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Prediction value of intercellular adhesion molecule-1 gene polymorphisms for epithelial ovarian cancer risk, clinical features, and prognosis

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ABSTRACT

Intercellular adhesion molecule-1 (ICAM-1, encoded by *ICAM-1*) is implicated in tumorigenesis and tumor progression. *ICAM-1* modulates the susceptibility to several types of cancer and the disease prognosis; however, its role in epithelial ovarian cancer (EOC) is unclear. Here, we evaluate single nucleotide polymorphisms (SNPs) in *ICAM-1* as predictors of EOC risk and prognosis. Six *ICAM-1* polymorphisms were genotyped in 408 patients with EOC and 520 controls using the MassARRAY system. The *ICAM-1* mRNA levels in 89 EOC tissues and 35 normal ovarian tissues were examined using quantitative PCR. The *ICAM-1* rs5498 G allele was associated with increased tumor grade (OR = 2.650) and EOC risk (OR = 1.405). This risk was more evident in females who had first-degree relatives (FDRs) with a tumor (OR = 3.475) or who experienced early menarche (OR = 2.774). The *ICAM-1* expression in the cancerous tissue was elevated compared with that of normal ovarian tissues ($p < 0.0001$), and it was associated with an rs5498 genotype ($p = 0.0002$). *ICAM-1* SNPs did not significantly predict the overall EOC survival ($p > 0.05$). However, the rs5498 G allele correlated with EOC survival time in patients whose FDRs suffered from a tumor ($p = 0.001$). *ICAM-1* rs5498 likely confers a high risk for EOC in G allele carriers accompanied by up-regulation of *ICAM-1* expression during carcinogenesis. The combination of *ICAM-1* rs5498 and tumor history predicts the EOC prognosis.

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1. Introduction

Epithelial ovarian cancer (EOC) is the main form of ovarian cancer and the most lethal gynecological carcinoma. Despite numerous efforts to understand its etiology, EOC is difficult to predict. It is well known that genetic factors play an important role in the etiology and pathogenesis of EOC and modulate EOC susceptibility. A few rare mutations in high-penetrance genes, including BRCA1, BRCA2 and HNPCC, elevate the familial EOC risk (Fasching et al., 2009), which accounts for just 10% of the total risk of developing EOC. Sporadic EOCs account for the majority of the cases and are mainly attributable to numerous common low-penetrance variants across the genome (Fasching et al., 2009). The identification of common variants that predispose individuals more weakly to EOC is a major challenge, but the results would be highly valuable for evaluating individual EOC risk, developing a new screening method and individualizing prevention approaches.

Intercellular adhesion molecule-1 (ICAM-1; also called CD54) is a member of the immunoglobulin superfamily of adhesion molecules. ICAM-1 plays an important role in cell–cell and cell–extracellular matrix interactions, and it mediates the invasion of immune cells into damaged tissue during the inflammatory and immune responses (Hubbard and Rothlein, 2000). Substantial evidence indicates that ICAM-1 is involved in tumorigenesis and tumor progression, specifically by facilitating tumor invasion and metastases (Brooks et al., 2008; Lin et al., 2006; Wang et al., 2006). Animal experiments indicated that inhibiting tumor cell *ICAM-1* expression reduces the metastatic capacity of tumor cells, thus supporting a role for this molecule in metastasis (Brooks et al., 2008; Lin et al., 2006; Miele et al., 1994; Wang et al., 2006). A potential explanation for this result is that the *ICAM-1* expression stimulated by vascular endothelial growth factor mediates endothelial cell migration and facilitates angiogenesis and local tumor cell invasion (Kevil et al., 2004; Kim et al., 2001). Clinical studies also revealed that *ICAM-1* expression is elevated in gastric (Maruo et al., 2002), breast (Schröder et al., 2011) and thyroid cancer tissues (Buitrago et al., 2011), and increased *ICAM-1* expression levels are associated with poor prognosis (Maruo et al., 2002; Schröder et al., 2011). *ICAM-1* is expressed in the surface epithelium of normal ovaries. It functions to recruit leukocytes into the preovulatory ovary, and it participates in the formation of the corpus luteum (Bonello et al., 2004). Moreover, *ICAM-1* expression levels were reduced in some ovarian adenocarcinoma cell lines and primary tumors,

Abbreviations: CI, confidence interval; EOC, epithelial ovarian cancer; FDR, first-degree relative; FPRP, false positive report probability; ICAM-1, Intercellular adhesion molecule-1; LD, linkage disequilibrium; LFA-1, lymphocyte function-associated protein-1; OR, odds ratio; SNP, single nucleotide polymorphism.

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suggesting that down-regulation of ICAM-1 expression may be a selective advantage to these cancer cells (Arnold et al., 2001). Similarly, the serum level of soluble ICAM-1 (sICAM-1) is also elevated in multiple cancers (Alexiou et al., 2003; Guney et al., 2008; O'Hanlon et al., 2002). Furthermore, the serum sICAM-1 level is positively correlated with several clinicopathological cancer features (e.g., tumor stage and metastases) and is a significant predictor of prognosis and survival (Alexiou et al., 2003; Guney et al., 2008).

Due to the critical role that ICAM-1 plays in tumorigenesis and tumor progression, the gene encoding ICAM-1 is thought to be a candidate tumor susceptibility gene. A large-scale association study confirmed that a region in chromosome 19p13.2, which includes *ICAM-1*, confers increased risk for breast and prostate cancer in two populations with European ancestry from Germany and Australia (Kammerer et al., 2004). Furthermore, two single nucleotide polymorphisms (SNPs) that were previously described in the human *ICAM-1* gene at codons 241 (glycine to arginine substitution; rs1799969) and 469 (a lysine to glutamic acid substitution; rs5498) were also shown to modulate the susceptibility for several types of cancers including prostate (Chen et al., 2006), colorectal (Qing-lei et al., 2009) and breast (Kammerer et al., 2004) cancers. The rs5498 SNP was also significantly correlated with colorectal cancer differentiation (Qing-lei et al., 2009) and gastric cancer prognosis (Tian et al., 2012). In addition, *ICAM-1* expression was affected by the rs5498 SNP genotype in human umbilical vein endothelial cells (Holder et al., 2008) and colorectal cancer tissues (Qing-lei et al., 2009).

Although *ICAM-1* variants affect the risk and biological behavior of multiple cancers, their role in EOC is unclear. The serum sICAM-1 level is elevated in benign and malignant ovarian tumors (Callet et al., 2000; Opala et al., 2003) and significantly correlates with the age at diagnosis (Callet et al., 2000) and tumor morphological score for an ovarian tumor (Opala et al., 2003), suggesting the involvement of ICAM-1 in EOC pathogenesis. In this study, we investigated the potential association of six *ICAM-1* SNPs with the risk, clinicopathological features and EOC prognosis.

2. Patients and methods

2.1. Subjects

A total of 408 patients with pathologically confirmed sporadic EOC were recruited from the inpatient gynecology department at our hospital from January 2006 to January 2012. Patients with a family history of ovarian/breast cancer or other malignancies were excluded. The clinical characteristics, including age at diagnosis, FIGO stage, histological type and tumor grade, were obtained from the medical records. Among the patients, the subjects who were inpatients between January 2006 and January 2008 were enrolled in a survival analysis so that the duration of follow-up could be more than three years. In addition, 520 age-matched healthy controls were recruited from subjects undergoing regular gynecological examinations at our hospital. The exposure history for several risk and protective factors for ovarian tumors for cases and controls, including smoking (Beral et al., 2012), obesity (body mass index > 25) (Beral et al., 2012), tumor occurrence in a first degree relative (FDR) (Tung et al., 2004), full-term pregnancy and age of menarche, were also collected from the medical records and/or interviews. All of the subjects were northern Han Chinese and provided written informed consent to participate in this study. The Ethics Committees of the Fourth Military Medical University approved this research.

2.2. SNP selection and genotyping

The HapMap database (release #27/phase II + III; population: Han Chinese in Beijing, HCB) was first consulted to obtain SNPs throughout the *ICAM-1* genomic region covering and flanking regions 2000 bp upstream and downstream of the gene. Fourteen SNPs were found in the HapMap HCB sample, and six that had a minor allele frequency > 0.05 were selected for our study, including rs281428, rs281432, rs5496, rs5498, rs281437 and rs3093030. Three to five milliliters of peripheral blood was collected from the subjects and preserved in tubes coated with EDTA. Genomic DNA was extracted using the TIANamp Blood DNA Kit (TIANGEN, Beijing, China) and stored at −20 °C until use. SNP genotyping was performed using the MassARRAY system, and the primers for the amplification and extension reactions were designed using MassARRAY Assay Design Version 3.1 software (Sequenom, San Diego, CA). The genotyping quality was examined by a detailed QC procedure consisting of a > 95% successful call rate, duplicate genotype calling, internal positive control samples and Hardy–Weinberg equilibrium (HWE) testing.

2.3. Tissue sample preparation and real-time quantitative PCR

Eighty-nine primary cancerous tissues and thirty-two adjacent normal ovarian tissues were collected from patients undergoing surgery. Morphologically normal ovarian epithelial cells and malignant EOC cells were obtained from these tissues by laser capture microdissection. Total RNA extraction and cDNA synthesis were performed as previously described (Buitrago et al., 2011). Real-time PCR was performed in duplicate using primer sets specific for *ICAM-1* (forward primer: 5′-TGCTGCTTTCCCG-3′ and reverse primer: 5′-GAAACCTCGTGCCTT CCCCTCC.

GGAAC-3′) and GAPDH (forward primer: 5′-CTCTGCTCCTCCTG TTCGAC-3′ and reverse primer: 5′-TTAAAAGCAGCCCTGGTGAC-3′), a housekeeping gene. A 25-μl reaction mixture containing 2.5 μl cDNA template, 12.5 μl TaqMan Universal PCR master mix (Applied Biosystems, CA) and 1.25 μl primer probe mixture was carried out using the following thermal cycler parameters: incubation at 50 °C for 2 min and denaturing at 95 °C for 10 min, then 40 cycles of the amplification step (denaturation at 95 °C for 15 s and annealing/extension at 60 °C for 1 min). The ICAM-1 gene expression values were normalized relative to GAPDH. The mean of the duplicate reference normalized expression measurements (ΔCt) was used to calculate the gene expression value according to the 2-ΔΔCt method (Arocho et al., 2006).

2.4. Statistical analysis

Pearson's chi squared (χ^2) test was used to evaluate the differences in the distribution of the categorical variables, including the known risk factors and frequencies of the *ICAM-1* genotypes, alleles and haplotypes. A logistic regression analysis was conducted to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations between the genetic polymorphisms and EOC risk and clinical features while controlling for known risk factors. To avoid a spurious association due to multiple testing, we calculated the false-positive report probability (FPRP) for a SNP from an estimated OR and the 95% CIs using the methodology described by Wacholder et al. (2004). Considering the positive associations between *ICAM-1* rs5498 and the risk of having multiple tumors (Chen et al., 2006; Kammerer et al., 2004; Qing-lei et al., 2009), the alteration in the encoded amino acids caused by rs5498 and the biological implications of *ICAM-1* in tumor development (Brooks et al., 2008; Kevil et al., 2004; Kim et al., 2001; Lin et al., 2006; Miele et al., 1994; Wang et al., 2006), a prior probability of 10% was assigned for the analysis of the association between rs5498 and EOC, while a more conservative prior probability of 1% was assigned for the other SNPs. In accordance with Wacholder et al. (2004), a standard FPRP cutoff of < 0.5 was selected with a cutoff of < 0.2 considered more stringent. The comparison of *ICAM-1* mRNA was performed by a non-parametric analysis of variance using ranks (Kruskal–Wallis) or the Mann–Whitney test. The survival time was calculated from the date of diagnosis to the date of death (from ovarian cancer) or censored on 1 July 2012 or at the time of death from another cause. The survival curves were plotted by the Kaplan–Meier method and compared using the log

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