Meta-analysis of Vitamin D-Binding Protein and Cancer Risk
Elena Tagliabue, Sara Raimondi, and Sara Gandini

Abstract

Background: Epidemiologic evidence supported a role for vitamin D and vitamin D receptor (VDR) polymorphisms in cancer risk. Beyond VDR, the biologic effects of vitamin D are mediated by the vitamin D-binding protein (DBP), a key protein in vitamin D metabolism. Furthermore, the gene encoding the DBP (GC, group-specific component) has an important role in the vitamin D pathway. Several studies investigated DBP serologic levels and GC polymorphisms in association with cancer risk with controversial results. Thus, we carried out a meta-analysis to investigate these associations.

Methods: We included 28 independent studies concerning the following tumors: basal cell carcinoma, bladder, breast, colon–rectum, endometrium, liver, esophagus, stomach, melanoma, pancreas, prostate, and kidney. Through random-effect models, we calculated the summary odds ratios (SOR) for serum DBP and the GC polymorphisms rs2282679, rs12512631, rs7041, rs4588, rs17467825, rs1155563, and rs1352844.

Results: We found a borderline decrease in cancer risk for subjects with high compared with low levels of DBP [SOR, 0.75; 95% confidence interval (CI), 0.56–1.00]. Dose-response meta-analysis indicates a nonsignificant decrease risk for an increase of 1,000 nmol/L of DBP (SOR, 0.96; 95% CI, 0.91–1.01). We found no significant alterations in cancer risk for subjects carrying any of the studied GC polymorphisms compared with wild-type subjects both in the main analysis and in analyses stratified by cancer type and ethnicity.

Conclusions: We found trends toward significance, suggesting a role of DBP in cancer etiology, which should be confirmed in further studies.

Impact: To our knowledge, this is the first study to investigate GC polymorphisms and DBP serologic levels in association with any type of cancer. Cancer Epidemiol Biomarkers Prev; 24(11): 1758–65. ©2015 AACR.

Introduction

Antiproliferative effects of 1,25-dihydroxy-vitamin D [1,25(OH)2D], the biologically active form of vitamin D, are well established in various cell types, including normal and malignant cells, by influencing cell differentiation and decrease cell proliferation, cell growth, invasion, angiogenesis, and metastasis (1). In addition, meta-analyses of epidemiologic studies showed that serum 25-hydroxy-vitamin D [25(OH)D] and vitamin D receptor polymorphisms (VDR) are associated with cancer risk at multiple sites (2–8).

Vitamin D is mainly synthesized following the skin’s exposure to solar UV radiation (UV-B). Alternatively, it can be found naturally in some foods or it can be ingested from supplements. Vitamin D is hydroxylated in the liver to produce 25(OH)D, which is then converted into 1,25(OH)2D by the VDR (1). Beyond VDR, the biologic effects of vitamin D are mediated by an abundance of the vitamin D-binding protein (DBP), which is a key protein in vitamin D metabolism. DBP is also a member of the albumin and alpha-fetoprotein gene family, and it is the major transport protein of vitamin D metabolites to different target organs (9–11). Indeed it has been hypothesized that levels of DBP may affect the delivery of 25(OH)D to the kidney and other organs, and of 1,25(OH)2D to target organs (10, 12).

The gene-encoding DBP protein, known as “group-specific component” (GC), is located on chromosome 4 (4q11–13) and is highly polymorphic (9, 12). Several nonsynonymous coding SNPs were described, two of them with common frequency: Glu416Asp (rs7041) and Thr420Lys (rs4588). rs7041 and rs4588 have been shown to alter plasma concentrations of 25(OH)D in candidate gene studies (10, 13). Furthermore, genome-wide association studies shown that GC rs2282679 and rs1155563 were associated with serum 25(OH)D levels (11, 14).

Association studies of several polymorphisms in the GC gene and of DBP level have been performed to investigate their role in different types of cancer development and have obtained controversial results (15–23). Thus, we decided to carry out a comprehensive literature search and meta-analysis to investigate the association between different GC polymorphisms, DBP level and cancer risk, providing quantitative summary risk estimates of the association and identifying sources of between-study heterogeneity.

Materials and Methods

Search strategy, inclusion criteria, and data abstraction
To identify published articles and abstracts on DBP serologic levels, GC polymorphisms and cancer, we carried out a comprehensive and systematic literature search updated to October 2014 using PubMed, EMBASE, and ISI Web of Knowledge. To identify...
the publications, we used combinations of the following keywords: "25-hydroxyvitamin D," "DBP," "GC," "vitamin D metabolites," "vitamin D polymorphism," and "cancer." We also checked the references from retrieved articles and reviews to identify any additional relevant study.

We considered eligible for the present analysis all independent studies reporting frequency and/or risk estimates with a corresponding measure of uncertainty [i.e., 95% confidence interval (CI), standard error, variance or P value of the significance of the estimate] of DBP serologic levels and/or any GC polymorphism for cancer of any type and controls.

We found 226 articles matching our keywords (Fig. 1), but we excluded 152 publications with title and/or abstract not relevant for the endpoint of this study. We considered full-text articles of the remaining 74 articles. Out of them, 30 were excluded because there were no data on DBP and/or GC polymorphisms, 13 were excluded because there were case-only studies, and 2 were excluded because there were not enough data to estimate odds ratios (ORs) and 95% CI. From the remaining 29 studies, we further excluded one study (24) because both cases and controls had HCV infection and could not therefore be considered as representative of the general at-risk population; and one study (25) because the study population overlapped with articles based on larger samples from the same population. Twenty-seven independent case–control studies were eventually considered for the present meta-analysis: 9 provided data on DBP levels and 18 on GC polymorphisms. For GC analysis, we selected studied polymorphisms for which appropriate data were available from at least three independent studies: rs2282679, rs12512631, rs7041, rs4588, rs17467825, rs1155563, and rs1352844.

For each study, we extracted adjusted ORs with 95% CI for each DBP quartile or quintile and/or for DBP unit increase, and for each GC polymorphism. Furthermore, we gathered cases and controls frequency data on wild-type (WT), heterozygous and variant homozygous alleles for each GC polymorphism according to cancer type. Further information was extracted from the selected articles, including study design, study country, publication year, source of controls, source of DNA, genotyping method, matching variables, and ethnicity.

Articles were reviewed and data were extracted and cross-checked independently by three investigators. Any disagreement was resolved by consensus among the three. In case of doubt about interpretation of the original data, we also contacted principal investigators of the study articles asking for clarifications.

Data analysis

First of all, we computed the summary OR (SOR) estimates for the "highest" versus the "lowest" category of the DBP level. When the information was available, we also calculated the summary estimates of the dose–response effect of the DBP level on cancer risk. The procedure is based on two steps: first, a linear model was fitted within each study to estimate the OR per unit of DBP level increase. When sufficient information was published (i.e., the number of subjects at each serum level category), the model was fitted according to the method proposed by Greenland and Longnecker (26). This method provides the natural logarithm of the OR, and an estimate of its standard error, taking into account that the estimates for separate categories are referred to the same reference category. When the number of subjects in each serum level category was not available from the publications, coefficients were calculated discounting the correlation between the estimates of risk at the separate exposure levels. In the second step, the SOR was estimated by pooling the different study-specific estimates using the random-effect models with summary effect size obtained from the estimation of maximum likelihood. Confidence intervals were computed assuming an underlying t distribution. When there were more than one OR calculated in a single study (i.e., analysis by different type of cancer), we adjusted the pooled estimates taking into account the correlation within studies by using the multivariate approach of van Houwelingen and colleagues (27).

Beyond DBP serologic levels, we performed a second analysis on GC. Through random-effect models, we calculated SORs with 95% CI, when possible, for heterozygous and variant homozygous genotype of each GC polymorphism, and according to the additive and dominant model of inheritance. When the included studies reported adjusted ORs, we used them instead of the crude ORs to take into account adjustment for possible confounders. We also verified the departure of frequencies of each GC polymorphism from expectation under Hardy–Weinberg equilibrium.

![Flowchart of selection of studies for inclusion in meta-analysis.](image-url)
(HWE) by the χ² test in controls for each available study. For the first step in the analysis of GC polymorphisms, we considered the association of each GC polymorphism with “any cancer site,” aggregating all sites. Then, we performed the analyses stratified by ethnicity (Caucasians, others) and by cancer sites for the two most-studied GC polymorphisms (rs7041 and rs4588), for which at least three estimates were available in each stratum. Because of the small number of studies on each cancer type, we aggregated the small number of studies on each cancer type, we aggregated

Table 1. Description of the studies included in the pooled-analysis for DBP serologic levels (A) and GC polymorphisms (B)

<table>
<thead>
<tr>
<th>(A) First author</th>
<th>PY</th>
<th>Country</th>
<th>Serum level (1 4 Q)</th>
<th>Controls type</th>
<th>Cancer type</th>
<th>Cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mondul (16)</td>
<td>2012</td>
<td>Finland</td>
<td>rs4588, rs7041</td>
<td>Population</td>
<td>Bladder</td>
<td>245/245</td>
</tr>
<tr>
<td>Mondul (55)</td>
<td>2012</td>
<td>USA</td>
<td>rs224–5017</td>
<td>Population</td>
<td>Bladder</td>
<td>369/364</td>
</tr>
<tr>
<td>Wang (17)</td>
<td>2014</td>
<td>USA</td>
<td>rs760–5588</td>
<td>Population</td>
<td>Breast</td>
<td>610/610</td>
</tr>
<tr>
<td>Anic (56)</td>
<td>2014</td>
<td>Finland</td>
<td>rs4369–6993</td>
<td>Population</td>
<td>Colorectal</td>
<td>418/418</td>
</tr>
<tr>
<td>Weinstein (18)</td>
<td>2015</td>
<td>USA</td>
<td>rs2460–5215</td>
<td>Population</td>
<td>Colorectal</td>
<td>476/476</td>
</tr>
<tr>
<td>Weinstein (57)</td>
<td>2012</td>
<td>Finland</td>
<td>rs4026–6721</td>
<td>Population</td>
<td>Pancreatic</td>
<td>254/234</td>
</tr>
<tr>
<td>Corder (34)</td>
<td>1995</td>
<td>USA</td>
<td>N.A.</td>
<td>Population</td>
<td>Prostate</td>
<td>181/181</td>
</tr>
<tr>
<td>Weinstein (58)</td>
<td>2013</td>
<td>Finland</td>
<td>rs4077–7058</td>
<td>Population</td>
<td>Prostate</td>
<td>948/948</td>
</tr>
<tr>
<td>Mondul (23)</td>
<td>2014</td>
<td>Finland</td>
<td>rs4396–6999</td>
<td>Population</td>
<td>Renal</td>
<td>262/262</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B) First author</th>
<th>PY</th>
<th>Country</th>
<th>Polymorphism</th>
<th>Controls type</th>
<th>Cancer type</th>
<th>Cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flohil (15)</td>
<td>2010</td>
<td>Netherlands</td>
<td>rs4588, rs7041</td>
<td>Population</td>
<td>Basal cell carcinoma</td>
<td>355/7,571</td>
</tr>
<tr>
<td>McCullogh (43)</td>
<td>2007</td>
<td>USA</td>
<td>rs4588, rs7041</td>
<td>Population</td>
<td>Breast</td>
<td>500/500</td>
</tr>
<tr>
<td>Abbas (44)</td>
<td>2008</td>
<td>Germany</td>
<td>rs4588, rs7041</td>
<td>Population</td>
<td>Breast</td>
<td>1,402/2,608</td>
</tr>
<tr>
<td>Anderson (48)</td>
<td>2011</td>
<td>Canada</td>
<td>rs4588, rs7041</td>
<td>Population</td>
<td>Breast</td>
<td>1,560/1,633</td>
</tr>
<tr>
<td>Dorigachoo (45)</td>
<td>2011</td>
<td>China</td>
<td>rs1155653, rs17467825, rs2282679, rs7041</td>
<td>Population</td>
<td>Breast</td>
<td>2,919/2,323</td>
</tr>
<tr>
<td>Poynter (42)</td>
<td>2010</td>
<td>USA</td>
<td>rs1155653, rs12512631, rs7041, rs1352844, rs17467825</td>
<td>Sibling</td>
<td>Colorectal</td>
<td>1,800/2,879</td>
</tr>
<tr>
<td>Hiriki (43)</td>
<td>2013</td>
<td>USA</td>
<td>rs2282679</td>
<td>Mixed¹</td>
<td>Colorectal</td>
<td>10,061/1,2768</td>
</tr>
<tr>
<td>Mahmoudi (59)</td>
<td>2014</td>
<td>Iran</td>
<td>rs4588</td>
<td>Hospital</td>
<td>Colorectal</td>
<td>303/354</td>
</tr>
<tr>
<td>Pibiri (60)</td>
<td>2014</td>
<td>USA</td>
<td>rs17467825, rs7041</td>
<td>Population</td>
<td>Colorectal</td>
<td>961/838</td>
</tr>
<tr>
<td>Zhou (49)</td>
<td>2012</td>
<td>China</td>
<td>rs4588</td>
<td>Population</td>
<td>Colorectal</td>
<td>964/1,187</td>
</tr>
<tr>
<td>Liu (19)</td>
<td>2013</td>
<td>USA</td>
<td>rs4588, rs7041</td>
<td>Population</td>
<td>Endometrial</td>
<td>572/572</td>
</tr>
<tr>
<td>Davies (35)</td>
<td>2011</td>
<td>UK</td>
<td>rs2282679¹</td>
<td>Mixed²</td>
<td>Melanoma</td>
<td>960/687</td>
</tr>
<tr>
<td>Schäfer (61)</td>
<td>2012</td>
<td>Germany</td>
<td>rs1155653, rs7041</td>
<td>Population</td>
<td>Melanoma</td>
<td>305/370</td>
</tr>
<tr>
<td>Peria-Chileto (20)</td>
<td>2013</td>
<td>Spain</td>
<td>rs1155653, rs12512631, rs7041, rs1352844, rs2282679, rs4588</td>
<td>Hospital</td>
<td>Melanoma</td>
<td>1,045/684</td>
</tr>
<tr>
<td>Anderson (21)</td>
<td>2013</td>
<td>Canada</td>
<td>rs2282679, rs4588, rs7041</td>
<td>Population</td>
<td>Pancreatic</td>
<td>628/1,939</td>
</tr>
<tr>
<td>Shui (46)</td>
<td>2012</td>
<td>USA</td>
<td>rs12512631, rs4588, rs7041</td>
<td>Population</td>
<td>Prostate</td>
<td>1,260/1,331</td>
</tr>
<tr>
<td>Karami (22)</td>
<td>2013</td>
<td>USA</td>
<td>rs12512631, rs4588, rs7041</td>
<td>Population</td>
<td>Prostate</td>
<td>776/444</td>
</tr>
<tr>
<td>Mondul (47)</td>
<td>2013</td>
<td>Mixed</td>
<td>rs2282679</td>
<td>Population</td>
<td>Prostate</td>
<td>10018/11052</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; PY, publication year; Q, quartile.

The analysis was carried out using SAS (version 9.2) and STATA (version 11.2).

Results
Table 1 summarizes the 9 studies about DBP and the 18 studies about GC included in the meta-analysis. With the exception of one study published in 1995 (34), the publication year ranges from 2007 to 2014. The majority of studies were carried out in Europe (N = 10/27, 37%) and the United States (N = 9/27, 33%). The investigated cancer sites were colon–rectum (number of estimates = 7), breast (5), prostate (5), melanoma (3), bladder (2), pancreas (2), basal cell carcinoma (1), endometrium (1), esophagus (1), kidney (1), liver (1), and stomach (1). Departure from HWE was observed in 3 studies (20, 22, 35) for rs2282679, rs12512631, and rs1251263 polymorphisms, respectively.

DBP serologic levels
Figure 2 represents ORs with 95% CI for DBP serologic levels comparing the highest quartile (or quintile, if available) with the lowest class for each study with available information. A borderline decrease in cancer risk was found for subjects with high levels of DBP compared with subjects with low levels of DBP (OR, 0.75; 95% CI, 0.56–1.00). Heterogeneity among study-specific estimates was high (I² = 67%), but it seems not attributable to any of the following variables evaluated in meta-regression analysis: source of controls, publication year, geographical area, ethnicity,
average age, and cancer site. Otherwise, the observed heterogeneity seems to be mainly due to one single study (23), with very low risk estimate. By excluding this study in sensitivity analysis, the between-study heterogeneity was no more evident ($I^2 = 0\%$, not shown), and the SOR (95% CI) increased to 0.88 (0.75–1.04).

Dose–response meta-analysis indicates a nonsignificant decrease risk for an increase of 1,000 nmol/L of DBP: SOR, 0.96 (95% CI, 0.91–1.01) with $I^2 = 71\%$. By excluding the renal cancer study, the SOR become borderline significant, 0.98 (95% CI, 0.96–1.00) because heterogeneity decreases significantly: $I^2 = 0\%$.

**GC polymorphisms**

SOR for an additive model could be calculated for all the studied polymorphisms (Table 2). We found no statistically significant association between each study polymorphism and cancer at any site.

When we investigated different models of inheritance for the two most studied polymorphisms, rs7041 and rs4588 (Table 3), we did not observe any significant increase of cancer risk at any site.

For these two polymorphisms, we had enough data to perform stratified analyses according to tumor site and race. Table 4 shows the results for different inheritance models. We did not find a significant association for the two polymorphisms neither with tumors previously associated or not with vitamin D, nor stratifying on Caucasian and other ethnic groups.

Sensitivity analyses excluding studies that do not respect HWE did not show important changes in results. Furthermore, funnel plots and Egger tests did not detect publication bias (results not shown).

### Discussion

We found a borderline decrease in cancer risk for subjects with high levels of DBP compared with subjects with low levels of DBP (SOR, 0.75; 95% CI, 0.56–1.00 for the highest versus the lowest quartile/quintile), with high between-study heterogeneity ($P^2 = 67\%$) due to the inclusion of one study on renal cancer (23) with a very low-risk estimate. After exclusion of this study in sensitivity analysis, the SOR was no longer significant, but the risk estimate from the dose–response model considering a linear increase of DBP became borderline significant (SOR, 0.98; 95% CI, 0.96–1.00). Therefore, the exclusion of this study does not substantially change our results of a borderline effect of DBP serologic levels in decreasing cancer risk. The renal cancer study has a prospective design, high-quality laboratory measurement of circulating 25(OH)D and DBP concentrations in fasting serum in two different time periods, and detailed information on (and adjustment for) many potential confounding factors. The very low cancer risk estimate found for DBP levels in this study may be
DBP may also affect carcinogenesis through its non-vitamin D metabolism and resorption.

DBP transports both 88% of 25(OH)D and 85% of 1,25(OH)2D, the active hormonal form of vitamin D, in circulation (9, 36, 37); thus, it has been hypothesized that levels of DBP may affect the delivery of 25(OH)D and of 1,25(OH)2D to target organs. Interestingly, it was found that 25(OH)D levels were highest in non-Hispanic whites, intermediate in Hispanics, and lowest in blacks, whereas levels of 1,25(OH)2D were similar among the three ethnic groups (13).

The importance of DBP comes from the consideration that controversy surrounds the precise level of total 25(OH)D at which calcium absorption declines or parathyroid hormone levels increase (38, 39). Thus, labeling the majority of the black subjects with low 25(OH)D levels as vitamin D deficient would be inconsistent with the observation that they had higher bone mineral density, higher calcium levels, and only slightly higher parathyroid hormone levels than their white counterparts, as observed in a previous study (40). The same study highlighted the importance of definition of bioavailable 25(OH)D, which is the circulating 25(OH)D not bound to DBP. The authors found that community-dwelling black Americans, as compared with whites, had low levels of total 25(OH)D, but also of DBP, resulting in similar concentrations of estimated bioavailable 25(OH)D. This reflects the importance of DBP as mediator of the effect of circulating 25(OH)D.

DBP may also affect carcinogenesis through its non-vitamin D–related biologic functions, including being a member of the extracellular actin scavenger system and by playing a role in chemotaxis, macrophage activation, apoptosis, and angiogenesis (9, 37).

Our meta-analysis did not suggest significant alterations in cancer risk for subjects carrying any of the studied GC polymorphisms compared with WT subjects. These results could be explained by the hypothesis that measurement of the circulating protein is more biologically effective than the role of mutations in genes that may only explain a portion of DBP status. Several previous studies have failed to identify significant association between GC polymorphism and cancer at different sites. Recently published data from the Ontario Pancreas Cancer Study (21), showed no significant association between GC rs2282679, rs7041, and rs4588 with pancreas cancer, with adjusted ORs around 1.00. Moreover, a pooled analysis of published case–control studies did not show a significant association between GC rs2282679 and colorectal cancer (41). Furthermore, other studies, including Colon Cancer Family Registry (42), Cancer Prevention Study II Nutrition Cohort (43), Marie Study (44), Nurses’ Health Study (19), Rotterdam Study (15), Shanghai Breast Cancer Study (45), and Health Professionals Follow-up Study (46), did not show significant association between GC rs7041 and/or rs4588 and cancer at different sites as colon—rectum, pancreas, breast, endometrium, skin and prostate. Otherwise, data from the Breast and Prostate Cancer Cohort Consortium (47) provided evidence of a significant association between the rs2282679 variant and prostate cancer risk, which is not confirmed by the present meta-analysis. Also one study within the Agricultural Health Study found a significant association between GC rs7041 and prostate cancer, but only in subjects exposed to the use of parathion pesticide (22). Peña-Chillet and colleagues (20) detected a strong association between rs12512631 and melanoma risk, whereas no association with melanoma was observed for the other studied polymorphisms (rs7041, rs4588, rs1155563, and rs1352844). The Ontario Women’s Diet and Health Study (48) found a significant association between breast cancer risk and rs7041, but not with rs4588. Finally, a Chinese study by Zhou and colleagues (49) investigated the association between the two most studied polymorphism (rs7041 and rs4588) and cancer risk at different sites such as liver, esophagus, stomach, and colon—rectum, and found only one significant association between rs4588 and colorectal cancer. The controversial results of these studies with our meta-analysis may attributable to the fact that kidney is the major organ affecting vitamin D, being responsible for vitamin D metabolism and resorption.

Table 3. SORs for different models of inheritance for the association between GC polymorphisms rs7041 and rs4588 and cancer at any site

<table>
<thead>
<tr>
<th>GC polymorphism</th>
<th>Model</th>
<th>SOR (95% CI)</th>
<th>P%</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs7041</td>
<td>Dominant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.01 (0.92–1.11)</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>GT vs. GG</td>
<td>0.99 (0.88–1.11)</td>
<td>33.6</td>
</tr>
<tr>
<td></td>
<td>TT vs. GG</td>
<td>1.08 (0.94–1.23)</td>
<td>0.0</td>
</tr>
<tr>
<td>rs4588</td>
<td>Dominant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.03 (0.94–1.12)</td>
<td>28.4</td>
</tr>
<tr>
<td></td>
<td>GT vs. GG</td>
<td>1.01 (0.93–1.10)</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>TT vs. GG</td>
<td>1.09 (0.91–1.30)</td>
<td>55.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Dominant model: GT+TT vs. GG.

Table 4. Stratified SORs for different models of inheritance for the GC polymorphisms rs7041 and rs4588 and cancer at any site

<table>
<thead>
<tr>
<th>GC polymorphism</th>
<th>Model</th>
<th>Vitamin D-associated tumors&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Vitamin D not associated tumors&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Caucasians</th>
<th>Others&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOR (95% CI)</td>
<td>SOR (95% CI)</td>
<td>SOR (95% CI)</td>
<td>SOR (95% CI)</td>
<td>SOR (95% CI)</td>
</tr>
<tr>
<td>rs7041</td>
<td>Additive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.01 (0.96–1.07) [5/7]</td>
<td>1.87 (0.65–5.36) [10/10]</td>
<td>1.30 (0.73–2.35) [8/8]</td>
<td>1.10 (0.76–1.63) [6/9]</td>
</tr>
<tr>
<td></td>
<td>Dominant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.01 (0.90–1.14) [2/4]</td>
<td>1.02 (0.34–3.27) [8/8]</td>
<td>1.05 (0.93–1.18) [6/6]</td>
<td>0.91 (0.66–1.23) [3/6]</td>
</tr>
<tr>
<td></td>
<td>GT vs. GG</td>
<td>0.99 (0.85–1.16) [2/4]</td>
<td>0.98 (0.31–3.16) [7/7]</td>
<td>1.05 (0.90–1.16) [5/5]</td>
<td>0.88 (0.62–1.25) [3/6]</td>
</tr>
<tr>
<td></td>
<td>TT vs. GG</td>
<td>1.08 (0.90–1.28) [2/4]</td>
<td>1.09 (0.27–4.37) [7/7]</td>
<td>1.09 (0.89–1.33) [5/5]</td>
<td>1.04 (0.63–1.72) [3/6]</td>
</tr>
<tr>
<td>rs4588</td>
<td>Additive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.04 (0.92–1.18) [4/6]</td>
<td>1.32 (0.72–2.64) [7/7]</td>
<td>1.01 (0.93–1.09) [7/7]</td>
<td>1.48 (0.57–1.84) [3/6]</td>
</tr>
<tr>
<td></td>
<td>Dominant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.02 (0.91–1.14) [2/4]</td>
<td>1.08 (0.46–2.53) [7/7]</td>
<td>1.00 (0.90–1.12) [6/6]</td>
<td>1.12 (0.44–2.79) [2/5]</td>
</tr>
<tr>
<td></td>
<td>GT vs. GG</td>
<td>0.99 (0.90–1.10) [2/4]</td>
<td>1.05 (0.42–2.62) [7/7]</td>
<td>0.99 (0.89–1.09) [6/6]</td>
<td>1.09 (0.40–2.99) [2/5]</td>
</tr>
<tr>
<td></td>
<td>TT vs. GG</td>
<td>1.18 (0.81–1.72) [2/4]</td>
<td>1.34 (0.41–4.35) [7/7]</td>
<td>1.03 (0.80–1.32) [6/6]</td>
<td>1.21 (0.42–3.74) [2/5]</td>
</tr>
</tbody>
</table>

<sup>a</sup>Tumors previously associated with vitamin D are basal cell carcinoma, breast, colorectal, and melanoma; not associated tumors are endometrial, esophageal, gastric, hepatocellular, pancreatic, and prostate.

<sup>b</sup>Chinese, African Americans, and mixed.

<sup>c</sup>Additive model: T allele vs. G allele.

<sup>d</sup>Dominant model: GT+TT genotypes vs. GG genotype.
be due either to sporadic association found by chance in previous studies, either to a possible specific role of some GC polymorphisms on cancer at specific sites. This may reflect the involvement of the GC gene in mechanisms that are cancer specific, rather than in general mechanisms involved in carcinogenesis process, as the ones in which vitamin D is involved: reduction of cell proliferation, cell growth, invasion, angiogenesis, and metastasis (1).

Unfortunately, we were unable to assess the association of each studied GC polymorphism with each cancer type due to the limited amount of published data. Furthermore, lack of significant associations between GC genes and cancer risk may be due to the fact that genetic variation may not have been captured by the variants taken into account.

To our knowledge, the present is the first meta-analysis that evaluates the association between DBP serologic level and several GC polymorphisms and risk of any type of cancer. Through this meta-analytic approach, we could provide powerful and robust summary risk estimates at least for the two most studied GC polymorphisms and according to different model of inheritance, and we were eventually able to provide a comprehensive review of the role of both DBP and GC in cancer risk.

One limitation of our meta-analysis is that we were not able to take into account other factors, like vitamin D intake, vitamin D levels, sun exposure, VDR, and 25(OH)D plasma levels that could modify the risk estimates, as reported in previous publications (50–54). Furthermore, the lack of data made it not possible to assess the association between DBP serologic levels and each cancer type so that our conclusions should be interpreted cautiously. Finally, it is also possible that other polymorphisms in the GC gene not here evaluated because of the low number of published studies, may in fact influence the risk of cancer.

In conclusion, we suggested a borderline reduction of cancer risk at any site for subjects with high serologic DBP levels compared with subjects with low serologic DBP levels. We did not observe any statistically significant association between variants in the GC gene and cancer risk in this meta-analysis. These results need to be validated in further studies.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: S. Raimondi, S. Gandini
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