TNFAIP8 variants as a potential epidemiological and predictive biomarker in ovarian cancer

Hongyu Gao  
Tumor Hospital of Harbin Medical University

Zhiran Zhang  
Tumor Hospital of Harbin Medical University

Liangliang Jiang  
Tumor Hospital of Harbin Medical University

Lei Zhang  
Tumor Hospital of Harbin Medical University

Ling Qin  
Tumor Hospital of Harbin Medical University

Shanshan Yang (dr_yss@126.com)  
Tumor Hospital of Harbin Medical University

Tianbo Liu (skyliu_1030@163.com)  
Tumor Hospital of Harbin Medical University  
https://orcid.org/0000-0001-6575-0310

Primary research

Keywords: TNFAIP8 polymorphism, ovarian cancer, susceptibility, metastasis, recurrence

DOI: https://doi.org/10.21203/rs.3.rs-29008/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Background

This research aimed to investigate the association between tumor necrosis factor-a-induced protein 8 (TNFAIP8) polymorphisms and ovarian cancer (OC) susceptibility.

Methods

A case-control study of 210 patients with OC and 231 healthy controls was conducted to assess the association between TNFAIP8 polymorphisms (rs11064, rs1045241, and rs1045242) and OC risk in Heilongjiang Province of China. Logistic regression analysis was applied to illustrate the underlying association.

Results

Our research found that TNFAIP8 rs11064 and rs1045242 were significantly connected with the susceptibility of OC. Additionally, rs1045242 increased the risk of OC, while rs11064 performed a protective role in the risk of OC. Data revealed that rs1045242 strongly related with advanced FIGO stage, larger residual tumor, and the presence of recurrence.

Conclusions

TNFAIP8 genetic variants, which may play difference roles, were significantly associated with OC susceptibility. The underlying molecular mechanism needs be clarified with scientific evidence.

Background

More than 3000 women a year were diagnosed ovarian cancer (OC) and two third of them ultimately die in the next five years [1, 2]. Furthermore, the incidence and mortality of Chinese women with OC has increased significantly [3]. However, no worthily diagnostic methods worldwide were applied for early detection of OC resulting in that OC were more common in advanced clinical stages. Regarding that OC is a multigenic disease [4, 5], the influence of environmental on its pathogenesis should not be neglected [6]. Therefore, it may be an interesting option to investigate key genes and their interaction with the environment for prevention and treatment of OC.

Tumor necrosis factor-a-induced protein 8 (TNFAIP8), as well as a TNFα-inducible gene in endothelial cells [7], was localized at chromosome 5 in the forward strand q23 region [8, 9]. TNFAIP8 takes part in the process of apoptosis and autophagy in different types of cells. Overexpression of TNFAIP8 is frequently observed in malignant tumors [8, 10–20], that is significantly correlated to excessive proliferation,
reduced apoptosis, enhanced invasion and metastasis, and drug resistance. Polymorphisms of TNFAIP8 gene are reported to be associated with risks of different cancers [9, 14, 21]. Additionally, we have demonstrated that elevated expression of TNFAIP8 protein implies poor prognosis and is related with resistance of OC [13, 22, 23]. However, there were no existing findings regarding the relationship of TNFAIP8 polymorphisms with OC risks. Therefore, we aimed to clarify the connection between TNFAIP8 polymorphism and OC susceptibility among people in Heilongjiang Province of China.

**Materials And Methods**

**Subjects and blood samples**

Totally 210 OC patients and 231 contemporaneously healthy individuals were recruited from the Harbin Medical University Cancer Hospital between September 2015 and February 2017. All OC cases were classified and evaluated according to the International Federation of Obstetricians and Gynecologists (FIGO) [24]. The pathological type was diagnosed as epithelial OC which contained serous, mucinous, endometrioid, and clear cell histological type. Any control subject with malignant tumor or digestive disease, or the family history of any cancers was excluded. Peripheral blood samples (5 mL) were collected from all subjects at the time of hospital admission.

The distributions of clinical data of all subjects are shown in Table 1 The study protocol was approved by Harbin Medical University Cancer Hospital Committee and all subjects provided signed informed consent from patients and controls. None of the recruited patients received preoperative chemo- or radiotherapy.

**Genotyping**

Peripheral blood (5 mL) from each subject was sampled in vacuum tubes with 5% ethylene diamine tetraacetic acid (EDTA). Then genomic DNA from whole blood was extracted using a blood genomic DNA extraction kit (Axygen Biotechnology, Union City, CA, USA) according to the manufacturer's instruction and stored at -20 °C for genotyping by polymerase chain reaction (PCR). Three TNFAIP8 SNPs (rs11064, rs1045241, and rs1045242) were selected in the present study according to our previous study [21]. The SNaPshot SNP assay was conducted to detect SNP genotype. The GeneMapperTM 4.0 Software (Applied Biosystems, Foster City, CA, USA) was applied to analyzed the resulting data. About 5% of the specimens were chosen randomly and genotyped twice to ensure the genotyping accuracy: the reproducibility was 100% [21].

**Statistical analysis**

All statistical analyses were performed with SPSS 22.0 (SPSS, Chicago, Illinois, USA). Genotype and allele distributions were assessed and the chi-square test was used to evaluated the Hardy–Weinberg equilibrium among the controls. Continuous variables were presented using mean ± SD and statistically analyzed using t-test. Categorical variables were statistically analyzed using the chi-square test or Fisher's text. The crude odds ratio (COR), adjusted odds ratio (AOR), and 95% confidence interval (CI) of logistic regression analysis was calculated in four genetic models (allele, co-dominant, dominant, and
recessive) to assess the association between TNFAIP8 single nucleotide polymorphisms (SNPs) and OC susceptibility with adjustment for age, smoking history, complication, and family history. All tests were two-tailed and \( P < 0.05 \) was considered statistical significance.

**Results**

### Demographic characteristics of the study population

The connection between TNFAIP8 SNPs and OC risk was explored in Heilongjiang Province of China. The basic information of all individuals was summarized in Table 1. The average ages of cases and controls were 53.24 ± 10.54 and 54.32 ± 9.58 years, respectively. Furthermore, no significant difference was observed between these two groups (\( P = 0.261 \)). In addition, there were no significant differences between the cases and controls in complication and smoking history (\( P > 0.05 \)). However, positive significance (\( P = 0.023 \)) between the case and control groups was presented in family cancer history (ovarian cancer).

### The relationship of TNFAIP8 polymorphism with OC risk

In this case-control study, three SNPs (rs11064, rs1045241, and rs1045242) in TNFAIP8 gene were selected and analyzed. The genotype frequencies of each SNP conformed to the Hardy-Weinberg equilibrium among controls (\( P > 0.05 \) for all). Displayed in Table 2, TNFAIP8 rs11064 A-allele (COR: 0.690, 95% CI: 0.491–0.971, \( P = 0.033 \) and AOR: 0.709, 95% CI: 0.504–0.997, \( P = 0.048 \)) and rs1045242 G-allele (COR: 1.619, 95% CI: 1.129–2.323, \( P = 0.009 \) and AOR: 1.628, 95% CI: 1.132–2.342, \( P = 0.009 \)) are risk factors for OC. However, the allele of TNFAIP8 rs1045241 had no effect on the risk of OC (\( P > 0.05 \)).

For further examination, we conducted the correlation between the genotypes of SNPs and OC risk by logistic regression analysis under the codominant, dominant, and recessive models (Table 3). Our results showed that rs11064 was significantly associated with increased OC susceptibility in codominant model (GG/AA, COR: 0.200, 95% CI: 0.057–0.706, \( P = 0.012 \) and AOR: 0.205, 95% CI: 0.058–0.726, \( P = 0.014 \)) and recessive model (GG/AA + AG, COR: 0.209, 95% CI: 0.060–0.731, \( P = 0.014 \) and AOR: 0.212, 95% CI: 0.060–0.744, \( P = 0.016 \)). Also, we demonstrated that rs1045242 was related to a higher risk of OC under codominant model (AG/AA, COR: 1.670, 95% CI: 1.091–2.558, \( P = 0.018 \) and AOR: 1.703, 95% CI: 1.108–2.618, \( P = 0.015 \)) and dominant model (AG + GG/AA, COR: 1.736, 95% CI: 1.149–2.623, \( P = 0.009 \) and AOR: 1.761, 95% CI: 1.162–2.670, \( P = 0.008 \)). However, there was no significant association between TNFAIP8 rs1045241 and OC risk.

Stratification analysis between TNFAIP8 SNPs and OC risk based on age, smoking history, complication, and family history

Aiming to deeply analyze the relationships of TNFAIP8 genotypes with OC susceptibility, we divided age into \( \leq 54 \) years old and > 54 years old, whether smoking, whether complication (patients with diabetes and cardio-cerebrovascular disease), and whether there is family history of OC. It revealed that rs1045242 mutation (AG + GG/AA) would significantly increase risk of OC (OR: 2.048, 95% CI: 1.116–3.757, \( P = \)
0.021) at age ≤ 54 years old (Supplementary Table 1). In subjects with no smoking history, the rs11064 mutation (GG) was a protective factor for OC (OR: 0.164, 95%CI: 0.036–0.742, \( P = 0.019 \)). On the contrary, the rs1045242 mutation (AG + GG) was a risk factor for OC (OR: 2.670, 95%CI: 1.141–6.247, \( P = 0.024 \)) in subjects with smoking history (Supplementary Table 2). As showed in Supplementary Table 3 and Table 4, the rs1045242 mutation (AG + GG) was a risk factor for OC in subjects with no complication (OR: 1.829, 95%CI: 1.109–3.018, \( P = 0.018 \)) and no family history of OC (OR: 1.746, 95%CI: 1.150–2.650, \( P = 0.009 \)). The rs11064 GG genotype was a protective factor for OC in subjects with no family history of OC (OR: 0.205, 95%CI: 0.058–0.724, \( P = 0.014 \)).

**Correlation between TNFAIP8 SNPs and clinicopathological characteristics of OC**

The correlation between three TNFAIP8 genotypes and the clinicopathologic data of OC is illustrated in Table 4. It was found that rs1045242 was related to an increased risk in OC patients with III/IV FIGO stage (\( P = 0.040 \) and \( P = 0.013 \), respectively) and presence of recurrence (\( P = 0.043 \) and \( P = 0.034 \), respectively) both under codominant and dominant models. For rs1045242, it was confirmed that AG + GG genotype was significantly associated with an increased OC risk in residual tumor more than 1 cm (\( P = 0.019 \)). rs1045241 SNP was strongly significant associated with FIGO stage (\( P = 0.025 \)) and residual tumor (\( P = 0.033 \)) under dominant model. Furthermore, rs11064 SNP was observed to be positively related to FIGO stage both under codominant (\( P = 0.024 \)) and dominant (\( P = 0.006 \)) models.

**Discussion**

In present study, we found that TNFAIP8 polymorphisms (rs11064 and rs1045242) were significantly associated with OC susceptibility. Furthermore, the GG-genotype of rs11640 was a protective factor and the AG + GG-genotype of rs1045242 was a risk factor for OC susceptibility. In addition, TNFAIP8 rs1045242 gene polymorphism was linked to advanced FIGO stage, larger residual tumor, and the presence of recurrence in OCs. Taken together, our current findings provided an crucial role of TNFAIP8 gene in the occurrence of OC, thus may give evidence on the potentially functional SNPs in TNFAIP8 and their clinical outcomes in OC patients.

TNFAIP8 polymorphism has been recently investigated in several disease including solid human cancer (cervical cancer and endometrial cancer) and Non-Hodgkin’s Lymphoma (NHL) which indicates that SNPs are the most common type of genetic variations caused by the heterogeneity among various types of human cancer [9, 14, 21]. Recent research suggests that genetic polymorphisms play a crucial role in the pathogenesis of OC [25–27]. To our knowledge, we illuminated the association between TNFAIP8 polymorphism and OC risk for the first time.

In cervical cancer, it revealed that the GG genotype of TNFAIP8 rs11064 was connected with an elevated risk compared with AA/AG genotypes [14]. Furthermore, the study of endometrial cancer (EC) [21] showed that the GG genotype and AG + GG genotype of TNFAIP8 rs11064 were both associated with increased risk compared with controls. However, our present research found that the G allele and GG allele of
TNFAIP8 rs11064 both played a reduced role in risk of OC (AOR: 0.709; 95%CI: 0.504–0.997 for G allele and AOR: 0.205; 95%CI: 0.058–0.726 for GG allele). The discordance of the above findings may be explained by that the effect of genetic factors often differs in different individuals.

No considerable relationship between TNFAIP8 rs1045241 and OC risk was identified in our present paper. Additionally, our previous study in EC had been in accordance with this result. Searching from the literature data, TNFAIP8 rs1045241 polymorphism was reported to have clinical significance in no other reports except that in NHL. Zhang et al. [9] demonstrated that the polymorphism of TNFAIP8 rs1045241 may lead to NHL susceptibility in a Chinese population. We believe that the related role of environmental factors may not be ignored. So far, no literature except our team has reported the relationship between TNFAIP8 rs1045242 polymorphism and tumor. Our results showed that TNFAIP8 rs1045242 G allele carriers showed increased risk of OC by 1.628 times compared to the A allele carriers. Also, the AG + GG genotype of TNFAIP8 rs1045242 increased 1.761 times risks of OC compared with AA genotype. These findings were consistent with previous study in EC [21]. The above provide evidence that TNFAIP8 rs1045242 polymorphism may involve in the onset of gynecological malignancy.

Besides, subgroup analysis revealed that TNFAIP8 rs1045242 polymorphism increased the risk of OC in patients with age ≤ 54 years old, smoking history, no complication, and no family cancer history, uncovering that individuals exposed to these factors are more susceptible to OC. In patients with no smoking history and no family cancer history, the GG allele of TNFAIP8 rs11064 SNPs played a protective factor for OC. However, the underlying mechanism that the same genotype performs opposite effects in different tumor types remains to be illuminated.

Moreover, we explored the connection between the TNFAIP8 genes polymorphism and clinical variables of OC. We suggested that TNFAIP8 genes polymorphism (rs11064, rs1045241, and rs1045242) were significantly connected with FIGO stage. In addition, TNFAIP8 rs1045242 polymorphism was also strongly associated with residual tumor, and recurrence, indicating its role of progression in OC. For rs11064, it was reported that it positively linked to deep myometrial invasion and lymph node metastasis under the codominant model in ECs [21]. In cervical cancer, it attempted to explore the relationship between TNFAIP8 rs11064 polymorphism and drug resistance, but with no sense [14]. The association between TNFAIP8 rs1045242 polymorphism and stage in NHL was observed.9

**Conclusions**

This study suggests that TNFAIP8 rs11064 and rs1045242 polymorphisms are remarkably linked with the risk of OC in Heilongjiang Province of China. However, the GG allele of TNFAIP8 in the two genotypes played the opposite roles in the risk of OC. Furthermore, we found that TNFAIP8 rs1045242 polymorphism had an effect on clinical significance of FIGO stage, residual tumor, and recurrence, indicating its progressive role in OC. Yet, there are some shortcomings. Whether TNFAIP8 rs1045242 polymorphism affected the protein expression status and its effect on prognosis remain to unclear. Thus,
well-designed larger, prospective study with functional analysis is an interesting direction and deserves further study which would give some new insights in the molecular mechanism of OC occurrence.

**Supplementary Materials**

**Supplementary Materials:** Supplementary Table 1, Supplementary Table 2, Supplementary Table 3, Supplementary Table 4,

**Declarations**

**Ethics approval and consent to participate**

The current study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital. A written consent from each participant was obtained after they were informed the purpose of this study.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All data generated and analyzed during this study are included in this published article and its additional file.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This study was supported by grants the Youth Elite Training Foundation of Harbin Medical University Cancer Hospital (JY2016-03), the Key Projects of Haiyan Foundation of Harbin Medical University Cancer Hospital (JJZD2019-02) and Outstanding Youth Programme of Harbin Medical University Cancer Hospital (JCQN2019-06).

**Authors’ contributions**

TB Liu and Honyu Gao conceived and designed the study. LL Jiang and ZR Zhang collected samples and processed data. L Qin and L Zhang provided technical support. SS Yang analyzed data. TB Liu drafted the manuscript. SS Yang revised the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

Not applicable.
References

1. Miller KD, Siegel RL, Lin CC. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016 Jul;66(4):271 – 89.

2. Wojciechowska U, Didkowska J, Zatonski W. Corpus uteri cancer. In: Zatonski W, editor. Cancer in Poland in 2006. Warsaw: Department of Epidemiology and Cancer Prevention; 2008. pp. 30–2.

3. Huang Z, Zheng Y, Wen W, Wu C, Bao P, Wang C, Zhong W, Gao YT, Jin F, Xiang YB, Shu XO, Beeghly-Fadiel A. Incidence and mortality of gynecological cancers: Secular trends in urban Shanghai, China over 40 years. Eur J Cancer. 2016 Aug;63:1–10.

4. Jones MR, Kamara D, Karlan BY, Pharoah PDP, Gayther SA. Genetic epidemiology of ovarian cancer and prospects for polygenic risk prediction. Gynecol Oncol. 2017 Dec;147(3):705–713.

5. Kar SP, Berchuck A, Gayther SA, Goode EL, Moysich KB, Pearce CL, Ramus SJ, Schildkraut JM, Sellers TA, Pharoah PDP. Common Genetic Variation and Susceptibility to Ovarian Cancer: Current Insights and Future Directions. Cancer Epidemiol Biomarkers Prev. 2018 Apr;27(4):395–404.

6. Pearce CL1, Rossing MA, Lee AW, Ness RB, Webb PM; for Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group, Chenevix-Trench G, Jordan SM, Stram DA, Chang-Claude J, Hein R, Nickels S, Lurie G, Thompson PJ, Carney ME, Goodman MT, Moysich K, Hodgall E, Jensen A, Goode EL, Fridley BL, Cunningham JM, Vierkant RA, Weber RP, Ziogas A, Anton-Culver H, Gayther SA, Gentry-Maharaj A, Menon U, Ramus SJ, Brinton L, Wentzensen N, Lissowska J, Garcia-Closas M, Massuger LF, Kiemeney LA, Van Altena AM, Aben KK, Berchuck A, Doherty JA, Iversen E, McGuire V, Moorman PG, Pharoah P, Pike MC, Risch H, Sieh W, Stram DO, Terry KL, Whittemore A, Wu AH, Schildkraut JM, Kjaer SK; Ovarian Cancer Association Consortium. Combined and interactive effects of environmental and GWAS-identified risk factors in ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2013 May;22(5):880 – 90.

7. Horrevoets AJ, Fontijn RD, van Zonneveld AJ, de Vries CJ, ten Cate JW, Pannekoek H. Vascular endothelial genes that are responsive to tumor necrosis factor-alpha in vitro are expressed in atherosclerotic lesions, including inhibitor of apoptosis protein-1, stannin, and two novel genes. Blood. 1999 May;15(10):3418–31. 93(.

8. Li Y, Jing C, Chen Y, Wang J, Zhou M, Liu X, Sun D, Mu L, Li L, Guo X. Expression of tumor necrosis factor α-induced protein 8 is upregulated in human gastric cancer and regulates cell proliferation, invasion and migration. Mol Med Rep. 2015 Aug;12(2):2636-42.

9. Zhang Y, Wang MY, He J, Wang JC, Yang YJ, Jin L, Chen ZY, Ma XJ, Sun MH, Xia KQ, Hong XN, Wei QY, Zhou XY. Tumor necrosis factor-α induced protein 8 polymorphism and risk of non-Hodgkin’s lymphoma in a Chinese population: a case-control study. PLoS One. 2012;7(5):e37846.

10. Kumar D, Gokhale P, Broustas C, Chakravarty D, Ahmad I, Kasid U. Expression of SCC-S2, an antiapoptotic molecule, correlates with enhanced proliferation and tumorigenicity of MDA-MB 435 cells. Oncogene. 2004 Jan 15;23(2):612-6.
11. Hadisaputri YE, Miyazaki T, Suzuki S, Yokobori T, Kobayashi T, Tanaka N, Inose T, Sohda M, Kuwano H. TNFAIP8 overexpression: clinical relevance to esophageal squamous cell carcinoma. Ann Surg Oncol. 2012 Jul;19(Suppl 3):589-96.

12. Liu K, Qin CK, Wang ZY, Liu SX, Cui XP, Zhang DY. Expression of tumor necrosis factor-alpha-induced protein 8 in pancreas tissues and its correlation with epithelial growth factor receptor levels. Asian Pac J Cancer Prev. 2012;13(3):847 – 50.

13. Liu T, Gao H, Chen X, Lou G, Gu L, Yang M, Xia B, Yin H. TNFAIP8 as a predictor of metastasis and a novel prognostic biomarker in patients with epithelial ovarian cancer. Br J Cancer. 2013 Sep;17(6):1685–92. 109(.

14. Shi TY, Cheng X, Yu KD, Sun MH, Shao ZM, Wang MY, Zhu ML, He J, Li QX, Chen XJ, Zhou XY, Wu X, Wei Q. Functional variants in TNFAIP8 associated with cervical cancer susceptibility and clinical outcomes. Carcinogenesis. 2013 Apr;34(4):770–8.

15. Zhang C, Kallakury BV, Ross JS, Mewani RR, Sheehan CE, Sakabe I, Luta G, Kumar D, Yadavalli S, Starr J, Sreenath TL, Srivastava S, Pollard HB, Eidelman O, Srivastava M, Kasid UN. The significance of TNFAIP8 in prostate cancer response to radiation and docetaxel and disease recurrence. Int J Cancer. 2013 Jul;133(1):31–42.

16. Liu T, Gao H, Yang M, Zhao T, Liu Y, Lou G. Correlation of TNFAIP8 overexpression with the proliferation, metastasis, and disease-free survival in endometrial cancer. Tumour Biol. 2014 Jun;35(6):5805–14.

17. Yang M, Zhao Q, Wang X, Liu T, Yao G, Lou C, Zhang Y. TNFAIP8 overexpression is associated with lymph node metastasis and poor prognosis in intestinal-type gastric adenocarcinoma. Histopathology. 2014 Oct;65(4):517–26.

18. Dong Q, Fu L, Zhao Y, Xie C, Li Q, Wang E. TNFAIP8 interacts with LATS1 and promotes aggressiveness through regulation of Hippopathway in hepatocellular carcinoma. Oncotarget. 2017 Feb 28;8(9):15689–15703.

19. Xiao M, Xu Q, Lou C, Qin Y, Ning X, Liu T, Zhao X, Jia S, Huang Y. Overexpression of TNFAIP8 is associated with tumor aggressiveness and poor prognosis in patients with invasive ductal breast carcinoma. Hum Pathol. 2017 Apr;62:40–9.

20. Xing Y, Liu Y, Liu T, Meng Q, Lu H, Liu W, Hu J, Li C, Cao M, Yan S, Huang J, Wang T, Cai L. TNFAIP8 promotes the proliferation and cisplatin chemoresistance of non-small cell lung cancer through MDM2/p53 pathway. Cell Commun Signal. 2018 Jul;31(1):43. 16(.

21. Liu T, Jiang L, Yu L, Ge T, Wang J, Gao H. Association of TNFAIP8 gene polymorphisms with endometrial cancer in northern Chinese women. Cancer Cell Int. 2019 Apr 23;19:105.

22. Wang J, Gao H, Liu G, Gu L, Yang C, Zhang F, Liu T. Tumor necrosis factor α-induced protein 8 expression as a predictor of prognosis and resistance in patients with advanced ovarian cancer treated with neoadjuvant chemotherapy. Hum Pathol. 2018 Dec;82:239–48.

23. Liu T, Xia B, Lu Y, Xu Y, Lou G. TNFAIP8 overexpression is associated with platinum resistance in epithelial ovarian cancers with optimal cytoreduction. Hum Pathol. 2014 Jun;45(6):1251–7.
24. Odicino F, Pecorelli S, Zigliani L, Creasman WT. History of the FIGO cancer staging system. Int J Gynaecol Obstet. 2008 May;101(2):205 – 10.

25. Couch FJ, Wang X, McGuffog L, Lee A, Olswold C, Kuchenbaecker KB, et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet. 2013;9(3):e1003212.

26. Amankwah EK, Lin HY, Tyrer JP, Lawrenson K, Dennis J, Chornokur G, et al. Epithelial-Mesenchymal Transition (EMT) Gene Variants and Epithelial Ovarian Cancer (EOC) Risk. Genet Epidemiol. 2015 Dec;39(8):689–97.

27. Vigorito E, Kuchenbaecker KB, Beesley J, Adlard J, Agnarsson BA, Andrulis IL, et al. Fine-Scale Mapping at 9p22.2 Identifies Candidate Causal Variants That Modify Ovarian Cancer Risk in BRCA1 and BRCA2 Mutation Carriers. PLoS One. 2016 Jul 27;11(7):e0158801.

### Tables

**Table 1. Demographic and clinicopathologic characteristics of 210 ovarian cancer cases and 231 healthy controls**

| Characteristics                          | Cases    | Controls   | \(^*P^\) |
|------------------------------------------|----------|------------|----------|
| Age                                      | 53.24±10.54 | 54.32±9.58 | 0.261    |
| Family cancer history (ovarian cancer)   |          |            | 0.023    |
| No                                       | 203      | 230        |          |
| Yes                                      | 7        | 1          |          |
| Complication\(^a\)                       |          |            | 0.060    |
| Yes                                      | 158      | 155        |          |
| No                                       | 52       | 76         |          |
| Smoking history                          | 159      | 180        | 0.583    |
| No                                       | 51       | 51         |          |
| Yes                                      |          |            |          |
| FIGO stage                               |          |            |          |
| I/II                                     | 94       |            |          |
| III/IV                                   | 116      |            |          |
| Histologic grade                         |          |            |          |
| G1/G2                                    | 95       |            |          |
| G3                                       | 115      |            |          |
| Histological type                        |          |            |          |
| serous                                   | 132      |            |          |
| mucinous                                 | 31       |            |          |
| endometrioid                             | 32       |            |          |
| clear cell                               | 15       |            |          |
| Residual tumor size                      |          |            |          |
| ≤ 1 cm                                   | 132      |            |          |
| > 1 cm                                   | 78       |            |          |
| Ascites                                  |          |            |          |
| ≤ 100 ml                                 | 64       |            |          |
| > 100 ml                                 | 146      |            |          |
| Serum CA-125 level                       |          |            |          |
| ≤ 35 U/mL                                | 45       |            |          |
| > 35 U/mL                                | 165      |            |          |
| Recurrence                               |          |            |          |
| No                                       | 124      |            |          |
| Yes                                      | 86       |            |          |

\(^*\)Two-sided chi-squared test or Fisher’s test or student’s t test.

\(^a\)Complication: patients with diabetes and cardio-cerebrovascular disease.

FIGO: the Federation of Gynaecology and Obstetrics; G1: Well differentiated; G2: moderately differentiated; G3: poorly differentiated.
Table 2. The distribution of allele frequencies of TNFAIP8 SNPs in cases and controls

|                | Cases(%) | Controls(%) | COR (95%CI) | AOR (95%CI) | *P     |
|----------------|----------|-------------|-------------|-------------|--------|
|                | n=420    | n=462       | P           |             |        |
| 352(83.8)      | 361(78.1)| 1.000       | 1.000       | 0.690       | 0.033  |
| 68(16.2)       | 101(21.9)| 0.971       | 0.709 (0.491-0.971) | 1.000       | 0.958 (0.684-0.997) | 0.048  |
| 341(81.2)      | 372(80.5)| 1.000       | 1.000       | 0.958       | 0.800  | 0.009  |
| 79(18.8)       | 90(19.5) | 0.684-      | 1.000       | 0.960       | 0.684- | 0.816  |
| 337(80.2)      | 401(86.8)| 1.340       | 1.349       | 1.349       | 1.000  | 0.009  |
| 83(19.8)       | 61(13.2) | 0.009       | 1.000       | 1.619       | 0.129- | 0.009  |

*Data were calculated by logistic regression, adjusted for age, smoking history, complication, family history

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval.

Table 3. Relationship of TNFAIP8 polymorphisms and ovarian cancer risk
| Cases (%) | Controls (%) | COR (95% CI) | P   | AOR (95% CI) | *P  |
|-----------|--------------|---------------|------|--------------|-----|
|           | n=210        | n=231         |      |              |     |
| **inant** |              |               |      |              |     |
| 145(69.0) | 145(62.8)    | 1.00          | 0.040| 1.000        | 0.048|
| 62(29.5)  | 71(30.7)     | 0.873         | (0.579-1.518) | 0.905 | (0.598-0.636) |
| 3(1.4)    | 15(6.5)      | 1.317         |  0.012 | 1.370       | 0.014|
| int       |              |               |      |              |     |
| 145(69.0) | 145(62.8)    | 0.200         | (0.057-0.726) | 0.205 | (0.058-0.226) |
| -GG       | 86(37.2)     | 0.166         |      |              |     |
| AG        |              |               |      |              |     |
| 3(1.4)    | 216(93.5)    | 0.756         | (0.509-0.782) | 0.524 | (0.016-0.359) |
| 15(6.5)   | 1.123        | 0.014         | 1.165|              |     |
| **inant** |              |               |      |              |     |
| 137(65.2) | 154(66.7)    | 0.209         | (0.060-0.276) | 0.212 | (0.060-0.214) |
| 67(31.9)  | 64(27.7)     | 0.731         | 0.440| 0.744        | 0.359|
| CC        |              |               |      |              |     |
| 137(65.2) | 154(66.7)    | 1.000         |      |              |     |
| 67(31.9)  | 64(27.7)     | 0.731         | 0.440| 0.744        | 0.359|
| int       |              |               |      |              |     |
| 73(34.8)  | 154(66.7)    | 1.177         | (0.779-0.752) | 1.216 | (0.801-0.674) |
| -TT       | 204(97.1)    | 1.778         |      |              |     |
| ive       | 6(2.9)       | 0.519         | (0.192-0.497) | 0.183 | (0.134-0.076) |
| -CT       | 13(5.6)      | 1.402         | 0.160| 1.350        | 0.008|
| **inant** |              |               |      |              |     |
| 135(64.3) | 175(75.8)    | 1.066         | (0.718-0.026) | 1.089 | (0.731-0.025) |
| 67(31.9)  | 52(22.5)     | 1.581         |      | 0.662        | 0.015|
| 8(3.8)    | 4(1.7)       | 0.126         |      |              |     |
| int       |              |               |      |              |     |
| 135(64.3) | 175(75.8)    | 0.493         | (0.184-0.468) | 0.174 | (0.080-0.076) |
| -GG       | 202(96.2)    | 1.322         | 0.009| 1.263        | 0.008|
| ive       | 8(3.8)       | 227(98.3)     |      |              |     |
| AG        | 4(1.7)       | 1.000         | 0.191| 1.000        | 0.218|
|           |              |              |      |              |     |

*Data were calculated by logistic regression, adjusted for age, smoking history, complication, family history

COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval.

Table 4. The association between TNFAIP8 polymorphisms and clinicopathological characteristics of ovarian cancer
| rs11064 | rs1045241 | rs1045242 |
|---------|-----------|-----------|
|         | rs11064   | rs1045241 | rs1045242 |
| AG      | G         | AG+G      |          |
| G       | CC        | CT        | TT       | CC+C     | AA      | AG    | GG    | AG+G |
| 0.024   | 0.006     | 0.025     | 0.040    |
| 19      | 1         | 20        | 69       | 23       | 2       | 25     | 69    | 23   | 2  |
| 43      | 2         | 45        | 68       | 44       | 4       | 48     | 66    | 44   | 6  |
| 27      | 1         | 28        | 0.674    | 63       | 30      | 2       | 32    | 0.766 | 62  |
| 35      | 2         | 37        | 74       | 37       | 4       | 41     | 73    | 37   | 5  |
| 0.463   | 0.446     | 0.430     |
| 40      | 3         | 43        | 0.280    | 0.098    | 0.064   |
| 9       | -         | 9         | 0.739    | 0.508    |
| 11      | -         | 11        | 0.557    | 0.694    | 0.561   |
| 2       | -         | 2         | 0.800    | 0.573    | 0.690   |
| 12      | 1         | 13        | 0.736    | 0.562    | 0.467   |
| 50      | 2         | 52        | 0.071    | 0.112    | 0.043   |
| 30      | 1         | 32        | 0.437    | 0.086    | 0.034   |
| 32      | 2         | 23        | 0.040    | 0.013    |         |

| AG      | G         | AG+G      |          |
|---------|-----------|-----------|-----------|
| G       | CC        | CT        | TT       | CC+C     | AA      | AG    | GG    | AG+G |
| 0.024   | 0.006     | 0.025     |          |
| 19      | 1         | 20        | 69       | 23       | 2       | 25     | 69    | 23   | 2  |
| 43      | 2         | 45        | 68       | 44       | 4       | 48     | 66    | 44   | 6  |
| 27      | 1         | 28        | 0.674    | 63       | 30      | 2       | 32    | 0.766 | 62  |
| 35      | 2         | 37        | 74       | 37       | 4       | 41     | 73    | 37   | 5  |
| 0.463   | 0.446     | 0.430     |
| 40      | 3         | 43        | 0.280    | 0.098    | 0.064   |
| 9       | -         | 9         | 0.739    | 0.508    |
| 11      | -         | 11        | 0.557    | 0.694    | 0.561   |
| 2       | -         | 2         | 0.800    | 0.573    | 0.690   |
| 12      | 1         | 13        | 0.736    | 0.562    | 0.467   |
| 50      | 2         | 52        | 0.071    | 0.112    | 0.043   |
| 30      | 1         | 32        | 0.437    | 0.086    | 0.034   |
| 32      | 2         | 23        | 0.040    | 0.013    |         |

| rs11064 | rs1045241 | rs1045242 |
|---------|-----------|-----------|
| AG      | G         | AG+G      |
| G       | CC        | CT        | TT       | CC+C     | AA      | AG    | GG    | AG+G |
| 0.024   | 0.006     | 0.025     |
| 19      | 1         | 20        |
| 43      | 2         | 45        |
| 27      | 1         | 28        |
| 35      | 2         | 37        |
| 0.463   | 0.446     |
| 40      | 3         | 43        |
| 9       | -         | 9         |
| 11      | -         | 11        |
| 2       | -         | 2         |
| 0.280   | 0.098     |
| 44      | 2         | 46        |
| 18      | 1         | 19        |
| 18      | -         | 18        |
| 44      | 3         | 47        |
| 12      | 1         | 13        |
| 50      | 2         | 52        |
| 30      | 1         | 32        |
| 32      | 2         | 23        |
"Two-sided chi-squared test or Fisher's text.

FIGO: the Federation of Gynaecology and Obstetrics; G1: Well differentiated; G2: moderately differentiated; G3: poorly differentiated.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTables.doc](#)