Meta-analysis on vitamin D receptor and cancer risk: focus on the role of TaqI, Apal, 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, Apal, 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 Apal 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 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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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).
Our previous meta-analysis (Gnagnarella et al., 2014; Raimondi et al., 2014) suggested that the most studied SNPs, FokI (rs2228570) and BsmI (rs1054410), 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 Cdx2g 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 χ²-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 (I² = 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 (I² ≤ 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-analyses 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 | |
|             | Ciciek et al. (2006) | USA | White | No | 439 | 479 | X | X | |
|             | Helick 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 | | |
|             | 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 | 2812 | X | X | |
|             | Chakraborty et al. (2009) | India | Asian | Yes | 160 | 140 | X | X | |
|             | Anderson et al. (2011) | Canada | White | No | 1546 | 1627 | 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 | |
|             | Yaylim-Eraltan et al. (2007) | Turkey | White | Yes | 26 | 52 | X | | |
|             | Ocho-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 | No | 2313 | 2032 | 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 | |
|             | Randerson-Moor et al. (2009)b | UK | White | No | 299 | 560 | 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 | |
|             | Lurie et al. (2007) | Mix | Asian | No | 93 | 172 | X | X | |
|             | Clendenen et al. (2008) | Mix | White | No | 170 | 329 | X | X | |
|             | Tworoger et al. (2009) | USA | White | 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 | Ruza et al. (2003) | Spain | White | No | 125 | 143 | X | X | |
|             | Anic et al. (2012) | USA | White | No | 564 | 605 | X | X | |
|             | Toptas et al. (2013) | Turkey | White | Yes | 100 | 122 | X | | |

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Table 1 (continued)

| Cancer site | References               | Country | Ethnicity | Hospital controls | Number of cases | Number of controls | TaqI | Apal | Cdx2 |
|-------------|--------------------------|---------|-----------|-------------------|----------------|-------------------|------|------|------|
| EAC         | Chang et al. (2012)      | Ireland | White     | No                | 202            | 234               |       |      |      |
| ESSC        | Li et al. (2008)         | China   | Asian     | Yes               | 126            | 169               |      |      |      |
| ESCH        | Gu et al. (2014)         | China   | Asian     | Yes               | 629            | 686               |      |      | X    |
| HCC         | Falleti et al. (2010)    | Italy   | White     | No                | 80             | 160               |      |      |      |
| Male breast | Kudlak et al. (2011)     | Turkey  | White     | Yes               | 25             | 96                |      |      |      |
| Myeloma     | Shafai et al. (2013)     | India   | Asian     | Yes               | 75             | 150               |      |      |      |
| NHL         | Smedby et al. (2011)     | Sweden  | White     | No                | 2303           | 1739              |      |      |      |
| NHL         | Purdue et al. (2007)     | USA     | Mixed     | No                | 2025           | 1751              |      |      |      |
| OSCC        | Bektas-Kayhan et al. (2010) | Turkey | White     | No                | 64             | 87                |      |      |      |
| OSCC        | Zelijc et al. (2012)     | Serbia  | White     | No                | 110            | 122               |      |      |      |
| HNC         | Liu et al. (2006)        | USA     | White     | No                | 719            | 821               |      |      |      |
| RCC         | Karan et al. (2008)      | Europe  | White     | Yes               | 925            | 1192              |      |      |      |
| RCC         | Obara et al. (2007)      | Japan   | Asian     | No                | 135            | 150               |      |      |      |
| TC          | Penna-Martinez et al. (2009) | Germany | White     | Yes               | 172            | 321               |      |      |      |
| Bladder     | Mittal et al. (2007)     | India   | Asian     | NS                | 130            | 346               |      |      |      |

Total studies (n = 18) 8509 8944

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.

The second Leeds case series (Leeds CCS1).

*The first Leeds case-control series (Leeds CCS1).

Table 2 Overall summary odds ratios for the association of VDR TaqI, Apal, 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  | 0.84 (0.78–1.12)         | 3        | 0.92 (0.76–1.12)       | 0.98 (0.54–1.79)                    |
|      | Breast          | 11                | Tt vs. TT  | 0.95 (0.80–1.12)         | 51       | 0.91 (0.72–1.13)       | 1.04 (0.79–1.36)                    |
|      | Colorectal      | 8                 | Tt vs. TT  | 1.00 (0.89–1.12)         | 20       | 1.00 (0.88–1.13)       |                                   |
|      | Skin            | 6                 | Tt vs. TT  | 0.98 (0.82–1.15)         | 34       | 0.99 (0.88–1.12)       | 1.08 (0.44–2.63)                    |
|      | Ovary           | 3                 | Tt vs. TT  | 1.04 (0.78–1.38)         | 54       | 1.01 (0.75–1.36)       |                                   |
|      | 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)                    |
|      | All sites       | 64                | Tt vs. TT  | 1.04 (0.94–1.16)         | 52       | 1.07 (0.94–1.23)       | 0.97 (0.85–1.12)                    |
| Apal | Prostate        | 9                 | Aa vs. AA  | 0.97 (0.73–1.43)         | 29       | 0.93 (0.63–1.38)       |                                   |
|      | Breast          | 8                 | Aa vs. AA  | 0.97 (0.68–1.57)         | 54       | 0.96 (0.61–1.51)       |                                   |
|      | Colorectal      | 5                 | Aa vs. AA  | 1.27 (0.84–1.90)         | 9        | 1.27 (0.84–1.90)       | 0.80 (0.52–1.38)                    |
|      | Other sites     | 3                 | Aa vs. AA  | 0.90 (0.47–1.71)         | 65       | 0.82 (0.42–1.58)       |                                   |
|      | All sites       | 36                | Aa vs. AA  | 1.13 (0.78–1.64)         | 50       | 1.24 (0.87–1.78)       |                                   |
| Cdx2 | Prostate        | 5                 | gg vs. GG  | 0.96 (0.80–1.15)         | 48       | 1.03 (0.72–1.26)       | 0.80 (0.52–0.95)                    |
|      | Breast          | 3                 | gg vs. GG  | 1.22 (0.70–2.12)         | 53       | 1.13 (0.59–2.15)       |                                   |
|      | Colorectal      | 5                 | gg vs. GG  | 1.24 (0.94–1.63)         | 64       | 1.24 (0.94–1.63)       |                                   |
|      | Skin            | 3                 | gg vs. GG  | 1.09 (0.96–1.24)         | 0        | 1.09 (0.96–1.24)       |                                   |
|      | Other sites     | 4                 | gg vs. GG  | 1.05 (0.85–1.29)         | 0        | 1.05 (0.85–1.29)       |                                   |

CI, confidence interval; SOR, summary odds ratio; VDR, vitamin D receptor.

*Bold indicates significant estimates.

*Estimates from < 2 studies were not pooled and they are not shown in the table.

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TAQI (tt vs. TT)

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.
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.
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; Xue 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.

A meta-analysis on ovarian cancer (Song and Lee, 2013) consistently showed an increased risk associated with FokI and Apal SNP. The FokI data are consistent with those reported by (Liu et al., 2013), even if Apal was not associated with the risk of ovarian cancer. Again, conflicting results have been reported for Apal 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).

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.
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 (Munindi 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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