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Original article

# Epistatic interaction between adiponectin and survivin gene polymorphisms in endometrial carcinoma

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ABSTRACT

Adiponectin appears to play an important role in the development and progression of several obesity-related malignancies. Also, overexpression of survivin, an inhibitor of apoptosis protein, is associated with increased risk of cancers. The aim of this study was to investigate the association between two polymorphisms in the adiponectin gene and endometrial cancer (EC) risk. We also investigated whether epistasis between surviving and adiponectin gene polymorphisms are associated with EC risk in an Iranian population.

The samples comprised formalin-fixed, paraffin-embedded tissue sections obtained from the archive of the pathology department, Imam-Khomeini Hospital and Firouzgar hospital. After DNA extraction the genotyping was performed using PCR-RFLP technique.

Single nucleotide polymorphisms (SNPs) in adiponectin (rs1063539, rs2241766) and survivin (rs9904341) gene were evaluated in the study. The increased frequency of *ADIPOQ* rs1063539C allele (CC + CG genotype) was associated with decreased EC risk [OR: 0.39(0.17–0.90)]. Survivin rs9904341C allele (CC + CG genotype) was associated with increased EC risk [crude OR: 2.75(1.27–5.95), adjusted OR: 2.93(1.27–6.76)]. We observed an epistatic interaction between survivin rs9904341 CC + CG genotype and *ADIPOQ* rs1063539 GG genotype increasing the risk of EC compared to those with other genotypes [OR: 4.86(1.88–12.54), $P = 0.001$].

Our findings indicate that adiponectin might have a modulatory effect on survivin role and function in EC, which requires further investigation.



## Introduction

Endometrial cancer (EC) is the most common gynecological malignancy of females in many countries [1]. The number of new cases is increasing worldwide. In the past decades, the incidence rate of EC has increased due to improved screening, change in dietary habits and lifestyle in developing countries. Although the etiology of EC has not been clearly understood, epidemiological studies have observed positive associations between obesity and EC risk [2,3].

Several proteins produced by adipocytes have been studied as a link between obesity and cancer risk. There is emerging evidence that adiponectin levels as one of the adipokins are inversely associated with the risk of several obesity-related malignancies such as breast, colorectal and endometrial cancers [4,5]. The studies have demonstrated that adiponectin may suppress cell proliferation, induce apoptotic responses and inhibit angiogenes [6,7]. Recently, several adiponectin gene (ADIPOQ) single nucleotide polymorphisms (SNPs) have been shown to influence the expression of the gene and subsequent cancer development [8,9]. Two of the most commonly studied SNPs at the ADIPOQ locus are a silent T to G substitution in exon 2 (rs2241766) and a G to C substitution in 3′

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UTR (rs1063539). However, association studies of these two SNPs, either independently or as a haplotype, have resulted in conflicting evidence in different population and sample types [10,11].

Survivin is a member of the inhibitor of apoptosis protein family (IAP) which regulates cell proliferation and apoptosis [12]. Although survivin is not expressed in most normal differentiated adult tissue, it is detected in fetal tissue and most cancers [13]. Overexpression of survivin correlates with increased metastasis and decreased survival in a variety of human cancers. We have recently reported the correlation of survivin gene polymorphism with EC risk [14]. Several oncogenic pathways such as phosphoinositide 3-kinase (PI3K)/Akt signaling, oncogene (Ras) expression, and Stat 3 (signal transducer and activator of transcription 3) activation, implicate survivin regulation in transformed cells [15,16]. Some effector molecules of adiponectin signaling pathway (e.g. Stat 3, Ras and Akt) participate in the regulation of survivin expression [17]. We hypothesized that over-expression of survivin in endometrial tumors may be influenced by adiponectin expression.

In the present study, we have evaluated the association between two SNPs in the ADIPOQ genes and endometrial cancer risk in an Iranian population. We also investigated the interaction between survivin gene polymorphism with SNPs in the ADIPOQ gene in EC risk.

## Materials and methods

### *Study population*

The study group comprised 58 patients with a preoperative histopathological diagnosis of endometrial carcinoma, according to either dilation and curettage or office biopsy examination. A control group ($n = 55$) was composed of patients who underwent dilation and curettage and were diagnosed as healthy after a pathological examination. Patients underwent surgical staging of endometrial cancer, including TAH + BSO + lymphadenectomy + cytology examination after hysterectomy. All sections were examined and interpreted according to the International Federation of Gynecology and Obstetrics (FIGO-1988) staging system, by the expert pathologists [18]. All speciments were examined by an expert pathologist (FF) and according to surgical and pathological data, surgico-pathological staging was done. Grading also was performed based on FIGO grade and nuclear grade. If nuclear grade did not match with FIGO grading, one grade was added to the tumor grade. Cases with clear cell carcinoma and papillary serous carcinoma were considered as high grade. All the grading and staging were perfomed on hysterectomy speciments. In adenocarcinoma with squamous differentiation, the nuclear grade of the glandular component determines the histologic grade. All patients were operated on in the Department of Gynecologic Oncology at Vali-E-Asr Hospital, and Firouzgar Hospital, Tehran University of Medical Sciences, Iran, between September 2008 and October 2012. Patients with a previous pelvic radiation, hormonal or chemotherapy treatment, and a coexisting second malignancy were excluded. The personal and demographic data of subjects were obtained from the patient files. Weight was recorded in light clothing to the nearest 0.1 kg on a SECA digital weighing scale (SECA, Germany), and height was measured without shoes to the nearest 0.1 cm. Body mass index (BMI) was calculated from weight and height [BMI = weight (kg)/height ($m^2$)].

Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL and/or current use of pharmacological treatment.

The study was approved by the Ethics Committee of Tehran University of Medical Sciences. Informed consent was obtained from those eligible subjects who desired to participate in the study.

### DNA extraction and genotyping

DNA extraction of paraffin-embedded tissue was performed according to standard protocol [19]. Primers were designed for genotyping adiponectin gene polymorphisms using PCR-RFLP technique.

The assay has been designed for genotyping Adiponectin rs1063539 and rs2241766 polymorphisms. The primer sequences for rs1063539 polymorphism were as follows:

Forward primer sequence: 5′-CTGGCTATGCTCACAGTCTCA-3′
Reverse primer sequence: 5′-ATGAAGCAAAAGCTGACAGAA-3′
The primer sequences for rs2241766 polymorphism were as follows:
Forward primer sequence: 5′-TTGTAGGTCCCAACTGGGTGTG-3′
Reverse primer sequence: 5′-CTTGAGTCGTGGTTTCCTGGTC-3′

PCR amplification was carried out in a final volume of 25 UL reaction mixture containing 50 ng DNA sample, 12.5 UL Ampliqon PCR master mixes (Skovlunde, Denmark) and 0.5 UL of each primers. Thermal cycle amplification conditions for rs1063539 polymorphism were: denaturation at 95 °C for 10 min and 14 cycles of 95 °C for 30 min, 60 °C decrease 0.5 °C per cycle for 45 s, 72 °C for 60 s and 24 cycles of 95 °C for 30 s, 53 °C for 45 s, 72 °C for 60 s with a final elongation at 72 °C for 5 min. For rs2241766 polymorphism the amplification condition was denaturation at 95 °C for 5 min and 39 cycles of 95 °C for 30 s, 60 °C for 45 s, 72 °C for 60 s, with a final elongation at 72 °C for 5 min. The PCR product size for rs1063539 polymorphism was 250 bps which after digestion with BsmaI restriction endunuclease the digested product yielding 20 bp, 100 bp, and 130 bp products for CC homozygous, 20 bp, 100 bp, 130 bp and 230 bp products for CG heterozygous and 20, 230 bp products for GG homozygous. PCR product length for rs2241766 polymorphism was 149 bps and after digestion with SmaIrestriction enzyme yields 14,912,128 bp products for TG heterozygous 12,128 bp products for GG homozygous and 149 bp undigested product for TT homozygous. PCR products were visualized on an agarose gel stained with SYBER green.

Survivin rs9904341 polymorphism genotyping was carried out based on the protocol has been described previously[20].

### *Statistical analysis*

Mean (standard deviation: SD) values for continuous and frequencies (%) for categorical variables of the baseline characteristics variables were compared between groups using student's *t*-test and $x^2$-test, respectively.

Strength of association between different groups and genotypes of adiponectin and survivin gene polymorphisms were estimated using odds ratios (ORs) and 95% confidence intervals (CIs) and existence of interactions was evaluated. Statistical analyses were performed with SPSS version 16.0 statistical package for Windows (SPSS Inc., Chicago, Illinois). *P* values ≤0.05 were considered to be statistically significant.

## Results

In this cross-sectional study, we included 58 patients with endometrial cancer and 55 healthy control groups. Patients' characteristics for histology examination grading and surgical staging according to are given in Table 1. Baseline characteristics of patients with EC and control group are summarized in Table 2. The mean age of subjects was 60.8 ± 8.6 years in patients with EC and 58.2 ± 6.9 years in the control group. EC had higher prevalence of hypertension and higher prevalence of post-menopause as compared with

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**Table 1**
The characteristics of patients with endometrial carcinoma.

| Carcinoma | $n=58$ |
|---|---|
| Histology of tumor | |
| Endometrioid | 44 |
| Mixed: | |
| Mucinous + Endometrioid | 1 |
| Endometrioid + Clear cell | 2 |
| Clear cell | 5 |
| Papillary serous | 3 |
| Adenosquamous | 3 |
| Grade of tumor: | |
| 1 | 31 |
| 2 | 12 |
| 3 | 15 |
| Surgical stage of tumor*: | |
| I | |
| IA | 17 |
| IB | 12 |
| IC | 7 |
| II | |
| IIA | 6 |
| IIB | 8 |
| III | |
| III A | 5 |
| III B | 0 |
| III C | 1 |
| IV | |
| IV A | 0 |
| IV B | 2 |

* International Federation of Gynecology and Obstetrics (FIGO-1988) staging system.

the controls. No significant case-control differences were observed for prevalence of diabetes and BMI.

The allele and genotype frequencies for each polymorphism were compared in cases and controls. Table 3 shows the distribution of allele and genotype frequencies for *survivin* gene polymorphism and *ADIPOQ* gene polymorphisms.

In Table 4, we found no evidence for association of *ADIPOQ* rs106353 and *ADIPOQ* SNP rs2241766 with stage and grade of cancer. We observed a significant association between survivin rs9904341 and grade of endometrial cancer ($P=0.005$). The risk of developing advanced diseases (grades 2 + 3) was greater for patients with *survivin* rs9904341C allele (CC or CG) than patients with G allele (GG) (OR = 3.29; CI: 1.10–9.79; $P=0.03$).

Table 5 shows that the presence of *ADIPOQ* rs1063539 C allele (CC or CG genotypes) was associated with decreased endometrial cancer risk [OR: 0.39 (0.17–0.90)]. In addition, presence of *survivin* rs9904341C allele (CC or CG) was associated with increased endometrial cancer risk [crude OR: 2.75 (1.27–5.95), adjusted OR: 2.93 (1.27–6.76)]. Individuals carrying survivin rs9904341C allele (CC or CG) and *ADIPOQ* rs1063539G allele (GG) had a higher risk of EC than those carrying other genotypes, independent of risk factors such as age [OR: 4.86 (1.88–12.54), $P=0.001$].

## Discussion

In this study, we found that an adiponectin gene polymorphism (rs1063539) and a survivin gene polymorphism (rs9904341) were significantly associated with endometrial cancer risk. This study also shows that there may be an interaction between adiponectin gene and surviving gene to predict EC risk.

We have previously shown an association between C allele carrier status for SNP rs9904341 of survivin and EC risk [14]. The presence of this polymorphism has been reported to be common in cancer cells and associated with increased survivin expression at both mRNA and protein levels [21]. Our result is in agreement with that reported by Xu et al., showing that the C allele of rs9904341 polymorphism may increase the risk of various cancers, especially in Asian populations [22]. Several studies have examined the potential association of the C allele carrier status for SNP rs9904341 of survivin with susceptibility to clinicopathologic characteristics of cancer [23–25]. We indicated that the risk of developing EC (grade 2 + 3) was significantly greater in individuals with the CC/CG genotype than in individuals with the GG genotype.

Regulation of survivin expression to provide a different cell survival threshold is the main mechanism in which survivin is utilized to protect cell from apoptosis. This effect might be implied by interactions between survivin and other molecules to apply antiapoptotic effects of survivin in response to the cell death stimulation [26,27].

There is increasing interest in the role of adiponectin in carcinogenesis. Several studies have reported the association between genetic polymorphisms in the adipokine genes and risk of cancer, and the results were not consistent [11,28]. Also, low plasma adiponectin concentration is associated with a decrease in insulin sensitivity, and the studies have shown that it can be predictive of future development of diabetes [29,30]. Our finding is in keeping with previous studies which reported that three of the 10 SNPs (rs374246, rs1063539 and rs12629945) in the *ADIPOQ* gene were significantly associated with endometrial cancer risk [11]. Another study found no association of genetic variants in the *ADIPOQ, ADIPOR1*, and *ADIPOR2* genes with breast cancer risk among postmenopausal women [31].

In the present study, we observed the individual carrying both the survivin and adiponectin risk genotypes (the C allele of the survivin and the G allele of rs1063539 of the adiponectin gene) had a higher risk of EC than those carrying other genotypes. Previous studies have shown that allele G of adiponectin rs1063539

**Table 2**
Baseline characteristics of subjects with endometrial cancer and healthy controls.

| Variables | Cases ($n=58$) | Controls ($n=55$) | *P*-value |
|---|---|---|---|
| Age (year) | $60.8 \pm 8.6$ | $58.2 \pm 6.9$ | 0.09 |
| Body mass index (kg/m$^2$) | $29.8 \pm 8.2$ | $31.2 \pm 5.1$ | 0.5 |
| Diabetes (%) | 27.5 | 22.9 | 0.4 |
| Postmenopause (%) | 91.9 | 68.6 | 0.01 |

Data are are mean (Standard Deviation) and number (%) where indicated.
$P \leq 0.05$ is significant.

**Table 3**
Genotype distributions of the polymorphisms of adiponectin and survivin genes.

| | Cases | Controls | *P*-value |
|---|---|---|---|
| *ADIPOQ*: SNP rs1063539 | | | |
| CC | 1.0(1.7) | 4.0(7.3) | 0.06 |
| CG | 11.0(19.0) | 18.0(32.7) | |
| GG | 46.0(79.3) | 33.0(60.0) | |
| Allele | | | |
| C | 13.0(11.2) | 26.0(23.6) | 0.01 |
| G | 103.0(88.9) | 84.0(76.4) | |
| *ADIPOQ*: SNP rs2241766 | | | |
| GG | 1.0(1.7) | 2.0(3.6) | 0.5 |
| TG | 23.0(3.7) | 24.0(43.6) | |
| TT | 32.0(55.2) | 29.0(52.7) | |
| Allele | | | |
| G | 25.0(22.3) | 28.0(25.5) | 0.5 |
| T | 87.0(77.7) | 82.0(74.5) | |
| *Survivin* SNP rs9904341 | | | |
| CC | 0.0(0.0) | 3.0(5.5) | 0.002 |
| CG | 32.0(55.2) | 14.0(25.5) | |
| GG | 26.0(44.8) | 38.0(69.1) | |
| Allele | | | |
| G | 84.0(72.4) | 20.0(18.2) | <0.001 |
| C | 32.0(27.6) | 90.0(81.8) | |

Values are percents (%), $P \leq 0.05$ is significant.

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**Table 4**
Genotype frequencies of adiponectin and survivin genes polymorphisms in patients with endometrial cancer according to grade and stage of tumors.

| | Grade of tumor | | | *P* value | Surgical stage of tumor | | | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | | I | II | III | IV | |
| ADIPOQ: SNP rs1063539 | | | | | | | | | |
| GG | 87.1 | 66.7 | 73.3 | | 86.1 | 71.4 | 50.0 | 100.0 | |
| CG | 9.7 | 33.3 | 0.0 | 0.2 | 11.1 | 28.6 | 50.0 | 0.0 | 0.3 |
| CC | 3.2 | 0.0 | 0.0 | | 2.8 | 0.0 | 0.0 | 0.0 | |
| ADIPOQ: SNP rs2241766 | | | | | | | | | |
| TT | 54.8 | 75.0 | 40.0 | | 55.6 | 64.3 | 16.7 | 100.0 | |
| TG | 41.9 | 16.7 | 53.3 | 0.3 | 41.7 | 21.4 | 83.3 | 0 | 0.2 |
| GG | 0.0 | 8.3 | 0.0 | | 0.0 | 7.1 | 0.0 | 0 | |
| Survivin SNP rs9904341 | | | | | | | | | |
| GG | 58.1 | 16.7 | 40.0 | | 52.8 | 21.4 | 66.7 | 0.0 | |
| CG | 41.9 | 83.3 | 60.0 | 0.005* | 47.2 | 78.6 | 33.3 | 100.0 | 0.07 |
| CC | 0.0 | 0.0 | 0.0 | | 0.0 | 0.0 | 0.0 | 0.0 | |

Values are percents (%), $P < 0.05$ is significant.
* Odds ratio of Grade 2 + 3 in individuals with CC/CG vs. individuals with GG was **3.29(1.10–9.79)** $P =$ **0.03**.

polymorphism is a low producer at the protein and mRNA level [32]. It is possible that the product of one of these genes interacts with the activity of the other gene. Recently, it has been reported that adiponectin decreases the transcript level of survivin [33]. Consistent with our findings, previous studies both *in vitro* and *in vivo* have shown that adiponectin expression at either the mRNA or protein level could be down-regulated by survivin activation [34,35], however, the exact molecular mechanisms through which these gene polymorphisms may influence risk of cancer, are not known.

The adiponectin and survivin gene polymorphisms could interact with each other in several ways. Adiponectin shows individual biological effects through differential activation of downstream signaling pathways. Signal transducer and activator of transcription 3 (Stat 3) is a common downstream effector of adiponectin. Furthermore, adiponectin suppresses constitutive Stat 3 activations in cancer cells. Also, promotion of tumor cell survival is partly mediated by activating Stat 3 through upregulation of the antiapoptotic protein survivin [34,36]. Because of its critical role in tumorigenesis, inhibitors of Stat 3 activation are being sought for both prevention and therapy of cancer, and it may constitute a universal signaling pathway to mediate pathophysiological effects of adiponectin on cancer [35].

**Table 5**
Odds ratios for endometrial cancer and the polymorphisms of adiponectin and survivin genes.

| SNPs | Crude OR (95%CI) | Adjusted OR (95%CI) |
|---|---|---|
| *ADIPOQ:* SNP rs2241766 | | |
| TT | 1.00 | 1.00 |
| TG/GG | 0.84(0.40–1.76) | 0.96(0.44–2.09) |
| *ADIPOQ:* SNP rs1063539 | | |
| GG | 1.00 | 1.00 |
| CC/CG | 0.39(0.17–0.90)* | 0.45(0.19–1.06) |
| *Survivin* SNP rs9904341 | | |
| GG | 1.00 | 1.00 |
| CC/CG | 2.75(1.27–5.95)* | 2.93(1.27–6.76)* |
| *ADIPOQ:* rs1063539/Survivin rs9904341** | 4.77(1.98–11.51)* | 4.86(1.88–12.54)* |

OR (95%CI); odds ratio (95% confidence interval), Adjusted OR; adjusted odds ratio for age.
* $P \leq 0.05$.
** *ADIPOQ* rs1063539/*Survivin* rs9904341: persons having GG genotype of *ADIPOQ* rs1063539 and CC/CG of *Survivin* rs9904341 compared with persons having CC/CG of *ADIPOQ* rs1063539 or GG of *Survivin* rs9904341.

Other mechanisms by which survivin maintains cell proliferation and promotes tumorigenesis might be through the PI3K/Akt pathway. PI3K regulates survivin expression through Akt activation. The previous studies have shown that activation of the PI3K/Akt pathway is necessary for up-regulation of survivin expression in various malignant cells [37,38]. Also, inhibition of the effect of several regulators of cell growth and signaling proteins is associated with adiponectin level of expression [39]. Adiponectin mediates inhibition of AKT phosphorylation through inactivation of P13K. Many reports show that inhibition of AKT, which has a key role in tumor suppression, takes place concurrent with the activation of AMPK [40]. It seems that adiponectin has an inhibitory effect on survivin in an interrelated metabolic pathway in malignant cells.

To our knowledge, this is the first study showing that the rs1063539 polymorphism of the adiponectin gene has a gene–gene interaction with rs9904341 of the survivin gene, increasing the risk of endometrial cancer.

A potential limitation of our study was the possibility that other genetic variants in the *ADIPOQ* and *survivin* genes in addition to those we studied which may play a role in endometrial cancer. Another limitation is that serum levels of adiponectin were not measured in this study. Therefore, we cannot evaluate whether concentrations of serum adiponectin were associated with these genetic variants. The effect of other risk factors such as smoking on our data could not be adequately evaluated because most of which were not available. Our findings need to be interpereted with causion and be confirmed in larger samples in different populations and also must further examine other polymorphisms in these genes and the association between them in patients with endometrial cancer.

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