Genetic Polymorphisms of Vitamin D Receptor Gene are Associated with Cervical Cancer Risk in Northeastern Thailand

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Abstract

Objective: This study aimed to explore whether VDR polymorphisms (Fok1, Apa1 and Taq1) are associated to the cervical cancer in Thai population. Materials and methods: Subjects of 204 cervical cancer patient and 204 age-matched healthy control were enrolled in the case-control study. VDR polymorphisms were detected by using real-time PCR. Haplotype analysis of three loci was applied to the obtained genotypes. Results: Significantly increased risk for cervical cancer was observed in carriers of TT genotype (p = 0.0388) and T allele (p = 0.0357) of Fok1 and TC genotype (p = 0.0001), CC genotype (p = 0.0160) and the C allele of Taq1 (p = 0.0001). Haplotype analyses revealed a significant correlation between C-T-C, T-G-C and T-T-C haplotypes and elevated risk for cervical cancer (OR = 2.06; 95%CI = 1.06-4.00; p = 0.0313, OR = 2.15; 95%CI = 1.22-3.80; p = 0.0078 and OR = 2.81; 95%CI = 1.53-5.16; p = 0.0006, respectively). Furthermore, haplotype carrying C allele of Taq1 (C-G-C + C-T-C + T-G-C + T-T-C) significantly increased cervical cancer risk with OR of 1.92 (95%CI = 1.32-2.79, p = 0.0006). Conclusion: Our finding revealed an association between VDR polymorphisms and cervical cancer risk. Taq1 C allele might be a molecular marker for cervical cancer development.

Keywords: Genetic polymorphism- Vitamin D receptor- cervical cancer

Introduction

Cervical cancer is currently one of the most common cancers in women worldwide (Bray et al., 2018). The underlying causes for cervical cancer are human papillomavirus (HPV) infection, genetic variation and environmental factors (Natphopsuk et al., 2012; Wang et al., 2010). In addition, there is several lines of evidence suggesting the role of calcitriol (1,25-dihydroxyvitamin D₃), active form of vitamin D, in female reproductive diseases including cervical cancer (Deuster et al., 2017; Kaabachi et al., 2014; Reichrath et al., 1998). However, VDR activity may be influenced by VDR genetic polymorphisms (Köstner et al., 2009), several of which have been identified. The frequently studied VDR polymorphisms such as Fok1, Apa1 and Taq1, all involving transitions (C>T in exon 2), (G>T in intron 8) and (T>C in exon 9), respectively (Köstner et al. 2009; McCullough et al. 2007; Wang et al. 2013). Fok1 produces an alternative transcription initiation site in which the T allele generates the VDR protein with three amino acid longer (427 amino acids) than the protein produced by C allele (424 amino acids). The longer protein exerts less transactivation capacity (Amadori et al., 2017). The Apa1 and Taq1 polymorphic sites are close to the 3’ untranslated region (3’-UTR) of VDR mRNA which affects mRNA D response elements (VDREs) on the target genes which then regulates the transcription (Pike and Meyer, 2012). In view of this control mechanism, calcitriol action thus depends on VDR activity (Uitterlinden et al., 2004).

The VDR protein is encoded by the VDR gene which is found in chromosome 12q13.11. This gene is expressed in normal and cancerous cervix, indicating the anti-tumor effects of calcitriol on the cervix (Deuster et al., 2017; Kaabachi et al., 2014; Reichrath et al., 1998). However, VDR activity may be influenced by VDR genetic polymorphisms (Köstner et al., 2009), several of which have been identified. The frequently studied VDR polymorphisms such as Fok1, Apa1 and Taq1, all involving transitions (C>T in exon 2), (G>T in intron 8) and (T>C in exon 9), respectively (Köstner et al. 2009; McCullough et al. 2007; Wang et al. 2013). Fok1 produces an alternative transcription initiation site in which the T allele generates the VDR protein with three amino acid longer (427 amino acids) than the protein produced by C allele (424 amino acids). The longer protein exerts less transactivation capacity (Amadori et al., 2017). The Apa1 and Taq1 polymorphic sites are close to the 3’ untranslated region (3’-UTR) of VDR mRNA which affects mRNA

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stability and the post-transcriptional process (Guo et al., 2018; Whitfield et al., 2001). Interestingly, *Fok1* have been shown to be linked with each other of 3'UTR indicating their interaction effects in modulating VDR activity (Israni et al., 2009; Kaabachi et al., 2014). As a result, most of studies have performed not only VDR genotype but also haplotype analysis in relation to cancer susceptibility but the results were inconsistent (Flügge et al., 2007; Kaabachi et al., 2014; Onen et al., 2008).

The study of VDR genetic polymorphisms is one approach to understand interindividual susceptibility to cervical cancer which have not been evaluated previously. Hence, this study provides the first report regarding the analysis of VDR polymorphisms (*Fok1*, *Apa1* and *Taq1*) individually and VDR haplotype on cervical cancer risk among Thai population.

**Materials and Methods**

**Study subjects**

The female volunteers were recruited from Srinagarind hospital, Khon Kaen University and Khon Kaen hospital, Khon Kaen, Thailand. Participants were divided into two groups that included 204 patients with pathologically diagnosed squamous cell carcinoma of the cervix (SCCA) and 204 age-matched healthy controls (5-years interval). Informed consent was obtained from all participants after which peripheral blood leukocytes were collected for VDR polymorphism analysis. The study was approved by the Ethic Committee of Khon Kaen university (Reference No. HE621103).

**Detection of VDR polymorphisms**

Genomic DNA (gDNA) was extracted from buffy coat using GF-1 Blood DNA Extraction Kit (Vivantis, USA). Real-time PCR with Taqman® probe (Applied Biosystems, USA) was used for *Fok1* (rs2228570), *Apa1* (rs7975232) and *Taq1* (rs731236) detection.

The real-time PCR conditions involved: a holding stage at 95°C for 10 minutes, followed by 40 cycles each of denaturation at 95°C for 15 seconds, annealing and extension at 60°C for 60 seconds.

**Statistical analyses**

Statistical analyses were performed using the STATA software. Deviation from Hardy-Weinberg equilibrium (HWE) for the genotype of each loci was tested with the Pearson’s chi-square ($\chi^2$) test). The haplotypes were inferred using PHASE algorithm version 2.1.1. Association between genotypes or haplotypes of VDR and cervical cancer risk was tested by calculating the odd ratios with (OR) 95% confidence intervals (95%CI) using logistic regression analyses. A two-tailed $p$-value of less than 0.05 was considered to be statistically significant.

**Results**

Table 1 presents association between VDR gene polymorphisms and cervical cancer risk. Genotype distribution of VDR (*Fok1*, *Apa1* and *Taq1*) polymorphisms among controls were consistent with HWE ($p > 0.05$). For the *Fok1* and *Taq1*, allele frequencies were found to differ significantly between the patients and the controls

### Table 1. Association between VDR Polymorphisms and Risk for Cervical Cancer

| Genotypes/Alleles | Control n (%) | Case n (%) | Crude OR [95%CI, $p$] | Adjusted OR* [95%CI, $p$] |
|-------------------|---------------|------------|-----------------------|---------------------------|
| **Fok1**<sup>a</sup> |               |            |                       |                           |
| CC                | 55 (29.6)     | 45 (22.06) | 1                     | 1                         |
| CT                | 106 (51.96)   | 96 (47.06) | 1.11 [0.67-1.84, 0.6790] | 1.44 [0.71-2.94, 0.313] |
| TT                | 43 (21.08)    | 63 (30.88) | 1.79 [1.03-3.11, 0.0388*] | 2.66 [1.17-6.04, 0.020*] |
| CT+TT             | 149 (73.04)   | 159 (77.94) | 1.3 [0.81-2.11, 0.2498] | 1.77 [0.90-3.46, 0.096] |
| C                 | 0.53          | 0.46       | 1                     | 1                         |
| T                 | 0.47          | 0.54       | 1.34 [1.02-1.77, 0.0357*] | NA                       |
| **Apa1**<sup>a</sup> |               |            |                       |                           |
| GG                | 100 (49.02)   | 94 (46.08) | 1                     | 1                         |
| GT                | 83 (40.69)    | 82 (40.2)  | 1.05 [0.68-1.63, 0.8143] | 1.11 [0.61-2.04, 0.728] |
| TT                | 21 (10.29)    | 28 (13.73) | 1.42 [0.72-2.82, 0.2771] | 1.96 [0.79-4.84, 0.144] |
| GT+TT             | 104 (50.98)   | 110 (53.92) | 1.13 [0.75-1.69, 0.5520] | 1.27 [0.72-2.24, 0.410] |
| G                 | 0.69          | 0.66       | 1                     | 1                         |
| T                 | 0.31          | 0.34       | 1.16 [0.86-1.55, 0.3302] | NA                       |
| **Taq1**<sup>a</sup> |               |            |                       |                           |
| TT                | 133 (65.2)    | 88 (43.14) | 1                     | 1                         |
| TC                | 58 (28.43)    | 95 (46.57) | 2.48 [1.59-3.87, 0.0001*] | 2.36 [1.28-4.35, 0.006*] |
| CC                | 13 (6.37)     | 21 (10.29) | 2.44 [1.10-5.58, 0.0160*] | 2.11 [0.73-6.10, 0.167] |
| TC+CC             | 71 (34.8)     | 116 (56.86) | 2.47 [1.62-3.76, 0.0001*] | 2.31 [1.30-4.11, 0.004*] |
| T                 | 0.79          | 0.66       | 1                     | 1                         |
| C                 | 0.21          | 0.34       | 1.95 [1.42-2.67, 0.0001*] | NA                       |

OR, odds ratio, CI: confidence interval, *p < 0.05, NA: not applicable, * no deviation from Hardy–Weinberg equilibrium ($p > 0.05$ by $\chi^2$ test); * adjusted multiple logistic regression for partners’ smoking, contraceptive use and HPV infection
Interestingly, the TT genotype and the T allele of Fok1 was significantly associated with increased risk for cervical cancer (crude OR = 1.79; 95%CI = 1.03-3.11; p = 0.0388 and adjusted OR = 2.66; 95%CI = 1.17-6.04; p = 0.020 for TT vs. CC and OR = 1.34; 95%CI = 1.02-1.77; p = 0.0357 for T vs. C). For Taq1 locus, TC and CC genotypes and the C allele significantly increased cervical cancer risk (crude OR = 2.48; 95%CI = 1.59-3.87; p < 0.0001 and adjusted OR = 2.36; 95%CI = 1.28-4.35; p = 0.006 for TC vs. TT and crude OR = 2.44; 95%CI = 1.10-5.58; p = 0.0160 and adjusted OR = 2.11; 95%CI = 0.73-6.10; p = 0.167 for CC vs. TT and OR = 1.95; 95%CI = 1.42-2.67; p < 0.0001 for C vs. T), whereas Apa1 was not associated with cervical cancer risk (p > 0.05).

Haplotype (Fok1-Apa1-Taq1) analysis regarding cervical cancer risk is presented in Table 2 where C-G-T was found to be the most common in both patients and controls. C-T-C, T-G-C and T-T-C haplotypes significantly increased the risk for cervical cancer compared to C-G-T haplotype with OR = 2.06; 95%CI = 1.06-4.00; p = 0.0313, OR = 2.15; 95%CI = 1.22-3.80; p = 0.0078 and OR = 2.81; 95%CI = 1.53-5.16; p = 0.0006, respectively. Interestingly, an elevated risk for cervical cancer was observed among haplotypes carrying C allele compared to T allele of Taq1; C-G-C vs. C-G-T (OR = 1.05; 95%CI = 0.57-1.92; p = 0.9334), C-T-C vs. C-T-T (OR = 3.22; 95%CI = 1.47-7.05; p = 0.0030), T-G-C vs. T-G-T (OR = 2.00; 95%CI = 1.12-3.56; p = 0.0181 and T-T-C vs. T-T-T (OR = 2.62; 95%CI = 1.31-5.25; p = 0.0059). Furthermore, carriers of Taq1 C haplotype (C-G-C + C-T-C + T-G-C + T-T-C) had 1.92 times higher risk for cervical cancer compared to C-G-T haplotype (95%CI = 1.32-2.79, p = 0.0006).

**Discussion**

To our knowledge, this study is the first to report an association between VDR polymorphisms and cervical cancer risk in a Thai population. Increased risks for cervical cancer observed among carriers of the TT genotype and the T allele of Fok1 polymorphism indicated this allele to be a susceptible risk allele. In agreement with these findings, the presence of the Fok1 T allele was a risk allele for ovarian, breast and renal cancers (Arjumand et al., 2012; Liu et al., 2013; Wang et al., 2013). The Fok1 T allele could decrease VDR transcription and translation efficacy which was reported to reduce anti-carcinogenic properties of calcitriol and contributes to an increased cancer susceptibility (Amadori et al., 2017; Chen et al., 2018; Feldman et al., 2014). Hence, this report confirms the role of Fok1 T allele in raising cancer susceptibility.

Our finding of an absence of correlation between Apa1 polymorphism and cervical cancer risk agrees with reports of other studies in prostate, breast and ovarian cancers (Clendenen et al., 2008; Wang et al., 2016). The Apa1 polymorphism found in the intron 8 does not change the VDR amino acid sequence (Köstner et al. 2009). Therefore, Apa1 would be less expected to mimic VDR expression and function as seen in earlier study which provided evidence that this polymorphism does not affect VDR expression level (Selvaraj et al., 2009).

Regarding Taq1 polymorphism, our results indicate a significant role of the C allele in the cervical cancer risk which was not previously observed in other cancers such as breast, prostate, and colorectal cancer (Bodiwala et al., 2004; Flügge et al., 2007; Gapska et al., 2009). A variant allele of Taq1 locus has been shown to regulate VDR mRNA stability which alters expression and transactivation capacity (McCullough et al., 2009; Whitfield et al., 2001). This mechanism might alter the state of VDR in the cancer susceptibility (Chen et al., 2018; Serrano et al., 2016). To our knowledge, the C allele of Taq1 might be a potential diagnostic biomarker for cervical cancer susceptibility. Nevertheless, these conflicting results provide a hypothesis that the influence of VDR on cancer susceptibility might depend on dietary and environmental factors that potentially influence calcitriol levels and VDR activity (Bodiwala et al., 2004; Köstner et al., 2009; McCullough et al., 2007). Hence, further studies should consider gene-environment interaction to clarify the role of calcitriol and VDR on cervical cancer susceptibility.

VDR haplotype (Fok1-Apa1-Taq1) analysis was performed to provide more conclusive information regarding genetic variation. In accordance with allele frequencies, C-G-T haplotype was predominant in the healthy Thai population as previously reported for another

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**Table 2. Association between VDR Haplotypes (Fok1-Apa1-Taq1) and Risk for Cervical Cancer**

| Fok1-Apa1-Taq1 | Control n (%) | Case n (%) | OR [95%CI, p] |
|----------------|--------------|------------|---------------|
| C-G-T          | 127 (31.13)  | 108 (26.47)| 1             | 1             |
| C-G-C          | 27 (6.62)    | 24 (5.88)  | 1.05 [0.57-1.92, 0.9334] | 1.05 [0.57-1.92, 0.9334] |
| C-T-T          | 46 (11.27)   | 25 (6.13)  | 0.64 [0.37-1.11, 0.1094] | 1             |
| C-T-C          | 16 (3.92)    | 28 (6.86)  | 2.06 [1.06-4.00, 0.0313*] | 3.22 [1.47-7.05, 0.0030*] |
| T-G-T          | 106 (25.98)  | 97 (23.77) | 1.08 [0.74-1.57, 0.7026] | 1             |
| T-G-C          | 23 (5.64)    | 42 (10.29) | 2.15 [1.22-3.80, 0.0078*] | 2 [1.12-3.56, 0.0181*] |
| T-T-T          | 45 (11.03)   | 41 (10.05) | 1.07 [0.65-1.76, 0.7847] | 1             |
| T-T-C          | 18 (4.41)    | 43 (10.54) | 2.81 [1.53-5.16, 0.0006*] | 2.62 [1.31-5.25, 0.0059*] |
| C-G-T          | 127 (31.13)  | 108 (26.47)| 1             | 1             |
| C-G-C + C-T-C + T-G-C + T-T-C | 84 (20.59) | 137 (33.57) | 1.92 [1.32-2.79, 0.0006*] | 1.92 [1.32-2.79, 0.0006*] |

OR, odds ratio; CI, confidence interval; * p < 0.05.
Asian population (Li et al., 2018).

Haplotypes containing the T allele of FokI or C allele of TaqI (C-T-C, T-G-C or T-T-C) were associated with statistically increased cervical cancer risks compared to the most common C-G-T haplotype. Nevertheless, haplotypes carrying only FokI T allele (T-T-C and T-T-T) were not correlated with increased cervical cancer risk, suggesting that the effect of FokI polymorphism might be depending on the interaction with TaqI loci. To clarify the possible significance of TaqI in cervical cancer risk, TaqI pair haplotypes analysis was performed. The presence of TaqI C allele was found to be strongly associated with an increased risk for cervical cancer, which was in line with the result of TaqI allelic analysis. Moreover, an increased cervical cancer risk observed in the haplotype analysis was higher than the risk observed in each allele. Thus, the role of VDR genetic variation on cervical cancer susceptibility is most likely influenced by the presence of the C allele of TaqI which produced less VDR activity and less responsive to calcitriol.

In conclusion, this study is the first to demonstrate the role of VDR polymorphisms, especially TaqI polymorphism in cervical cancer risk among Northeastern Thai women. Thus, the TaqI C allele might be considered an important molecular marker for cervical cancer risk that may predict possible cervical cancer development.

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