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Cyclin D1 G870A polymorphism and squamous cell carcinoma of the uterine cervix in Korean women

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Abstract

Though many investigators have reported relationships between the *CCND1* polymorphism and susceptibility to various carcinomas, to our knowledge, no report has been issued concerning its relationship with uterine cervical cancer. Thus, we undertook this study to investigate the association between *CCND1* polymorphisms and susceptibility to cervical cancer in Korean women. This study was carried on 222 patients with squamous cell carcinoma of uterine cervix and on 314 normal controls. *CCND1* genotyping was determined by polymerase chain reaction and restriction fragment length polymorphism. The allelic frequencies of the cases (A, 0.53; G, 0.47) were not significantly different from those of the controls (A, 0.49; G, 0.51) ($P=0.238$). Regression analysis after adjusting for age showed that the *CCND1* G870A genotypes are not related to the risk of squamous cell carcinoma of the uterine cervix. Our findings suggest that the *CCND1* polymorphism is not associated with an increased risk of squamous cell carcinoma of uterine cervix in Korean women.

Keywords: Cervical cancer; Cyclin D1; Polymorphism

1. Introduction

Cervical cancer is second only to breast cancer as the most common cancer in women worldwide [1]. Though the incidence of cervical cancer has reduced during the last decade, it remains the most common malignancy of the female genital tract in Korea [2].

Human papillomavirus (HPV) is the primary cause of cervical cancer development, and though HPV infections are widespread in the general population only a small proportion of infected women develop cervical dysplasia or cancer [3]. In other words, HPV infection appears to be necessary but insufficient in itself to cause cervical cancer. Other factors such as

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viral load, viral persistence, cervical cancer screening program attendance, and a host factors play important additional roles in cervical cancer development [4].

Certainly, individual differences play a critical role in determining the fate of HPV infections and precancerous lesions of the cervix. Several studies have found that the genetic background of the host is an important aspect of cervical cancer susceptibility [5,6]. In addition, recent studies upon single nucleotide polymorphism of several genes support the role of a host genetic component in the development of the cervical cancer [7,8].

Cyclin D1 plays an important role in the transition of the cell cycle from the G1 phase to the S phase, and cyclin D1 has been suggested to act as an active switch that regulates cell cycle progression [9]. Moreover, it is known that the cyclin D1 gene (*CCND1*) has a single base polymorphism (G870A) in exon 4 that increases the frequency of alternate splicing [10]. The protein encoded by the alternate transcript lacks the last 55 amino acids at the carboxy-terminus, which are replaced by a shorter 43-amino-acid sequence encoded by intron 4. As a result, the carboxy-terminal end of the alternate transcript lacks sequences important for protein turnover and thus may have a longer half-life [10]. Moreover, elevated cyclin D1 levels might allow cells to escape the cell-cycle checkpoint machinery. Recent studies showed that the *CCND1* polymorphism is associated with elevated risks of colorectal, urinary bladder, lung, head and neck, prostate, and esophageal cancers [11–17]. However, to the best of our knowledge, no study has been performed on the relation between the *CCND1* polymorphism and squamous cell carcinoma of the uterine cervix (SCCUC).

Therefore, we conducted this case-control study to characterize the association between this single nucleotide polymorphism and susceptibility to SCCUC in Korean women.

2. Materials and methods

2.1. Study subjects

All patients with a new diagnosis of SCCUC ($n=229$) were consecutively included from 1999 to 2002. All received an operation and were followed at the Department of Obstetrics and Gynecology, Seoul National University Hospital. The non-cancer control group ($n=323$) was composed of healthy Korean women that visited our hospital to participate in a routine cancer detection program for gynecologic cancer. These controls had no history of cervical neoplastic disease, a normal cervical cytology in at least two consecutive annual examinations, and were without evidence of cervical pathology. Women with any malignant disease, those who had received blood transfusion, and those with any systemic problem, such as, chronic liver disease, were also excluded from the control group. The patients and controls were all Korean, meaning that they belonged to the same ethnic group. Informed consent and 10 ml of peripheral blood were obtained from each participant. Before beginning this study, the study protocol was approved by the Institutional Review Board of Seoul National University Hospital.

2.2. Genotyping

DNA was extracted from the peripheral blood samples collected from all study participants. A 167 bp fragment encompassing the G–A polymorphism site in the *CCND1* exon 4 terminal region, was amplified using the specific primers 5′-GTGAAGTT-CATTTCCAATCCGC-3′ in exon 4 and 5′-GGGA-CATCACCCTCACTTAC-3′ in intron 4. PCR was carried out using 0.1 μg of DNA, 1 unit of Taq polymerase, 10 mM of Tris-HCl (pH 8.3), 50 mM KCl, 1.0 mM $MgCl_2$, 20 μM of each dNTP, and 20 pM of primer. The PCR conditions were as follows; 5 min of incubation, 1 min at 95 °C (denaturation), 35 amplification cycles [1 min at 61 °C (annealing), 2 min at 72 °C (extension)], and a final 7 min at 72 °C final extension in a thermal cycler. After confirming a successfulness of PCR by 1.5% agarose gel electrophoresis, each PCR product was digested overnight with 5 units of *Scr*FI enzyme (New England Biolabs Inc., Beverly, MA) at 37 °C, and electrophoresed in 3.0% agarose gel. The 167 bp PCR fragment obtained was split into 146 and 22 bp fragments when the *Scr*FI site was present. Genotypes were designated as G or A when the *Scr*FI restriction site was present or absent, respectively [10]. Direct DNA sequencing was performed in each genotype samples and they were used as positive controls.