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ORIGINAL ARTICLE

17β-hydroxysteroid dehydrogenase type Gene *1937* A > G Polymorphism as a Risk Factor for Cervical Cancer Progression in the Polish Population

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Abstract The role of 17β-estradiol (E2) in the development of cervical tumor (CT) has been demonstrated. 17β Hydroxysteroid dehydrogenase type 1 (HSD17B1) converts estrone (E1) into E2. We aimed to study the distribution of the *HSD17B1937* A > G (rs605059) single nucleotide polymorphism (SNP) in women (n = 383) with CT and controls (n = 401) from the Polish population. The p-trend value evaluated for *HSD17B1* rs605059 was 0.0233 for all patients. The A/A vs G/G genotype significantly contributed to all patients with CT, and the Odds Ratio (OR) was 1.570 (95 % CI = 1.053–2.343; p = 0.0266). Stratification of the patients based on tumor stage and histological grade indicated the contribution of *HSD17B1*937 A > G to stages III and IV. The p-value was 0.0010. The OR for the A/A vs G/G genotype was 2.992 (95 % CI = 1.627–5.502, p = 0.0003), the OR for the A/G vs G/G genotype was 2.545 (95 % CI = 1.410–4.593, p = 0.0015) and the OR for the A/A and A/G vs G/G genotype was 2.724 (95 % CI = 1.546–4.799, p = 0.0004). Moreover, we observed a contribution of the rs605059 SNP to histological grade G3 status. The p-value was 0.0042. The OR for the A/A vs G/G genotype was 5.632 (95 % CI = 1.644–19.290, p = 0.0026), the OR for the A/G vs G/G genotype was 4.213 (95 % CI = 1.244–14.265, p = 0.0113) and the OR for the A/A and A/G vs G/G genotype was 4.780 (95 % CI = 1.456–15.687, p = 0.0033). Our study indicated that the *HSD17B1937 A > G* transition is a risk factor for CT, especially for stages III and IV and histological grade G3.

Keywords Cervical carcinoma · *HSD17B1* · Polymorphisms

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Introduction

Cervical tumors (CTs) are the second most common malignancies in women worldwide, and approximately 500,000 newly diagnosed CTs caused 20,000 deaths in 2010 [1]. The human papillomavirus (HPV) has been considered the major causative factor of CTs [2]. HPV oncoproteins E6 and E7 inactivate p53 and members of the pRb family and destabilize the mechanisms that control the cell cycle [3]. Moreover, during mitosis, E6 and E7 oncoproteins impair chromosome duplication and segregation, which leads to severe chromosomal instability [4]. There are other risk factors that contribute to the development of CT, including an active sexual history, contraceptive use, cigarette smoking, multiparity, weakened immune system function and environmental pollution [5–8]. Despite infection with high-risk HPV, the majority of the HPV particles (90 %) are removed by the hosts' immune system as found in three-year follow-up studies, and merely 1–2 % of the remaining 10 % become chronic and lead to precancerous lesions termed cervical intraepithelial neoplasias (CINs) and CT development [9, 10]. These findings suggest that long-term infection with high-risk HPV is associated with cervical carcinogenesis; however, such infection is insufficient to result in CT alone [9–11].

Recently, increasing evidence has demonstrated the role of 17β-estradiol (E2) in the development of CT [12–21]. The biosynthesis of E2 generally occurs in the ovaries, although E2 may also be produced by other pathways in peripheral

tissues [22–24]. 17β-Hydroxysteroid dehydrogenase type 1 (HSD17B1) is a member of the HSD17Bs superfamily of short-chain dehydrogenases/reductases that control sex steroid levels via the oxidation or reduction of sex steroid precursors [25]. HSD17B1 is responsible for the transformation of estrone (E1) into E2, which is a more biologically active estrogen [26]. The sustained expression of this enzyme has been identified in the ovarian granulosa, but it is also present in different peripheral tissues in which E1 is converted to E2 [26–28]. *HSD17B1* single-nucleotide polymorphisms (SNPs) may potentially cause changes to the biological functions of HSD17B1 enzymes that might contribute to hormone-related disorders [29, 30]. One *HSD17B1* SNP is the 937 A > G (rs605059) transition situated in exon 6 that results in an amino acid change from serine to glycine at position 312 [29, 30]. Many studies have demonstrated that *HSD17B1*937 A > G is a genetic risk factor that is involved in various estrogen-related cancers [31–34]. However, little is known about the contribution of *HSD17B1*937 A > G to cervical carcinogenesis. Therefore, we aimed to study the association of *HSD17B1* rs605059 with CT development in the Polish population. Moreover, we evaluated the contributions of this SNP to disparate stages, histological grades and types of CT.

Patients and Methods

Study Subjects

Three hundred eighty-two women with cervical cancer and diagnosed stages, histological grades and cervical tumor types based on the criteria of the International Federation of Gynecology and Obstetrics (FIGO) were included in this study. The patient data were provided for the women with cervical cancer who attended the Department of Radiotherapy of the Greater Poland Cancer Center in Poznań, Poland between August 2008 and March 2014 (Table 1). The controls included four hundred one unrelated healthy female volunteers collected during routine examinations at the Gynecologic and Obstetrical University Hospital at Poznan University of Medical Sciences, Poland (Table 1). All cases and controls were Caucasians from the Wielkopolska area of Poland. Informed consent was obtained from all patients and controls. The study methods were approved by the Local Ethical Committee of the Poznań University of Medical Sciences.

Genotyping of the *HSD17B1*937 A > G (rs605059) Transition

DNA was obtained from peripheral blood cells via a salting-out procedure. The *HSD17B1*937 A > G transition DNA fragment (121 bp) was amplified using the primers F: 5′ CCAGGGGACAAAGAAGGG 3′ and R: 5’TGGGGCAG AGGACGAGG 3′. The *HSD17B1*937 A > G polymorphism was then genotyped via high-resolution melting (HRM) curve analysis using HOT FIREPol EvaGreen (Solis BioDyne, Tartu, Estonia) with a LightCycler 480 system (Roche Diagnostics, Mannheim, Germany). The presence of this transition was validated by Sanger sequencing analyses of randomly selected samples comprising 15 % of the samples from all of the women.

Table 1 Clinical and demographics characteristics of patients and controls

Characteristic	Patients (n = 383)	Controls (n = 401)
[a]Mean age ± SD	48.8 ± 10.6	47.1 ± 8.9
Tumour stage		
IA	55 (14.4 %)	
IB	56 (14.6 %)	
IIA	47 (12.3 %)	
IIB	54 (14.1 %)	
IIIA	79 (20.6 %)	
IIIB	67 (17.5 %)	
IVA	8 (2.1 %)	
IVB	17 (4.4 %)	
Histological grade		
G1	87 (22.7 %)	
G2	167 (43.6 %)	
G3	54 (14.1 %)	
Gx	75 (19.6 %)	
Histological type		
Squamous Cell Carcinoma	352 (91.9 %)	
Adenocarcinoma	22 (5.7 %)	
Other	9 (2.4 %)	
HPV genotypes		
16 and 18	264 (68.9 %)	
16, 18, 31, 33, 35, 39,45,51,52,56,58,59 and 68	379 (99 %)	

[a] age at first diagnosis

Data Analysis

The genotype distributions of the cases and controls were investigated for divergences from Hardy-Weinberg (HW) equilibrium using the χ^2 test. The *HSD17B1*937 A > G transition was examined as a genetic susceptibility factor for cervical cancer using the Cochran-Armitage p-trend test (p_{trend}). The chi-squared (χ^2) test and the Fisher exact test were used to determine the differences in the genotypic and allelic

distributions between the patients and controls, and p values <0.05 were considered statistically significant. Odds ratios (ORs) and confidence intervals (95 % CIs) were also calculated. The statistical analyses were conducted with Statistica version 10 (2011, Stat Soft, Inc., Tulsa, USA).

Results

Prevalence of the *HSD17B1*937 A > G (rs605059) Genotype in the Patients in Stages I, II, III and IV

The values from the χ^2 tests for HW equilibrium were 0.699 and 0.719 for the controls and women with cervical cancer, respectively. The p-trend values evaluated for *HSD17B1* rs605059 was statistically significant (p_{trend} = 0.0233). The frequencies of the *HSD17B1* A/A genotype in the cases and controls were 38 % and 31 %, respectively (Table 2). The distributions of the *HSD17B1* A/G genotype were 45 % and 47 % in the patients and controls, respectively (Table 2). Statistical analysis demonstrated that the A/A vs G/G genotype significantly contributed to CT with an OR of 1.570 (95 % CI = 1.053–2.343), p = 0.0266). However, we did not find significant contributions of the A/G vs G/G or A/A and A/G vs G/G genotypes (Table 2).

Prevalence of the *HSD17B1*937 A > G (rs605059) Genotype in Patients in Stages I and II

The frequency of the homozygous A/A genotype was increased, but the heterozygous A/G genotype was decreased in the women with CT in stages I and II compared with the controls (Table 2). The p_{trend} observed for the *HSD17B1* A > G transition was not statistically significant (p_{trend} = 0.5242). There were also no contributions of the *HSD17B1* A > G transition to stages I or II CT (Table 2).

Prevalence of the *HSD17B1*937 A > G (rs605059) Genotype in the Patients in Stages III and IV

The p-trend calculated for the *HSD17B1* A > G polymorphism was statistically significant (p_{trend} = 0.0010). The *HSD17B1* A/A genotype was 1.3-fold more frequent in the cases than the healthy individuals (40 % and 31 %, respectively). We also observed an increased A/G heterozygote frequency in the cases compared with the controls (51 % and 47 %, respectively; Table 2). There were significant associations of the *HSD17B1* A > G transition with stages III and IV CT. The OR for the A/A vs G/G comparison was 2.992 (95 % CI = 1.627–5.502, p = 0.0003), the OR for the A/G vs G/G comparison was 2.545 (95 % CI = 1.410–4.593, p = 0.0015) and the OR for the A/A and A/G vs G/G comparison was 2.724 (95 % CI = 1.546–4.799, p = 0.0004; Table 2).

Prevalence of the *HSD17B1*937 A > G (rs605059) Genotype in Patients with Different Histological Grades

The p-trend calculated for the *HSD17B1* A > G polymorphism was statistically significant (p_{trend} = 0.0042) in the patients with histological grade G3. There was a significant association of the *HSD17B1* A > G transition with grade G3 cervical cancer. The OR for A/A vs G/G comparison was 5.632 (95 % CI = 1.644–19.290, p = 0.0026), the OR for A/G vs G/G comparison was 4.213 (95 % CI = 1.244–14.265, p = 0.0113) and the OR for A/A and A/G vs G/G comparison was 4.780 (95 % CI = 1.456–15.687, p = 0.0033; Table 2). However, we did not observe a contribution of the *HSD17B1* *A > G* genotype among the patients with histological grades G1, G2 or Gx (Table 2). Additionally, we did not find any associations of the HPV strains with the *HSD17B1* A > G genotype for stages I, II, III and IV, the histological grades G1, G2, G3 and Gx or the histological type of CT (data not shown).

Discussion

HSD17B1 is situated on chromosome 17q12-q21, and its protein has been identified in the ovaries, placenta, endometrium, testis, cancerous and noncancerous breast epithelium, and prostate cancer cells [35–37]. Recently, we identified the HSD17B1 transcript and protein in primary cervical cancer cells and noncancerous cervical cells [38]. Moreover, we observed the presence of the HSD17B1 transcript and protein in HeLa, SiHa, Ca Ski and C-33 A cervical cancer cells, which were able to transform E1 to E2 in vitro [38]. Several studies have demonstrated the role of estrogen in supporting cervical carcinogenesis [12–21]. The treatment of SiHa cells with E2 results in a several-fold elevation in HPV-16 transcripts [15]. Moreover, there are seven regions in the HPV-16 genome that contain sequences similar to the estrogen-responsive element [15]. E2 also modulates p53 protein levels, which are related to status of the E6/E7 protein in HPV-infected cells [16]. E2 inhibits the apoptosis of CT cells and increases their proliferation while increasing the cells' susceptibility to mutations [17, 18]. In transgenic HPV16 *E6* and *E7* mice, synergistic interactions of the expressions of E6 and E7 oncoproteins with E2 treatment that lead to the malignant transformations of vaginal and cervical squamous epithelia have been observed [20]. Shai et al. (2007) used E6 transgenic mice and found that the *E6* oncogene synergizes with E2 to induce the occurrence of CTs after 9 months of exposure to E2 [12]. In another study, the reduced occurrence of CTs in HPV16-transgenic mice that were exposed to E2 for 6 months followed by 3 months without exogenous E2 relative to mice that were continuously exposed to E2 for 9 months was attributed to reduced tumor incidence, reduced aggressiveness and smaller tumor sizes

Table 2 Distribution of the *HSD17B1*937 A > G (rs605059) polymorphism among patients with cervical cancer and controls

	Genotype distribution				Odds ratio (95 % CI) p value[b]	Odds ratio (95 % CI) p value[b]	Odds ratio (95 % CI) p value[b]	
	(frequency %)			MAF[a](%)	A/A vs G/G	A/G vs G/G	A/A or A/G vs G/G	p_{trend}
n	**A/A**	**A/G**	**G/G**					
controls	125 (31)	188 (47)	88 (22)	45				
n = 401								
Cervical cancer								
stage I - IV	145 (38)	173 (45)	65 (17)	40	**1.570 (1.053–2.343)**	1.246 (0.8508–1.824)	1.375 (0.9629–1.965)	**0.0233**
n = 383					***p* = 0.0266**	*p* = 0.2582	*p* = 0.0790	
stage I and II	77 (36)	86 (41)	49 (23)	43	1.106 (0.7052 1.736)	0.8215 (0.5330–1.266)	0.9353 (0.6285–1.392)	0.5242
n = 212					*p* = 0.6601	*p* = 0.3728	*p* = 0.7412	
stage III and IV	68 (40)	87 (51)	16 (9)	35	**2.992 (1.627–5.502)**	**2.545 (1.410–4.593)**	**2.724 (1.546–4.799)**	**0.0010**
n = 171					***p* = 0.0003**	***p* = 0.0015**	***p* = 0.0004**	
histological grade G1	32 (37)	39 (45)	16 (18)	19	1.408 (0.7282–2.722)	1.141 (0.6048–2.152)	1.248 (0.6903–2.255)	0.2840
n = 87					p = 0.3076[c]	*p* = 0.6836	*p* = 0.4630	
histological grade G2	59 (63)	74 (33)	34 (4)	21	1.222 (0.7390–2.019)	1.019 (0.6313–1.644)	1.100 (0.7049–1.716)	0.3903
n = 167					*p* = 0.4345	*p* = 0.9393	*p* = 0.6750	
histological grade G3	24 (68)	27 (24)	3 (8)	20	**5.632 (1.644–19.290)**	**4.213 (1.244–14.265)**	**4.780 (1.456–15.687)**	**0.0042**
n = 54					**p = 0.0026[c]**	**p = 0.0113[c]**	***p* = 0.0033**	
histological grade Gx	30 (40)	33 (51)	12 (9)	35	1.760 (0.8541–3.627)	1.287 (0.6363–2.612)	1.476 (0.7619–2.859)	0.1042
n = 75					*p* = 0.1221	*p* = 0.4835	*p* = 0.2460	

Statistically significant results are highlighted in bold

[a] Minor allele frequency

[b] Uncorrected X^2 test

[c] Fisher exact test

[21]. Moreover, it has been suggested that CTs exhibit a similar dependence on estrogen for tumor development and that antiestrogen therapy for the treatment of CTs should be reconsidered [21]. Recent studies have revealed new interactions between the HPV16 E7 oncoprotein and E2 treatment in the induction of cervical carcinogenesis [14]. Microarray analyses of transgenic HPV16 E7 mice exposed to E2 have revealed many differentially expressed genes that regulate the immune response and cellular metabolism [14]. The effect of the E2 level in the blood plasma on cervical carcinogenesis has also been evaluated in case–control studies [39]. Long-term treatment of postmenopausal women with E2-progestin has been linked to increased development of cervical malignancies [39].

In the present study, we found a statistically significant *p*-value trend for the *HSD17B1*937 A > G transition for all patients. We also observed a significant association of the 937 A/A genotype with CT in all of the assessed women. Further, the stratification of patients based on tumor stage and grade revealed a significant p-value trend and separate and combined contributions of the *HSD17B1* A/A and A/G genotypes to stages III and IV and histological grade G3 cervical cancer.

The meta-analysis conducted by Yao et al. (2010) suggested that the *HSD17B1*937*G* **(**312 Gly) allele may be protective against breast cancer development in Caucasians [31]. Moreover, the *HSD17B1*937 G (312 Gly) allele displays a protective effect on the breast cancer risk of women who have used any hormone replacement therapy for 10 years or longer [33]. Iwasak et al. (2010) demonstrated that polymorphisms in *HSD17B1* rs605059 may modify the association between isoflavone intake and breast cancer risk [34]. The frequencies of the *HSD17B1*937 AA (312 Ser) genotype and the A allele are significantly increased in Chinese women with uterine leiomyomas compared with healthy controls [40].

In our previous studies, we identified significant upregulations of the HSD17B1 transcript and protein levels in primary cervical cancer tissues compared with normal cervical tissues [38]. Our studies suggest that the HSD17B1937 A (321Ser) protein variant is a risk factor for the development of stages III and IV CTs. This finding suggests the role of this protein variant in the increased extension and spread of cancerous cells to the surrounding tissues. In our studies, the HSD17B1 321Ser protein variant was also found to be a risk factor for histological grade G3 CTs, which tend to grow rapidly and spread faster than lower-grade tumors.

Setiawan et al. (2004) demonstrated that the A/A genotype, which corresponds to the HSD17B1 321Ser protein variant, is associated with elevated E2 levels in lean women [41]. In a study of women with CT and CIN3, Rinaldi et al. (2011) suggested the possible role of E2 in the invasiveness of CTs [42]. Recently, Huang et al. (2012) demonstrated that the sex steroid E2 may enhance the invasiveness of CTs. These authors indicated that E2 acts as an activator of the phosphatidylinositol 3-kinase signaling pathway in vitro, and this activation results in a reduction in tissue inhibitors of metalloproteinases [19].

CT is considered an estrogen related cancer, and the functional *HSD17B1*937 A > G polymorphism might act as a biomarker in optimizing therapy. Therefore, the monitoring of the *HSD17B1*937 A > G SNP might be useful not only as predictive factor of cancer expansion but in the future may be considered in treatments of CT with HSD17B1 inhibitors.

Our study demonstrated a weak association of the *HSD17B1*937 A > G transition with all stages of CT. However, stratification of the patients based on the CT stages and grades revealed that the *HSD17B1*937 A gene variant was a strong contributor to stages III and IV and grade G3. Our study is the first to demonstrate the involvement of the *HSD17B1*937 A > G transition in cervical carcinogenesis. Therefore, this investigation should be repeated in much larger groups that include various ethnicities.

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