequence or structure of the protein. However, we understand that the variant 1506T>C was associated with and increased risk of ovarian cancer and the decreased survival of the patient. Furthermore, GADD45A functions downstream of BRCA1 and p53 in the DNA damage pathway. GADD45A expression is regulated by multiple transcription factors, such as p53, BRCA1, WT1, Oct-1,

![Fig 3. GADD45A genotypes and ovarian cancer prognosis. A, Genotype TT+TC of GADD45A had longer relapse-free survival (P = 0.018). B, Genotype TT+TC of GADD45A had longer overall survival (P = 0.0093).](image-url)
NF-YA, ATF4, AP-1, c-myc, and ZBRK1, which typically bind to the promoter or intronic regions of GADD45A [16, 20, 21, 29]. Thus, we hypothesized that this variant might disrupt transcription factor binding sites, thereby altering GADD45A expression and affecting tumor genesis. Consistent with findings obtained in other cancer studies [22–24], GADD45A mRNA expression was lower in ovarian patients than controls. Moreover, GADD45A mRNA expression was lower in patients with the CC genotype compared to patients carrying the T allele (TT +TC), and the survival of patients with the CC genotype was poorer. Thus, carrying the C allele (TC+CC) was associated with an increased risk of positive CA125. Those results were consistent with the function of GADD45A. GADD45A is implicated in active DNA demethylation, apart from the maintenance of genomic stability, DNA repair and suppression of cell growth [29,30].

As previously indicated, the participants involved in our study were mainly residents of Shandong Province, China. Because the Chinese population is generally more genetically homogeneous than other ethnic populations, we predict that these findings will be consistent in larger sample sizes across China, but determining the applicability of our findings to other ethnic populations (both within and outside Asia) requires further investigation in different patient populations, and larger sample sizes are required before these data can be extrapolated to other ethnicities [30].

In conclusion, we found, for the first time, that the GADD45A (1506T>C) polymorphism may be correlated with ovarian cancer susceptibility, clinicopathological characteristics, GADD45A expression levels and ovarian cancer prognosis. Because GADD45A has been demonstrated to be a key regulator in a complex network of oncogenic pathways, further investigations are needed to elucidate the functional role of this gene and its association with ovarian carcinogenesis and development. The variants of GADD45A may prove to be useful markers for the identification of ovarian cancer-susceptible patients or prognostic indicators of disease progression, and they may also serve as potential targets for future therapies.

In this study, for the first time, we demonstrate that the GADD45A (1506T>C) polymorphism is associated with ovarian cancer susceptibility and prognosis. A relationship was observed between the GADD45A (1506T>C) polymorphism and GADD45A expression levels. These data suggest that GADD45A (1506T>C) is a new tumor susceptibility gene and could be a useful molecular marker for assessing ovarian cancer risk and for predicting ovarian cancer patient prognosis.

**Author Contributions**

Conceived and designed the experiments: CZY KS BHK. Performed the experiments: CZY XYL XLL NY ZPL. Analyzed the data: CZY XYL. Contributed reagents/materials/analysis tools: SY XYL XLL NY KS. Wrote the paper: CZY KS.

**References**

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64(1):9–29. Epub 2014/01/09. doi: 10.3322/caac.21208 PMID: 24399786.
2. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst. 1998; 90(23):1774–86. Epub 1998/12/05. PMID: 9893917.
3. Meindl A, Hellebrand H, Wiek C, Erven V, Wappenschmidt B, Niederacher D, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet. 2010; 42(5):410–4. Epub 2010/04/20. doi: 10.1038/ng.569 PMID: 2040964.
4. Loveday C, Turnbull C, Ramsay E, Hughes D, Ruark E, Frankum JR, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet. 2011; 43(9):879–82. Epub 2011/08/09. doi: 10.1038/ng.893 PMID: 21822267.
5. Yin J, Lu K, Lin J, Wu L, Hildebrandt MA, Chang DW, et al. Genetic variants in TGF-beta pathway are associated with ovarian cancer risk. PLoS One. 2011; 6(9):e25559. Epub 2011/10/11. doi: 10.1371/journal.pone.0025559. PMID: 2194931; PubMed Central PMCID: PMC3184159.

6. Ma X, Zhang J, Liu S, Huang Y, Chen B, Wang D. Polymorphisms in the CASP8 gene and the risk of epithelial ovarian cancer. Gynecol Oncol. 2011; 122(3):554–9. Epub 2011/07/01. doi: S0090-8285(11) 00428-8 [pii]. doi: 10.1016/j.ygyno.2011.05.031 PMID: 21714991.

7. Permuth-Wey J, Kim D, Tsai YY, Lin HY, Chen YA, Bamholtz-Sloan J, et al. LIN28B polymorphisms influence susceptibility to epithelial ovarian cancer. Cancer Res. 2011; 71(11):3896–903. Epub 2011/04/13. doi: 0008-5472.CAN-10-4167 [pii] doi: 10.1158/0008-5472.CAN-10-4167 PMID: 21482675; PubMed Central PMCID: PMC3107389.

8. Braem MG, Schouten LJ, Peeters PH, den Brandt PA, Onland-Moret NC. Genetic susceptibility to sporadic ovarian cancer: A systematic review. Biochim Biophys Acta. 2011; 1816(2):132–46. Epub 2011/06/07. doi: S0304-419X(11)00023-0 [pii] doi: 10.1016/j.bbcan.2011.05.002 PMID: 21641967.

9. Pettitri LM, Heikkinen T, Thompson D, Kallioniemi A, Schleuter J, Holli K, et al. RAD51C is a susceptibility gene for ovarian cancer. Hum Mol Genet. 2011; 20(16):3278–88. Epub 2011/05/28. doi: ddr229 [pii] doi: 10.1093/hmg/ddr229 PMID: 21616938.

10. Ramus SJ, Antoniou AC, Kuchenbaecker KB, Soucy P, Beesley J, Chen X, et al. Ovarian cancer susceptibility alleles and risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Hum Mutat. 2012. Epub 2012/01/19. doi: 10.1002/humu.22025 PMID: 22233144.

11. Yuan C, Wang C, Liu X, Kong B. Analyze association of the progesterone receptor gene polymorphism PROGINS with ovarian cancer risk. Mol Biol Rep. 2013; 40(10):6001–9. Epub 2013/09/24. doi: 10.1007/s11033-013-2709-x PMID: 24027083.

12. Yi Siafakas A, Richardson DR. Growth arrest and DNA damage-45 alpha (GADD45alpha). Int J Biochem Cell Biol. 2009; 41(9):1816–21. Epub 2009/05/05. doi: 10.1016/j.biocel.2008.06.018 PMID: 18760377.

13. Bolton KL, Tyrer J, Song H, Ramus SJ, Notaridou M, Jones C, et al. Common variants at 19p13 are associated with susceptibility to ovarian cancer. Nat Genet. 2010; 42(10):880–4. Epub 2010/09/21. doi: ng.666 [pii] doi: 10.1038/ng.666 PMID: 20852633; PubMed Central PMCID: PMC3125495.

14. Goode EL, Chenevix-Trench G, Song H, Ramus SJ, Notaridou M, Lawrenson K, et al. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet. 2010; 42(10):874–9. Epub 2010/09/21. doi: ng.668 [pii] doi: 10.1038/ng.668 PMID: 20852622; PubMed Central PMCID: PMC3020231.

15. Song H, Ramus SJ, Tyrer J, Bolton KL, Gentry-Maharaj A, Wozniak E, et al. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. Nat Genet. 2009; 41(9):996–1000. Epub 2009/08/04. doi: ng.424 [pii] doi: 10.1038/ng.424 PMID: 19648919; PubMed Central PMCID: PMC2844110.

16. Rosemary Siafakas A, Richardson DR. Growth arrest and DNA damage-45 alpha (GADD45alpha). Int J Biochem Cell Biol. 2009; 41(5):986–9. Epub 2008/09/02. doi: S1357-2725(08)00252-5 [pii] doi: 10.1016/j.biocel.2008.06.018 PMID: 18760377.

17. Levrero M, De Laurenzi V, Costanzo A, Gong J, Wang JY, Melino G. The p53/p63/p73 family of transcription factors: overlapping and distinct functions. J Cell Sci. 2000; 113 (Pt 10):1661–70. Epub 2000/04/19. doi: 10769197.

18. Hoffman B, Liebermann DA. GADD45 in modulation of solid tumors and leukemia. Adv Exp Med Biol. 2013; 793:21–33. Epub 2013/10/10. doi: 10.1007/978-1-4614-8289-5_2 PMID: 24104471.

19. Zhan Q, Chen IT, Antinore MJ, Fornace AJ Jr. Tumor suppressor p53 can participate in transcriptional induction of the GADD45 promoter in the absence of direct DNA binding. Mol Cell Biol. 1998; 18(5):2768–78. Epub 1998/05/05. PMID: 9566896; PubMed Central PMCID: PMC110656.

20. Gao M, Dong W, Hu M, Yu M, Guo L, Qian L, et al. GADD45alpha mediates arsenite-induced cell apoptotic effect in human hepatoma cells via JNKs/AP-1-dependent pathway. J Cell Biochem. 2010; 109(6):1264–73. Epub 2010/02/27. doi: 10.1002/jcb.22509 PMID: 20186883.

21. Zerbini LF, Liebermann TA. Life and death in cancer. GADD45 alpha and gamma are critical regulators of NF-kappaB mediated escape from programmed cell death. Cell Cycle. 2005; 4(1):18–20. Epub 2004/12/23. doi: 1363 [pii] PMID: 15613850.

22. Zhu N, Shao Y, Xu L, Yu L, Sun L. Gadd45alpha and Gadd45-gamma utilize p38 and JNK signaling pathways to induce cell cycle G2/M arrest in Hep-G2 hepatoma cells. Mol Biol Rep. 2009; 36(8):2075–85. Epub 2008/12/03. doi: 10.1007/s11033-008-9419-9 PMID: 19048389.
23. Higashi H, Vallbohmer D, Warnecke-Eberz U, Hokita S, Xi H, Brabender J, et al. Down-regulation of Gadd45 expression is associated with tumor differentiation in non-small cell lung cancer. Anticancer Res. 2006; 26(3A):2143–7. Epub 2006/07/11. PMID: 16827157.

24. Reddy SP, Britto R, Vinnakota K, Aparna H, Sreepathi HK, Thota B, et al. Novel glioblastoma markers with diagnostic and prognostic value identified through transcriptome analysis. Clin Cancer Res. 2008; 14(10):2978–87. Epub 2008/05/17. doi: 10.1158/1078-0432.CCR-07-4821 PMID: 18483363.

25. Wang W, Huper G, Guo Y, Murphy SK, Olson JA Jr., Marks JR. Analysis of methylation-sensitive transcriptome identifies GADD45a as a frequently methylated gene in breast cancer. Oncogene. 2005; 24(16):2705–14. Epub 2005/03/01. doi: 10.1038/sj.onc.1208464 PMID: 15735726.

26. Yuan C, Li X, Yan S, Yang Q, Liu X, Kong B. The MTDH (-470G>A) Polymorphism Is Associated with Ovarian Cancer Susceptibility. PLoS One. 2012; 7(12):e51561. Epub 2012/12/15. doi: 10.1371/journal.pone.0051561 PONE-D-12-30681 PMID: 23240043; PubMed Central PMCID: PMC3519849.

27. Jiang F, Li P, Fornace AJ Jr., Nicosia SV, Bai W. G2/M arrest by 1,25-dihydroxyvitamin D3 in ovarian cancer cells mediated through the induction of GADD45 via an exonic enhancer. J Biol Chem. 2003; 278(48):48030–40. Epub 2003/09/25. doi: 10.1074/jbc.M308430200 PMID: 14506229.

28. Jiang T, Soprano DR, Soprano KJ. GADD45A is a mediator of CD437 induced apoptosis in ovarian carcinoma cells. J Cell Physiol. 2007; 212(3):771–9. Epub 2007/05/03. doi: 10.1002/jcp.21073 PMID: 17474084.

29. Liebermann D, Tront JS, Sha X, Mukherjee K, Mohamed-Hadley A, Hoffman B. Gadd45 stress sensors in malignancy and leukemia. Crit Rev Oncog. 2011; 16(1–2):129–40. Epub 2011/12/14. doi: 10.1080/10633090.2011.570660 PMID: 22159033; PubMed Central PMCID: PMC3268054.

30. Liu X, Zhang N, Li X, Moran MS, Yuan C, Yan S, et al. Identification of novel variants of metadherin in breast cancer. PLoS One. 2011; 6(3):e17582. Epub 2011/03/17. doi: 10.1371/journal.pone.0017582 PMID: 21408129; PubMed Central PMCID: PMC3050918.