

Review



ESR1 Pvull (rs2234693 T>C) polymorphism and cancer susceptibility: Evidence from 80 studies

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Abstract

Emerging epidemiological researches have been performed to assess the association of ESR1 Pvull (rs2234693 T>C) polymorphism with the risk of cancer, yet with conflicting conclusions. Therefore, this updated meta-analysis was performed to make a more accurate evaluation of such relationship. We adopted EMBASE, PubMed, CNKI, and WANFANG database to search relevant literature before January 2018. Odds ratios (ORs) and 95% confidence intervals (Cls) were employed to estimate the relationship strengths. In final, 80 studies (69 publications) involving 26428 cases and 43381 controls were enrolled. Our results failed to provide significant association between overall cancer risk and Pvull polymorphism under homozygous (TT vs. CC) and heterozygous (TT vs. CT) models. Statistically significant relationship was only observed for Pvull polymorphism in allele model T vs. C (OR=0.95, 95% CI=0.91-0.99). Stratification analysis by cancer type suggested that T genotype significantly decreased prostate cancer risk (TT vs. CC: OR=0.79, 95% CI=0.66-0.94; T vs. C: OR=0.89, 95% CI=0.82-0.98), Leiomyoma risk (T vs. C: OR=0.82, 95% CI=0.68-0.98), and HCC risk (TT vs. CC: OR=0.45, 95% CI=0.28-0.71; T vs. C: OR=0.67, 95% CI=0.47-0.95). Furthermore, significantly decreased risk was also found for Africans, population-based and hospital-based studies in the stratified analyses. These results suggest that ESRI Pvull (rs2234693 T>C) polymorphism may only have little impact on cancer susceptibility. In the future, large-scale epidemical studies are warranted to verify these results.

Key words: meta-analysis, *ESR1*, PvuII, polymorphism, cancer risk

Introduction

Worldwide, cancer still ranks the number one killer that threatens people's life. Approximately 14.1 million new cancer cases and 8.2 million cancer-caused deaths occurred globally in 2013 [1]. In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States [2]. By now, the definitive etiology of cancer remains unknown. However, a myriad of evidence has suggested that cancer is a complex disease caused by both genetic and environmental factors [3, 4]. Numerous functional polymorphisms have been found to be implicated in the development of cancers [5-7].

Previous researches have reported that hormonal factors play crucial roles in the development of some cancers. Common genetic variants in hormonal-related genes were associated with cancer susceptibility [8]. Among them, estrogen receptor (ER) was the most related-hormone in cancer risk. Estrogen receptor (ER) has two forms, which is alpha and beta [9]. Estrogen receptor-α plays a critical mediating hormonal role in response in estrogen-sensitive tissues. It consists of several domains important for hormone regulation, activation of transcription and DNA binding. Evidence points to estrogen receptor-a as the main receptor correlated to

initiation of cancer [10]. Estrogen receptor- α , a transcription factor, is encoded by the *ESR1* gene.

The ESR1 gene, comprises of 8 exons and 7 introns, is located on chromosome 6q25.1. Several SNPs of *ESR1* gene have been identified to influence the risk of cancer, but the most popular studied SNP is ESR1 PvuII (rs2234693 T>C) polymorphism [11]. Although increasing studies have been performed, the conclusions of the roles of ESR1 PvuII (T>C) polymorphism in cancer risk are conflicting. The inconsistent conclusions between ESR1 PvuII (rs2234693 T>C) polymorphism and cancer risk may be due to the limitations in the sample size of the corresponding studies or the inadequate statistical power in genetic studies with complex characteristics. Several meta-analyses regarding this issue have been performed to resolve the conflicting situation but somehow failed. With the aim to solve such embarrassment, we conducted this comprehensive meta-analysis by adopting all published articles.

Materials and methods

Publication search

We first inputted the following key words: "single nucleotide polymorphism or polymorphism or variant or SNP" and "ESR1 or ESRa or Estrogen Receptor a or Estrogen Receptor 1", and "cancer or tumor or neoplasm or carcinoma)" in database of PubMed and EMBASE. In addition, we also searched the Chinese database CNKI and WANFANG to include more eligible studies. Further, additional studies were also manually extracted from the references of the above obtained publications. The date of the final literature search was set on January 2018. We did not set any language publication restrictions here. The article will be considered as different studies if it contains more than two ethnicities. If the searched articles have overlapping data, the largest one will be selected.

Eligibility criteria

The evaluating publications in this meta-analysis should fulfill all the following requirements: 1) unrelated case-control studies; 2) original epidemiological studies; 3) analyzing the relationship between *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer risk; 4) enough data to obtain odds ratios (ORs) and 95% confidence intervals (CIs); 5) articles written in English or in Chinese.

Data extraction

Two authors separately extracted data by screening all eligible studies. They collected the information regarding first author's surname, country, publication year, ethnicity, genotyping methods, the source of controls, and numbers of cases and controls with CC, CT and TT genotypes. All the disagreed information was settle down after fully discussed by the two authors.

Statistical methods

Hardy-Weinberg equilibrium (HWE) in the controls was determined using goodness-of-fit χ^2 test. P<0.05 was considered as departure from HWE. Three genetic models, homozygous model (TT vs. CC), heterozygous model (TT vs. CT), and allele comparison (T vs. C), were applied to assess the association between ESR1 PvuII (rs2234693 T>C) polymorphism and cancer risk. The strength of such association was assessed by calculating ORs with the corresponding 95% CIs. Stratification analyses were also conducted by ethnicity, cancer type, source of control, and HWE in controls, in all studies. Chi square-based Q-test was adopted to monitor between-study heterogeneity. The fixed-effects model (the Mantel-Haenszel method) was chosen to estimate the pooled OR, if the studies were homogeneous (P>0.10 for the Q test). Otherwise, the random-effects model (the DerSimonian and Laird method) was used. Sensitivity analysis was conducted by excluding each study individually and re-calculating the ORs and 95% CIs. Begg's funnel plot and Egger's linear regression were used to evaluate whether there exists publication bias [12, 13]. The asymmetric plot and P value less than 0.5 was considered as the existence of publication bias. We also conducted quality assessment to detect the quality of each study using the quality assessment criteria [14]. The version 11.0 STATA software was adopted to perform all statistical analysis (Stata Corporation, College Station, TX). All the statistics were two-sided with P value of <0.05 as significant findings.

Results

Study characteristics

Our first research in databases identified 185 candidate publications. After screening the title and abstract, we kept 64 publication s in the analysis [15-78]. Moreover, we further extracted 5 articles from the references of the retrieval articles [79-83]. The flow chart of screening process was graphically shown in **Figure 1**. In final, 80 studies (69 publications) with 26428 cases and 43381 controls were included in the pooled analysis (**Table 1**). Among them, 38 studies focused on Asians, 36 on Caucasians, 3 on Africans, 1 on Hispanic Sand 1 on non-Hispanic Caucasians, 1 on Hispanic Caucasians. 44 studies were hospital-based design, 36 were population-based design. The controls' genotype frequencies were in agreement with HWE (*P*>0.05) in 74 studies, except for 6 studies.



Figure 1. Flowchart of study selection process.

Table 1. The baseline characteristics of all q	jualified studies in this meta-analysis
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Surname	Year	Country	Ethnicity	Cancer type	Control Source	Genotype method	Case				Cont	rol			HWE	Score
							TT	CT	CC	All	TT	CT	CC	All		
Modugno	2001	USA	Caucasian	Prostate	PB	PCR	26	34	21	81	85	109	43	237	0.438	8
Massart	2001	Italy	Caucasian	Leiomyoma	HB	PCR	35	57	27	119	46	77	33	156	0.941	5
Suzuki	2003	Japan	Asian	Prostate	PB	PCR	46	43	12	101	29	59	26	114	0.702	9
Massart	2003	Italy	Caucasian	Leiomyoma	HB	PCR-RFLP	54	91	43	188	66	111	48	225	0.917	5
Iwamoto	2003	Japan	Asian	Endometrial	HB	PCR-RFLP	25	54	13	92	25	28	12	65	0.408	4
Shin	2003	Korea	Asian	Breast	PB	PCR-RFLP	75	91	35	201	64	105	26	195	0.095	8
Tanaka	2003	Japan	Asian	Prostate	HB	PCR	23	63	29	115	39	113	48	200	0.061	6
Cai	2003	China	Asian	Breast	PB	PCR-RFLP	415	516	138	1069	430	546	190	1166	0.452	12
Fukatsu	2004	Japan	Asian	Prostate	HB	PCR-RFLP	37	57	22	116	81	110	47	238	0.384	6
wedren	2004	Sweden	Caucasian	Breast	PB	PCR-RFLP	390	634	268	1292	384	651	313	1348	0.248	10
Lu	2005	China	Asian	Breast	HB	PCR-RFLP	54	65	19	138	50	69	21	140	0.723	78
Modugno	2005	USA	Caucasian	Breast	PB	PCR-RFLP	53	115	80	248	819	1810	1272	3901	0.000	6
Onland-Moret	2005	Netherlands	Caucasian	Breast	PB	PCR-RFLP	89	150	69	308	88	153	96	337	0.093	9
Low	2006	UK	Caucasian	Prostate	PB	TaqMan	13	41	21	75	49	84	25	158	0.266	2
Al-Hendy	2006	USA	African	Leiomyoma	HB	PCR-RFLP	22	34	36	92	9	9	3	21	0.760	3
Al-Hendy	2006	USA	Caucasian	Leiomyoma	HB	PCR-RFLP	21	23	17	61	57	99	1	157	0.000	2
Al-Hendy	2006	USA	Hispanic	Leiomyoma	HB	PCR-RFLP	14	23	8	45	27	18	6	51	0.284	11
Zhai	2006	China	Asian	HCC	PB	PCR-RFLP	74	117	53	244	91	116	30	237	0.457	6
Chen	2006	China	Asian	Leiomyoma	HB	PCR-RFLP	35	37	11	83	31	38	9	78	0.604	5
Denschlag	2006	Germany	Caucasian	Leiomyoma	PB	PCR	33	66	31	130	40	59	40	139	0.075	9
Hernandez	2006	USA	Caucasian	Prostate	PB	TaqMan	47	55	18	120	129	131	43	303	0.300	11
Hernandez	2006	USA	Caucasian	Prostate	PB	TaqMan	115	216	100	431	154	296	132	582	0.653	9
Hernandez	2006	USA	African	Prostate	PB	TaqMan	9	22	16	47	50	113	50	213	0.373	11
Shen	2006	China	Asian	Breast	PB	PCR-RFLP	98	120	29	247	107	124	43	274	0.480	10
Cunningham	2007	Minnesota	Caucasian	Prostate	PB	PCR	257	454	213	924	120	249	120	489	0.684	9
Berndt	2007	USA	Caucasian	Prostate	HB	PCR	121	238	111	470	152	316	135	603	0.230	9
Hsieh	2007	China	Asian	Leiomyoma	PB	PCR-RFLP	25	75	6	106	60	44	6	110	0.571	7
Hu	2007	China	Asian	Breast	HB	PCR-RFLP	39	58	16	113	49	45	19	113	0.128	7
Kadiyska	2007	Bulgaria	Caucasian	Colorectal	HB	PCR-RFLP	34	79	27	140	23	35	19	77	0.438	11
Kjaergaard	2007	Danmark	Caucasian	Prostate	PB	TaqMan	35	55	26	116	1203	1972	830	4005	0.676	11
Kjaergaard	2007	Danmark	Caucasian	Breast	PB	TaqMan	398	613	245	1256	727	1225	537	2489	0.621	7
Wang	2007	USA	Caucasian	Breast	PB	PCR	117	188	87	392	214	393	176	783	0.862	4
Onsory	2008	India	Asian	Prostate	HB	PCR-RFLP	28	54	18	100	42	48	10	100	0.487	
González-Mancha	2008	Spain	Caucasian	Breast	PB	PCR-RFLP	153	209	82	444	193	361	150	704	0.435	6
Sobti	2008	India	Asian	Prostate	HB	PCR	52	77	28	157	64	90	16	170	0.050	6
Gonzalez-Zuloeta	2008	Netherlands	Caucasian	Breast	PB	PCR-RFLP	72	94	24	190	1602	1648	453	3703	0.359	6
Dunning	2009	UK	Caucasian	Breast	PB	TaqMan	1260	2164	938	4362	1318	2296	934	4548	0.253	8
Ashton	2009	Australia	Caucasian	Endometrial	PB	PCR-RLFP	39	95	57	191	96	129	65	290	0.088	11
Iwasaki	2009	Japan	Asian	Breast	HB	TaqMan	144	180	64	388	115	196	77	388	0.692	10
Iwasaki	2009	Japan	Asian	Breast	HB	TaqMan	25	39	15	79	22	43	14	79	0.374	9
Iwasaki	2009	Japan	Asian	Breast	HB	TaqMan	107	187	85	379	122	194	63	379	0.338	10

Surname	Year	Country	Ethnicity	Cancer type	Control Source	Genotype method	Case	:			Cont	trol			HWE	Score
							ΤT	CT	CC	All	TT	CT	CC	All	•	
Sonestedt	2009	Sweden	Caucasian	Breast	РВ	MassARRAY	158	273	108	539	316	539	218	1073	0.667	10
Beuten	2009	USA	non-Hispanic Caucasians	Prostate	PB	PCR	167	304	138	609	222	421	200	843	0.988	7
Beuten	2009	USA	Hispanic Caucasians	Prostate	PB	PCR	75	92	28	195	186	246	82	514	0.964	7
Beuten	2009	USA	African	Prostate	PB	PCR	18	41	23	82	54	105	50	209	0.940	7
Anghel	2009	Romania	Caucasian	Bladder	HB	PCR	0	6	9	15	18	48	48	114	0.309	5
Anghel	2009	Romania	Caucasian	Colorectal	HB	PCR	2	13	3	18	18	48	48	114	0.309	5
Anghel	2009	Romania	Caucasian	AML	HB	PCR	0	5	10	15	18	48	48	114	0.309	5
Anghel	2009	Romania	Caucasian	HCC	HB	PCR	2	6	4	12	18	48	48	114	0.309	5
Anghel	2009	Romania	Caucasian	Breast	HB	PCR	4	65	32	101	15	38	37	90	0.333	6
Wang JY	2010	China	Asian	Leiomyoma	HB	PCR-RFLP	24	46	22	92	51	100	42	193	0.592	6
Wang XL	2010	China	Asian	Leiomyoma	HB	PCR-RFLP	42	48	12	102	35	49	16	100	0.867	6
Gupta	2010	India	Asian	Prostate	HB	PCR-RFLP	52	77	28	157	64	90	16	170	0.049	6
Park	2010	China	Asian	Gallbladder	PB	PCR-RFLP	41	100	94	235	108	356	314	778	0.658	11
Sonoda	2010	Japan	Asian	Prostate	HB	PCR	60	89	31	180	61	87	29	177	0.828	5
Sakoda	2011	China	Asian	Breast	PB	PCR	229	290	93	612	327	427	120	874	0.298	12
Deng	2011	China	Asian	Breast	HB	PCR-RFLP	42	63	23	128	52	61	17	130	0.892	7
Wang	2011	China	Asian	Cervical	HB	PCR-RFLP	39	45	18	102	32	52	18	102	0.692	6
Sissung	2011	USA	Caucasian	Prostate	PB	TaqMan	25	75	28	128	46	60	20	126	0.952	3
de Giorgi	2011	Italy	Caucasian	Melanoma	HB	PCR-RFLP	32	49	31	112	56	98	41	195	0.876	6
Balistreri	2011	Italy	Caucasian	Prostate	HB	PCR-RFLP	37	11	2	50	84	7	0	91	0.702	4
Han	2011	China	Asian	Breast	PB	TaqMan	353	399	107	859	324	402	151	877	0.171	9
Szendroi	2011	Hungary	Caucasian	Prostate	HB	PCR-RFLP	43	122	39	204	31	47	25	103	0.392	7
Lundie	2012	USA	Caucasian	Endometrial	PB	PCR	116	184	91	391	194	369	146	709	0.223	9
Srivastava	2012	India	Asian	Gallbladder	PB	PCR-RFLP	59	218	133	410	19	110	91	220	0.075	12
Safarinejad	2012	Iran	Asian	Prostate	PB	PCR-RFLP	11	94	57	162	65	169	90	324	0.373	6
Chang	2012	China	Asian	Lung	HB	PCR-RFLP	21	60	3	84	62	132	40	234	0.034	4
Tang	2013	China	Asian	Breast	HB	MALDI-TOF	293	374	127	794	334	375	136	845	0.076	9
Jurecekova	2013	Slovak	Caucasian	Prostate	HB	PCR	78	154	79	311	81	126	49	256	1	5
Pazarbasi	2013	Turkey	Caucasian	Prostate	HB	PCR	14	14	6	34	10	7	10	27	0.012	3
Ramalhinho	2013	Portugal	Caucasian	Breast	HB	PCR-RFLP	28	60	19	107	45	60	16	121	0.566	7
Liu	2014	China	Asian	HCC	HB	PCR	34	54	19	107	57	38	10	105	0.331	6
Chattopadhyay	2014	India	Asian	Breast	PB	PCR-RFLP	157	164	39	360	136	162	62	360	0.252	11
Lu	2014	China	Asian	Breast	HB	PCR-RFLP	227	258	57	542	425	454	137	1016	0.368	5
Madeira	2014	Brazil	Asian	Breast	HB	PCR-RFLP	6	49	9	64	25	39	8	72	0.211	6
Taghizade	2014	Iran	Asian	Leiomyoma	HB	PCR-RFLP	78	133	65	276	50	74	33	157	0.563	7
Cao	2014	China	Asian	Breast	HB	PCR-RFLP	70	109	42	221	79	124	49	252	0.978	7
Lu	2015	Japan	Asian	Prostate	HB	TaqMan	67	191	94	352	80	175	97	352	0.949	7
Nyante	2015	USA	Caucasian	Breast	PB	PCR	518	984	470	1972	469	908	398	1775	0.297	11
Han	2017	China	Asian	Prostate	HB	PCR	94	102	48	244	92	112	28	232	0.492	8

Abbreviations: HB, hospital based; PB, population based; PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; HCC, hepatocarcinoma; AML, acute myeloid leukemia; HWE, Hardy-Weinberg equilibrium.

Meta-analysis results

The summary results of meta-analysis were presented in **Table 2** and **Figure 2**. In all, no significant association between the *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer risk was observed under homozygous model (TT vs. CC: OR=0.92, 95% CI=0.84-1.01) and heterozygous model (TT vs. CT: OR=0.94, 95% CI=0.88-1.001). Statistically significant relationship was only observed for PvuII in allele model T vs. C (OR=0.95, 95% CI=0.91-0.99).

In subgroup analysis by cancer type, we found that the T genotype significantly decreased prostate cancer risk (TT vs. CC: OR=0.79, 95% CI=0.66-0.94; T vs. C: OR=0.89, 95% CI=0.82-0.98), Leiomyoma risk (T vs. C: OR=0.82, 95% CI=0.68-0.98), and HCC risk (TT vs. CC: OR=0.45, 95% CI=0.28-0.71; T vs. C: OR=0.67, 95% CI=0.47-0.95). However, no relationship between *ESR1* PvuII polymorphism and any other types of cancer was observed. Ethnicity subgroup analysis revealed that significant association between *ESR1* PvuII genotype and cancer risk was detected among African (TT vs. CC: OR=0.54, 95% CI=0.30-0.98), and Hispanics (TT vs. CT: OR=0.41, 95% CI=0.17-0.99; T vs. C: OR=0.55, 95% CI=0.30-0.99). Such association was not observed for the Asians and Caucasians. In terms of source of controls, we found that the *ESR1* PvuII T genotype help to decrease cancer risk in hospital-based group (T vs. C: OR=0.89, 95% CI=0.83-0.96) and in population-based group (TT vs. CC: OR=0.81, 95% CI=0.70-0.94; TT vs. CT: OR=0.86, 95% CI=0.78-0.96). Further subgroup analysis by HWE in controls also failed to detect positive association, except for heterogenous model in HWE>0.05 subgroup (TT vs. CT: OR=0.94, 95% CI=0.88-1.00). Subgroup analysis of quality revealed that *ESR1* PvuII T genotype help to decrease cancer risk in group with quality score ≤9.

Heterogeneity and sensitivity analysis

Between-study heterogeneity was first calculated by using Q test and l^2 statistics. We used the random-effect model as significant heterogeneity was observed among all three genetic models (P<0.001) in the pooled analysis (TT vs. CC: P<0.001, I^2 = 59.1%; TT vs. CT: P<0.001, I^2 = 49.4%; T vs. C:

P<0.001, I² = 61.0%). In addition, sequential leave-one-out sensitivity analysis was adopted to evaluate the stability of the results. After removing each study, no substantial changes in pooled results were found (**Figure 3**).

Publication bias

The shape of Begg's funnel plots was quite symmetry (**Figure 4**). Moreover, statistical evidence of Egger's test also provided the none-existence of publication bias among the studies (data not shown).

Discussion

In this meta-analysis, we comprehensively evaluated the association between *ESR1* PvuII (rs2234693 T>C) polymorphism with cancer susceptibility. The obtained results suggested *ESR1* PvuII (rs2234693 T>C) polymorphism may influence overall cancer risk in a low impact effect manner. So far, this meta-analysis represents the most powerful investigation in elucidating the role of *ESR1* PvuII (rs2234693 T>C) in cancer risk.

The polymorphism of *ESR1*, PvuII (rs2234693 T>C), can affect *ESR1* transcription activity and further contribute to the carcinogenesis. A myriad of studies has investigated the role of *ESR1* PvuII (rs2234693 T>C) polymorphisms in cancer risk. In 2001, Massart et al. claimed that the PvuII and XbaI polymorphisms in the *ESR1* gene do not produce different risks of developing uterine leiomyomas [52]. In another study performed in urban Shanghai with 1069 breast cancer patients and 1166 controls, Cai et

found that ESR1 PvuII (rs2234693 T>C) al. polymorphism conferred to an enhanced risk of breast cancer among subjects carrying Pp (CT) and pp (TT) genotypes [21]. Yet, AI-Hendy et al. claimed that the ESR1PvuII PP (CC) genotype contributed to a significantly increased risk of uterine leiomyomas in black and white women, but not in Hispanic women [15]. Many meta-analyses have been conducted aiming to obtain a clear association between ESR1 PvuII (rs2234693 T>C) and cancer risk. In 2010, Li et performed a meta-analysis regarding the al. association of several potentially functional SNPs in ESR1 with breast cancer risk. This analysis on 10,300 breast cancer cases and 16,620 controls in PvuII (rs2234693 T>C) polymorphism revealed a borderline significant decreased breast cancer risk for CC and CC/CT carriers (CC vs. TT: OR=0.92, 95% TT: CI=0.86-0.99; CC/CT vs. OR=0.95, 95% CI=0.89-1.00) [84]. In a meta-analysis updated to April 2014, 41 studies were included to analyze the relationship between ESR1 PvuII (rs2234693 T>C) and cancer risk. Results of the pooled analysis suggested a null relationship between PvuII (rs2234693 T>C) polymorphism and overall cancer risk. Subgroup analysis indicated that PvuII (rs2234693 T>C) polymorphism was associated with a decreased risk of gallbladder cancer, in contrast with the increased risk of prostate cancer and hepatocellular carcinoma (HCC). They also failed to observe significant association in Asian and Caucasian populations [85].

Table 2. Meta-analysis of the association between ESR1 Pvull polymorphism and cancer risk

Variables	No. of studies	Homozygous		Heterozygous		Allele	
		TT vs. CC		TT vs. CT		T vs. C	
		OR (95% CI)	P het	OR (95% CI)	P het	OR (95% CI)	P het
All	80	0.92 (0.84-1.01)	< 0.001	0.94 (0.88-1.001)	< 0.001	0.95 (0.91-0.99)	< 0.001
Cancer type							
Breast	28	1.08 (0.98-1.19)	0.001	1.01 (0.94-1.08)	0.015	1.03 (0.99-1.08)	0.004
Prostate	26	0.79 (0.66-0.94)	< 0.001	0.89 (0.78-1.01)	0.006	0.89 (0.82-0.98)	< 0.001
Leiomyoma	11	0.72 (0.49-1.06)	0.016	0.83 (0.61-1.12)	0.003	0.82 (0.68-0.98)	0.006
HCC	3	0.45 (0.28-0.71)	0.353	0.63 (0.39-1.04)	0.191	0.67 (0.47-0.95)	0.145
Endometrial	3	0.73 (0.43-1.24)	0.067	0.73 (0.40-1.35)	0.005	0.84 (0.63-1.11)	0.046
Others	9	1.26 (0.85-1.90)	0.070	1.06 (0.88-1.40)	0.203	1.06 (0.88-1.28)	0.042
Ethnicity							
Asian	38	0.94 (0.80-1.10)	< 0.001	0.93 (0.84-1.04)	< 0.001	0.96 (0.89-1.03)	< 0.001
Caucasian	36	0.93 (0.83-1.04)	< 0.001	0.95 (0.88-1.04)	0.003	0.96 (0.90-1.01)	< 0.001
African	3	0.54 (0.30-0.98)	0.292	0.83 (0.52-1.32)	0.870	0.70 (0.49-1.001)	0.185
Hispanics	1	0.39 (0.11-1.34)	-	0.41 (0.17-0.99)	-	0.55 (0.30-0.99)	-
Non-Hispanic Caucasian	1	1.09 (0.81-1.47)	-	1.04 (0.81-1.34)	-	1.04 (0.90-1.21)	-
Hispanic Caucasian	1	1.18 (0.71-1.96)	-	1.08 (0.75-1.55)	-	1.08 (0.85-1.38)	-
Control source							
HB	44	1.02 (0.91-1.13)	< 0.001	0.99 (0.92-1.08)	0.009	0.89 (0.83-0.96)	< 0.001
PB	36	0.81 (0.70-0.94)	< 0.001	0.86 (0.78-0.96)	< 0.001	0.99 (0.95-1.05)	< 0.001
HWE							
>0.05	74	0.94 (0.86-1.02)	< 0.001	0.94 (0.88-1.00)	< 0.001	0.96 (0.92-1.001)	< 0.001
≤0.05	6	0.74 (0.33-1.67)	< 0.001	0.98 (0.80-1.21)	0.672	0.90 (0.70-1.14)	0.009
Quality score							
>9	17	1.07 (0.92-1.23)	0.386	1.04 (0.98-1.11)	0.327	1.03 (0.96-1.10)	< 0.001
≤9	63	0.86 (0.77-0.96)	0.008	0.88 (0.81-0.96)	< 0.001	0.92 (0.87-0.97)	< 0.001
Abbreviations: Het, heterogene	ity: HB, hospital based: F	B. population based.					

Masar (2001) Masar (2003) Masar (2003) Masar (2003) Salin (2003) Cal (200	0.79 (0.55, 1.13) 0.97 (0.69, 1.36) 1.91 (1.29, 2.83) 0.96 (0.73, 1.26) 0.87 (0.55, 1.37) 1.01 (0.76, 1.34) 0.99 (0.71, 1.36) 1.12 (0.99, 1.26) 0.97 (0.71, 1.34) 1.09 (0.98, 1.21) 1.10 (0.78, 1.55) 1.01 (0.85, 1.22) 1.19 (0.96, 1.49) 0.59 (0.40, 0.88) 0.41 (0.20, 0.82) 0.54 (0.30, 0.99) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.94, 1.28) 0.99 (0.83, 1.17) 0.99 (0.83, 1.21) 1.10 (0.94, 1.28) 0.97 (0.75, 1.26) 1.10 (1.00, 1.21) 1.06 (0.89, 1.26) 0.63 (0.42, 0.94) 1.22 (1.03, 1.45) 0.57 (0.54, 0.19)	0.95 1.03 0.85 1.30 0.68 1.25 1.08 2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
Namer (2001) Stank (2003) Stank (2003) Tanka (2003) Tanka (2003) Tanka (2003) Tanka (2004) Stank (2005) Matter (2005) Databater (2006) Hermander (2006) Barnander (2006) Barnander (2006) Stank (2007) Stater (2007)	$\begin{array}{c} 1.9, 1.0, 9, 1.36 \\ 1.91 (1.29, 2.83) \\ 0.96 (0.73, 1.26) \\ 0.87 (0.55, 1.37) \\ 1.01 (0.76, 1.34) \\ 0.99 (0.71, 1.36) \\ 1.12 (0.99, 1.26) \\ 0.97 (0.71, 1.34) \\ 1.09 (0.98, 1.21) \\ 1.10 (0.78, 1.55) \\ 1.01 (0.85, 1.22) \\ 1.19 (0.96, 1.49) \\ 0.59 (0.40, 0.88) \\ 0.41 (0.20, 0.82) \\ 0.59 (0.40, 0.88) \\ 0.41 (0.20, 0.82) \\ 0.59 (0.40, 0.88) \\ 0.41 (0.20, 0.82) \\ 0.59 (0.40, 0.88) \\ 0.41 (0.20, 0.82) \\ 0.59 (0.40, 0.88) \\ 0.41 (0.20, 0.82) \\ 0.59 (0.40, 0.88) \\ 0.41 (0.20, 0.82) \\ 0.59 (0.40, 0.88) \\ 0.41 (0.20, 0.82) \\ 0.59 (0.40, 0.88) \\ 0.41 (0.20, 0.82) \\ 0.59 (0.44, 0.59) \\ 0.59 (0.44, 0.59) \\ 0.59 (0.43, 0.99) \\ 0.70 (0.54, 0.91) \\ 1.02 (0.64, 1.60) \\ 1.03 (0.65, 1.42) \\ 0.99 (0.83, 1.17) \\ 0.49 (0.33, 0.74) \\ 0.88 (0.60, 1.28) \\ 1.00 (0.67, 1.48) \\ 0.97 (0.75, 1.26) \\ 1.10 (1.00, 1.21) \\ 1.06 (0.89, 1.26) \\ 1.05 (0.42, 0.94) \\ 1.22 (1.03, 1.45) \\ 0.56 (0.42, 0.94) \\ 1.22 (1.03, 1.45) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.42) \\ 0.56 (0.51) \\ 0.56 $	1.03 0.85 1.30 0.68 1.25 1.08 2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 0.84 1.36 2.36 1.89
<pre>ivach (200)</pre>	1.91 (1.29, 2.83) $0.96 (0.73, 1.26)$ $0.87 (0.55, 1.37)$ $1.01 (0.76, 1.34)$ $0.99 (0.71, 1.36)$ $1.12 (0.99, 1.26)$ $0.97 (0.71, 1.34)$ $1.09 (0.98, 1.21)$ $1.10 (0.78, 1.55)$ $1.01 (0.78, 1.55)$ $1.01 (0.78, 1.52)$ $1.19 (0.96, 1.49)$ $0.59 (0.40, 0.88)$ $0.41 (0.20, 0.82)$ $0.54 (0.30, 0.99)$ $0.70 (0.54, 0.91)$ $1.02 (0.64, 1.60)$ $1.03 (0.74, 1.45)$ $0.91 (0.87, 1.24)$ $0.99 (0.83, 1.19)$ $0.74 (0.47, 1.16)$ $1.10 (0.38, 1.42)$ $1.09 (0.84, 1.28)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.83, 1.17)$ $0.99 (0.84, 1.28)$ $0.97 (0.75, 1.24)$ $1.00 (0.67, 1.48)$ $0.97 (0.75, 1.26)$ $1.10 (1.00, 1.21)$ $1.06 (0.89, 1.26)$ $0.63 (0.42, 0.94)$ $1.22 (1.03, 1.45)$	0.85 1.30 0.68 1.25 1.08 2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.88 0.84 1.36 0.84 1.36 1.36 1.39
raard(203) imato(200) imato(203) imato($\begin{array}{c} 0.96 \ (0.73 \ 1.26) \\ 0.96 \ (0.73 \ 1.26) \\ 0.87 \ (0.55 \ 1.37) \\ 1.01 \ (0.76 \ 1.34) \\ 0.99 \ (0.71 \ 1.36) \\ 1.12 \ (0.99 \ 1.26) \\ 0.97 \ (0.71 \ 1.34) \\ 1.09 \ (0.98 \ 1.21) \\ 1.10 \ (0.78 \ 1.55) \\ 1.01 \ (0.85 \ 1.22) \\ 1.19 \ (0.96 \ 1.49) \\ 0.59 \ (0.40 \ 0.88) \\ 0.41 \ (0.20 \ 0.82) \\ 0.54 \ (0.30 \ 0.99) \\ 0.70 \ (0.54 \ 0.91) \\ 1.02 \ (0.54 \ 0.91) \\ 1.02 \ (0.54 \ 0.91) \\ 1.02 \ (0.54 \ 0.91) \\ 1.02 \ (0.54 \ 0.91) \\ 1.02 \ (0.54 \ 1.45) \\ 0.91 \ (0.65 \ 1.24) \\ 0.99 \ (0.83 \ 1.19) \\ 0.74 \ (0.47 \ 1.16) \\ 1.10 \ (0.86 \ 1.42) \\ 1.10 \ (0.94 \ 1.28) \\ 0.99 \ (0.83 \ 1.17) \\ 0.49 \ (0.33 \ 0.74) \\ 0.88 \ (0.60 \ 1.28) \\ 1.00 \ (0.67 \ 1.48) \\ 0.97 \ (0.75 \ 1.26) \\ 1.00 \ (0.67 \ 1.48) \\ 0.97 \ (0.75 \ 1.26) \\ 1.00 \ (0.67 \ 1.48) \\ 0.97 \ (0.75 \ 1.26) \\ 1.00 \ (0.67 \ 1.48) \\ 0.97 \ (0.75 \ 1.26) \\ 1.00 \ (0.67 \ 1.48) \\ 0.97 \ (0.75 \ 1.26) \\ 1.00 \ (0.67 \ 1.48) \\ 0.97 \ (0.75 \ 1.26) \\ 1.00 \ (0.67 \ 1.48) \\ 0.97 \ (0.75 \ 1.26) \\ 1.00 \ (0.67 \ 1.48) \\ 0.97 \ (0.75 \ 1.26) \\ 1.06 \ (0.48 \ 1.26) \\ 0.65 \ (0.42 \ 0.94) \\ 1.22 \ (1.33 \ 1.45) \\ 0.5 \ (0.42 \ 0.94) \\ 1.22 \ (1.33 \ 1.45) \\ 0.5 \ (0.41 \ 0.94) \\ 0.5 \ (0.41 \ 0.94) \\ 0.5 \ (0.41 \ 0.94) \\ 0.5 \ (0.41 \ 0.94) \\ 0.5 \ (0.42 \ 0.94) \\ 0.5 \ (0.42 \ 0.94) \\ 0.5 \ (0.5 \ 0.14) \\ 0.5 $	1.30 0.68 1.25 1.08 2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.34 0.75 0.34 0.75 0.34 0.75 0.34 0.75 0.34 0.75 0.34 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.88 0.88 0.84 1.36 2.36 1.89
amote (2003) in (2003) ada (2003) id (2003) (20090)	0.87 (0.55, 1.37) 1.01 (0.76, 1.34) 0.99 (0.71, 1.36) 1.12 (0.99, 1.26) 0.97 (0.71, 1.34) 1.09 (0.98, 1.21) 1.10 (0.78, 1.55) 1.01 (0.85, 1.22) 1.19 (0.96, 1.49) 0.59 (0.40, 0.88) 0.41 (0.20, 0.82) 0.54 (0.30, 0.99) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.96, 1.42) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.96, 1.42) 1.10 (0.96, 1.28) 0.99 (0.83, 1.17) 0.48 (0.60, 1.28) 1.00 (0.67, 1.24) 0.99 (0.83, 1.17) 0.48 (0.60, 1.28) 1.00 (0.67, 1.24) 0.97 (0.75, 1.26) 1.10 (1.00, 1.21) 1.06 (0.89, 1.26) 0.63 (0.42, 0.94) 1.22 (1.03, 1.45) 0.56 (0.42)	0.68 0.68 1.25 1.08 2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 1.86 0.69 1.41 1.80 0.80 0.88 0.84 1.36 0.84 1.36 1.36 1.39
aamou (ano) / in (2003) in	$\begin{array}{c} 0.87 \ (0.55, 1.37) \\ 1.01 \ (0.76, 1.34) \\ 0.99 \ (0.71, 1.36) \\ 1.12 \ (0.99, 1.26) \\ 0.97 \ (0.71, 1.34) \\ 1.09 \ (0.88, 1.21) \\ 1.10 \ (0.78, 1.55) \\ 1.10 \ (0.78, 1.55) \\ 1.01 \ (0.85, 1.22) \\ 1.91 \ (0.96, 1.49) \\ 0.59 \ (0.40, 0.88) \\ 0.41 \ (0.20, 0.82) \\ 0.59 \ (0.40, 0.88) \\ 0.41 \ (0.20, 0.82) \\ 0.54 \ (0.30, 0.99) \\ 0.70 \ (0.54, 0.91) \\ 1.02 \ (0.64, 1.60) \\ 1.03 \ (0.74, 1.45) \\ 0.91 \ (0.87, 1.24) \\ 0.99 \ (0.83, 1.19) \\ 0.74 \ (0.44, 1.66) \\ 1.01 \ (0.36, 1.42) \\ 1.10 \ (0.94, 1.28) \\ 0.99 \ (0.83, 1.17) \\ 0.49 \ (0.33, 0.74) \\ 0.88 \ (0.66, 1.28) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.42, 0.94) \\ 1.22 \ (1.33, 1.45) \\ 0.56 \ (0.42, 0.94) \\ 1.22 \ (1.33, 1.45) \\ 0.56 \ (0.44, 0.94) \\ 1.26 \ (1.68, 1.66) \\ 1.05 \ (0.42, 0.94) \\ 1.26 \ (1.68, 1.66) \\ 1.05 \ (0.42, 0.94) \\ 1.26 \ (1.68, 1.66) \\ 1.05 \ (0.42, 0.94) \\ 1.26 \ (1.68, 1.66) \\ 1.05 \ (0.42, 0.94) \\ 1.26 \ (1.68, 1.66) \\ 1.01 \ (0.56 \ 1.64) \\ 1.01 \ (0.56 \ 1.$	0.68 1.25 1.08 2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.34 0.75 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.88 0.88 0.84 1.36 2.36 1.89
hin (2003) ia (2003) ia (2003) ia (2003) ia (2005) hand-Marc (2005) ov (2006) i + Heary (2007) i + Heary (2007)	$\begin{array}{c} 1.01 \left(0.76, 1.34\right)\\ 0.99 \left(0.71, 1.36\right)\\ 1.12 \left(0.99, 1.26\right)\\ 0.97 \left(0.71, 1.34\right)\\ 1.09 \left(0.98, 1.21\right)\\ 1.10 \left(0.78, 1.55\right)\\ 1.11 \left(0.85, 1.22\right)\\ 1.19 \left(0.96, 1.49\right)\\ 0.59 \left(0.40, 0.88\right)\\ 0.41 \left(0.20, 0.82\right)\\ 0.41 \left(0.20, 0.82\right)\\ 0.54 \left(0.35, 0.83\right)\\ 0.70 \left(0.54, 0.91\right)\\ 1.02 \left(0.64, 1.60\right)\\ 1.03 \left(0.74, 1.45\right)\\ 0.91 \left(0.67, 1.24\right)\\ 0.99 \left(0.83, 1.19\right)\\ 0.74 \left(0.47, 1.16\right)\\ 1.10 \left(0.94, 1.28\right)\\ 0.99 \left(0.83, 1.17\right)\\ 0.49 \left(0.33, 0.74\right)\\ 0.88 \left(0.60, 1.28\right)\\ 1.00 \left(0.67, 1.48\right)\\ 0.97 \left(0.75, 1.26\right)\\ 1.10 \left(1.094, 1.28\right)\\ 1.06 \left(0.48, 1.26\right)\\ 1.56 \left(0.42, 0.94\right)\\ 1.22 \left(1.03, 1.45\right)\\ 0.56 \left(0.42, 0.94\right)\\ 1.25 \left(1.04, 1.45\right)\\ 0.56 \left(0.42, 0.94\right)\\ 1.25 \left(1.05, 1.45\right)\\ 0.56 \left(0.42, 0.94\right)\\ 1.25 \left(1.04, 1.45\right)\\ 0.56 \left(0.42, 0.94\right)\\ 1.56 \left(0.42, 0.94\right)\\ 1$	1.25 1.08 2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.34 0.75 0.34 0.75 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.38 1.41 1.82 1.41 1.82 1.38 1.39 1.39 1.39 1.39 1.39 1.39 1.39 1.39 1.39 1.39 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.36 1.38 1.36 1.36 1.38 1.36 1.38 1.36 1.38 1.36 1.38 1.36 1.38 1.36 1.38 1.36 1.89
<pre>index (2003)</pre>	0.99 (0.71, 1.36) 1.12 (0.99, 1.26) 0.97 (0.71, 1.34) 1.09 (0.98, 1.21) 1.10 (0.78, 1.55) 1.01 (0.85, 1.22) 1.19 (0.96, 1.49) 0.59 (0.40, 0.88) 0.41 (0.20, 0.82) 0.54 (0.30, 0.83) 0.54 (0.30, 0.99) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.94, 1.28) 0.99 (0.83, 1.17) 0.49 (0.33, 0.74) 0.88 (0.60, 1.28) 1.00 (0.67, 1.24) 0.97 (0.75, 1.26) 1.00 (0.67, 1.28) 0.97 (0.75, 1.26) 1.00 (1.00, 1.21) 1.06 (0.89, 1.26) 0.63 (0.42, 0.94) 1.22 (1.03, 1.45) 0.76 (0.51)	1.08 2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
ai (203) defer (204) it (205) halad-Maret (205) vo (206) H-Heady (2006) H-Heady (2006) H-Heady (2006) H-Heady (2006) exenching (2007) exenching (2007) exenching (2007) exenching (2007) adi yaka (2007) adi yaka (2007) adi yaka (2007) adi yaka (2007) adi yaka (2007) yaka (20	$\begin{array}{c} 1.12 \ (0.99, 1.26) \\ 0.97 \ (0.71, 1.34) \\ 1.09 \ (0.98, 1.21) \\ 1.10 \ (0.78, 1.55) \\ 1.01 \ (0.85, 1.22) \\ 1.91 \ (0.96, 1.49) \\ 0.59 \ (0.40, 0.88) \\ 0.41 \ (0.20, 0.82) \\ 0.54 \ (0.35, 0.83) \\ 0.54 \ (0.35, 0.83) \\ 0.54 \ (0.36, 0.99) \\ 0.70 \ (0.54, 0.91) \\ 1.02 \ (0.64, 0.91) \\ 1.02 \ (0.64, 0.91) \\ 1.02 \ (0.64, 0.91) \\ 1.02 \ (0.64, 1.60) \\ 1.03 \ (0.74, 1.45) \\ 0.91 \ (0.87, 1.24) \\ 0.99 \ (0.83, 1.19) \\ 0.74 \ (0.47, 1.16) \\ 1.10 \ (0.94, 1.28) \\ 0.99 \ (0.83, 1.17) \\ 0.49 \ (0.33, 0.74) \\ 0.88 \ (0.66, 1.28) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.64, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.63 \ (0.42, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.76 \ (0.56 \ 1.04) \\ \end{array}$	2.21 1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 0.88 0.84 1.36 1.36 1.36 1.36 1.39
aksts (2091) cdre(2004) cdre(2005) baland-Maret (2005) ow (2006) 1-Heady (2006) 1-Heady (2006) erandare (2007) ing (2007)	0.97 (0.71, 1.34) 1.09 (0.98, 1.21) 1.10 (0.78, 1.55) 1.01 (0.85, 1.22) 1.19 (0.96, 1.49) 0.59 (0.40, 0.88) 0.41 (0.20, 0.82) 0.54 (0.35, 0.83) 0.54 (0.35, 0.83) 0.54 (0.35, 0.83) 0.54 (0.35, 0.83) 0.54 (0.36, 0.99) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.91 (0.67, 1.24) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.84, 1.42) 1.10 (0.94, 1.28) 0.99 (0.83, 1.17) 0.49 (0.33, 0.74) 0.88 (0.40, 1.28) 1.00 (0.67, 1.48) 0.97 (0.75, 1.26) 1.00 (1.00, 1.21) 1.06 (0.89, 1.26) 0.63 (0.42, 0.94) 1.22 (1.03, 1.45)	1.11 2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
deric (2004) i (2005) i (2005) i lander - Meret (2005) i Hendry (2006) i - Hendry (2006) i - Hendry (2006) i - Hendry (2006) i encoldag (2007) i encoldag	$\begin{array}{c} 1.09 \ (0.38, 1.21) \\ 1.10 \ (0.78, 1.55) \\ 1.01 \ (0.85, 1.22) \\ 1.19 \ (0.36, 1.49) \\ 0.59 \ (0.40, 0.88) \\ 0.41 \ (0.20, 0.82) \\ 0.59 \ (0.40, 0.88) \\ 0.41 \ (0.20, 0.82) \\ 0.54 \ (0.30, 0.99) \\ 0.70 \ (0.54, 0.91) \\ 1.02 \ (0.64, 1.60) \\ 1.03 \ (0.74, 1.45) \\ 0.91 \ (0.87, 1.24) \\ 0.99 \ (0.83, 1.19) \\ 0.74 \ (0.47, 1.16) \\ 1.10 \ (0.34, 1.28) \\ 0.99 \ (0.83, 1.17) \\ 0.49 \ (0.33, 0.74) \\ 0.88 \ (0.60, 1.28) \\ 1.09 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.10 \ (1.04, 1.21) \\ 1.06 \ (0.48, 1.26) \\ 1.06 \ (0.42, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.56 \ (0.42, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.56 \ (0.42, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.56 \ (0.44) \\ 0.56 \ (0.45) \ (0.45) \\ 0.56 \ (0.45) \ (0.45) \\ 0.56 \ (0.45) \ (0.45) \\ 0.56 \ (0.45) \ (0.45) \ (0.56) \ (0.45) \\ 0.56 \ (0.45) \ (0.45) \ (0.56) \ (0.45) \ (0.56) \ (0.45) \ (0.56) \ (0.45) \ (0.56) \ (0.45) \ (0.56) \ (0.45) \ (0.56) \ (0.45) \ (0.56) \ (0.45) \ (0.56) \ (0.45) \ (0.56) \ (0.56) \ (0.45) \ (0.56) \ (0.56) \ (0.45) \ (0.56) \ ($	2.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
aud (1009) inder More (2005) sw (2006) i-Hendy (2006) i-Hendy (2006) i-Hendy (2006) i-at (2006) i-at (2006) i-at (2006) i-at (2007) i-at ($\begin{array}{c} 1.0 \ (0.78, 1.21) \\ 1.10 \ (0.78, 1.55) \\ 1.01 \ (0.85, 1.52) \\ 1.19 \ (0.96, 1.49) \\ 0.59 \ (0.40, 0.88) \\ 0.54 \ (0.30, 0.82) \\ 0.54 \ (0.30, 0.99) \\ 0.70 \ (0.54, 0.91) \\ 1.02 \ (0.54, 0.91) \\ 1.02 \ (0.54, 0.91) \\ 1.02 \ (0.54, 1.60) \\ 1.03 \ (0.74, 1.45) \\ 0.91 \ (0.67, 1.24) \\ 0.99 \ (0.83, 1.19) \\ 0.74 \ (0.47, 1.16) \\ 1.10 \ (0.84, 1.28) \\ 0.99 \ (0.83, 1.17) \\ 0.49 \ (0.33, 0.74) \\ 0.88 \ (0.50, 1.28) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.10 \ (1.00, 1.21) \\ 1.66 \ (0.48, 1.26) \\ 0.63 \ (0.42, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.76 \ (0.51 \ 0.48) \\ 1.26 \ (0.48, 1.26) \\ 0.65 \ (0.42, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.76 \ (0.51 \ 0.48) \\ 1.26 \ (1.04) \ (1.04) \\ 1.26 \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04) \ (1.04$	1.29 1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.88 0.88 0.84 1.36 2.36 1.89
lu (u00) hand-Marc (2005) wo (2006) l-Heady (2006) l-Heady (2006) wenching (2006) wenching (2006) mennadez (2006) mennadez (2006) mennadez (2006) mennadez (2006) mennadez (2006) mennadez (2007) mennadez (2007) mennade (2008) mennade (2009) mennade (2009)	$\begin{array}{c} 1.10 \ (0.8, 1.53) \\ 1.01 \ (0.85, 1.22) \\ 1.19 \ (0.96, 1.49) \\ 0.59 \ (0.40, 0.88) \\ 0.41 \ (0.20, 0.82) \\ 0.54 \ (0.35, 0.83) \\ 0.54 \ (0.35, 0.83) \\ 0.54 \ (0.35, 0.83) \\ 0.54 \ (0.35, 0.83) \\ 0.70 \ (0.54, 0.91) \\ 1.02 \ (0.64, 1.60) \\ 1.03 \ (0.74, 1.45) \\ 0.91 \ (0.67, 1.24) \\ 0.99 \ (0.83, 1.19) \\ 0.74 \ (0.47, 1.16) \\ 1.10 \ (0.86, 1.42) \\ 1.10 \ (0.94, 1.28) \\ 0.99 \ (0.83, 1.17) \\ 0.49 \ (0.33, 0.74) \\ 0.58 \ (0.40, 1.28) \\ 1.09 \ (0.67, 1.24) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (1.20, 1.21) \\ 1.06 \ (0.89, 1.22) \\ 1.06 \ (0.89, 1.26) \\ 0.63 \ (0.42, 0.94) \\ 1.22 \ (1.33, 1.45) \\ 0.76 \ (0.55 \ 1.04) \\ \end{array}$	1.01 1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
lodupin (2005) wic (2005) Heady (2006) Heady (2006) heady (2006) wenching (2006) wenching (2006) wenching (2006) wenching (2006) wenching (2007) wenching (2007) wenc	$\begin{array}{c} 1.01 \ (0.85, 1.22) \\ 1.19 \ (0.96, 1.49) \\ 0.59 \ (0.40, 0.88) \\ 0.41 \ (0.20, 0.82) \\ 0.54 \ (0.30, 0.99) \\ 0.70 \ (0.54, 0.91) \\ 1.02 \ (0.64, 1.60) \\ 1.03 \ (0.74, 1.45) \\ 0.91 \ (0.87, 1.24) \\ 0.99 \ (0.83, 1.19) \\ 0.74 \ (0.47, 1.16) \\ 1.10 \ (0.84, 1.28) \\ 0.99 \ (0.83, 1.17) \\ 0.49 \ (0.33, 0.74) \\ 0.88 \ (0.60, 1.28) \\ 1.09 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.49, 1.22) \\ 1.00 \ (0.49, 1.22) \\ 1.00 \ (0.49, 1.22) \\ 1.00 \ (0.49, 1.22) \\ 1.00 \ (0.49, 1.22) \\ 1.00 \ (0.49, 1.22) \\ 1.00 \ (0.49, 1.22) \\ 1.00 \ (0.49, 1.22) \\ 1.00 \ (0.49, 1.24) \\ 1.06 \ (0.49, 1.26) \\ 0.63 \ (0.42, 0.94) \\ 1.22 \ (1.33, 1.45) \\ 0.27 \ (0.51 \ 0.14) \\ 0$	1.82 1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
https://www.cit/colors/section/	$\begin{array}{c} 1.19 \left(0.96, 1.49 \right) \\ 0.59 \left(0.40, 0.88 \right) \\ 0.41 \left(0.20, 0.82 \right) \\ 0.54 \left(0.30, 0.99 \right) \\ 0.70 \left(0.54, 0.91 \right) \\ 1.02 \left(0.64, 1.60 \right) \\ 1.03 \left(0.74, 1.45 \right) \\ 0.99 \left(0.83, 1.19 \right) \\ 0.74 \left(0.47, 1.16 \right) \\ 1.10 \left(0.84, 1.22 \right) \\ 0.99 \left(0.83, 1.19 \right) \\ 0.74 \left(0.47, 1.16 \right) \\ 1.10 \left(0.94, 1.28 \right) \\ 0.99 \left(0.83, 1.17 \right) \\ 0.49 \left(0.33, 0.74 \right) \\ 0.88 \left(0.60, 1.28 \right) \\ 1.00 \left(0.67, 1.48 \right) \\ 0.97 \left(0.75, 1.26 \right) \\ 1.06 \left(0.88, 1.26 \right) \\ 1.10 \left(1.04, 1.21 \right) \\ 1.66 \left(0.88, 1.26 \right) \\ 0.63 \left(0.42, 0.94 \right) \\ 1.22 \left(1.03, 1.45 \right) \\ 0.76 \left(0.51 \left(1.04 \right) \\ 0.56 \left(0.42 \right) \\ 0.5$	1.60 0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.88 0.84 1.36 2.36 1.89
vow (2006) 1-Heady (2006) 1-Heady (2006) head (2006) exendable (2006) ermadable (2007) side (2007) side (2007) side (2007) jaergaard (2007) jaergaard (2007) jaergaard (2007) side (2008) obtic (2009) staski (2010) <td>0.59 (0.40, 0.88) 0.41 (0.20, 0.82) 0.54 (0.35, 0.83) 0.54 (0.35, 0.83) 0.54 (0.35, 0.83) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.86, 1.42) 1.10 (0.94, 1.28) 0.99 (0.83, 1.17) 0.99 (0.83, 1.17) 0.99 (0.33, 1.17) 0.49 (0.33, 0.74) 0.88 (0.60, 1.28) 1.00 (0.67, 1.48) 0.97 (0.75, 1.26) 1.10 (1.00, 1.21) 1.06 (0.89, 1.26) 0.63 (0.42, 0.94) 1.22 (1.03, 1.45) 0.76 (0.51)</td> <td>0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89</td>	0.59 (0.40, 0.88) 0.41 (0.20, 0.82) 0.54 (0.35, 0.83) 0.54 (0.35, 0.83) 0.54 (0.35, 0.83) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.86, 1.42) 1.10 (0.94, 1.28) 0.99 (0.83, 1.17) 0.99 (0.83, 1.17) 0.99 (0.33, 1.17) 0.49 (0.33, 0.74) 0.88 (0.60, 1.28) 1.00 (0.67, 1.48) 0.97 (0.75, 1.26) 1.10 (1.00, 1.21) 1.06 (0.89, 1.26) 0.63 (0.42, 0.94) 1.22 (1.03, 1.45) 0.76 (0.51)	0.85 0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
I-Heady (2006) I-Heady (2006) I-Heady (2006) watchlag (2006) emandate (2006) inigham (2007) algosta (2007) jaergard (2007) vaski (2009) vaski (2009) vaski (2009) vaski (2009) vaski (2009) jagle	0.41 (0.20, 0.82) 0.54 (0.35, 0.83) 0.54 (0.35, 0.83) 0.54 (0.36, 0.99) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.94, 1.28) 0.99 (0.83, 1.17) 0.49 (0.33, 0.74) 0.88 (0.66, 1.28) 1.00 (0.67, 1.48) 0.97 (0.75, 1.26) 1.00 (0.67, 1.48) 0.97 (0.75, 1.26) 1.10 (1.00, 1.21) 1.06 (0.89, 1.22) 1.06 (0.42, 0.94) 1.22 (1.03, 1.45) 0.76 (0.51 0.14)	0.34 0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
H-Heady (2006) H-Heady (2006) encaded (2006) encaded (2006) encaded (2006) encaded (2006) encaded (2006) with (2007) with (2007) sich (2008) sich (2008) sich (2008) sich (2009) sigle (2010) sigle (20	0.54 (0.35, 0.83) 0.54 (0.30, 0.99) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.91 (0.67, 1.24) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.86, 1.42) 1.10 (0.86, 1.42) 1.00 (0.86, 1.42) 1.00 (0.86, 1.28) 1.09 (0.83, 0.74) 0.88 (0.60, 1.28) 1.00 (0.67, 1.48) 0.97 (0.75, 1.26) 1.10 (1.00, 1.21) 1.06 (0.89, 1.22) 1.66 (0.42, 0.94) 1.22 (1.03, 1.45) 0.76 (0.51 (0.41)	0.75 0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
Theoly (2006) thi (2006) encode(2006) encode(2006) encode(2006) encode(2006) encode(2006) encode(2007) side (2007) side (2007) side (2007) side (2007) sigergand(2007) angostation sigergand(2007) sigergand(2008) unsigergand(2009) scalic (2009) scalic (2001)	0.54 (0.30, 0.99) 0.70 (0.54, 0.91) 1.02 (0.64, 1.60) 1.03 (0.74, 1.45) 0.91 (0.67, 1.24) 0.99 (0.83, 1.19) 0.74 (0.47, 1.16) 1.10 (0.86, 1.42) 1.10 (0.86, 1.42) 1.00 (0.88, 1.42) 1.00 (0.88, 1.42) 1.00 (0.67, 1.48) 0.97 (0.75, 1.26) 1.00 (0.67, 1.48) 0.97 (0.75, 1.26) 1.10 (1.00, 1.21) 1.06 (0.89, 1.22) 1.06 (0.49, 1.24) 1.22 (1.03, 1.45) 0.76 (0.51 (0.41)	0.45 1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
Table (2006) enclose() enclose() <tr< td=""><td>$\begin{array}{c} 0.70 \ (0.54, 0.91) \\ 0.70 \ (0.54, 0.91) \\ 1.02 \ (0.64, 1.60) \\ 1.03 \ (0.74, 1.45) \\ 0.91 \ (0.87, 1.24) \\ 0.99 \ (0.83, 1.19) \\ 0.74 \ (0.47, 1.16) \\ 1.10 \ (0.94, 1.28) \\ 0.99 \ (0.83, 1.17) \\ 0.49 \ (0.33, 0.74) \\ 0.88 \ (0.60, 1.28) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.10 \ (1.00, 1.21) \\ 1.66 \ (0.89, 1.22) \\ 1.66 \ (0.42, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.27 \ (1.03, 1$</td><td>1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89</td></tr<>	$\begin{array}{c} 0.70 \ (0.54, 0.91) \\ 0.70 \ (0.54, 0.91) \\ 1.02 \ (0.64, 1.60) \\ 1.03 \ (0.74, 1.45) \\ 0.91 \ (0.87, 1.24) \\ 0.99 \ (0.83, 1.19) \\ 0.74 \ (0.47, 1.16) \\ 1.10 \ (0.94, 1.28) \\ 0.99 \ (0.83, 1.17) \\ 0.49 \ (0.33, 0.74) \\ 0.88 \ (0.60, 1.28) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.00 \ (0.67, 1.48) \\ 0.97 \ (0.75, 1.26) \\ 1.10 \ (1.00, 1.21) \\ 1.66 \ (0.89, 1.22) \\ 1.66 \ (0.42, 0.94) \\ 1.22 \ (1.03, 1.45) \\ 0.27 \ (1.03, 1$	1.38 0.68 1.03 1.14 1.86 0.69 1.41 2.00 1.90 0.80 0.88 0.84 1.36 2.36 1.89
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ang (2011)	1.15 (0.78, 1.71)	0.84
issung (2011)	0.63 (0.44, 0.89)	0.98
e Giorgi (2011)	0.87 (0.63, 1.21)	1.06
alistreri (2011)	0.23 (0.09, 0.58)	0.20
an (2011)	1.21 (1.05, 1.39)	2.11
	0.02 (0.66 1.20)	1.04
	0.95 (0.00, 1.29)	1.04
(2012)	0.99 (0.83, 1.18)	1.87
rivastava (2012)	1.37 (1.08, 1.74)	1.47
afarinejad (2012)	0.65 (0.49, 0.86)	1.30
hang (2012)	1.28 (0.89, 1.83)	0.95
ang (2013)	0.95 (0.82, 1.09)	2.09
resetura (2013)	0.77 (0.61, 0.09)	1 51
	0.77 (0.01, 0.98)	1.51
Izarbasi (2013)	1.62 (0.78, 3.33)	0.32
amalhinho (2013)	0.73 (0.50, 1.05)	0.90
iu (2014)	0.51 (0.34, 0.76)	0.81
hattopadhyay (2014)	1.30 (1.05, 1.61)	1.62
a (2014)	1.07 (0.92 1.25)	2.00
	0.56 (0.25, 0.01)	2.00
Jacera (2014)	0.56 (0.35, 0.91)	0.63
aghizade (2014)	0.88 (0.67, 1.17)	1.28
ao (2014)	1.02 (0.79, 1.31)	1.38
a (2015)	0.94 (0.77, 1.16)	1.65
vante (2015)	0.97 (0.89, 1.06)	2.39
	0.83 (0.64, 1.09)	1.26
	0.05 (0.04, 1.06)	1.30
verant (1-squared = 01.070, p = 0.000)		100.00
OTF: Weights are from random effects analysis	0.95 (0.91, 1.00)	

Figure 2. Forest plot for the overall cancer susceptibility associated with the *ESR1* Pvull (T>C) polymorphism under allele comparison model. Notes: The horizontal lines represent the study-specific ORs and 95% Cls, respectively. The diamond represents the pooled results of OR and 95% Cl.



Figure 3. Sensitivity analysis of the association between ESR1 Pvull (T>C) polymorphism and cancer susceptibility. Each point represents the recalculated OR after deleting a separate study.



Figure 4. Funnel plot analysis to detect publication bias for ESR1 Pvull (T>C) polymorphism under allele comparison model. Notes: Each point represents a separate study for the indicated association.

From then on, several new case-control studies with larger samples were available. In addition, the former meta-analysis conducted only included studies published in English. To provide a robust clarification, we performed the updated meta-analysis by involving all the eligible studies published. Overall, statistically significant relationship was only observed for PvuII in allele model T vs. C (OR=0.95, 95% CI=0.91-0.99). However, we did not detect any significant relationship between *ESR1* PvuII

(rs2234693 T>C) polymorphism and cancer risk in the pooled analysis under homozygous and heterozygous model. Cancer type by subgroup analysis indicated that T genotype significantly decreased prostate cancer risk, Leiomyoma risk, and HCC risk. Yet no association was observed in other types of cancers. These data suggested that the PvuII (rs2234693 T>C) polymorphism on ESR1 may function in a wide manner regarding the different cancer types. When stratified by population, no significant association between ESR1 PvuII genotype and cancer risk among African, and Hispanics was detected. Such association was observed for the Africans. The limited statistical power caused by relatively small number of studies in Africans should be considered. In this meta-analysis, several measurements were performed to enhance the credibility of our conclusion. First, we adopted every effort to expand numbers of included studies, such the incorporating all publications written both in Chinese and in English. The relatively large number of including studies was one of the important merits of the current study. We also performed publication bias and the sensitivity analysis under the guidance of Cochrane protocol. The sensitivity analysis and publication bias analysis revealed the strength of our conclusions. Although this meta-analysis has its own merits, limitations still exist. First, we only used unadjusted estimates to determine whether there is a relationship between ESR1 PvuII (rs2234693 T>C) polymorphism and cancer risk. Adjustment analysis was absence due to the lack of patient's clinical data such as life habit, smoking and drinking status, exposing factors, and gene-environment interactions, which restrains our further analysis for confounding factors. Second, the validity of conclusion was impaired as significant between-study heterogeneity was detected in some comparisons. Such heterogeneity might result from different quality of studies, and might impair the strength of the conclusion. Third, selection bias and language bias were inevitable, as only published studies and papers written in English or Chinese were analyzed, respectively. Moreover, selection bias might also generate as most of the studies included in this meta-analysis were from candidate gene based, but not from GWAS. Fourth, the sample size of subgroup analysis was relatively small in some strata, impaired the statistical power to estimate the real association. Last, the analyzed case-control studies were mostly performed using Caucasians and Asians populations. Therefore, more trials using different population background, especially Africans, are essential to further confirm such conclusion, due to the genetic and geographical differences.

Conclusion

In conclusion, the current meta-analysis suggests that *ESR1* PvuII (rs2234693 T>C) polymorphism may not be strong enough to impact the risk of cancer, based on the pooled results of the published articles. Such relationship further helps to explain the etiology of cancer. Yet, further epidemiological studies with larger sample sizes, standardized unbiased design are warranted to confirm this conclusion.

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Competing Interests

The authors have declared that no competing interest exists.

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