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# The Joint Effect of hOGG1 Genotype and Smoking Habit on Endometriosis in Taiwan

**Chia-Wen Tsai[1, 2, *], Chien-Yi Ho[1, *], Liang-Chun Shih[1, *], Tsung-Ho Ying[3], Yi-Hsien Hsieh[4], Ya-Chien Chen[1], Wen-Shin Chang[1, 2, 5], Chung-Yu Huang[6, 7], Sin-Bao Pan[6], Hao-Ai Shui[7], Chang-Peng Chen[1, 8], Paulus S. Wang[2, 9], and Da-Tian Bau[1, 2, 5]**

[1]*Terry Fox Cancer Research Laboratory, China Medical University Hospital, Taichung 40447*
[2]*Graduate Institute of Basic Medical Science, China Medical University, Taichung 40402*
[3]*Department of Obstetrics and Gynecology, School of Medicine, College of Medicine Chung Shan Medical University, Taichung 40201*
[4]*Institute of Biochemistry and Biotechnology, College of Medicine Chung Shan Medical University, Taichung 40201*
[5]*Graduate Institute of Clinical Medical Science, China Medical University, Taichung 40402*
[6]*Taichung Armed Forces General Hospital, Taichung 41152*
[7]*Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei*
[8]*Lin-Shin Hospital, Taichung 40867*
*and*
[9]*Department of Biotechnology, Asia University, Taichung 41354, Taiwan, Republic of China*

## Abstract

**This study has two aims: [1] to evaluate the association between *hOGG1* genotypic polymorphism and endometriosis risk, and [2] to investigate the joint effects of *hOGG1* genotype and smoking habit on endometriosis susceptibility in Taiwan. For this purpose, the well-known polymorphic variants of *hOGG1*, codon 326, was genotyped and analyzed of its association with the risk of endometriosis. In total, 153 patients with endometriosis and 636 non-endometriosis healthy controls were recruited and genotyped. The methodology for genotyping is polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Pearson's *Chi*-square test was performed to compare the distributions of the genotypes between case and control groups. The results showed that the *hOGG1* codon 326 genotypes were not differently distributed between the endometriosis and non-endometriosis control groups in both genotypic ($P = 0.6212$) and allelic ($P = 0.4006$) frequency analysis. We have further analyzed the genotypic-smoking joint effects on endometriosis risk and found an obvious interaction between *hOGG1* codon 326 genotypes and smoking status. The *hOGG1* codon 326 genotypes were increased in endometriosis risk only in the smoker groups ($P = 0.0061$), but not in the non-chewer group ($P = 0.0648$). Our results provide the evidence that the *hOGG1* codon 326 genotype may have a joint effect with smoking on the development of endometriosis.**

**Key Words: endometriosis, hOGG1, single nucleotide polymorphism, smoking**

## Introduction

Endometriosis, which is defined as the presence of ectopic endometrial glands and stroma outside the uterus, is a common cause of pelvic pain and infertility, affecting as many as 10% of premenopausal women while its etiology remains unclear (2, 3). The prevalence of endometriosis is around 3-20% in the general

Corresponding author: Dr. Da-Tian Bau, Terry Fox Cancer Research Laboratory, China Medical University Hospital, 2 Yuh-Der Road, Taichung 40447, Taiwan, R.O.C. Tel: +886-4-22052121 ext. 1523, Fax: +886-4-22052121 ext. 1543, E-mail: datian@mail.cmuh.org.tw; artbau2@gmail.com
*These authors contribute equally to this study.
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population and as high as 20-50% in infertile women (2, 3, 16). Endometriosis, one type of metaplases of eutopic endometrial cells, displays some features of malignancy, including local invasion and aggressive spread to distant organs. Ectopic endometriosis constitutes the growth of endometrial tissue in a place other than the uterine cavity. It is well known that DNA repairing system is essential for the maintenance of genome stability against carcinogenesis. Then it is logical to suspect some genetic variants of DNA repair genes might contribute to endometriosis pathogenesis.

Smoking is reported to generate reactive oxygen species (ROS) including superoxide anion radicals and hydrogen peroxide, which may induce lots of DNA single and double strand breaks. Sustained oxidative stress, such as smoking related chemicals exposure, may induce oxidative DNA adducts in human genome, and 8-hydroxy-2-deoxyguanine (8-OH-dG) was found to be the major adduct (13, 32). The 8-OH-dG is mutagenic which if not repaired immediately after its formation, may cause severe GC to TA transversions on genes such as oncogenes and tumor suppressor genes, which may lead to carcinogenesis (13, 32). Among the DNA repair pathways, the base excision repair subpathway is in charge of the removal of 8-OH-dG and other oxidative DNA adducts from our genome (17). The human OGG1 (*hOGG1*) gene encodes a DNA glycosylase which catalyzes the cleavage of the glycosylic bond between the oxidized base and the sugar moiety, leaving an abasic apurinic/apyrimidinic site in altered DNA (9, 14). The resulting apurinic/apyrimidinic site is then incised, and the repair is completed by successive actions of a phosphodiesterase, a DNA polymerase, and a DNA ligase (9, 14).

In the human genome, the *hOGG1* gene maps to chromosome 3p26.2. Three *hOGG1* variants with different repair activities were identified due to a C to G shifting at 1245 bp (C1245G) in exon 7. This variation causes a serine (Ser) to cysteine (Cys) substitution at codon 326 during translation. This phenomenon is also called *hOGG1* Ser326Cys polymorphism (rs1052133), which has been demonstrated to affect the hOGG1 function (19). Those cells with Cys genotype exhibited a reduced DNA repair activity (19), and this genotypic-phenotypic correlation has been reported in many types of cancers in recent years (23, 29-31). However, no paper had investigated the role of genotype of *hOGG1* in endometriosis before, and not to mention its interaction with smoking habit. In the present study, we aimed at analyzing the *hOGG1* Ser326Cys genotypes in a Taiwan endometriosis population, and investigated the interaction of *hOGG1* Ser326Cys genotypes and smoking habits.

## Materials and Methods

*Study Population and Sample Collection*

One hundred and fifty three patients diagnosed with endometriosis were recruited at the outpatient clinics of general surgery during 2000-2010 at Chung Shan Medical University Hospital in Taiwan. The endometriosis patients were diagnosed by laparoscopy and classified according to the American Society for Reproductive Medicine and all the patients were confirmed histologically of the disease. Among the endometriosis patients, the disease was found to be minimal/mild (stages I and II) in 62 cases (40.5%) and moderate/severe (stages III and IV) in 91 cases (59.5%). Patients with pathological confirmation or clinical suspicion of leiomyoma, adenomyosis, or invasive carcinoma of the uterine cervix or ovary were excluded from this study. No patient had received hormone therapy during the preceding 12 months. The mean age of the endometriosis patients was 40.3 ± 4.9 years, and 55 of them (35.9%) did not have a child or full pregnancy. The basal FSH level was 7.2 ± 1.4 IU/l. The non-endometriosis statuses were confirmed after detail ultrasonography. All operations were performed by experienced surgeon Dr. Yin and his colleagues. All women accepted to provide their peripheral blood sampling for genotype analyses with their informed consents. The experiment was approved by the Ethical Committee and Institutional Review Board of the Chung Shan Medical University Hospital. About four-fold amounts of non-endometriosis healthy volunteers as the controls were selected by matching for their age, gender and habits after initial random sampling from the Health Examination Cohort of China Medical University Hospital. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other or unknown origin, and any familial diseases. Both groups completed a well-informed questionnaire which included the individual smoking habits. Smokers were defined as daily or almost daily smokers, who had smoked at least five packs of cigarettes in their lifetime. Smokers were asked for the age of initiation, whether they were currently smoking or had already quit, and if so, when they had quit, and on average, how many cigarettes they smoked or had smoked daily.

*Genotyping Assays*

Genomic DNA was prepared from peripheral blood leukocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed according to previous studies (4, 6-8, 10-12, 21, 25, 27, 28, 34). The polymerase chain reaction plus

**Table 1. The sequences of the forward and reverse primers, polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) conditions for *hOGG1* genotyping work**

| Polymorphism (Location) | Primers Sequences (5' to 3') | Restriction Enzyme | SNP Sequence | DNA Fragment Size (bp) |
|---|---|---|---|---|
| Codon 326 | F: ACTGTCACTAGTCTCACCAG | *Fnu4HI* | C (Ser) | 200 |
| (rs1052133) | R: GGAAGGTGGGAAGGTG | 37°C for 2 h | G (Cys) | 100 + 100 |

*F and R indicate forward and reverse primers, respectively.

**Table 2. Genotypic and allelic frequencies for *hOGG1* codon 326 gene polymorphism in endometriosis patients and non-endometriosis controls**

| Codon 326 rs1052133 | Controls | % | Patients | % | *P*-Value[a] | OR (95% CI) |
|---|---|---|---|---|---|---|
| Genetic frequency | | | | | 0.6212 | |
| GG | 276 | 43.4% | 73 | 47.7% | | 1.00 (Ref) |
| CG | 255 | 40.1% | 56 | 36.6% | | 0.83 (0.56-1.22) |
| CC | 105 | 16.5% | 24 | 15.7% | | 0.86 (0.52-1.44) |
| CG+CC | 360 | 56.6% | 80 | 52.3% | | 0.84 (0.59-1.20) |
| Allele frequency | | | | | 0. 4006 | |
| Allele G | 807 | 63.4% | 202 | 66.0% | | 1.00 (Ref) |
| Allele C | 465 | 36.6% | 104 | 34.0% | | 0.89 (0.68-1.16) |

[a] Based on *Chi*-square test.

restriction fragment length polymorphism (PCR-RFLP) cycling conditions were: one cycle at 94°C for 5 min; 35 cycles at 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec, and a final extension at 72°C for 10 min (22). Then the PCR products were digested by the specific restriction enzymes for 2 h, and 3% DNA gel electrophoresis was performed. Pairs of PCR-RFLP primer sequences and restriction enzyme for each DNA product are all listed in Table 1. The representative PCR-based restriction results and analyses for *hOGG1* codon 326 were shown in Fig. 1.

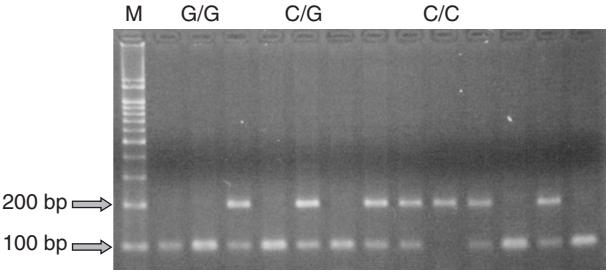


Fig. 1. PCR-RFLP results of the codon 326 polymorphism of *hOGG1* gene shown on 3% agarose electrophoresis. M: 100 bp DNA size marker, G/G: divisible homozygote, C/G: heterozygote, and C/C: indivisible homozygote PCR products.

*Statistical Analyses*

Only those subjects with both genotypic and clinical results were recruited in the final analysis. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *hOGG1* codon 326 in the controls from those expected under the Hardy-Weinberg equilibrium was examined by the goodness-of-fit test. Pearson's *Chi*-square test was performed to compare the distributions of the genotypes between case and control groups. Cancer risk associated with the genotypes was estimated as odds ratio (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. Data were recognized as statistically significant when individual *P*-value was less than 0.05.

## Results

The genotypic and allelic frequencies for *hOGG1* codon 326 gene polymorphism in endometriosis patients and non-endometriosis controls are summarized and analyzed in Table 2. The genotype distributions of *hOGG1* codon 326 were not different between endometriosis and non-endometriosis groups ($P$ = 0.6212) (Table 2). The data also showed that the C allele of the *hOGG1* codon 326 polymorphism was not significantly associated with a slightly higher endometriosis risk ($P$ = 0.4006). It is more convincing to provide the results from multiple approaches so we

**Table 3. Distribution of *hOGG1* codon 326 genotypes in endometriosis patients after stratification by individual smoking habits**

| Variable | *hOGG1* codon 326 genotype | | | |
|---|---|---|---|---|
| | GG (%) | CG (%) | CC (%) | *P*-Value |
| Non-Smokers | | | | 0.0648 |
| Controls | 206 (45.8%) | 174 (38.7%) | 70 (15.5%) | |
| Patients | 58 (51.3%) | 47 (41.6%) | 8 (7.1%) | |
| Smokers | | | | **0.0061** |
| Controls | 70 (37.6%) | 81 (43.5%) | 35 (18.8%) | |
| Patients | 15 (38.3%) | 9 (22.5%) | 16 (40.0%) | |

**Table 4. Genotypic frequencies of *hOGG1* codon 326 polymorphism in different stages of endometriosis women and controls**

| codon 326 | Subgroup | Total n | Genotypes | | *P*-Value | OR (CI 95%) |
|---|---|---|---|---|---|---|
| | | | n (%) GG | n (%) CG+CC | | |
| | Control | 636 | 276 (43.4) | 360 (56.6) | | Reference |
| | Stage 1 | 29 | 15 (51.7) | 14 (48.3) | 0.5709 | 0.72 (0.34-1.51) |
| | Stage 2 | 33 | 16 (48.5) | 17 (51.5) | 0.8476 | 0.81 (0.40-1.64) |
| | Stage 3 | 44 | 22 (50.0) | 22 (50.0) | 0.6834 | 0.77 (0.42-1.41) |
| | Stage 4 | 47 | 20 (42.6) | 27 (57.4) | 0.6814 | 1.04 (0.57-1.88) |

have also performed the analysis of odds ratio for endometriosis risk among the variant genotypes. The odds ratio analysis showed that those who carry heterozygous CG and homozygous CC have 0.83- and 0.86-fold of endometriosis risk (95% CI = 0.56-1.22 and 0.52-1.44), compared with those with homologous GG, respectively. A combination of CG+CC *vs.* GG has a similar level of risk compared with those with homologous GG (odds ratio = 0.84, 95% CI = 0.59-1.20). The conclusive finding deduced from the data in Table 2 is that the C allele of *hOGG1* codon 326 seems not to be associated with higher risk for endometriosis in Taiwan.

It may be that the genetic polymorphism of a low-penetrate gene, such as *hOGG1*, may not contribute to the susceptibility of endometriosis as much as the environmental factors, such as the individual smoking habit. Thus, we are interested in analyzing the interaction of genotype of *hOGG1* codon 326 and the smoking habits. As show in Table 3, the genotype distribution of various genetic polymorphisms of *hOGG1* codon 326 was significantly different between endometriosis and non-endometriosis control groups who have smoking habit ($P = 0.0061$), which is not observed in the non-smokers ($P = 0.0648$) (Table 3).

We are interested in that whether the C allele of *hOGG1* codon 326 could serve as a protective biomarker among different stages of endometriosis in Taiwan. To examine this hypothesis, the distributions of genotypic frequency of *hOGG1* codon 326 polymorphisms among different stages of endometriosis women and controls were analyzed and presented in Table 4. For the stage 1 to 3, the C allele of *hOGG1* codon 326 seemed to serve as a protective biomarker, while for the stage 4, it seemed to serve as a risky biomarker. However, the differential distribution among the subgroups was not statistically significant (Table 4).

## Discussion

The role of *hOGG1* in endometriosis was largely unknown. Thus in this study, we investigated the role of the most popular polymorphic genotype of the *hOGG1* gene in the susceptibility for the endometriosis in a Taiwanese population. We found that none of the genotype of *hOGG1* codon 326 was significantly associated with a higher susceptibility for endometriosis (Table 2). The data suggested that the effects of the *hOGG1* codon 326 genotype on endometriosis may not be as high-penetrate as other polymorphic genotypes we have found previously (5, 18, 35).

The hOGG1 protein plays a central role in base excision repair. Kohno *et al*. had reported that 326Ser (C)-coding hOGG1 protein has a 7-fold higher 8-oxdG repair activity than 326Cys(G)-coding hOGG1 (19). This was further augmented by Yamane *et al*., whose findings suggested that 326Cys(G)-coding

hOGG1 has a lower capacity to prevent 8-ox-dG-caused mutagenesis *in vivo* in human cells than 326Ser (C)-coding hOGG1 protein (33). In literature, the association of the OGG1 GG genotype with increased risk of various types of cancer has been reported (1, 20, 22, 24, 26). However, we did not find a significant association of any *hOGG1* genotype with endometriosis risk in this study.

In 2002, *hOGG1* codon 326 polymorphism was reported to be associated with risk for smoking- and/or alcohol-related cancer in USA (15). In their results, the homozygous G/G genotype was associated with increased orolaryngeal cancer risk in the Caucasian population. In addition, the risky G allele had obvious joint effects with both smoking and alcohol drinking on orolaryngeal carcinogenesis (15). To compare the difference between Caucasian and oriental populations, we have also analyzed the association between *hOGG1* codon 326 genotypes and endometriosis risk in patients and controls who have a smoking habit in Taiwan, an oriental population. Interestingly, the interaction between *hOGG1* codon 326 and smoking habit is obvious, and the C allele, not G allele as in the Caucasian population, had joint effect with smoking habit on endometriosis risk (Table 3). This ethnic difference is commonly happened in genomic study and needs to be verified in larger populations in the future. We have also checked the possibility of the C allele to serve as a predictive biomarker for different endometriosis stage. However, the distributions of C allele of *hOGG1* codon 326 among the four stages of endometriosis patients and controls were not significantly different (Table 4).

One limitation of the study is its sample size, for in the cases the sample size is quite less bases on the low incidence of disease. To enhance the analyzing power of this study, we have recruited more than 4-fold of non-endometriosis controls in this study. In the future, we should continuously recruit more patients of endometriosis to enlarge the sample size, which would be more representative for the Taiwanese women population. In our previous studies, is was found that Arg/Pro and Pro/Pro genotypes for p53 codon 72 had a 1.84- and 2.74-fold increased risk of endometriosis compared to those with Arg/Arg, while the variant genotype of CDKN1A codon 31 was not associated (35). As for the DNA repair system genotypes, we have reported that the G allele of XRCC1 codon 399 (5), the XRCC4 codon 247*A and XRCC4 promoter-1394*T related genotypes and alleles, but not XRCC4 intron 3 I/D polymorphism, were associated with endometriosis susceptibilities and pathogenesis (18).

In conclusion, we have found that smoking is an environmental factor for endometriosis in Taiwan, and genotype of *hOGG1* had joint effects with smoking habit on endometriosis risk. Our results indicate that the C allele of *hOGG1* codon 326 may interact with smoking habits, affecting the whole progress of endometriosis. From the adaptive medicine viewpoint, we strongly suggested that Taiwanese women not to cultivate a smoking habit, which showed here to enhance the susceptibility of endometriosis of women. In the future, more comprehensive genotyping and haplotyping are warranted in revealing novel clinically applicable predictive biomarkers. Also, more functional studies are also required to evaluate genotype and phenotype correlation in endometriosis.

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