Meta-analysis on vitamin D receptor and cancer risk: focus on the role of TaqI, ApaI, and Cdx2 polymorphisms

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Vitamin D plays a significant role in our health, including cancer incidence and mortality. Vitamin D receptor (VDR) single-nucleotide polymorphisms (SNPs) may affect its activity, influencing the risk of cancer. Several studies have investigated VDR SNPs, but the association with the risk of cancer is controversial. Here, we present a meta-analysis to assess the association of *TaqI*, *ApaI*, and *Cdx2* SNPs with the risk of cancer. A systematic literature search was performed following a predefined protocol and using validated search strategies. This meta-analysis shows the summary odd ratio (SOR) overall, by cancer sites and by ethnicity. Up to January 2014, we identified 73 independent studies with 35 525 cases and 38 675 controls. The meta-analysis of *Cdx2 gg* versus *GG* showed a significant 12% increased risk for all cancers [SOR = 1.12; 95% confidence interval (CI): 1.00–1.25]. The other SNPs analyzed did not show an overall significant association with the risk of cancer: SOR = 0.98 (95% CI: 0.90–1.07) and 1.06 (95% CI: 0.95–1.19) for *TaqI tt* versus *TT* and *ApaI aa* versus *AA*, respectively. *TaqI* shows a significant 43% increased risk for colorectal cancer (SOR = 1.43; 95% CI: 1.30–1.58 for *tt* vs. *TT*). Strong frequency variations are present among different ethnic groups. This meta-analysis showed an overall increased risk of cancer associated with *Cdx2 SNP* and a specific higher risk of colorectal cancer associated with the *TaqI* polymorphism. The VDR genotype might become more relevant when clustered in a specific haplotype, associated with other SNPs of genes involved in vitamin D metabolism, or for specific tumors and/or patient characteristics. *European Journal of Cancer Prevention* **25:85–96**

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Introduction

Vitamin D comes from two sources: endogenous, which is produced in the skin on exposure to sunlight, and exogenous, to a minor extent, which is ingested in food. Vitamin D is transported by vitamin D-binding protein (GC) and hydroxylated in the liver into 25-hydroxyvitamin D [25(OH)D], the more stable circulating metabolite. 25(OH)D is further hydroxylated into 1,25-dihydroxyvitamin D [1,25(OH)2D] in the kidney. This is the biologically active metabolite that binds to nuclear vitamin D receptors (VDR). VDR is expressed in bone, intestine, and in many other tissues and cells including cancer cells.

So far, vitamin D has mainly been studied for its role in the maintenance of calcium and phosphate homeostasis, and bone health. However, it is also involved in a wide range of other health issues, cardiovascular diseases, metabolic disorders, allergy, and cancer (Deeb *et al.*, 2007; Liu *et al.*, 2008; Minambres *et al.*, 2012). Numerous in-vitro studies have indicated that 1,25(OH)2D can inhibit cell proliferation and promote cell differentiation in tumor tissue, suggesting that vitamin D may be protective against cancer (Deeb *et al.*, 2007). Concomitantly, epidemiological studies have shown an inverse relationship between the incidence of cancer, mortality, and plasma levels of vitamin D (Autier and Gandini, 2007; Gandini *et al.*, 2011).

Vitamin D activity is mediated by its receptor (VDR). The VDR is a type II nuclear receptor that interacts with the promoters of vitamin-D-responsive genes. VDR is found bound to DNA in the presence of corepressors; when 1,25(OH)2D binds to the VDR, it triggers a series of conformational changes including the release of corepressors and the recruitment of coactivators (Strugnell and DeLuca, 1997). VDR is differentially expressed in many types of cancer including breast, cervix, ovary, and many others (Friedrich *et al.*, 2003). Its expression, together with the enzyme involved in vitamin D hydroxylation, suggests a paracrine/autocrine vitamin D metabolism at cancer sites.

Several VDR single-nucleotide polymorphisms (SNPs) have been identified that may deregulate vitamin D activity, interfering with its role in the risk of cancer (Uitterlinden *et al.*, 2004; Kostner *et al.*, 2009).

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Our previous meta-analysis (Gnagnarella *et al.*, 2014; Raimondi *et al.*, 2014) suggested that the most studied SNPs, *FokI* (rs2228570) and *BsmI* (rs1544410), can determine risk factors for cancer. More recently, other SNPs have been investigated: *TaqI* (rs731236), *ApaI* (rs7975232), and *Cdx2* (rs11568820). *TaqI* and *ApaI* polymorphisms, located near the 3′-UTR of the VDR gene, do not alter the protein's amino acid sequence, and it remains difficult to explain how these variants might influence VDR function. However, even if they do not have a direct action, they can be in linkage with other gene polymorphisms and act as markers (Kostner *et al.*, 2009) of other sequences in the VDR gene that regulate transcription, translation, or RNA processing (Durrin *et al.*, 1999; Whitfield *et al.*, 2001). *Cdx2*, located in the 5′ region of the VDR, has been suggested to modulate promoter activity, and the *Cdx2 g* allele showed 30% less transcriptional activity compared with the *a* allele (Arai *et al.*, 2001). To clarify the possible role of *TaqI*, *ApaI*, and *Cdx2* VDR polymorphisms in the risk of cancer, we carried out a comprehensive literature search and meta-analysis of published studies. We calculated risk estimates for each specific SNP for any cancer and for specific organs, and we examined extensively estimate inconsistencies, variability, and between-study heterogeneity.

Methods

A systematic literature search and quantitative analysis were planned, carried out, and reported following MOOSE guidelines on the meta-analysis of observational studies (Stroup *et al.*, 2000).

Published reports were obtained from the following databases using validated search strategies: PUBMED, Ovid Medline, EMBASE, and ISI Web of Knowledge up to January 2014. We used the MeSH index terms 'VDR', 'Vitamin D receptor', or '*TaqI*', '*ApaI*,' and '*Cdx2*' in combination with 'cancer' or 'tumor'. We also performed manual searches of references cited in the retrieved articles and preceding reviews on the topic. Ecological studies, case reports, reviews, and editorials were not considered eligible. We screened titles, looked at abstracts and, if the abstract content was relevant, full copies of articles were retrieved and read by at least two coauthors.

We selected studies reporting the minimum information on relative risks necessary to carry out an adequate meta-analysis:

(1) Sufficient information to estimate the relative risk and 95% confidence intervals (95% CI) for the association between *TaqI*, *ApaI*, or *Cdx2* polymorphisms and cancer [odds ratios (OR), relative risks or crude data and corresponding SEs, variance, CIs, or *P*-value of the significance of the estimates].

(2) Studies had to be independent and not duplicate results published in another article. When some articles studied the same population, results from the publication using the largest sample of patients were used.

A standardized data-collection protocol was used to gather the relevant data from each selected article. When data were reported by ethnicity or by cancer sites, the estimates were extracted separately for the two factors.

We excluded studies evaluating the risk of colorectal adenoma and benign prostatic hyperplasia as our endpoint was the risk of cancer and we included studies with disease-free controls.

When possible, we considered fully adjusted estimates of the association between VDR polymorphisms and cancer, both for heterozygous and minor allele homozygous patients compared with wild-type patients.

Data extraction was carried out by one coauthor in a predefined database and then revised by a second coauthor. For each study selected for this meta-analysis, we extracted information on authors, journal and year of publication, country, ethnicity of the study population, source of controls (hospital or population), number of cases and controls, risk estimates, and the corresponding CI along with variables adjusted for in the analysis.

Statistical analysis

The summary odds ratios (SORs) for heterozygous carriers and homozygous mutant carriers compared with wild-type patients were calculated. As cancer is a relatively rare disease, we ignored the distinction between the various estimates of relative risk (i.e. OR, rate ratio, risk ratio) and all measures were interpreted as relative risk. Every measure of association, and corresponding CIs, was transformed into log relative risks, and the corresponding variance was calculated using the formula proposed by Greenland (1987). When no estimates were given, crude estimates were calculated from tabular data. We used Woolf's formula to evaluate the SE of the log relative risk.

The SOR was estimated by pooling the study-specific estimates with random-effects models as described by Van Houwelingen *et al.* (2002), with summary effect size obtained from maximum likelihood estimation. CIs were computed assuming an underlying *t*-distribution.

The measure of heterogeneity I^2 has been considered to compare heterogeneities for different numbers of pooled studies. It can be interpreted as the percentage of total variation across several studies that is attributable to heterogeneity: larger values of I^2 indicate greater heterogeneity. A threshold of I^2 below 50% is generally considered an acceptable level of variability (Higgins and Thompson, 2002).

We presented SORs overall and separately for each cancer site (for which at least three papers were found unless differentially indicated), and stratified by ethnicity (White and other than White); moreover, we produced forest plots including the single studies and the SOR.

To assess the influence of possible sources of bias, we considered the STROBE checklist proposed for observational epidemiologic studies (Von Elm *et al.*, 2008). According to the STROBE checklist, using metaregression, we evaluated between-study heterogeneity assessing the influence of different study features, such as the study population and study design. We also examined changes in results after exclusion of specific studies to evaluate the stability of the pooled estimates. Metaregressions and subgroup analyses were carried out to quantify between-study heterogeneity (Greenland, 1987). Heterogeneity was investigated by examining possible factors that could influence the estimates: ethnicity, source of SNP determination (blood vs. tissue), type of controls, race, adjustment for confounding factors, etc.

Furthermore, deviations from the Hardy–Weinberg (H–W) equilibrium for frequency of VDR genotypes of *TaqI*, *ApaI*, and *Cdx2* polymorphisms in controls were assessed using the χ^2-test.

Publication bias was evaluated graphically with a funnel plot and we carried out the Macaskill test (Macaskill *et al.*, 2001), which is more powerful than the Egger test when fewer than 20 estimates are included in the analysis.

All the statistical analyses were carried out using SAS software (version 9.2; SAS Institute Inc., Cary, North Carolina, USA).

Results

In this meta-analysis, we investigated the associations between the VDR gene polymorphisms *TaqI*, *ApaI*, and *Cdx2* and the risk of cancer. Seventy-three independent studies were identified. Some of them reported different estimates within the same manuscript (Table 1). Information on allele frequencies for each SNP, deviation from H–W equilibrium, and information on adjusting variables are presented in Supplementary Table 1. In Table 2, the SORs are reported, overall, by cancer site (prostate, breast, colorectal, skin, and ovary, and all the remaining organs grouped in 'other sites') and by ethnic groups, separately for *TaqI*, *ApaI*, and *Cdx2*. Estimates of between-study heterogeneity are also reported.

TaqI

The role of *TaqI* polymorphism in the risk of cancer was investigated in 64 studies (Table 1). A total of 24 439 cases and 26 406 controls were included. Seventeen studies published results on the associations with prostate cancer, 11 with breast cancer, eight with colorectal, six with skin cancer, three with ovarian cancer, and 17 with other cancer sites. Overall, no significant association with the risk of cancer was observed for all cancer sites SOR = 0.98 (95% CI: 0.9–1.07) and 1.04 (95% CI: 0.94–1.16) for *tt* and *Tt* versus the *TT* genotype, respectively (Table 2 and Fig. 1 and Supplementary Figure 1), and no major differences have been observed as stratified by ethnicity (White vs. other than White). The *TaqI tt* genotype has shown an increased risk for colorectal cancer, SOR 1.43 (95% CI: 1.30–1.58); the data lose significance in Caucasians [SOR = 1.21 (95% CI: 0.89–1.64)]. An opposite trend was found in ovarian cancer, with an 18% risk reduction for the *Tt* genotype [SOR = 0.82 (95% CI: 0.72–0.93], but with a large heterogeneity between study estimates ($I^2 = 83\%$), probably related to the inclusion in this analysis of different ethnic groups. Indeed, the calculated SOR for Caucasians was in the opposite direction, suggesting a possible risk reduction only for patients other than Caucasians (data not shown). A similar risk reduction was also observed for other cancer groups [SOR 0.88 (95% CI: 0.78–1.00].

The range of allele frequencies is relatively broad among the controls, the allele frequency ranging from 4 to 48%. Interestingly, in Asian populations, the *t* allele appears to be quite rare (Supplementary Table 1), and several studies from an Asian cohort do not have homozygote *tt* carriers, but only patients with the *tT* genotype. In five studies, a significant departure from H–W equilibrium was observed (Supplementary Table 1).

ApaI

The role of *ApaI* polymorphism in the risk of cancer has been investigated for a total of 12 542 cases and 13 574 controls (Table 1). The allele frequencies range from 23 to 70% for the *a* allele (Supplementary Table 1). In seven studies, a significant departure from H–W equilibrium was observed (Supplementary Table 1).

No significant association with the risk of cancer has been observed for any cancer site: SORs were 1.06 (95% CI: 0.95–1.19) and 1.06 (95% CI: 0.96–1.18) for *aa* and *Aa* versus the *AA* genotype, respectively (Table 2, Fig. 2 and Supplementary Figure 2).

Cdx2

A total of 25 studies (17 425 cases and 21 384 controls) were analyzed for the association between the *Cdx2* polymorphism and the risk of cancer. *Cdx2* showed a modest but significant association with all cancer sites: SOR was 1.12 (95% CI: 1.00–1.25) and 1.03 (95% CI: 0.96–1.10) for *gg* and *Gg* versus the *GG* genotype, respectively, with acceptable between-study heterogeneity ($I^2 \leq 22\%$). Even if they do not reach statistical significance similar to the *TaqI* polymorphism, the non-Caucasians might predominantly contribute to the cancer risk association SOR 1.40 (95% CI: 0.89–2.19) (Table 2, Fig. 3 and Supplementary Figure 3).

Table 1 Characteristics of the studies included in the meta-analysys on the association between VDR *TaqI*, *ApaI*, and *Cdx2* polymorphism and different types of cancer

Cancer site	References	Country	Ethnicity	Hospital controls	Number of cases	Number of controls	*TaqI*	*ApaI*	*Cdx2*
Prostate	Ma *et al.* (1998)	USA	White	No	372	591	X		
	Correa-Cerro *et al.* (1999)	France	White	No	105	132	X		
	Blazer *et al.* (2000)	USA	White	No	70	179	X		
	Blazer *et al.* (2000)	USA	A-A	No	7	14	X		
	Habuchi *et al.* (2000)	Japan	Asian	Yes	222	128	X	X	
	Medeiros *et al.* (2002)	Portugal	White	Yes	162	206	X		
	Suzuki *et al.* (2003)	Japan	Asian	Yes	81	105	X	X	
	Huang *et al.* (2004)	Taiwan	Asian	Yes	103	106	X	X	
	Oakley-Girvan *et al.* (2004)	USA	White	No	232	171	X	X	
	Oakley-Girvan *et al.* (2004)	USA	A-A	No	113	121	X	X	
	Maistro *et al.* (2004)	Brazil	Mix	No	165	200	X	X	
	John *et al.* (2005)	USA	White	No	425	437	X		X
	Andersson *et al.* (2006)	Sweden	White	Yes	137	176	X		
	Chaimuangraj *et al.* (2006)	Thailand	Asian	Yes	28	30	X	X	
	Cicek *et al.* (2006)	USA	White	No	439	479	X	X	X
	Holick *et al.* (2007)	USA	White	No	630	565	X		
	Mikhak *et al.* (2007)	USA	White	No	684	684			X
	Onen *et al.* (2008)	Turkey	White	Yes	133	157	X	X	
	Torkko *et al.* (2008)	USA	White	No	444	488			X
	Torkko *et al.* (2008)	USA	Hispanic	No	141	273			X
	Bai *et al.* (2009)	China	Asian	No	122	130	X	X	
	Holt *et al.* (2009)	USA	White	No	705	716	X		
	Rowland *et al.* (2012)	USA	A-A	No	533	250			X
Total studies ($n=20$)					6053	6338			
Breast	Curran *et al.* (1999)	Australia	White	Yes	135	110	X	X	
	Dunning *et al.* (1999)	UK	White	No	508	426	X		
	Hou *et al.* (2002)	Taiwan	Asian	Yes	34	169	X	X	
	Buyru *et al.* (2003)	Turkey	White	NA	78	27	X		
	Sillanpaa *et al.* (2004)	Sweden	White	No	483	482	X	X	
	Barroso *et al.* (2008)	Spain	White	Mix	549	556	X		
	Abbas *et al.* (2008)	Germany	White	No	1408	2612	X		X
	Chakraborty *et al.* (2009)	India	Asian	Yes	160	140	X	X	
	Anderson *et al.* (2011)	Canada	White	No	1546	1627	X	X	X
	Dalessandri *et al.* (2012)	USA	White	No	164	174		X	
	Engel *et al.* (2012)	USA	White	No	269	552	X	X	
	Yao *et al.* (2012)	USA	White	No	381	382			X
	Yao *et al.* (2012)	USA	A-A	No	547	461			X
	Mishra *et al.* (2013)	USA	A-A	Yes	115	73	X	X	
	Mishra *et al.* (2013)	USA	Hispanic	Yes	117	276	X	X	
Total studies ($n=13$)					6394	8067			
CRC	Park *et al.* (2006)	Korea	Asian	No	190	318	X	X	
	Flugge *et al.* (2007)	Russia	White	Yes	256	256	X	X	X
	Yaylim-Eraltan *et al.* (2007)	Turkey	White	Yes	26	52	X		
	Ochs-Balcom *et al.* (2008)	USA	White	No	250	246	X		X
	Theodoratou *et al.* (2008)	UK	White	No	3005	3072		X	X
	Slattery *et al.* (2009)	USA	White	No	2313	2902			X
	Mahmoudi *et al.* (2010)	Iran	Asian	Yes	452	452	X	X	
	Hughes *et al.* (2011)	Czech Republic	White	Yes	717	615	X	X	
	Bentley *et al.* (2012)	New Zealand	White	No	199	191	X		X
	Gunduz *et al.* (2012)	Turkey	White	Yes	43	42	X		
Total studies ($n=10$)					7451	8146			
Skin	Hutchinson *et al.* (2000)	UK	White	Yes	316	108	X		
	Han *et al.* (2007)	USA	White	No	215	854			X
	Han *et al.* (2007) (BCC)	USA	White	No	285	854			X
	Han *et al.* (2007) (SCC)	USA	White	No	278	854			X
	Li *et al.* (2008)	USA	White	Yes	805	841	X		
	Gapska *et al.* (2009)	Poland	White	No	725	765	X		
	Randerson-Moor *et al.* (2009)[a]	UK	White	No	1028	402	X	X	X
	Randerson-Moor *et al.* (2009)[b]	UK	White	No	299	560	X	X	X
	Pena-Chilet *et al.* (2013)	Spain	White	Mix	530	314	X		
	Lesiak *et al.* (2011)	Poland	White	Yes	142	142	X	X	
	Kostner *et al.* (2012)	Germany	White	Yes	82	51	X	X	
Total studies ($n=8$)					4705	4037			
Ovary	Lurie *et al.* (2007)	Mix	White	Yes	71	144s	X	X	X
	Lurie *et al.* (2007)	Mix	Asian	No	93	172	X	X	X
	Clendenen *et al.* (2008)	Mix	White	No	170	323	X	X	
	Tworoger *et al.* (2009)	USA	Mix	Yes	1392	1893			X
	Grant *et al.* (2013)	USA	White	No	513	532	X	X	
	Grant *et al.* (2013)	USA	A-A	No	74	79	X	X	
Total studies ($n=4$)					2313	3143			
Other sites									
Bone	Ruza *et al.* (2003)	Spain	White	No	125	143	X	X	
Brain	Anic *et al.* (2012)	USA	White	No	564	605	X		X
Brain	Toptas *et al.* (2013)	Turkey	White	Yes	100	122	X		

Table 1 (*continued*)

Cancer site	References	Country	Ethnicity	Hospital controls	Number of cases	Number of controls	*TaqI*	*ApaI*	*Cdx2*
EAC	Chang *et al.* (2012)	Ireland	White	No	202	234	X	X	
ESCC	Li *et al.* (2008)	China	Asian	Yes	126	169	X		
ESCC	Gu *et al.* (2014)	China	Asian	Yes	629	686			X
HCC	Falleti *et al.* (2010)	Italy	White	No	80	160	X	X	
Male breast	Kizildag *et al.* (2011)	Turkey	White	Yes	25	96	X	X	
Myeloma	Shafia *et al.* (2013)	India	Asian	Yes	75	150		X	
NHL	Smedby *et al.* (2011)	Sweden	White	No	2303	1789	X		
NHL	Purdue *et al.* (2007)	USA	Mixed	No	2025	1751	X		
OSCC	Bektas-Kayhan *et al.* (2010)	Turkey	White	No	64	87	X		
OSCC	Zeljic *et al.* (2012)	Serbia	White	No	110	122	X	X	
HNC	Liu *et al.* (2005)	USA	White	No	719	821	X		
RCC	Karami *et al.* (2008)	Europe	White	Yes	925	1192	X		
RCC	Obara *et al.* (2007)	Japan	Asian	No	135	150	X		
TC	Penna-Martinez *et al.* (2009)	Germany	White	Yes	172	321	X	X	
Bladder	Mittal *et al.* (2007)	India	Asian	NS	130	346	X		
Total studies ($n=18$)					8509	8944			

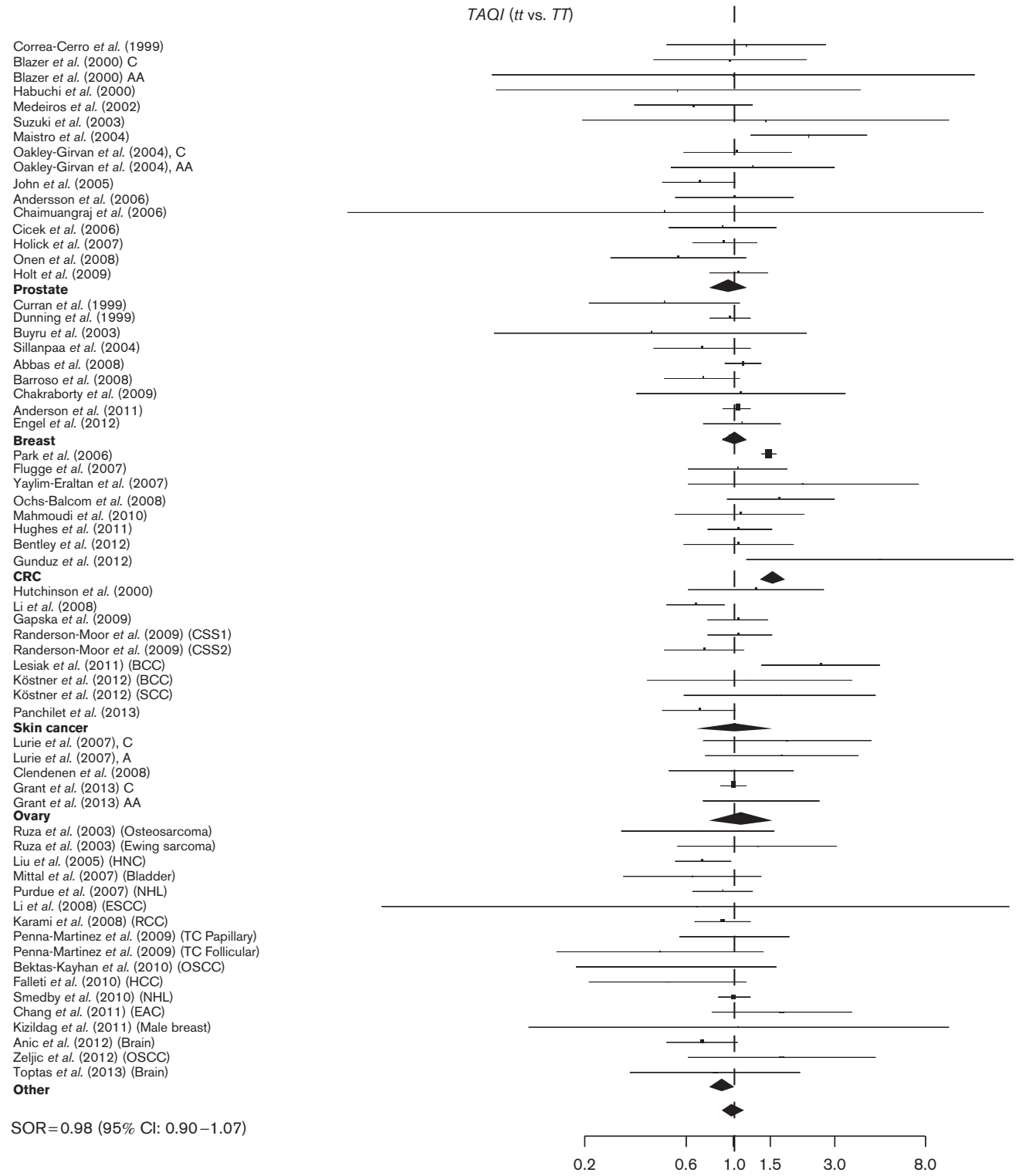
TaqI or rs731236; *ApaI* or rs7975232; *Cdx2* or rs1156882.
A-A, African-American; BCC, basal cell carcinoma; CRC, colorectal cancer; EAC, esophageal adenocarcinoma; HCC, hepatocellular carcinoma; HNC, head and neck cancer; NA, not available; NHL, non-Hodgkin lymphoma; OSCC, oral squamous cell carcinoma; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; TC, thyroid carcinoma; VDR, vitamin D receptor.
[a]The first Leeds case–control series (Leeds CCS1).
[b]The second Leeds case series (Leeds CCS2).

Table 2 Overall summary odds ratios for the association of VDR *TaqI*, *ApaI*, and *Cdx2* polymorphism with different types of cancer and ethnicity

VDR	Cancer	Number of studies	Comparison	All patients SOR (95% CI)	I^2 (%)	Caucasians SOR (95% CI)	Other than Caucasians SOR (95% CI)
TaqI	Prostate	17	*tt* vs. *TT*	0.94 (0.78–1.12)	3	0.92 (0.76–1.12)	0.98 (0.54–1.79)
			Tt vs. *TT*	0.95 (0.80–1.12)	51	0.91 (0.72–1.13)	1.04 (0.79–1.36)
	Breast	11	*tt* vs. *TT*	1.00 (0.89–1.12)	20	1.00 (0.88–1.13)	[a]
			Tt vs. *TT*	1.00 (0.89–1.11)	34	0.99 (0.88–1.12)	1.08 (0.44–2.63)
	Colorectal	8	*tt* vs. *TT*	**1.43 (1.30–1.58)**	26	1.21 (0.89–1.64)	[a]
			Tt vs. *TT*	1.01 (0.83–1.24)	21	1.06 (0.77–1.46)	0.93 (0.42–2.05)
	Skin	6	*tt* vs. *TT*	1.01 (0.71–1.45)	61	1.09 (0.72–1.66)	[a]
			Tt vs. *TT*	1.09 (0.82–1.45)	55	1.14 (0.79–1.64)	[a]
	Ovary	3	*tt* vs. *TT*	1.04 (0.78–1.38)	0	1.01 (0.75–1.36)	[a]
			Tt vs. *TT*	**0.82 (0.72–0.93)**	83	1.25 (0.82–1.91)	[a]
	Other sites	17	*tt* vs. *TT*	**0.88 (0.78–1.00)**	0	0.90 (0.78–1.03)	0.68 (0.34–1.37)
			Tt vs. *TT*	1.25 (0.94–1.67)	0	1.35 (0.88–2.07)	1.01 (0.73–1.40)
	All sites	64	*tt* vs. *TT*	0.98 (0.9–1.07)	57	0.97 (0.92–1.03)	1.06 (0.82–1.36)
			Tt vs. *TT*	1.04 (0.94–1.16)	52	1.07 (0.94–1.23)	0.97 (0.85–1.12)
ApaI	Prostate	9	*aa* vs. *AA*	1.00 (0.74–1.36)	29	[a]	0.93 (0.63–1.38)
			Aa vs. *AA*	0.97 (0.68–1.37)	54	[a]	0.96 (0.61–1.51)
	Breast	8	*aa* vs. *AA*	0.96 (0.80–1.15)	48	1.03 (0.72–1.48)	0.80 (0.02–30.8)
			Aa vs. *AA*	1.00 (0.80–1.25)	54	1.02 (0.78–1.34)	0.69 (0.00–185.0)
	Colorectal	5	*aa* vs. *AA*	1.21 (0.82–1.78)	64	1.06 (0.77–1.46)	[a]
			Aa vs. *AA*	1.06 (0.91–1.24)	35	1.02 (0.79–1.32)	[a]
	Skin	3	*aa* vs. *AA*	1.16 (0.72–1.89)	0	1.16 (0.72–1.89)	[a]
			Aa vs. *AA*	1.27 (0.84–1.90)	9	1.27 (0.84–1.90)	[a]
	Ovary	3	*aa* vs. *AA*	0.90 (0.47–1.71)	65	0.82 (0.42–1.58)	[a]
			Aa vs. *AA*	1.06 (0.64–1.76)	0	1.03 (0.60–1.79)	[a]
	Other sites	8	*aa* vs. *AA*	1.13 (0.78–1.64)	50	1.24 (0.87–1.78)	[a]
			Aa vs. *AA*	1.07 (0.76–1.49)	59	[a]	0.86 (0.17–4.34)
	All sites	36	*aa* vs. *AA*	1.06 (0.95–1.19)	45	1.05 (0.96–1.15)	1.14 (0.81–1.60)
			Aa vs. *AA*	1.06 (0.96–1.18)	44	1.05 (0.98–1.13)	1.00 (0.77–1.31)
Cdx2	Prostate	5	*gg* vs. *GG*	1.09 (0.73–1.64)	59	0.79 (0.47–1.34)	[a]
			Gg vs. *GG*	1.01 (0.83–1.22)	0	0.98 (0.75–1.27)	[a]
	Breast	3	*gg* vs. *GG*	1.22 (0.70–2.12)	53	1.13 (0.59–2.15)	[a]
			Gg vs. *GG*	0.97 (0.70–1.36)	64	0.96 (0.69–1.34)	[a]
	Colorectal	5	*gg* vs. *GG*	1.24 (0.94–1.63)	0	1.24 (0.94–1.63)	[a]
			Gg vs. *GG*	1.09 (0.96–1.24)	0	1.09 (0.96–1.24)	[a]
	Skin	3	*gg* vs. *GG*	1.05 (0.15–7.60)	0	1.05 (0.15–7.60)	[a]
			Gg vs. *GG*	0.95 (0.40–2.29)	0	0.95 (0.40–2.29)	[a]
	Other sites	4	*gg* vs. *GG*	0.96 (0.68–1.36)	0	0.94 (0.49–1.79)	[a]
			Gg vs. *GG*	1.12 (0.93–1.34)	57	1.15 (0.87–1.53)	[a]
	All sites	18	*gg* vs. *GG*	**1.12 (1.00–1.25)**	17	1.08 (0.95–1.22)	1.40 (0.89–2.19)
			Gg vs. *GG*	1.03 (0.96–1.10)	22	1.02 (0.96–1.10)	1.06 (0.72–1.55)

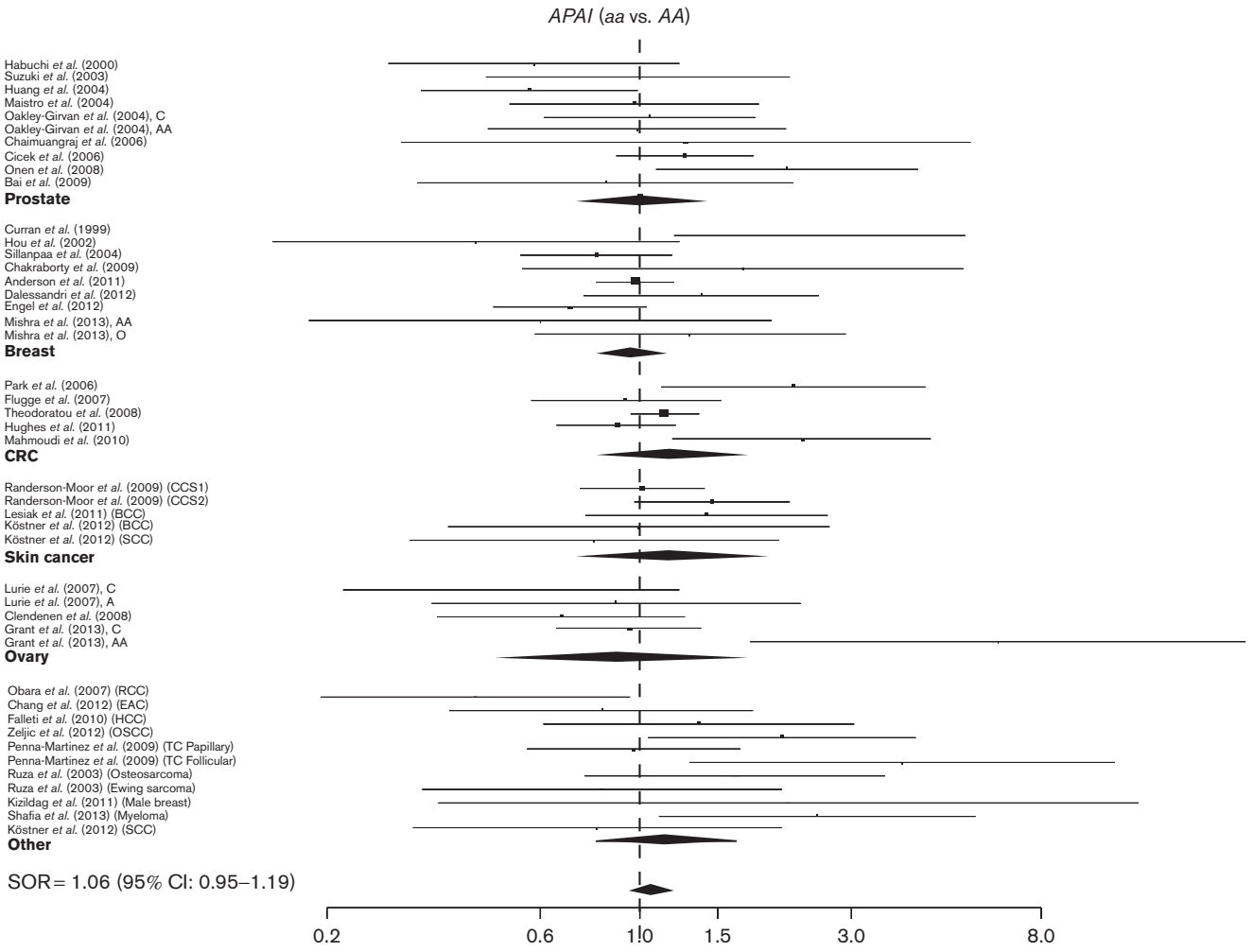
CI, confidence interval; SOR, summary odds ratio; VDR, vitamin D receptor.
Bold indicates significant estimates.
[a]Estimates from ≤ 2 studies were not pooled and they are not shown in the table.

Fig. 1



Study-specific SORs with 95% confidence intervals forest plot for the association between the development of cancer and *TaqI tt* versus *TT* genotype by cancer sites and overall. CRC, colorectal cancer; SORs, summary odds ratios.

Fig. 2



Study-specific SORs with 95% confidence intervals for the association between the development of cancer and *ApaI aa* versus *AA* genotype by cancer sites and overall. CRC, colorectal cancer; SORs, summary odd ratios.

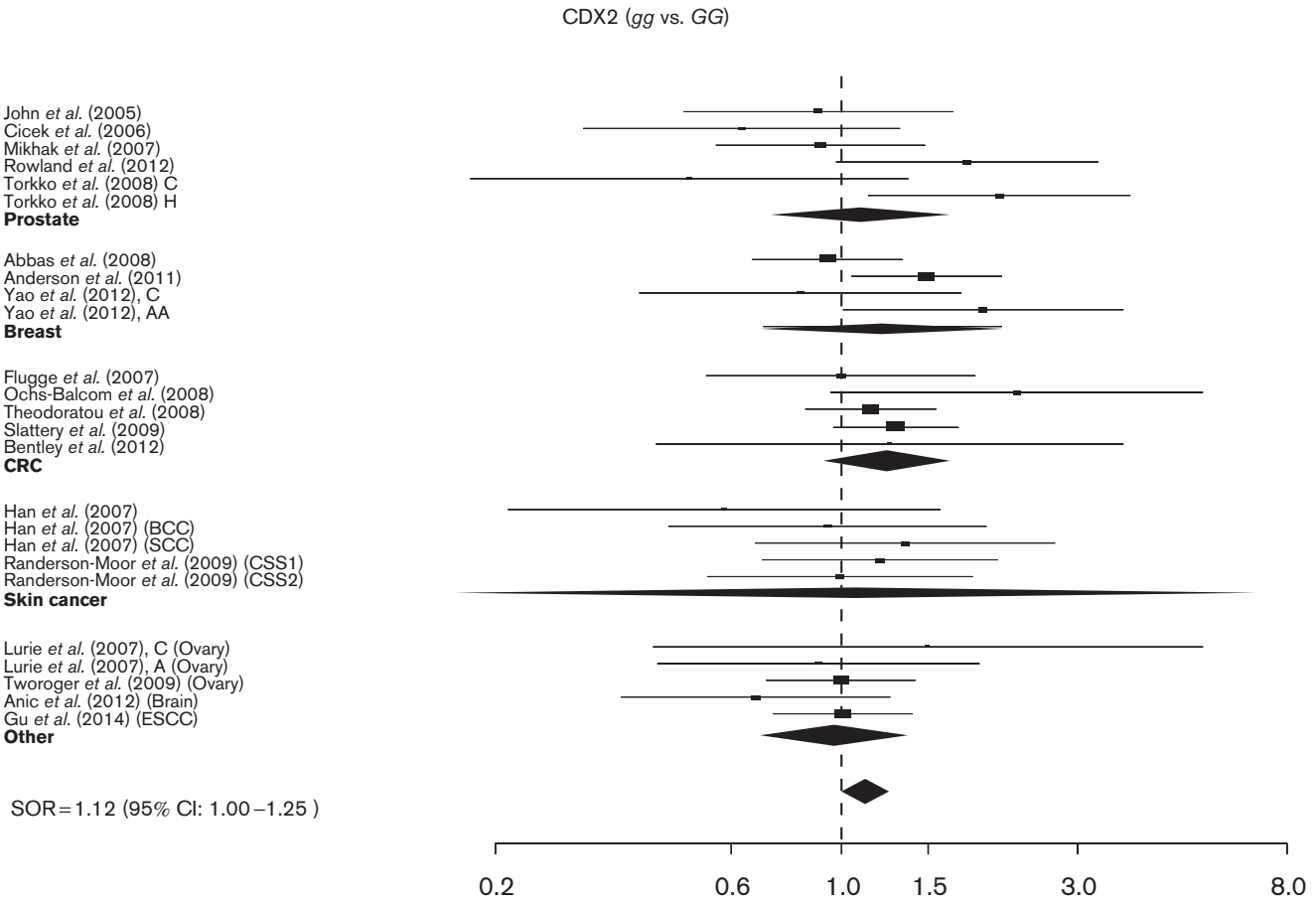
Overall, the allele frequency ranged from 19 to 79% for the *g* allele (Supplementary Table 1). In Caucasians and Asian populations, it ranged from 20 to 45%, whereas in African-Americans *g* ranged from 73 to 79%. In three studies, a significant departure from H–W equilibrium was observed (Supplementary Table 1).

No evidence of publication bias was found for any of the investigated VDR polymorphisms and cancer sites.

Discussion

The role of VDR polymorphisms in the risk of cancer is controversial. To better define the possible clinical relevance, we carried out a comprehensive meta-analysis of *TaqI*, *ApaI*, and *Cdx2* VDR polymorphisms. We found that the *Cdx2 gg* genotype was associated with a 12% increased risk of cancer overall. In-vitro reported gene assays found that the *Cdx2* protein binds more efficiently to the *a* than to the *g* allele, and the *g* allele has been shown to drive transcription less efficiently (Crofts *et al.*, 1998). The *g* allele has also been associated with lower bone mineral density in candidate gene studies (Arai *et al.*, 2001) and in genome-wide association studies (Styrkarsdottir *et al.*, 2008). The *g* allele frequency is particularly high in African Americans and it is possible that the association found in our meta-analysis was driven by non-White populations. Overall *TaqI* and *ApaI* variant genotypes did not show a significant association with the risk of cancer. For specific cancer sites, colorectal cancer showed a 43% increased risk with the *tt TaqI* genotype. Polymorphism frequencies have a very broad range, with a very low *TaqI t* allele frequency among Asians; the frequencies are consistent with the one reported in the literature (Uitterlinden *et al.*, 2004).

Fig. 3



Study-specific SORs with 95% confidence intervals for the association between the development of cancer and *Cdx2 gg* versus *GG* genotype by cancer sites and overall. CRC, colorectal cancer; SORs, summary odds ratios.

Some VDR meta-analyses have been published (Touvier *et al.*, 2011; Bai *et al.*, 2012; Guo *et al.*, 2012; Huang *et al.*, 2013; Liu *et al.*, 2013; Song and Lee, 2013; Wang *et al.*, 2013; Xu *et al.*, 2014), but differently from others, here we analyzed all cancer sites with a panel of different SNPs and we investigated sources of heterogeneity, including ethnicity, which seems to explain much of the between-study variation. The Huang group showed an overall 16% increased risk, increasing to 31% in African-American patients for *Cdx2* SNP (variant homozygous condition versus the heterozygote plus the wild-type genotype) for any cancer. These data are similar to those we have reported here. *BsmI* was found to be associated with an increased risk of cancer by Xu *et al.* (2014). In his meta-analysis, *FokI*, *TaqI*, and *ApaI* did not show an overall cancer risk association, but only for specific cancer sites. The meta-analysis on colorectal cancer by Touvier *et al.* (2011) and a second one by Bai *et al.* (2012) reached similar conclusions: the *BsmI* polymorphism was found to be associated with a reduced risk of cancer, whereas *FokI TaqI*, *ApaI*, and *Cdx2* did not show an association with the risk of colorectal cancer. In our meta-analysis, the *TaqI tt* genotype was associated with a 43% increased risk. Our analysis included eight studies, whereas the Bai *et al.* (2012) publication analyzed nine studies, including three studies on adenoma risk, which might weaken the data. The study by Touvier *et al.* (2011) had a smaller sample size. The *TaqI* polymorphism has been suggested to be associated with the risk of prostate cancer in Asian populations (Guo *et al.*, 2012).

A meta-analysis on ovarian cancer (Song and Lee, 2013) consistently showed an increased risk associated with *FokI* and *ApaI* SNP. The *FokI* data are consistent with those reported by (Liu *et al.* (2013), even if *ApaI* was not associated with the risk of ovarian cancer. Again, conflicting results have been reported for *ApaI* and breast cancer by the Wang group (Wang *et al.*, 2013) that suggested an association in Asian populations, whereas Luo *et al.* (2014) did not report this association. *Cdx2* might be associated with the risk of breast cancer in African-Americans (Zhou *et al.*, 2013), consistent with the data reported by Huang *et al.* (2013).

These data reinforce the hypothesis that VDR SNPs, and overall vitamin D metabolism, are correlated to the risk of cancer, and might be more relevant in specific ethnic groups. Moreover, single studies have suggested a correlation with vitamin D plasma level and tumor characteristics. The *TaqI* polymorphism, as reported by Ma *et al.* (1998), showed a reduction in the risk of prostate cancer only in patients with lower circulating vitamin D. Low vitamin D level and *Cdx2* SNP were also associated with poorly differentiated prostate cancer (Mikhak *et al.*, 2007). In colon cancer, vitamin D plasma level and BMI may interact with VDR SNPs (Yaylim-Eraltan *et al.*, 2007; Ochs-Balcom *et al.*, 2008; Gunduz *et al.*, 2012). In breast cancer, the estrogen receptor status and vitamin D level may interact with VDR polymorphisms (Swami *et al.*, 2000; Engel *et al.*, 2012; Yao *et al.*, 2012).

To strengthen the role of the VDR polymorphisms, some authors have defined haplotypes, analyzing more SNPs simultaneously, but this approach is difficult in a meta-analytic context, because of the inconsistent analysis throughout the different studies and generally low statistical power for haplotype analyses (McCullough *et al.*, 2007; Abbas *et al.*, 2008; Engel *et al.*, 2012).

Most likely, to identify a clinically relevant VDR phenotype, it is necessary to include in the analysis the 25 (OH)D plasma levels and other genes involved in vitamin D activity, such as the binding protein (*GC*) and the anabolic and catabolic enzymes (*CYP27A1*, *CYP27B1*, *CYP24A1*, and *CYP2R1*) (Lauridsen *et al.*, 2005; Deeb *et al.*, 2007). The multifunctional plasma protein *GC* is the major transporter of vitamin D metabolites in the circulation. Plasma 1,25(OH)2D and 25(OH)D levels are related to the *GC* genotype (Lauridsen *et al.*, 2005). *GC* SNPs may have a dual effect and may be associated with lower or higher vitamin D, and also the response to vitamin D supplementation may be modified (Muindi *et al.*, 2013). In a recent genome-wide association study, the combination of *GC* (rs2282679), *DHCR7* (rs12785878), and *CYP2R1* (rs10741657) SNPs conferred an approximately two-fold increase in the risk of vitamin D deficiency (Wang *et al.*, 2010). In addition, for specific *GC* SNP, an association with the risk of cancer for melanoma and hepatocellular carcinoma has also been shown; for colon cancer *GC* SNP may correlate with the prognosis, whereas the association with the risk of cancer has not been confirmed (Hiraki *et al.*, 2013; Lange *et al.*, 2013; Pena-Chilet *et al.*, 2013; Szkandera *et al.*, 2013). One more factor is the variability within the tumor tissue of the complex vitamin D metabolisms' differential exposure of VDR and other enzymes to promote vitamin D anabolisms or catabolism within the tumor itself (Anderson *et al.*, 2006; Thill *et al.*, 2010).

In conclusion, our study represents an updated and comprehensive meta-analysis on the role of *TaqI*, *ApaI*, and *Cdx2* VDR polymorphisms and the risk of cancer at any site including 23 cancer types and provided a complete picture of the role of VDR polymorphisms in the risk of cancer. Among the SNPs included in this meta-analysis, the *Cdx2* polymorphism has shown a general trend toward an increased risk of cancer. *TaqI* has been found to be associated with an increased risk for colorectal cancer, whereas overall, *ApaI* is not associated significantly with the risk of cancer. Limitations are because of the low number of studies available for some cancer sites or for some ethnic groups.

The VDR genotype might become more clinically relevant clustered in a specific haplotype, considering the *CG*-binding protein or for specific tumors and/or patient characteristics.

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Conflicts of interest

There are no conflicts of interest.

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