

## RESEARCH ARTICLE

# Variants on ESR1 and their Association with Prostate Cancer Risk: A Meta-analysis

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### Abstract

**Background:** Epidemiological studies evaluating the association of two variants rs9340799 and rs2234693 on estrogen receptor 1 (ESR1) with prostate risk have generated inconsistent results. **Methods:** A meta-analysis was here conducted to systematically evaluate the relationship of these two variants with prostate cancer susceptibility. **Results:** For rs9340799, heterozygosity of T/C carriers showed a significant increased prostate cancer risk with a pooled odds ratio (OR) of 1.34 (95% CI = 1.06-1.69) while homozygote C/C carriers showed an increased but not statistically significant association with prostate cancer risk (pooled OR = 1.29, 95% CI = 0.94-1.79). Compared to the homozygous TT carriers, the allele C carriers showed a 31% increased risk for prostate cancer (pooled OR = 1.31, 95% CI = 1.06-1.63). No significant association between the rs2234693 and prostate cancer risk was found with the pooled OR of 1.15 (95% CI = 0.97-1.39, T/C and C/C vs. T/T) under the dominant genetic model. Compared to the homozygote T/T carriers, the heterozygous T/C carriers did not show any significantly different risk of prostate cancer (pooled OR = 1.13, 95% CI = 0.94-1.36) and the homozygous C/C carriers also did not show a significant change for prostate cancer risk compared to the wide-type T/T carriers (pooled OR = 1.26, 95% CI = 0.98-1.62). **Conclusions:** These data suggested that variant rs9340799, but not rs2234693, on ESR1 confers an elevated risk of prostate cancer.

**Keywords:** ESR1 - prostate cancer - polymorphisms - meta-analysis

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### Introduction

Prostate cancer is a leading cause of death for the men in the developed countries and the incidence rate in the Asian and Central or Eastern European countries is increasing (Jemal et al., 2011). According to the latest statistics, prostate cancer is accounting for 14% (about 903,500 cases) of the total new cancer cases and 6% (about 258,400 cases) of the total cancer deaths for males in 2008 (Jemal, et al. 2011). Many factors that lead to the prostate cancer development have been reported (Iwasaki et al., 2005; Hsing et al., 2006). Of them, the endocrine system has drawn much attention in the etiology of the prostate cancer for its important roles in the prostatic tissue growth and development. Thus, roles of sex steroid hormones including androgens and estrogens, which are produced in the periphery as well as in the prostate itself, have been extensively studied for the past years. Epidemiological and experimental studies have suggested that although androgen deprivation and administration of estrogens have been recognized as the therapies for prostate cancer patients, early exposure to estrogens may lead to the prostate cancer development (Nelles et al., 2011).

Estrogens exert effects via their cognate receptors, estrogen receptor (ER) alpha (ESR1) and ER beta (ESR2). Both receptors are located in the prostate glands and they have been postulated to have important effects on these glands (Harkonen et al., 2004). Many previous studies have investigated the relation between genes that are involved in the estrogen metabolism pathway and the risk of prostate carcinoma (Celhay et al., 2010; Muthusamy et al., 2011). Variants on the gene ER alpha (ESR1) have been reported to be significantly associated with the risk of other sex steroid hormone-related carcinomas, such as breast cancer (Li et al., 2010), endometrial cancer (Einarsdottir et al., 2009) and ovarian carcinoma (Doherty et al., 2010). Many studies also evaluated the variants on ESR1 especial for the PvuII (IVS1-397, rs2234693) and XbaI (IVS1-351, rs9340799) polymorphisms and their association with prostate cancer; however, inconsistent results were found for the reports.

Herein, we conducted a meta-analysis to systematically assess the association between the two variants and prostate cancer risk and we found that rs9340799 but not rs2234693 may contribute to the prostate cancer susceptibility.

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## Materials and Methods

### Identification and selection of the related studies

We systematically searched the MEDLINE and PubMed databases to identify potential studies that have evaluated the association between the two polymorphisms on ESR1 and prostate cancer susceptibility, which has been published online before June 2012. We used the term “prostate cancer” in combination with “ESR1”, “estrogen receptor”, “rs9340799”, “rs2234693”, “XbaI” or “PvuII” to identify the potential eligible studies. The references of the identified publications were checked to identify any missing studies in the database search by the authors independently.

The eligible studies were those provided the detailed data about the polymorphisms of rs9340799 and rs2234693 and the risk of prostate cancer and should also provided sufficiency data for the allele frequency of the genotypes or sufficient data to calculate the allele frequency. If the study did not provide the detailed data about the allele frequency, the authors were contacted for the detail data.

If overlapping study population was existed between the studies, only the study that provided the most complete information or the latest report was included in the final meta-analysis studies. Eligible studies should be cohort, case-control, or cross-sectional studies that reported in English.

### Data extraction

Detailed data that were extracted from the identified publications including: first author’s name and the publication year, the design of the study, the area or country of the conducted, the sample size of the study, and the allele frequency of the selected variants in the cases and controls (Table 1 and Table 2). If an article consisted of more than one population study group then each subgroup was recognized as an individual subgroup study except for one study reported by Cunningham et al. (S-Cunningham et al., 2007), which contain a common control group for the familial and sporadic prostate cancer patients and the allele frequency were put together in the cases before the final analysis.

**Table 1. Main characteristics of the 9 Studies Included in the Meta-analysis for ESR1 (XbaI, IVS1-351, rs9340799)**

Study (First Author, Year)	Study type	Location	Sample Size (case/control)	Genotype Distribution (case/control)		
				TT	TC	CC
Modugno, 2001	Population based Case-Control	Pennsylvania, USA	88/241	34/116	38/93	10/28
Suzuki, 2003	Population based Case-Control	Maebashi, Japan	101/114	72/75	24/30	5/9
Fukatsu, 2004	Hospital based Case-Control	Japan	147/266	74/163	37/68	6/11
Cunningham, 2007	Population based Case-Control (Familial)	USA	425/487	188/189	186/227	51/71
Cunningham, 2007	Population based Case-Control (Sporadic)	USA	493/487	192/189	231/227	70/71
Beuten, 2009 (non-Hispanic Caucasians)	Population based Case-Control	Texas, USA	609/843	258/335	277/393	74/115
Beuten, 2009 (Hispanic Caucasians)	Population based Case-Control	Texas, USA	195/514	91/224	84/88	20/59
Beuten, 2009 (African American)	Population based Case-Control	Texas, USA	82/209	37/118	36/78	9/13
Gupa, 2010	Hospital based Case-Control	Indian	157/170	71/87	75/72	11/11
Sissung, 2011	Population based Case-Control	USA	129/127	42/58	69/61	18/8
Szendroi, 2011	Hospital based Case-Control	Budapest, Hungary	204/102	35/29	111/54	59/18
Safarinejad, 2012	Population based Case-Control	Tehran, Iran	162/324	20/81	108/187	34/56

**Table 2. Main Characteristics of the 15 Studies Included in the Study for ESR1 (PvuII, IVS1-397, rs2234693)**

Study (First Author, Year)	Study type	Location	Sample Size (case/control)	Genotype Distribution (case/control)		
				TT	TC	CC
Modugno, 2001	Population based Case-Control	Pennsylvania, USA	88/241	26/85	34/109	21/43
Suzuki, 2003	Population based Case-Control	Maebashi, Japan	101/114	46/29	43/59	12/26
Tanaka, 2003	Hospital based Case-Control	Izumo, Japan	115/200	23/39	63/113	29/48
Fukatsu, 2004	Hospital based Case-Control	Japan	147/266	37/81	57/110	22/47
Low, 2006	Nested Case-Control	Norfolk, UK	89/178	13/49	41/84	21/25
Berndt, 2007	Nested Case-Control	USA	488/617	121/152	238/316	111/135
Cunningham, 2007	Population based Case-Control (Familial)	USA	430/489	129/120	206/249	95/120
Cunningham, 2007	Population based Case-Control (Sporadic)	USA	494/489	128/120	248/249	118/120
Kjaergaard, 2007	Prospective Cohort	USA	116/4005	35/1203	55/1972	26/830
Onsory, 2008	Hospital based Case-Control	Chandigarh, India	100/100	28/42	54/48	18/10
Beuten, 2009 (non-Hispanic Caucasians)	Population based Case-Control	Texas, USA	609/843	167/222	304/421	138/200
Beuten, 2009 (Hispanic Caucasians)	Population based Case-Control	Texas, USA	195/514	75/186	92/246	28/82
Beuten, 2009 (African American)	Population based Case-Control	Texas, USA	82/209	18/54	41/105	23/50
Gupa, 2010	Hospital based Case-Control	Indian	157/170	52/64	77/90	28/16
Sonoda, 2010	Hospital based Case-Control	Japan	180/177	60/61	120/116	
Sissung, 2011	Population based Case-Control	USA	128/126	25/46	75/60	28/20
Szendroi, 2011	Hospital based Case-Control	Budapest, Hungary	204/102	43/31	122/47	39/25
Safarinejad, 2012	Population based Case-Control	Tehran, Iran	162/324	11/65	94/169	57/90

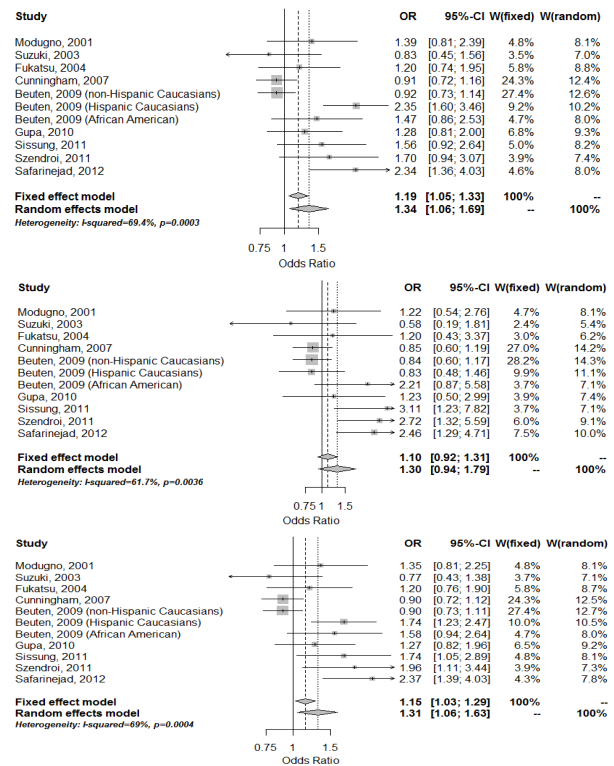
### Statistical methods

The standard inverse variance weighting method was used to calculate the pooled ORs and its 95% CI under the fixed-effects model and the DerSimonian-Laird method was used to calculate the pooled estimate under the random-effects model. For each study, the association of the two variants and prostate cancer susceptibility was presented as the odds ratio (OR) and its 95% confidence interval (CI). We also used the Fisher's exact test to test whether the identified study was in accordance with Hardy-Weinberg equilibrium (HWE) of the genotype distribution in the control group.

The Cochran's Q-test in combination with the  $I^2$  statistic, which represents the percentage of variability across studies that is attribute to heterogeneity rather than chance were used to quantify the heterogeneity between the studies. Significantly heterogeneity among studies was defined when P value was less than 0.1 for the Q statistic, or the  $I^2$  value was greater than 25%. If there were significant heterogeneity, the overall pooled estimate under the random-effects model rather than the fixed-effects model was acceptable, and vice versa. Publication bias of the studies was examined with the funnel plots and further assessed by the Begg's adjusted rank correlation method (Begg et al., 1994). If significant publication bias for the published reports was found, the trim and fill method was used to correct the publication bias and re-calculate the pooled estimate (Peters et al., 2007). P values less than 0.05 were considered as statistically significant in the meta-analysis. All the statistical analysis was performed with the R software and the Meta package of the R (www.r-project.org).

### Results

rs9340799 and the susceptibility of prostate cancer From the database search, we have identified ten studies that have reported the association of the variant of rs9340799 (XbaI, IVS1-351) and prostate cancer (Modugno et al., 2001; Suzuki et al., 2003; Fukatsu et al., 2004; Hernandez et al., 2006; Cunningham et al., 2007; Beuten et al., 2009; Gupta et al., 2010; Sissung et al., 2011; Szendroi et al., 2011; Safarinejad et al., 2012); however, one study reported by Hernandez et al. (2006) had the same study population with the other study reported by Beuten et al. (2009) and the it was excluded from our further study. In total, nine studies that have recruited a total of 2,792 prostate cancer patients and 3,397 controls with eleven individual study groups were included in the meta-analysis study (Table 1). No departure from Hardy-Weinberg equilibrium of the variant rs9340799 in the control groups was found. Of them, three studies reported a significant increased prostate cancer for the variant rs9340799 (Sissung et al., 2011; Szendroi et al., 2011; Safarinejad et al., 2012), while the other studies did not report a significant association for the variant and prostate cancer. From the meta-analysis, we found that compared to the TT carriers, the TC carriers showed a 34% increased prostate cancer (pooled OR = 1.34, 95% CI = 1.06-1.69; Figure 1a) under the random effects model ( $Q = 32.63$ ,  $df = 10$ ,  $P = 0.0003$ ;  $I^2 = 69.4\%$ ). However,

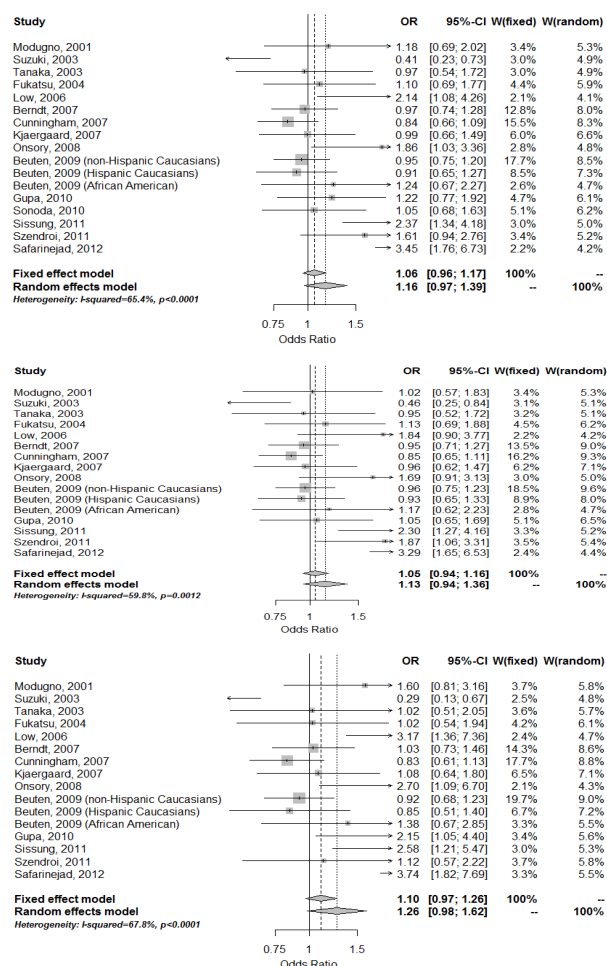


**Figure 1. Forest Plot of the Prostate Cancer Associated with (A) rs9340799 heterozygosity (T/C vs. T/T); (B) rs9340799 homozygosity (C/C vs. T/T); (C) allele C carrier status (T/C and C/C vs. T/T)**

the homozygote CC carriers did not show a significant association with prostate cancer risk (pooled OR = 1.29, 95% CI = 0.94-1.79; Figure 1b) under the random effects model ( $Q = 26.1$ ,  $df = 10$ ,  $p = 0.0036$ ;  $I^2 = 61.7\%$ ). Under the dominant genetic effect model, we found that allele C carriers showed a 31% increased risk for prostate cancer compared to the homozygosity TT carriers using the random effects model (pooled OR = 1.31, 95% CI = 1.06-1.63; Figure 1c). Significant heterogeneity between the studies was with the  $I^2$  value was 69% and the P value was 0.0004 for the Q-test ( $Q = 32.27$ ,  $df = 10$ ). The sensitivity analysis suggested that none study significantly influence the pooled results. No significant publication bias was found with the Begg's rank test ( $p = 0.1391$ ). These results indicated that rs9340799 may be a risk factor for prostate cancer and it may acts as a dominant model.

rs2234693 and the susceptibility of prostate cancer

In total, 17 individual studies were identified in the literature search stage that have evaluated the association between the rs2234693 and prostate cancer (Modugno et al., 2001; Suzuki et al., 2003; Tanaka et al., 2003; Fukatsu et al., 2004; Hernandez et al., 2006; Low et al., 2006; Berndt et al., 2007; Cunningham et al., 2007; Kjaergaard et al., 2007; Onsory et al., 2008; Sobti et al., 2008; Beuten et al., 2009; Gupta et al., 2010; Sonoda et al., 2010; Sissung et al., 2011; Szendroi et al., 2011; Safarinejad et al., 2012). Two of them were excluded for overlapping studied populations (Hernandez et al., 2006; Sobti et al., 2008). 15 individual reports with 17 subgroups that have recruited a total of 3,885 cases and 8,575 controls were included in the meta-analysis (Table 2). No deviation of Hardy-Weinberg equilibrium was found for the variant rs2234693 for any study. Of them, six reports found a significant



**Figure 2. Forest Plot of the Prostate Cancer Associated with (A) rs2234693 allele C carriers (T/C and C/C vs. T/T); (B) rs2234693 heterozygosity (T/C vs. T/T); (C) rs2234693 homozygosity (C/C vs. T/T)**

association for the variant and prostate cancer risk while the others did not found such association (Suzuki et al., 2003; Low et al., 2006; Onsory et al., 2008; Gupta et al., 2010; Sissung et al., 2011; Safarinejad et al., 2012). From the meta-analysis, no significant association between the rs2234693 and prostate cancer risk was found with the pooled OR was 1.15 (95% CI = 0.97-1.39) under dominant genetic model (Figure 2a). Significant heterogeneity between the studies was found ( $Q = 46.28$ ,  $df = 16$ ,  $P < 0.0001$ ;  $I^2 = 65.4\%$ ). For significant publication bias was existing for the reports (Begg's test,  $p = 0.001$ ), the trim and fill method was applied for the bias adjustment and the results also indicated no significant association between the rs2234693 and prostate cancer (pooled OR = 0.94, 95% CI = 0.77-1.14). Compared to the homozygote TT carriers, the heterozygosity TC carriers did not showed any significant different risk for the prostate cancer (pooled OR = 1.13, 95% CI = 0.94-1.36;  $Q = 37.27$ ,  $df = 15$ ,  $p = 0.0012$ ;  $I^2 = 59.8\%$ ; Figure 2b). The homozygosity CC carriers also did not show an increased prostate cancer risk compared to the wide-type TT carriers (pooled OR = 1.26, 95% CI = 0.98-1.62; Figure 2c). For each test, significant publication bias was identified by the Begg's test ( $P = 0.004$  and  $0.004$ , respectively). After we applied the trim and fill method to adjust the publication bias, no significant association was found for any of the meta-

analysis. These results suggested that rs2234693 may not contribute to the prostate cancer susceptibility.

## Discussion

For the current meta-analysis studies, we have evaluated the association between the two widely studies variants on ESR1 with the prostate cancer risk, we have found that variant rs9340799 may contribute to the susceptibility of prostate cancer risk, but not for the variant rs2234693. However, care must be taken when interpreting these data because significant publication bias was identified for the individual studies that recruited in the meta-analysis studies, especially for rs2234693.

rs9340799 locates in the intron 1 of the ESR1 gene. Modugno et al. firstly evaluated its correlation with prostate cancer risk and they found that for those with a shorter CAG repeat in exon 1 of the androgen receptor (AR), the allele C carriers showed a significant increased prostate cancer, but for not for those with higher AR (CAG) repeat (Modugno et al., 2001). Safarinejad et al. reported that compared to those of TT genotype, carriers of XbaI TC genotype had significantly higher SHBG levels and significant differences in total and free T and E2 levels between the genotypes were also found (Safarinejad et al., 2010). From a meta-analysis conducted by Ioannidis et al. have found that for women who were homozygous for the absence of an XbaI recognition site, the adjusted odds of all fractures were reduced by 19% (OR = 0.81, 95% CI = 0.71-0.93) and vertebral fractures by 35% (OR = 0.65, 95% CI = 0.49-0.87) (Ioannidis et al., 2004). Wedren et al. found that allele C was associated with a significant reduced risk for endometrial cancer risk (Wedren et al., 2008), but another study conducted by Ashton et al. found that allele C was a risk factor for endometrial cancer risk, which may be due to the population diversity (Ashton et al., 2009). Wang et al. found that the variant was associated with a protective effect on breast cancer (Wang et al., 2007); however, a meta-analysis suggested no correlation for the variant and breast cancer risk was found (Li et al., 2010). For prostate cancer risk, inconsistent results were found for the association between rs9340799, which also may be due to the population diversity and/or smaller sample size; however, from the meta-analysis, we found the allele C carriers showed a significant increased prostate cancer. The results indicated that rs9340799 could be a risk factor for prostate cancer and ESR1 pathway may be involved in the carcinogenesis of prostate cancer.

rs2234693 is another variant that also locates in the intron 1 of ESR1, and the association between the allele and prostate cancer was also firstly evaluated by Modugno et al. (2001); however, no significant association was found in that study. Suzuki et al. found that the T/T genotype of the variant was significantly associated with the risk of developing prostate carcinoma and the results were repeated by several other reports, but not for all the following reports. Our current meta-analysis suggested that there was no significant association for the variant and prostate cancer risk and significant publication bias for the reports was also identified. The allele C of the variant has been reported to be associated with reduced odds of

obesity of in white postmenopausal women (Goulart et al., 2009). A recent meta-analysis have been evaluated the association of the variants on ESR1 and breast cancer risk, the pooled estimate for a total of 10,300 breast cancer cases and 16,620 controls of rs2234693 showed a borderline significant decreased breast cancer risk for CC and CC/CT carriers compared to the TT carriers (Li et al., 2010); however, no significant association was found for the rs9340799. These data suggested that the variants on ESR1 may have different effect on the etiology of the estrogen related diseases.

We acknowledged that there are several limitations for our current meta-analysis study. First, the sample size is still relatively small and all the data are from case-control studies, more studies with larger sample size are needed. Second, the ethnicity of the participants is not specified, and most of the studies were conducted in the Americans, so there is a lack of evidence from other populations. Third, a significant publication bias was found for the studies that reported the association between the rs2234693 and prostate cancer risk, which may lead to a bias for the current meta-analysis results. Thus, more future studies that evaluated the associations of the two polymorphisms and prostate cancer are warranted.

In summary, the overall results from our meta-analysis suggest that variant rs9340799 on ESR1 was statistically associated with an increased risk of prostate cancer but not for the variant rs2234693; however, more studies are warranted to confirm the results and the underlying molecular mechanisms that are involved also need further investigation.

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