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Polymorphism of *HSD17B1* Ser312Gly with Cancer Risk: Evidence from 66,147 Subjects

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Hydroxysteroid (17-beta)dehydrogenase 1(*HSD17B1*) plays a central role in sex steroid hormone metabolism. *HSD17B1* polymorphic variants may contribute to cancer susceptibility. Numerous investigations have been conducted to assess the association between *HSD17B1* Ser312Gly polymorphism and cancer risk in multiple ethnicities, yet these have produced inconsistent results. We therefore performed this comprehensive meta-analysis to attempt to provide a quality assessment of the association of interest. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the strength of associations. After a systematic literature search of several major public databases, 20 studies involving 29,460 cases and 36,687 controls were included in this meta-analysis. No significant association was found between *HSD17B1* Ser312Gly polymorphism and cancer risk. However, Ser312Gly polymorphism showed a significantly decreased risk for Caucasians (there were 44,284 Caucasians for analysis, comprising 19,889 cases and 24,395 controls) in the subgroup analysis by ethnicity (dominant: OR = 0.958, 95% CI = 0.919–0.998; and allele comparing: OR = 0.973, 95% CI = 0.947–0.999). And there was the same trend towards risk in the population-based (PB) controls (homozygous: OR = 0.951, 95% CI = 0.908–0.997 and allele comparing: OR = 0.976, 95% CI = 0.954–0.999), but not among Asians or hospital-based (HB) controls. In addition, no association was observed in the stratified analysis for breast cancer studies by source of control, ethnicity and quality score. These findings suggested that the *HSD17B1* Ser312Gly polymorphism might confer genetic cancer susceptibility in an ethnic-dependent manner, especially among Caucasians. Well-designed, large-scale studies are warranted to validate these findings.

■ **Keywords:** *HSD17B1*, Ser312Gly, polymorphism, cancer, risk

It has been suggested that estrone and 17-βestradiol are endogenous estrogens that are associated with carcinogenesis of various tissue types (Drzewiecka et al., 2014; Santen et al., 2014; Yager, 2014). A study conducted by Yager (2014) indicated that the carcinogenicity of estrogen is related to aberrant activities of both estrogen receptor (ER) and non-receptor signaling pathways, two complementary pathways. The ER regulates cell proliferation, while the non-receptor pathway is involved in the formation of DNA adducts and oxidative DNA damage. Under pathological conditions, excessive cell divisions resulting from both continuous hormonal stimulus and DNA damage-induced genetic instability could promote cancer development. The 17β-hydroxysteroid dehydrogenase type 1 *(HSD17B1)* gene, located on chromosome 17q12–q21, encodes a 17HSDtype 1 enzyme. This enzyme plays a central role in sex steroid hormone metabolism by catalyzing the conversion of estrone to its most potent form, 17-βestradiol (Puranen et al., 1997). However, some research has also indicated that individual genetic variation might increase one's susceptibility to cancer (Dai et al., 2007; Zhang et al., 2014).

To date, more than 450 single nucleotide polymorphisms (SNPs) in the *HSD17B1* gene have been reported in the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/). Among these, the Ser312Gly polymorphism (rs605059) has been widely investigated. The non-synonymous A→G polymorphism in codon 312 of exon six changes the amino acid serine to glycine (Mannermaa et al., 1994; Silva et al., 2006). Although current evidence indicates that this SNP

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does not affect the function of the enzyme (Johnson et al., 2005; Puranen et al., 1994), the level of estradiol as well as the ratio of estradiol to estrone in the blood were dramatically increased in the carriers of AA genotype of the *HSD17B1* Ser312Gly polymorphism in comparison to non-carriers (Setiawan et al., 2004). Excessive estradiol alters expression of affected genes through the phosphorlation of extracellular signal-regulated kinase (Erk) 1/2, and then further increases cell proliferation, thereby modulating cancer susceptibility (Elloumi-Mseddi et al., 2014).

Over the past decades, numerous molecular epidemiology studies have been carried out to assess the association of *HSD17B1* Ser312Gly polymorphism with susceptibility to a board spectrum of cancers among different ethnic populations, including endometrial cancer (Ashton et al., 2010; Dai et al., 2007; Setiawan et al., 2004), breast cancer (Abbas et al., 2010; Feigelson et al., 2006; Gaudet et al., 2008; Iwasaki et al., 2010; Justenhoven et al., 2008; Kato et al., 2009; Mannermaa et al., 1994; Obazee et al., 2013; Plourde et al., 2008; Sakoda et al., 2008; Sangrajrang et al., 2009; Setiawan et al., 2004; Wang et al., 2009; Wu et al., 2003), prostate cancer (Kraft et al., 2005), uterine leiomyoma (Cong et al., 2012), and lung cancer (Wu et al., 2014). However, results were rather inconsistent or even contradictory. The discrepancy among studies is partially due to the relatively small sample size in each of published studies. We performed this comprehensive meta-analysis to provide a more precise assessment of the association between *HSD17B1* Ser312Gly polymorphism and the risk of cancer.

Materials and Methods

Literature Search Strategy

We identified eligible publications that examined the association between the *HSD17B1* gene polymorphism and cancer risk from PubMed, Embase, China National Knowledge Infrastructure (CNKI) and Wan Fang (WF) databases using the following search items: '*HSD17B1* or *17β- hydroxysteroid dehydrogenase type 1* or *EDH17B1*', 'polymorphism or variant or variation' and 'cancer or carcinoma' (the search was last updated on July 30, 2015). Extra eligible studies were retrieved by manually searching the reference lists of retrieved studies. No language restrictions were included in the search strategy. In the case of the appearance of the same subjects in multiple studies, we only included the study with the largest sample size or the latest one in our meta-analysis.

Inclusion and Exclusion Criteria

The studies included in our meta-analysis met the following criteria: (1) full-text research article; (2) evaluated *HSD17B1* Ser312Gly polymorphisms and cancer risk; (3) case-control study, cohort study, or nested case-control study on human subjects; (4) independent from other investigations; (5) provided adequate data to calculate ORs and the corresponding 95% CIs. Case-only studies were excluded. In addition, reviews, conference abstract, case reports, studies without detailed data, and meta-analyses were also excluded.

Data Extraction

Information was extracted from eligible studies by two authors working independently. Conflicts were resolved by discussion between these two investigators until consensuses were reached, or a third investigator would step in to adjudicate potential disagreement when needed. The following information was collected: the surname of first author, publication date, country of origin, ethnicity, source of control groups (HB or PB), genotyping method, p values of the chi-square test for Hardy–Weinberg equilibrium (HWE) for the control subjects, and genotype counts of cases and controls (Table 1).

Quality Assessment

The two authors evaluated the quality of each study using the quality assessment criteria derived from previously published meta-analyses conducted by Thakkinstian et al. (2011) and Xue et al. (2014); see Table 2. A score ranging from 0 to15 was used to weigh up the quality of studies. Zero was deemed to the lowest quality, while 15 indicated the highest quality. Investigations with scores ≤ 9 were considered as low quality, while those with scores >9 were categorized as high quality. Disagreements were judged impartially by a third investigator.

Statistical Analysis

The crude ORs and 95% CIs were used to evaluate the strength of associations between the *HSD17B1* Ser312Gly polymorphism and cancer risk. The pooled risk estimations were performed under different genetic models, including homozygous model (Gly/Gly vs. Ser/Ser), heterozygous model (Gly/Ser vs. Ser/Ser), recessive model (Gly/Gly vs. Gly/Ser+ Ser/Ser), dominant model (Gly/Gly + Gly/Ser vs. Ser/Ser), and allele comparison model (Gly vs. Ser). Deviation from the HWE in controls were examined by chi-square goodness-of-fit test, and $p < .05$ was considered a significant deviation from the HWE (Rohlfs & Weir, 2008). Heterogeneity across studies was tested by a chi-square-based Q test (heterogeneity was considered to exist between studies when $p < .10$ and $I^2 > 25\%$ for the Q test, with $25\% < I^2 < 50\%$ regarded as low heterogeneity, $50\% \leq I^2 \leq 75\%$ regarded as moderate heterogeneity, and $I^2 > 75\%$ as high heterogeneity). We calculated pooled ORs with a fixed-effects model if there was no heterogeneity; where the p value was $<.10$, a random-effect model was adopted (Tan et al., 2014). If heterogeneity was observed, meta-regression analyses would be performed to explore the potential source of the heterogeneity (Higgins & Thompson 2004; Thompson & Higgins, 2002). Stratification analyses

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TABLE 1

Characteristics of Investigations Included in Meta-Analysis

Investigators	Year	Cancer type	Race	Case			Control			Control source	Methods	HWE	Quality score
				AA	GA	GG	AA	GA	GG				
Kraft et al.	2005	Prostate	Caucasian	2,299	3,932	1,845	2,521	4,409	2,141	PB	TaqMan	0.0126	13
Ashton et al.	2010	Endometrial	Caucasian	64	84	43	91	147	52	PB	PCR–RFLP	0.5803	12
Setiawan et al.	2004	Endometrial	Caucasian	69	96	54	181	316	167	HB	TaqMan	0.2183	12
Dai et al.	2007	Endometrial	Asian	186	465	380	174	487	358	PB	TaqMan	0.703	12
Cong et al.	2012	Myoma	Asian	40	66	15	55	111	51	PB	PCR–RFLP	0.7304	10
Mannermaa et al.	1994	Breast	Caucasian	43	83	64	36	106	48	PB	PCR–SSCP	0.0974	7
Wu et al.	2003	Breast	Asian	40	80	58	125	313	210	PB	PCR–RFLP	0.6645	11
Feigelson et al.	2006	Breast	Mix	1,406	2,588	1,139	2,011	3,610	1,580	PB	TaqMan	0.5963	13
Gaudet et al.	2008	Breast	Caucasian	2,066	3,120	1,310	2,058	3,323	1,407	PB	TaqMan	0.3297	12
Justenhoven et al.	2008	Breast	Caucasian	180	296	113	159	319	142	PB	MALDI–TOFMS	0.458	11
Plourde et al.	2008	Breast	Caucasian	15	29	6	19	42	12	HB	PCR	0.168	8
Sakoda et al.	2008	Breast	Asian	116	289	209	152	417	305	PB	PCR	0.6447	15
Kato et al.	2009	Breast	African	40	95	42	57	86	46	HB	TaqMan	0.2325	11
Sangrajrang et al.	2009	Breast	Asian	154	299	107	145	239	99	HB	TaqMan	0.9773	10
Iwasaki et al.	2010	Breast	Mix	78	199	108	88	187	109	HB	TaqMan	0.985	10
Wang et al.	2009	Breast	Asian	54	83	63	35	82	83	PB	AS-PCR	0.0662	11
Setiawan et al.	2004	Breast	Caucasian	254	467	211	338	625	251	HB	TaqMan	0.2231	13
Abbas et al.	2010	Breast	Caucasian	924	1,603	619	1,632	2,746	1,107	PB	MALDI–TOFMS	0.4353	14
Obazee et al.	2013	Breast	Mixed	84	108	33	44	50	20	PB	TaqMan	0.3806	8
Wu et al.	2014	Lung	Asian	96	246	161	111	261	136	HB	TaqMan	0.4982	10

Note: PB = population based; HB = hospital based.

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TABLE 2

Quality Assessment Criteria For Article

Criteria	Score
Representativeness of case	
Selected from population cancer registry	2
Selected from hospital	1
No method of selection described	0
Representativeness of control	
Population based	3
Blood donors	2
Hospital based	1
Not described	0
Ascertainment of NHL case	
Histopathologic confirmation	2
By patient medical record	1
Not described	0
Control selection	
Controls matched with cases by age and sex	2
Controls matched with cases only by age or by sex	1
Not matched or not described	0
Genotyping examination	
Genotyping done blindly and quality control	2
Only genotyping done blindly or quality control	1
Unblinded and without quality control	0
HWE	
HWE in the control group	1
HWD in the control group or not mentioned	0
Total sample size	
>1,000	3
501–1,000	2
201–500	1
≤200	0

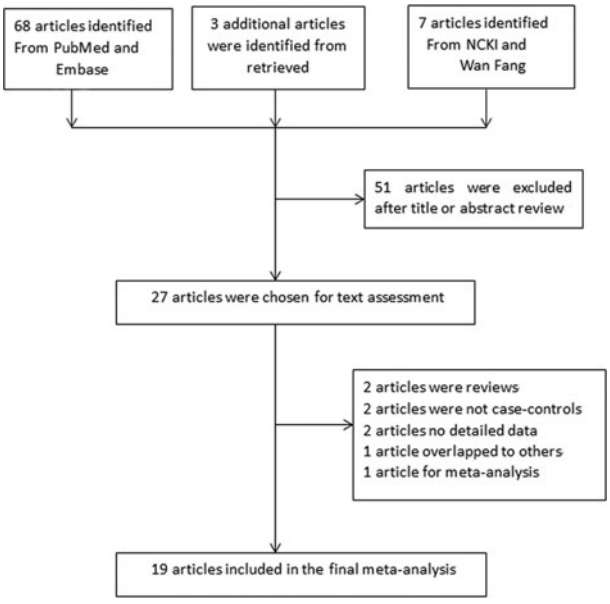

FIGURE 1

Flow diagram of selection of studies included in the current meta-analysis for the association between HSD17B1 gene polymorphisms and cancer susceptibility.

were conducted to explore the effects of covariates on the association of interest, such as ethnicity (Caucasians, Asians, and Mixed, which contained more than one ethnic group), source of control, quality score of investigations, and type of cancer (if a cancer type encompassed less than three individual investigations, it was classified into the 'other cancers' group).

The Begg's funnel plot and Egger's regression asymmetry test were conducted to detect the underlying publication bias: a p value less than .05 was considered as significant publication bias (Peters et al., 2006). We performed sensitivity analysis to estimate the stability of the results by consecutively excluding eligible studies individually and recalculating the pooled ORs and 95% CIs.

The significant results further underwent a false-positive report probability (FPRP) analysis (Hua et al., 2014; Tan & Chen, 2014). To determine the FPRP value for an association between the studied SNP and cancer risk, we adopted a prespecified prior probability of 0.1 and statistical power to determine the OR of 0.67 (for protective effects) or 1.50 (for risk effects). The threshold of a FPRP value was 0.2. Only the significant associations with an FPRP value of less than 0.2 were deemed as noteworthy.

The FPRP was performed using SAS software (version 9.1; SAS Institute, Cary, NC). The rest of statistical tests were conducted by STATA version 11.1 (Stata Corporation. USA). All p values were two-sided, and a p value less than .05 was considered statistically significant.

Results

Characteristics of Relevant Studies

As shown in Figure 1, using search terms described in the methods section, a total of 68 relevant articles were initially retrieved from EMBASE and PubMed databases, and an additional three articles were identified from the reference lists of the retrieved studies; a further seven articles written in Chinese were obtained from the NCKI and WF databases. Of the total number of articles, 51 were excluded after title and abstract screening. Among the remaining 27 articles, two reviews, one meta-analysis, and two articles with a case-only design were further excluded. Another two articles were excluded due to failure to provide detailed genotype data. As a result, 19 articles that met the inclusion criteria remained for final analysis. Of these, one publication was considered to consist of two individual studies, since it reported data on breast cancer and endometrial cancer separately. Ultimately, 19 publications, consisting of 20 individual studies with 29,460 cases and 36,687 controls, were included in the present meta-analysis (Table 1). Among these studies, there were 14 studies conducted on breast cancer, three on endometrial cancer, and three on 'other cancers' (prostate cancer, uterine leiomyoma and lung cancer; Table 1). In terms of ethnicity, nine studies were performed among Caucasians, seven among Asians, and four among mixed ethnic groups (only one study was conducted on African Americans, which was sorted into the 'mixed' category). When sorted by the source of control, 13 studies were PB and seven were HB (Table 1). Furthermore,

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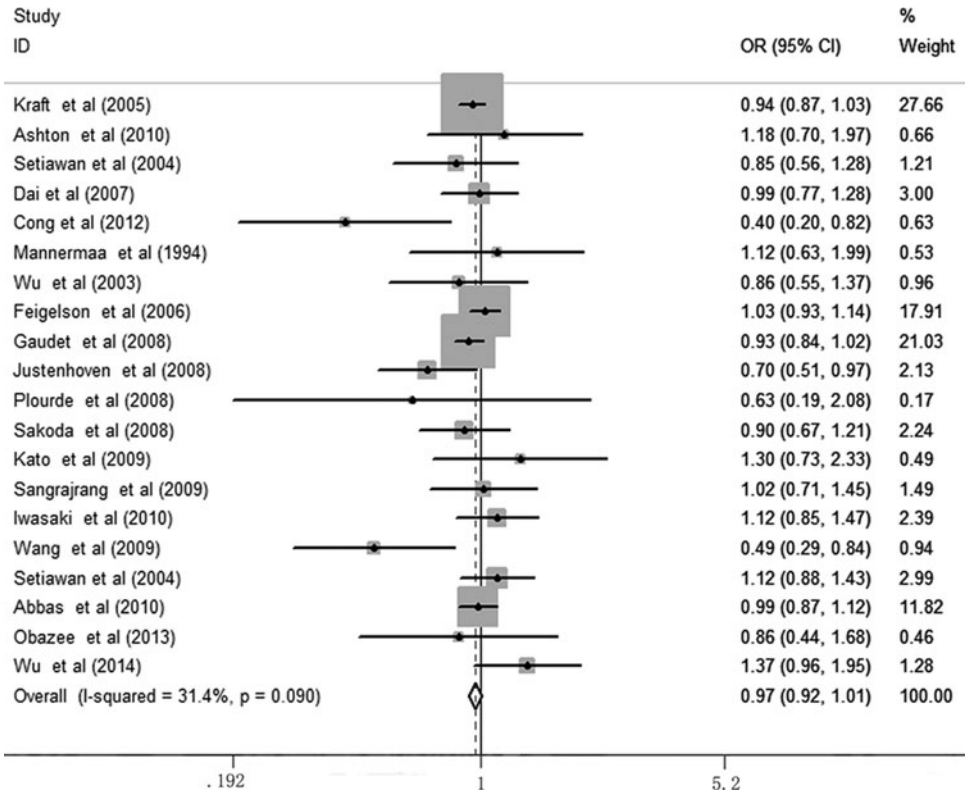

FIGURE 2

Forest plots of effect estimates for HSD17B1 Ser312Gly polymorphism and cancer susceptibility (GG vs. AA). For each study, the estimation of OR and its 95% CI are plotted with a box and a horizontal line. e, pooled ORs and its 95% CIs.

17 studies were classified as high quality and three as low quality. All cases were confirmed pathologically.

Meta-Analysis Results

As shown in Table 3 and Figure 2, a pooled analysis did not yield any significant association between *HSD17B1* Ser312Gly polymorphism and cancer risk (homozygous: OR = 0.966, 95% CI = 0.925–1.010; heterozygous: OR = 0.978, 95% CI = 0.943–1.015; dominant: OR = 0.975, 95% CI = 0.942–1.009; recessive: OR = 0.984, 95% CI = 0.948–1.021; allele comparing: OR = 0.984, 95% CI = 0.963–1.006).

However, subgroup analysis by ethnicity indicated that this variant significantly decreased the risk of developing cancer among Caucasians (dominant: OR = 0.958, 95% CI = 0.919–0.998; allele comparing: OR = 0.973, 95% CI = 0.947–0.999). Moreover, stratification analysis by source of control revealed that this variant is associated with a significantly decreased risk of cancer for PB studies (homozygous: OR = 0.951, 95% CI = 0.908–0.997; allele comparing: OR = 0.976, 95% CI = 0.954–0.999). No significant association was found in the subgroup analysis by quality of studies and cancer type. In addition, in light of this study strongly comprised of breast cancer samples (14 out of 20 investigations), we further conducted subgroup analyses for breast cancer studies by source of control, ethnicity and quality score, but observed no evidence of the association in any of subgroups (Table 4).

The significant results then underwent FPRP analysis. Since the *HSD17B1* polymorphism was associated with protection against cancer, FPRP values were computed using a preset prior probability of 0.1, statistical power to detect an OR of 0.67, and our significant results (ORs and *p* values). The FPRP values suggested that the significant association between decreased cancer risk and the *HSD17B1* protective genotypes in PB subgroup was not noteworthy (homozygous model: FPRP = 0.24; allele comparison model: FPRP = 0.279). Likewise, for Caucasians, the FPRP value for the significantly decreased cancer risk associated with this variant was: dominant model: FPRP = 0.274; allele comparison model: FPRP = 0.228. The result of the FPRP indicated some bias due to the small sample size in subgroups. Thus, further validation of these findings by studies with larger sample sizes are needed.

Heterogeneity and Sensitivity Analyses

A chi-square Q test and I^2 statistic were performed to evaluate the heterogeneity among the studies. There was no heterogeneity under the heterozygous model, dominant and recessive models ($p = 0.353$, $I^2 = 8.3\%$; $p = .198$,

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TABLE 3

Meta-Analysis of the HSD17B1 Gene Polymorphism and Cancer Risk

		GG vs. AA			GA vs. AA			Dominant model			Recessive model		
Variable	*n*	OR (95% CI)	p^a	p^b	OR (95% CI)	p^a	p^b	OR (95% CI)	p^a	p^b	OR (95% CI)	p^a	p^b
Total	20	0.966 (0.925–1.010)	.128	.090	0.978 (0.943–1.015)	.242	.353	0.975 (0.942–1.009)	.149	.198	0.984 (0.948–1.021)	.389	.132
Ethnicity													
Asian	7	0.874 (0.689–1.109)	.268	.014	0.943 (0.832–1.068)	.357	.412	0.942 (0.837–1.059)	.315	.118	0.945 (0.792–1.127)	.527	.023
Caucasian	9	0.948 (0.899–1.000)	.051	.507	0.962 (0.921–1.005)	.084	.457	0.958 (0.919–0.998)	.042	.560	0.973 (0.929–1.018)	.235	.274
Mixed	4	1.043 (0.950–1.146)	.374	.766	1.047 (0.968–1.132)	.251	.379	1.030 (0.958–1.108)	.426	.682	1.013 (0.937–1.096)	.746	.889
Cancer type													
Breast	14	0.972 (0.921–1.026)	.303	.207	0.986 (0.943–1.031)	.573	.193	0.991 (0.951–1.033)	.675	.818	0.983 (0.939–1.029)	.464	.425
Endometrial	3	0.982 (0.805–1.197)	.855	.619	0.853 (0.711–1.022)	.084	.849	0.898 (0.758–1.064)	.212	.796	1.083 (0.931–1.260)	.303	.566
Others	3	0.903 (0.586–1.391)	.642	.008	0.980 (0.914–1.049)	.555	.636	0.970 (0.910–1.035)	.359	.167	0.932 (0.660–1.316)	.688	.008
Control source													
PB	13	0.951 (0.908–0.997)	.035	.084	0.970 (0.933–1.008)	.119	.395	0.965 (0.930–1.000)	.052	.239	0.974 (0.936–1.013)	.184	.078
HP	7	1.103 (0.964–1.262)	.152	.633	1.058 (0.943–1.186)	.336	.412	1.072 (0.962–1.194)	.210	.416	1.067 (0.956–1.191)	.246	.657
Quality score													
High	17	0.967 (0.925–1.010)	.133	.043	0.980 (0.944–1.017)	.276	.318	0.976 (0.942–1.010)	.166	.113	0.982 (0.946–1.019)	.341	.156
Low	3	0.946 (0.628–1.425)	.790	.664	0.876 (0.630–1.218)	.431	.336	0.910 (0.666–1.244)	.554	.699	1.143 (0.815–1.603)	.439	.168

Note: [a]The pooled *p* value; [b]*p* value for heterogeneity test. PB = population based; HB = hospital based.

TABLE 4

Meta-Analysis of the HSD17B1 Gene Polymorphism and Breast Cancer Risk

		GG vs. AA			GA vs. AA			Dominant model			Recessive model		
Variable	*n*	OR (95% CI)	p^a	p^b	OR (95% CI)	p^a	p^b	OR (95% CI)	p^a	p^b	OR (95% CI)	p^a	p^b
Total	14	0.972 (0.921–1.026)	.303	.207	0.986 (0.943–1.031)	.573	.193	0.991 (0.951–1.033)	.675	.818	0.983 (0.939–1.029)	.464	.425
Ethnicity													
Asian	4	0.856 (0.707–1.035)	.109	.165	0.946 (0.796–1.123)	.524	.184	0.961 (0.817–1.131)	.633	.496	0.911 (0.786–1.056)	.216	.360
Caucasian	6	0.950 (0.884–1.019)	.154	.277	0.959 (0.906–1.016)	.155	.320	0.974 (0.924–1.027)	.338	.717	0.978 (0.920–1.040)	.473	.165
Mixed	4	1.043 (0.950–1.146)	.374	.766	1.047 (0.968–1.132)	.251	.379	1.030 (0.958–1.108)	.426	.682	1.013 (0.937–1.096)	.746	.889
Control source													
PB	9	0.955 (0.902–1.012)	.123	.121	0.973 (0.928–1.020)	.254	.201	0.983 (0.940–1.027)	.434	.713	0.975 (0.929–1.025)	.321	.219
HP	5	1.099 (0.941–1.283)	.234	.851	1.092 (0.959–1.244)	.184	.485	1.060 (0.938–1.198)	.351	.795	1.036 (0.911–1.177)	.590	.765
Quality score													
High	11	0.972 (0.921–1.027)	.316	.099	0.988 (0.945–1.034)	.607	.153	0.993 (0.952–1.035)	.732	.729	0.980 (0.936–1.027)	.397	.536
Low	3	0.946 (0.628–1.425)	.790	.664	0.876 (0.630–1.218)	.431	.336	0.910 (0.666–1.244)	.554	.699	1.143 (0.815–1.603)	.439	.168

Note: [a]The pooled *p* value; [b]*p* value for heterogeneity test. PB = population based; HB = hospital based.

$I^2 = 20.7\%$; $p = .132$, $I^2 = 26.7\%$) in the overall analysis. In contrast, significant heterogeneity was observed under the homozygous and allele comparison models ($p = .090$, $I^2 = 31.4\%$; $p = .071$, $I^2 = 33.7\%$). Then, a meta-regression was performed to determine the source of heterogeneity by types of cancer, source of controls, ethnicity, and quality score. We found that none of these factors contributed to the heterogeneity in the current meta-analysis (data shown in Supplementary Table 1). Moreover, sensitivity analysis, by consecutively excluding studies one at a time, indicated that the removal of any of studies did not substantially alter the pooled ORs, suggesting the stability of the meta-analysis results.

Publication Bias

For the significant results, the shape of the funnel plot for Caucasians in the dominant and allele comparing model, as well as PB controls in the homozygous and allele comparing model, did not show obvious asymmetry (Figure 3). Moreover, Begg's and Egger's tests suggested no evidence of publication bias in these models, respectively (Caucasian subgroup: homozygous model, Begg's test, $p = .835$, Egger's test, $p = .308$; heterozygous model, Begg's test, $p = .211$, Egger's test, $p = .707$; dominant model, Begg's test, $p = .211$, Egger's test, $p = .674$; recessive models, Begg's test, $p = .404$, Egger's test, $p = .201$; allele comparison model, Begg's test, $p = .835$, Egger's test, $p = .289$ and PB controls subgroup: homozygous model, Begg's test, $p = .222$, Egger's test, $p = .784$; heterozygous model, Begg's test, $p = .088$, Egger's test, $p = .344$; dominant model, Begg's test, $p = .067$, Egger's test, $p = .292$; recessive models, Begg's test, $p = .714$, Egger's test, $p = .899$; allele comparison model, Begg's test, $p = .393$, Egger's test, $p = .876$). Similarly, in the pooled analysis and other subgroup analysis, the shape of the funnel plot did not show any obvious asymmetry for the Ser312Gly polymorphism and cancer risk.

Discussion

In this current meta-analysis for the association between *HSD17B1* Ser312Gly polymorphism and cancer risk, 20 studies with a total of 29,460 cases and 36,687 controls were included. This meta-analysis observed no significant association between *HSD17B1* Ser312Gly polymorphism and overall cancer risk in all the genetic models. However, further stratified analyses by ethnicity indicated that the Ser312Gly polymorphism decreased cancer risk among Caucasians, but not other ethnic groups. When the analyses were stratified by the source of control, such association was observed for a PB, but not a HB, subgroup. There was no significant association between *HSD17B1* Ser312Gly polymorphism and the risk of cancer when subgroup analyses were performed by cancer type and quality score. To date, this is the first meta-analysis to assess the relationship between *HSD17B1* Ser312Gly polymorphism and cancer susceptibility.

The *HSD17B1* gene is located at chromosome17q21.2. The protein product of the gene is a metabolizing enzyme that converts estrone to estradiol, the more bioactive form of estrogen (Vihko et al., 2001). So far, several SNPs in the *HSD17B1* gene have been extensively investigated. Among these SNPs, the Ser312Gly polymorphism in the exon 6 that may modulate genetic cancer predisposition (Gaudet et al., 2008; Iwasaki et al., 2010) is the most common non-synonymous polymorphism. The non-conservative amino acid substitution of serine to glycine in the HSD17B1 protein caused by this variant may influence transcriptional activation of the *HSD17B1* enzyme. Potentially functional polymorphisms in the estrogen-metabolizing genes may influence their biological function, and thereby influence the susceptibility to hormone-related cancer (Abbas et al., 2010; Tsuchiya et al., 2005). A meta-analysis including 13,987 cases and 17,066 controls was carried out in 2010 to estimate the relationship between *HSD17B1* Ser312Gly and risk of breast cancer, and no significant association was observed (Yao et al., 2010). With the inclusion of more investigations, our meta-analysis replicated this previously reported null association. However, we failed to confirm some of the significant results presented in the previous meta-analysis. For example, our study could not duplicate the finding that the *HSD17B1* Ser312Gly polymorphism was associated with decreased breast cancer risk among Caucasian. The association was no longer significant upon the inclusion of five more investigations in our meta-analysis. Alternatively, significant association was obtained in stratified analyses by ethnicity, probably owing to biological or genetic differences between various races. Furthermore, genetic and environmental differences by race may play an important role in the disparities of cancer susceptibility (Pinheiro et al., 2005; Reding et al., 2012; Setiawan et al., 2006). The source of control may also contribute to the results. For example, controls who were recruited from hospital could not fully represent the population from which the cases originated, which may weaken the value of risk. Moreover, although a subgroup analysis by ethnicity and control source found an association between Caucasian and PB controls, the result should be considered with caution as the p value was only moderate.

The FPRP analyses were performed for the significant findings to rule out false positive findings resulting from multiple comparisons. While FPRP values at the preset prior probability of 0.1 suggested that Ser312Gly polymorphism might not be able to influence the cancer risk, there are several possible interpretations of these outcomes. First, multiple comparisons and the limited sample size in the subgroups would make a certain effect in some findings. Second, the significant association for PB studies and Caucasians was based on a moderation p value. Third, between-study heterogeneity was observed in the pool analysis.

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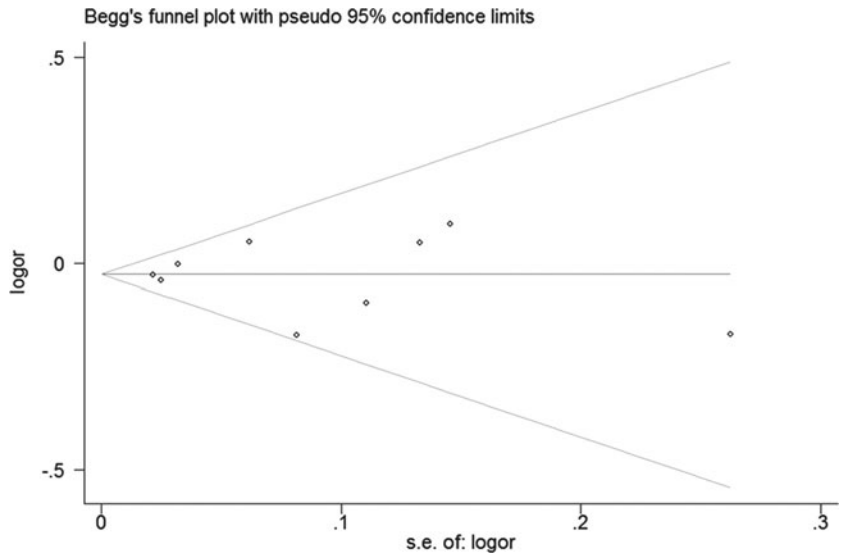

FIGURE 3

Funnel plot analysis to detect publication bias for HSD17B1 Ser312Gly polymorphism by allele comparison model for Caucasian subgroup analysis. Each point represents a separate study for the indicated association.

However, the meta-regression did not determine the source of the heterogeneity, which is probably because only slight heterogeneity existed across studies. Moreover, the sample sizes were reduced when stratification analysis was performed to identify the source of heterogeneity. Several factors may contribute to the heterogeneity among the pooled analysis. Discrepancies in lifetime environmental factors and genetic background could conceivably contribute to surveyed racial differences in the incidence of cancer (Laiyemo et al., 2010; Reding et al., 2012; Sucheston et al., 2012). Furthermore, the same SNP may play a different role in tumor susceptibility because multi-genetic and multi-factorial factors are involved in carcinogenesis. The disparity of pathogenesis in different tumors may also interpret the heterogeneity. Heterogeneity should be explored in more investigations in the future.

There were also some limitations to be addressed in this meta-analysis. First, there were some studies with a relatively small sample size (less than 500) included in our study. Second, in some subgroup analysis, only a moderate number of individual studies were included. For instance, subgroups with endometrial cancer and other cancers only comprised three studies. As a result, the statistical power to detect the potential association was reduced. Third, conference abstracts and unpublished studies were omitted. Finally, this current meta-analysis was solely dependent on unadjusted estimates. If possible, ORs adjusted for gender, age, smoking status, drinking, occupational exposures, as well as hormonal replacement therapy, would be more accurate.

In summary, no significant association was found between *HSD17B1* Ser312Gly polymorphism and overall cancer risk. Nevertheless, stratified analysis by ethnicity suggested that this variant might confer decreased cancer risk among Caucasians, indicating that *HSD17B1* Ser312Gly might be an ethnicity-specific SNP. Finally, large-scale studies should be performed to confirm these findings.

Supplementary Material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/thg.2016.6.S1832427416000062.

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