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Ethnicity as modifier of risk for Vitamin D receptors polymorphisms: Comprehensive meta-analysis of all cancer sites

Patrizia Gnagnarella [a,*], Sara Raimondi [b], Valentina Aristarco [c], Harriet Johansson [c], Federica Bellerba [b], Federica Corso [b], Simone Pietro De Angelis [b], Pietro Belloni [b,d], Saverio Caini [e], Sara Gandini [b]

[a] Division of Epidemiology and Biostatistics, IEO European Institute of Oncology IRCCS, Milan, Italy
[b] Department of Experimental Oncology, IEO European Institute of Oncology IRCCS, Milan, Italy
[c] Division of Cancer Prevention and Genetics, IEO European Institute of Oncology IRCCS, Milan, Italy
[d] Department of Statistical Sciences, University of Padua, Italy
[e] Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy

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ABSTRACT

Vitamin D receptors polymorphisms are found to be associated with several cancers. Since their prevalence vary across ethnicities and ethnicity itself seems to influence the cancer risk, a comprehensive meta-analysis was performed to investigate the role of VDR Fok1, Bsm1, Taq1, Apa1, Cdx2 and cancer risk at specific organ sites. Odds ratios, calculated with random-effects models, summarized one-hundred-ninety-two independent studies for twenty-two cancer sites. Evidence was provided that *Fok1*, *Bsm1*, *Cdx2*, *Apa1* and *Taq1* are linked to cancer susceptibility for colorectal, lung, ovarian, skin, multiple myeloma and brain cancer. Stratifying by ethnicity, some differences were found, partially explained by minor allele frequency (MAF), for colorectal cancer, ovarian and prostate cancer in Caucasian and prostate cancer in Asian populations. In summary, ethnicity may be a modifier of cancer risk, in particular for hormone dependent cancers and it should be considered evaluating the effect of VDR on cancer risk.

1. Introduction

According to the GLOBOCAN (Bray et al., 2018), cancer ranks from the first to fourth leading cause of death worldwide in most high-income countries. Incidence and mortality rates vary across regions depending on the degree of socioeconomic status and associated life style factors, but genetic factors also have an established broad influence on cancer risk (Hung et al., 2004; Bandera et al., 2017). Of note, most of the hereditary component of cancer risk cannot explained by mutations in known high penetrance genes (e.g. BRCA), and variants in moderate-to-low risk genes are instead thought to be the most common basis of genetic susceptibility to cancer.

Numerous studies investigated the extra-skeletal activities of vitamin D (VD) over the last two decades, suggesting a protective role on the onset, progression and prognosis of several chronic disease, such as autoimmune diseases, metabolic syndromes, cardiovascular disease, cancers, and all-cause mortality (Hewison, 2012; Muscogiuri et al., 2012; Pilz et al., 2012; Souberbielle et al., 2010). Regarding carcinogenesis, there is in vitro and in vivo evidence that VD may affect all steps of tumorigenesis, from initiation to metastasis (Skrajnowska and Bobrowska-Korczak, 2019; Chen et al., 2018a; Evans et al., 1996). The active VD metabolite, 1,25(OH)2D, exerts its activity by binding to the intracellular vitamin D receptor (VDR), which mediates transcriptional activation and repression of target genes (Prufer and Barsony, 2002; Haussler et al., 1998). Specifically, VDR interacts with VD response elements (VDRE) on the DNA to produce biological effects (Ramagopalan et al., 2010; Zhang and Song, 2014; Bouillon et al., 2008). VDR is active in virtually all tissues and cell types, including cancer cells (Wang et al., 2012; Lee et al., 2018).

Genetic variation may influence individual VD status limiting

Abbreviations: RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism; VD, Vitamin D; VDR, vitamin D receptor; OR, odds ratio; CI, confidence interval; H-W, Hardy-Weinberg; vs, versus; CRC, Colorectal Cancer; BCC, Basal Cell Carcinoma; SCC, Squamous Cell Carcinoma; MAF, minor allele frequency; VD, vitamin D; SOR, summary odds ratio; WT, wild-type; Hom, homozygous; Het, heterozygous.

* Corresponding author at: Division of Epidemiology and Biostatistics, European Institute of Oncology IRCCS, Viale Ripamonti, 435, 20141 Milan, Italy.
E-mail address: Patrizia.gnagnarella@ieo.it (P. Gnagnarella).

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synthesis in the skin, hydroxylation in the liver and kidney, transportation, metabolism, and degradation, and could potentially influence the binding of 1,25(OH)2D to its receptor VDR, the transcriptional activity of the receptor and its binding to VDRE, thus affecting its activity in multiple aspects (Tagliabue et al., 2015; Rai et al., 2017). Therefore, VDR and other common polymorphisms of genes associated with VD metabolism were hypothesized to be associated with cancer risk (Kostner et al., 2009).

To date, the most frequently studied single nucleotide polymorphisms (SNPs) of the VDR are *Fok1* (rs10735810), *Bsm1* (rs1544410), *Apa1* (rs7975232), *Taq1* (rs731236) and *Cdx2* (rs11568820). Our group previously published numerous meta-analysis (Gandini et al., 2009; Raimondi et al., 2009, 2014; Gnagnarella et al., 2014; Serrano et al., 2016) and narrative reviews (Tagliabue et al., 2015; Gandini et al., 2014) addressing associations between VDR polymorphisms and site-specific cancer risk. We found some significant associations for all genotypes with numerous cancer sites, but other ethnicities rather than Caucasian were not associated with cancer risk. Due to the increasing number of published studies, it is now possible to explore the effect of SNPs in modulating cancer risk among ethnic sub-groups. It is well established that VDR genotypes vary widely among ethnic sub-groups as reported by differences in allele frequency across populations (Uitterlinden et al., 2004; Tayeb et al., 2003). The most recent meta-analysis found some significant associations for breast and lung cancer in African American and Asian respectively (Li et al., 2018, 2019; Yu et al., 2018) but the number of papers for some populations are still limited. Here we performed an updated comprehensive meta-analysis covering twenty-two cancer sites and assessing heterogeneity of effect by ethnicity as well.

2. Materials and methods

2.1. Publication strategy

A systematic literature search was conducted and reported following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (Stroup et al., 2000). Published reports were gathered from the following databases: PUBMED, Ovid Medline, EMBASE, and ISI Web of Knowledge up to August 2020. We used any of the following MeSH terms and text words: "VDR", "Vitamin D receptor", or "*Fok1*", "*Bsm1*" "*Taq1*", "*Apa1*" and "*Cdx2*", in combination with "cancer" or "tumor", without any restriction. We also performed manual searches of references cited in the retrieved articles and preceding reviews on the topic.

2.2. Study selection

The articles were selected according with the following inclusion criteria: 1) Sufficient information to estimate the relative risk and 95 % confidence intervals (CIs) for the association between VDR polymorphism and cancer. This includes odds ratio (OR), relative risks or crude data and corresponding standard errors, 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. We excluded studies evaluating the risk of benign conditions (e.g. colorectal adenoma); studies that considered benign hyperplasia as controls; and studies with zero subjects in the wild-type group for cases or controls. Furthermore, we excluded studies that did not include risk estimates for homozygous or heterozygous variants vs. wild-type.

2.3. Data extraction and quality assessment

A standardized data-collection protocol was used to gather the relevant data from each selected article. 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 (PG, HJ and AV). Any disagreements were settled down by discussion. For each study we pulled out information on authors, journal and year of publication, country, ethnicity of study population, source of controls, number of cases and controls (separately for genotypes), relative risk estimates and the corresponding CI, along with possible confounders considered in the adjusted risk estimates and minor allele frequency (MAF). When data were reported by ethnicity or by cancer sites, the estimates were extracted separately for the two factors.

2.4. Statistical analysis

Risk estimates assessing the association between VDR polymorphisms and cancer risk comparing heterozygous carriers and homozygous carriers with wild-type subjects were retrieved from all included studies. When no estimates were given, crude estimates were calculated from tabular data. We used Woolf's formula to evaluate the standard error of the log relative risk. Every measure of association, and corresponding confidence intervals, were transformed into log relative risks, and the corresponding variance was calculated using the formula proposed by (Greenland (1987)).

The Summary Odd Ratios (SORs) were estimated by pooling the study-specific estimates with the random effects models as described by van Houwelingen (van Houwelingen et al., 2002), with summary effect size obtained from maximum likelihood estimation. Confidence intervals were computed assuming an underlying t-distribution.

We assessed the homogeneity of the effects across studies by the I^2, that could be interpreted as the percentage of total variation across several studies that is attributable to 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 were found at least three studies) and stratified by ethnicity; moreover we produced forest plots including both the OR from each single study and the SOR.

To assess the influence of possible sources of bias, we considered the STROBE checklist proposed for observational epidemiologic studies (von et al., 2008). According to the STROBE checklist, we used meta-regression and subgroup analysis to assess the influence on between-study heterogeneity of study features (such as the study population and study design) and other factors that could influence the estimates, such as the source of SNP determination (blood vs. tissue), type of controls, ethnicity, adjustment for confounding factors, and others.

Furthermore, deviations from the Hardy-Weinberg (H-W) equilibrium for frequency of VDR genotypes in controls were assessed using Chi-square test. Sensitivity analyses were carried out excluding the studies that were not in H-W equilibrium and the studies for which the reported MAF differed from HapMap (http://hapmap.ncbi.nlm.nih.gov/) when the reported MAF were 50 % less or double than the closest ethnic group.

Publication bias was evaluated graphically with a funnel plot, and formally assessed by applying the Macaskill test (Macaskill et al., 2001). Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC; version 9.2) and R Statistical Software (Version 3.6.1).

3. Results

3.1. Study characteristics

According to our research strategy, we identified 606 articles. After applying inclusion and exclusion criteria (Fig. 1), we ended up with 192 independent studies included, involving 78,628 cases and 98,209 cancer-free controls. Selected studies presented data for twenty-two cancer sites: bladder, brain, breast, male breast, colorectal (CRC), esophageal, gallbladder, gastric, head and neck, kidney, leukemia, liver, lung, multiple myeloma, non-Hodgkin lymphoma, ocular, ovary, pancreas, prostate, sarcoma, skin (melanoma and non-melanoma skin

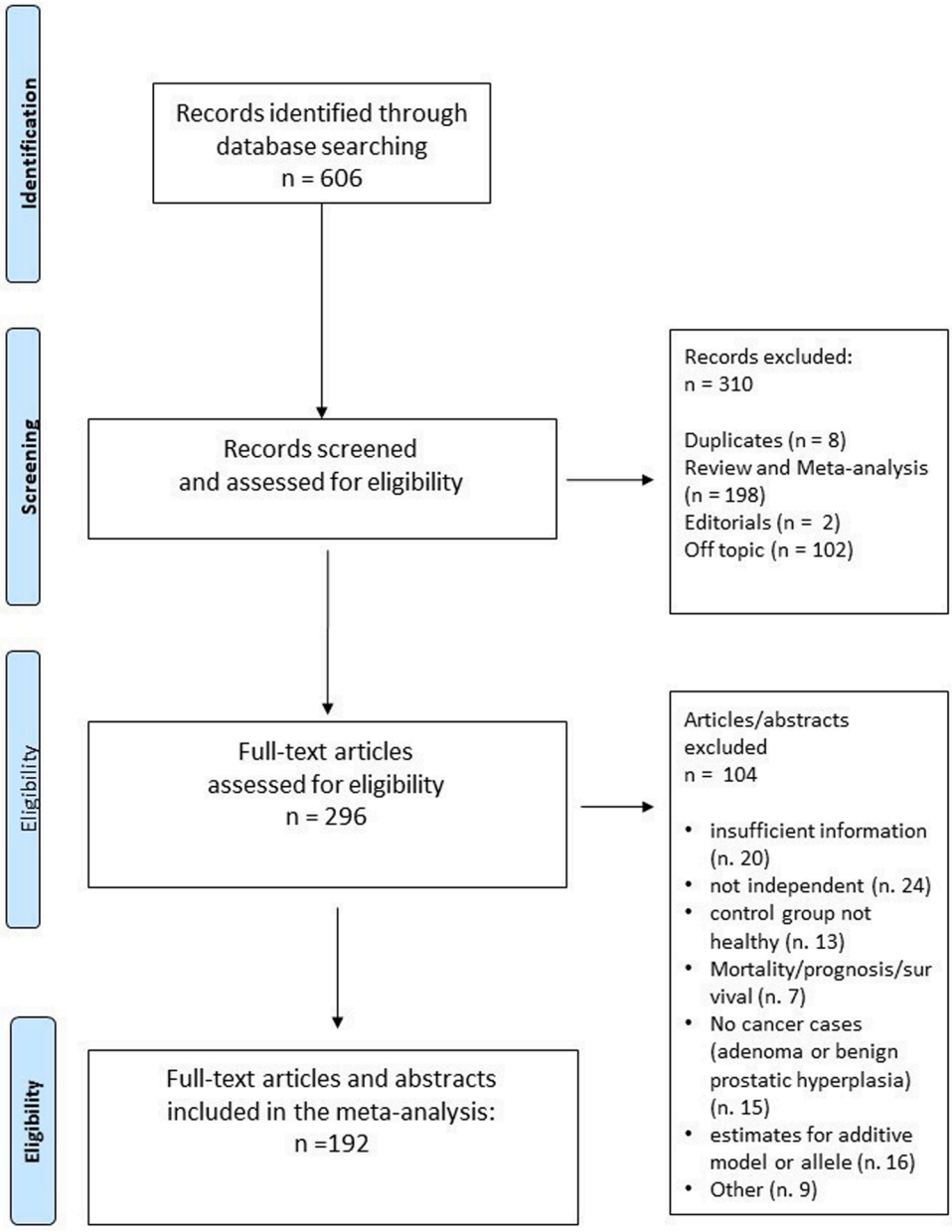

Fig. 1. Study flow chart for the process of selecting the enrolled studies.

cancer), pediatric solid tumor and thyroid (follicular, medullary and papillary). We included one paper evaluating tobacco-related cancer risk and VDR polymorphisms association (Deschasaux et al., 2015). Among the 543 estimates from 192 studies, 92 were based on Caucasian, 37 on Asian, 23 on African-American and African, 6 on Hispanic, 7 on mixed ethnicities and 47 on other ethnicities (i.e., Indian, Bangladeshi, Turkish and Iranian). The characteristics of the included studies are presented in Supplementary Table 1.

Significant associations are reported in the Tables 1 and 2. Forest plots for homozygous variants vs. wild-type stratified by ethnicities are reported in Supplementary figures (Supplementary Figs. 1–28). We did not find any evidence of publication bias for the significant associations found.

3.2. Association between the VDR polymorphism cancer risk at specific organ sites

3.2.1. Breast cancer

Between 1999 to 2019 forty-five studies published results on the association of any of *Fok1*, *Bsm1, Taq1, Apa1,* or *Cdx2* with breast cancer risk, for a total of 25,937 cases and 34,632 controls. Most of them were carried out in USA and Canada (n = 13) and in European countries (n = 10). Seventeen studies were case-control studies with population-based controls and fifteen analyzed a Caucasian population (Supplementary Table 1).

Overall, no significant associations were observed between any VDR polymorphism and breast cancer risk, neither for the homozygous, nor the heterozygous group compared to wild-type subjects (Supplementary Figs. 3–7). In the subgroup analysis by ethnicity (Table 2), our results suggested a significant breast cancer risk reduction for *Apa1* polymorphism among Asian considering the heterozygote variant vs. wild-type (*Aa* vs. *AA* SOR = 0.44, 95 % CI: 0.31–0.62) with no evidence of

Table 1
Overall significant summary odds ratios for the association of VDR polymorphisms with different types of cancer.

Contrasts	Cancer	VDR	N of estimates	OR	Low 95 % CI	Up 95 % CI	I^2%
Hom vs WT	Colorectal	*Bsm1*	24	0.61	0.38	0.97	96
	Ovary	*Fok1*	7	1.21	1.07	1.36	0
	Lung	*Bsm1*	4	0.80	0.69	0.92	0
		Taq1	4	0.83	0.69	0.99	0
	Multiple Myeloma	*Fok1*	3	2.95	1.54	5.64	52
		Apa1	3	2.04	1.33	3.13	2
Het vs WT	Colorectal	*Bsm1*	24	0.72	0.55	0.94	95
		Cdx2	6	1.10	1.01	1.19	0
	Ovary	*Fok1*	7	1.11	1.01	1.21	0
		Bsm1	7	1.17	1.01	1.35	12
	Skin	*Bsm1*	11	0.87	0.79	0.96	0
	Brain	*Fok1*	3	0.75	0.60	0.94	0
	Multiple Myeloma	*Fok1*	3	1.52	1.25	1.85	0

Hom: homozygous; WT: wild-type; Het: heterozygous; OR – Odds ratio; I^2 - heterogeneity.

between-study heterogeneity ($I^2 = 0\%$) (Guo et al., 2015; Huang et al., 2012; Hou et al., 2002), but only three studies were included (Table 2). Performing sensitivity analyses excluding studies with inconsistencies in H-W equilibrium (John et al., 2007; Anderson et al., 2011; Barroso et al., 2008; Mishra et al., 2013; Talaneh et al., 2017; Akilzhanova et al., 2013) or studies for which the reported MAF differed from reference (http://hapmap.ncbi.nlm.nih.gov/), we did not find any significant associations.

3.2.2. Prostate cancer

Forty-one eligible studies were published between 1998 and 2020 (Supplementary Table 1; Supplementary Figs. 21–25) analyzing the association with prostate cancer risk. A total of 8449 cases and 9820 controls were included. Fourteen studies were carried out in USA and Canada, twenty-two were case-control studies with hospital-based controls and twenty-one analyzed a Caucasian population. The pooled results indicated that VDR polymorphisms are not associated with prostate cancer risk in the overall population, but we found a significant increased risk of 8% for the Caucasian population for *Fok1* polymorphism comparing the heterozygote group vs. wild-type (*Ff* vs. *FF* SOR = 1.08, 95 % CI: 1.01–1.16), with no evidence of between-study heterogeneity ($I^2 = 0\%$) (Table 2). In the subgroup analysis by ethnicity, our results suggested also a significant prostate cancer risk reduction for *Apa1* polymorphism considering the homozygote variant vs. wild-type (*Aa* vs. *AA* SOR = 0.70, 95 % CI: 0.49–0.99) with no evidence of between-study heterogeneity ($I^2 = 0\%$) (Guo et al., 2015; Huang et al., 2012; Hou et al., 2002) including five studies (Table 2).

3.2.3. Colorectal cancer

A total of thirty-six studies examined the association between CRC and VDR polymorphisms, including 17,122 cases and 20,082 controls (Supplementary Table 1; Supplementary Figs. 8 and 9). They analyzed cancer risk associations mainly in Caucasian (n = 16), Asian (n = 8), and other populations (n = 12). Twenty-two studies were case-control studies with hospital-based controls. The results of our meta-analysis suggested a significant risk reduction of CRC for carriers of both *BB* and *Bb* genotype compared to carriers of *bb* genotype, respectively SOR = 0.61 (95 %CI: 0.38−0.97) and SOR = 0.72 (95 %CI: 0.55−0.94) with a high between-study heterogeneity ($I^2 = 96$ % and $I^2 = 95$ % respectively) in both comparisons (Table 1). The subgroup analysis of Caucasian population confirm only the significant risk reduction comparing for *BB* vs. *bb* genotype (SOR = 0.87; 95 %CI: 0.80−0.95), with no evidence of between-study heterogeneity ($I^2 = 0\%$) (Table 2; Supplementary Fig. 9). Excluding studies that showed inconsistencies concerning H–W equilibrium (Alkhayal et al., 2016; Gunduz et al., 2012; Laczmanska et al., 2014; Li et al., 2009; Rasool et al., 2014; Theodoratou et al., 2008), we did not find any significant associations. Contrasting result were found for *Cdx2* polymorphism comparing the heterozygote group vs. wild-type. The Gg compared to GG genotype (wild-type) was found to carry a significantly increased risk of 10 % for the overall population with no evidence of heterogeneity (all the studies were performed on Caucasian population) (Table 1). In sensitivity analysis, these results were not confirmed.

3.2.4. Skin cancer

A total of eleven studies examined the association between skin cancer and VDR polymorphisms, including 4639 cases and 3833 controls (Supplementary Table 1; Supplementary Figs. 26 and 27). There were 8 estimates evaluating risk association for cutaneous melanoma, 3 estimates for basal cell carcinoma (BCC), two for squamous cell carcinoma (SCC) and one for BCC or SCC (Burns et al., 2017). Seven studies were from Europe and three from USA (Supplementary Table 1). Seven studies were hospital-based and four population-based and all studies presented results for a Caucasian population. We found a significantly decreased skin cancer risk by 13 % for *Bsm1* polymorphism comparing heterozygous group vs. wild-type (*bB* vs. *bb* SOR = 0.87, 95 % CI: 0.79−0.96) with no evidence of between-study heterogeneity ($I^2 = 0\%$) among Caucasians (Table 2).

In the subgroup analysis by ethnicity, our results suggested also a significantly increased skin cancer risk for *Taq1* polymorphism considering the heterozygote variant vs. wild-type (*Tt* vs. *TT* SOR = 1.22, 95 % CI: 1.00–0147) with a 56 % of between-study heterogeneity (Table 2).

3.2.5. Ovarian cancer

Seven studies evaluated the association with ovarian cancer (Supplementary Table 1, Supplementary Fig. 20), including 4091 cases and 6750 controls. Only one study was hospital-based (Mostowska et al., 2016), three studies were conducted in USA (Grant et al., 2013; Lurie et al., 2007; Tworoger et al., 2009), two in USA and Europe (Lurie et al., 2011; Clendenen et al., 2008), one in India (Mohapatra et al., 2013) and one in Poland (Mostowska et al., 2016). Six studies presented results for Caucasian populations. The pooled results indicated that *Fok1* and *Bsm1*

Table 2
Significant summary odds ratios for the association of VDR polymorphisms with different types of cancer and ethnicity.

Contrasts	Cancer	Ethnicity	VDR	N of estimates	OR	Low 95 %CI	Up 95 %CI	I^2%
Hom vs WT	Colorectal	Caucasian	*Bsm1*	12	0.87	0.80	0.95	0
	Ovary	Caucasian	*Fok1*	5	1.20	1.06	1.36	0
	Prostate	Asian	*Apa1*	5	0.70	0.49	0.99	0
Het vs WT	Colorectal	Caucasian	*Cdx2*	6	1.10	1.01	1.19	0
	Ovary	Caucasian	*Fok1*	5	1.10	1.01	1.21	0
			Bsm1	5	1.20	1.04	1.39	14
	Prostate	Caucasian	*Fok1*	14	1.08	1.01	1.16	0
	Breast	Asian	ApaI	3	0.44	0.31	0.62	0
	Skin	Caucasian	*Bsm1*	11	0.87	0.79	0.96	0
			Taq1	10	1.22	1.00	1.47	56

Hom: homozygous; WT: wild-type; Het: heterozygous; OR – Odds ratio; I^2 - heterogeneity.

polymorphisms were positively associated with ovarian cancer risk (Table 1). We found a significantly increased risk by 21 % and 11 % for *Fok1* polymorphism comparing the homozygous group vs. wild-type (*ff* vs. *FF*: SOR = 1.21, 95 % CI: 1.07–1.36) and heterozygous group vs. wild-type (*Ff* vs. *FF*: SOR = 1.11, 95 % CI: 1.01–1.21) with no evidence of between-study heterogeneity ($I^2 = 0\%$) (Supplementary Fig. 20). The subgroup analysis of Caucasian population confirms the significant increased risks for both genotypes (Table 2).

We also found a significant increased risk of 17 % for the *Bsm1* polymorphism in the heterozygous group (*Bb* vs *bb*: SOR = 1.17, 95 % CI: 1.01–1.35, $I^2 = 12\%$) (Table 1) and in Caucasian (*Bb* vs *bb*: SOR = 1.20, 95 % CI: 1.04–1.39, $I^2 = 14\%$) (Table 2), but not confirmed in sensitivity analysis excluding studies with inconsistencies with H–W equilibrium.

3.2.6. Other cancers

Fifty-two studies were published investigating the association of *Fok1*, *Bsm1, Taq1, Apa1, Cdx2* with remaining sixteen cancer sites (Supplementary Table 1). Two additional papers evaluated the risk estimates for pediatric solid tumors (Bienertova-Vasku et al., 2016) and for tobacco-related cancers (Deschasaux et al., 2015). We were able to calculate an overall risk estimate only for lung, bladder, brain, kidney, thyroid, head and neck, liver, gastric, multiple myeloma, sarcoma and non-Hodgkin lymphoma (Supplementary Figs. 1 and 2; 10–19; 28) because they had estimates from at least three studies. For lung cancer, we found a significant decreased risk by 20 % and 17 % for *Bsm1* and *Taq1* polymorphisms in the homozygote group vs. wild-type (*BB* vs. *bb* SOR = 0.80, 95 % CI: 0.69−0.92 and *tt* vs. *TT* SOR = 0.83, 95 % CI: 0.69−0.99) with no evidence of between-study heterogeneity ($I^2 = 0\%$) (Table 1; Supplementary Fig. 18). For multiple myeloma, we found a significant more than two-fold increased risk for *Fok1* and *Apa1* polymorphisms in the homozygote group vs. wild-type (*ff* vs. *FF* SOR = 2.95, 95 % CI: 1.54–5.64 and *aa* vs. *AA* SOR = 2.04, 95 % CI:1.33−3.13) with evidence of between-study heterogeneity ($I^2 = 52\%$ and $I^2 = 2$ respectively) (Table 1; Supplementary Fig. 14). In the heterozygotes model, we observed a significant 52 % increased risk only for *Fok1*, but only 3 studies were included.

We found a significant risk reduction of 25 % for brain cancer for *Fok1* polymorphism comparing the heterozygous group vs. wild-type model (*Ff* vs. *FF* SOR = 0.75, 95 % CI: 0.60−0.94, $I^2 = 0\%$) (Table 1; Supplementary Fig. 1).

In the subgroup analysis for ethnicity, no significant associations were observed between VDRs polymorphisms and these cancer sites (Table 2).

3.2.7. Results from previous meta-analyses

We compared our results with recent meta-analyses published from 2016 until now. We found eighteen meta-analysis (Table 3) analyzing the association between *Fok1*, *Bsm1*, *Taq1*, *Apa1*, *Cdx2* polymorphisms and risk with breast (Li et al., 2018; Iqbal and Khan, 2017; Lu et al., 2016), CRC (Pan et al., 2018; Sheng et al., 2017), lung (Li et al., 2019; Yu et al., 2018), ovarian (Li et al., 2018; Chen and Zhu, 2018), prostate (Chen et al., 2018b; Fei et al., 2016; Kang et al., 2016, 2018; Mi et al., 2017; Wang et al., 2016) and skin (BCC and SCC) cancer (VON Schuckmann et al., 2016). They found significant associations for *Bsm1*, *Cdx2*, *Fok1* and *Taq1* (Table 4). Eight new meta-analysis have been published on *Apa1* polymorphism in association with breast, CRC, lung, ovarian and prostate cancer (Li et al., 2018, 2019; Yu et al., 2018; Iqbal and Khan, 2017; Pan et al., 2018; Wang et al., 2016) but no significant estimates were found. Two meta-analysis found significant associations for breast cancer (Li et al., 2018; Iqbal and Khan, 2017). Iqbal found an increased risk for the *Bsm1* homozygote variant in the overall population (Iqbal and Khan, 2017), and Li et al. (2018) observed an increased breast cancer risk in African-American for the homozygotes variant of the *Cdx2*, including only two studies (Li et al., 2018). The results are contrasting for *Taq1* polymorphism (Table 4). Li et al. (2018) suggested an increased breast cancer risk for *tt* genotype vs *TT* in all populations and in Caucasians (Li et al., 2018), while Iqbal and Khan (2017) found an overall 11 % risk reduction.

Table 3
Meta-analysis published by cancer sites and VDR from 2016 to 2018.

Cancer type	Author	*Apa1*	*Fok1*	*Bsm1*	*Cdx2*	*Taq1*
Breast	Iqbal, 2017 (Burns et al., 2017)	x	x	x	x	x
	Li, 2018 (Mostowska et al., 2016)	x	x	x	x	x
	Lu, 2016 (Grant et al., 2013)	x	x	x		x
Colorectal	Cho, 2018	x	x	x	x	x
	Pan, 2018 (Lurie et al., 2007)	x	x	x	x	x
	Sheng, 2017 (Tworoger et al., 2009)					x
Lung	Li, 2019 (Lurie et al., 2011)	x		x	x	x
	Yu, 2018 (Clendenen et al., 2008)			x		
Ovary	Duan, 2020	x	x	x	x	x
	Chen, 2018 (Mohapatra et al., 2013)		x			
	Li, 2018 (Mostowska et al., 2016)	x	x	x	x	x
	Chen, 2018 (Bienertova-Vasku et al., 2016)					x
Prostate	Fei, 2016 (Iqbal and Khan, 2017)					x
	Kang, 2016 (Lu et al., 2016)		x			
	Kang, 2018 (Pan et al., 2018)			x		x
	Mi, 2017 (Sheng et al., 2017)		x			
Skin (BCC and SCC)	Wang, 2016 (Chen and Zhu, 2018)	x			x	
	Von Schuckmann, 2016 (Chen et al., 2018b)		x	x		

For CRC, only one meta-analysis found a significant 21 % risk reduction for the *BB* variant vs wild-type (Pan et al., 2018). Regarding lung cancer the most recent reports found a significant risk reduction with lung cancer (Li et al., 2019; Yu et al., 2018; Duan et al., 2020) for the homozygote and heterozygote variant compared to wild-type of *Bsm1* polymorphim (Li et al., 2019; Yu et al., 2018) (Table 4) and this effect was stronger in Asian population.

Regarding prostate cancer, five meta-analysis have been recently published, two for *Fok1* (Kang et al., 2016; Mi et al., 2017) and three for *Taq1* polymorphims (Chen et al., 2018b; Fei et al., 2016; Kang et al., 2018). An increased risk was observed in Caucasians for the *ff* genotype by Mi (Mi et al., 2017) and for *ff* and *Ff* vs *FF* by Kang (Kang et al., 2016). A risk reduction for *tt* compared to *TT* carriers was observed in the overall population (Chen et al., 2018b; Fei et al., 2016) and in Asian population (Chen et al., 2018b; Kang et al., 2018) (Table 4).

Significant associations were found for *Fok1* polymorphism with ovarian cancer in two meta-analyses (Table 4) comparing *ff* and *fF* with *FF* carriers (Li et al., 2018; Chen and Zhu, 2018).

4. Discussion

The present meta-analysis represents the most comprehensive and critical synthesis of available data investigating the associations between VDR *Fok1* (rs2228570), *Bsm1* (rs1544410), *Taq1* (rs731236), *Apa1* (rs7975232), *Cdx2* (rs11568820) and site-specific cancer risk, overall and by ethnicity. Pooling together the available estimates, we provide evidence that *Fok1*, *Bsm1*, *Cdx2, Apa1* and *Taq1* are linked to cancer susceptibility for specific cancer sites: CRC, lung, ovarian, skin

Table 4
Significant estimates found in the meta-analyses retrieved.

Contrast	Cancer	Overall/Ethnicity	VDR	Author	n. study	OR	Low 95 %	Up 95 %	I^2, %
Hom vs WT	Breast	Overall	***Bsm1***	Iqbal, 2017 (Burns et al., 2017)	*20*	**1.18**	**1.05**	**1.32**	57.4
		African-American	***Cdx2***	Li, 2018 (Mostowska et al., 2016)	2	**1.90**	**1.03**	**3.49**	0
		Overall	***Taq1***	Iqbal, 2017 (Burns et al., 2017)	*13*	**0.89**	**0.81**	**0.98**	9.4
				Li, 2018 (Mostowska et al., 2016)	15	**1.11**	**1.00**	**1.22**	7.1
		Caucasian		Li, 2018 (Mostowska et al., 2016)	11	**1.11**	**1.00**	**1.23**	3.1
	Colorectal	Overall	***Bsm1***	Pan, 2018 (Lurie et al., 2007)	23	**0.79**	**0.64**	**0.97**	85.5
		Asian		Li, 2019 (Lurie et al., 2011)	4	**0.23**	**0.10**	**0.54**	
	Lung	Asian	***Bsm1***	Yu, 2018 (Clendenen et al., 2008)	4	**0.23**	**0.10**	**0.55**	0
		Overall			8	**0.76**	**0.60**	**0.96**	38.4
		Overall		Duan, 2020	10	**0.63**	**0.40**	**0.99**	50
		Caucasian	***Fok1***	Kang, 2016 (Lu et al., 2016)	*15*	**1.11**	**1.01**	**1.22**	0
				Mi, 2017 (Sheng et al., 2017)	14	**1.06**	**1.00**	**1.13**	0
	Prostate	Overall/Asian		Chen, 2018 (Bienertova-Vasku et al., 2016)	13	**0.50**	**0.30**	**0.83**	0
		Overall	***Taq1***	Fei, 2016 (Iqbal and Khan, 2017)	*24*	**0.84**	**0.70**	**0.99**	34.4
		Asian		Kang, 2018 (Lu et al., 2016)	*14*	**0.63**	**0.41**	**0.95**	0
	Ovary	Overall	***Fok1***	Chen, 2018 (Mohapatra et al., 2013)	*7*	**1.18**	**1.05**	**1.32**	0
				Li, 2018 (Mostowska et al., 2016)	12	**1.15**	**1.03**	**1.29**	
Het vs WT		Asian		Li, 2019 (Lurie et al., 2011)	4	**0.37**	**0.25**	**0.54**	
		Overall			8	**0.59**	**0.39**	**0.88**	77.9
		Asian	***Bsm1***	Yu, 2018 (Clendenen et al., 2008)	4	**0.37**	**0.28**	**0.48**	15
	Lung	Overall			6	**0.46**	**0.30**	**0.71**	73
		Overall		Duan, 2020	10	**0.53**	**0.40**	**0.77**	86
		Overall	***Cdx2***	Li, 2019 (Lurie et al., 2011)	2	**0.80**	**0.66**	**0.98**	0
		Asian	***Taq1***	Li, 2019 (Lurie et al., 2011)	3	**0.62**	**0.43**	**0.90**	
	Ovary	Overall	***Fok1***	Chen, 2018 (Mohapatra et al., 2013)	*7*	**1.12**	**1.03**	**1.22**	26.6
				Li, 2018 (Mostowska et al., 2016)	12	**1.09**	**1.01**	**1.19**	32.9
	Prostate	Caucasian	***Fok1***	Kang, 2016 (Lu et al., 2016)	*15*	**1.07**	**1.00**	**1.15**	0

Hom: homozygous; WT: wild-type; Het: heterozygous; OR – Odds ratio; I^2 - heterogeneity.

and multiple myeloma. With increasing number of independent studies, we aimed at evaluating the effect of SNPs in modulating cancer risk among ethnic sub-groups. Ethnicity accounted for some of the heterogeneity in cancer risk associated with VDR polymorphisms, because of the underlying differences in MAF across populations for CRC, ovarian, skin and prostate cancer in Caucasian and breast and prostate cancer in Asian populations. Notably, high differences between the MAF and the reference values were found, in particular for the Asian populations, and these differences may partially explain some contrasting results, but the number of studies available is limited to give a firm conclusion.

In our meta-analysis, it is of interest to note that we found an increased risk for ovarian cancer for *Bsm1* polymorphism, not previously found (Raimondi et al., 2014; Li et al., 2018) and in the opposite direction compared to other cancer site (CRC, lung, skin). The *Bb* genotype showed an association with a 17 % increased risk, especially in Caucasian (20 %), not found in the homozygotes model (*BB* vs *bb*). However the hospital based study conducted in Poland (Mostowska et al., 2016), that suggested a significantly 56 % higher risk of ovarian cancer for carriers of *Bb* compared to *bb* genotype, presented data for the MAF much lower than usually reported for Caucasians. Pooling together the available estimates, we provide evidence that *Fok1* may be associated with ovarian cancer in line with our previous meta-analysis (Gnagnarella et al., 2014) and two recent meta-analyses (Li et al., 2018; Chen and Zhu, 2018). A significantly increased risk was found among both *ff* and *Ff* carriers compared to the wild-type *FF* genotype. These results are confirmed in the subgroup analysis, in Caucasian, but not in the sensitivity analysis taking into account the quality of studies. From a functional point of view, the *f* allele of the *Fok1* restriction fragment length polymorphism, located in the coding region of the VDR gene, results in the production of a VDR protein that is three amino acids longer. The longer the VDR amino acid chain, the less responsive it becomes to 1,25 (OH)2D, and the lower the transcription rate (Colin et al., 2000). This may contribute to reduce immunity response, thus potentially influencing tumorigenesis. Moreover, we may speculate that VDR polymorphisms interfere in the complex relationship between VD and cancer pathogenesis of hormone dependent cancers (such as the down-regulation of the oestrogen receptor signalling pathway (Li et al., 2018)) in an ethnic-group specific way, but further investigations on other genetic or environmental specific factors are warranted.

We provide evidence that *Cdx2* and *Bsm1* are associated with CRC risk. For *Cdx2* we found a 10 % significant increase risks in CRC, comparing the *Gg* vs. GG genotypes in Caucasian population (Theodoratou et al., 2008; Flugge et al., 2007; Ochs-Balcom et al., 2008; Slattery et al., 2009). The *Cdx2* polymorphism (A/G) is located in the core sequence for the *Cdx*2 binding in the promoter region of the VDR gene affecting the transcriptional activity. Ecological studies indicate a strong correlation between frequency of *Cdx-2 A*-allele and the incidence rates of hip fracture from different ethnic groups (Fang et al., 2003). As reported by Fang (Fang et al., 2003), the hip fracture incidence rates appeared to be highest in subjects of northern European and lowest in those of Asian and African origin whereas the *A*-allele frequency is lower in North European (19 %) and higher in Asian and African subjects (43 % and 74 % respectively) suggesting a protective effect of this allele and an impact on vitamin D status (Arai et al., 2001). These different frequencies can partially explain the effect of ethnicity interference in the complex relationship between VD and cancer pathogenesis.

Moreover, we provide evidence that *Bsm1* was associated with a significant reduced CRC risk in both the homozygotes and heterozygotes models, confirming previous meta-analysis (Raimondi et al., 2014; Pan et al., 2018). As reported by Slattery (Slattery et al., 2004) the presence of the *B*, *A*, and *t* RFLP alleles for *Bsm1*, *Apa1*, and *Taq1*, either alone or in combination, has been associated with increased mRNA expression of the VDR gene, increased serum levels of 1,25-dihydroxy vitamin D, and increased levels of osteocalcin (Morrison et al., 1994; Evans et al., 2000), reported to be protective against the development of colonic adenomas (Slattery et al., 2004).

Our meta-analysis identified a significant association of *Bsm1* polymorphism with skin cancer risk in the heterozygote model (*Bb* vs. *bb*) confirming our previous meta-analysis (Raimondi et al., 2014) but we failed to find a significant association in the homozygotes model.

Lung cancer was found significantly associated with *Bsm1* and *Taq1* polymorphisms (overall). These results were not confirmed in the subgroup and sensitivity analysis due to the few studies included (4 studies).

Three meta-analyses have been recently published (Li et al., 2019; Yu et al., 2018) (Duan, 2020) with similar results.

Our meta-analysis found for the first time an association between *Fok1* polymorphism and **brain cancer and multiple myeloma**, based on three studies. A significant 25 % risk reduction comparing the heterozygous genotype vs. wild-type, not found in the homozygotes variant model. While *Fok1* was found to be associated with an increased risk for multiple myeloma in the homozygotes and heterozygotes model, but further studies are necessary to clarify these observations.

We failed to found a significant association with breast cancer risk for VDR genotypes and in particular for *Bsm1* polymorphisms, as reported by a recent meta-analysis (Li et al., 2018; Iqbal and Khan, 2017) (an 18 % increased risk). We observed a protective effect for *Apa1* in the heterozygotes model in Asian population, but only 3 studies were included.

In our meta-analysis, it is of interest to note that we found a prostate cancer risk reduction for *Apa1* in the homozygotes model in Asian population, while in Caucasian we observed an increased risk for *Fok1* polymorphism for the heterozygous model compared to wild-type, as reported by Kang (Kang et al., 2016).

Our meta-analysis has several strengths. We abided by established guidelines for conducting rigorous systematic reviews and meta-analysis (Higgins and Thompson, 2002; Tricco et al., 2015) and calculated summary risk estimates for the association between the most studied VDR polymorphisms possible and cancer risk at twenty-one body sites, thus providing a comprehensive and updated critical appraisal of the role of VDR polymorphisms on cancer risk considering ethnicity. In conducting this meta-analysis, we paid particular attention to include only independent papers and studies including healthy subjects as controls. Our group has gained experiences in retrieving as many relevant reports as possible, reducing risk of selection and publication bias. Finally, we reviewed all previously published meta-analyses and found several inaccuracies in the interpretation of risk estimates. In numerous articles, we found data obtained applying different genetic models (homozygote, heterozygous, dominant, recessive and allele genetic model) and in some cases using also different referent allele to test the effect of the polymorphism.

Our study has some limitations as well. Several publications included in our meta-analysis provided little information in their manuscript and the authors did not respond to our attempts to retrieve the missing data (Chen et al., 2017; Yousaf et al., 2014). Furthermore, we extracted fully adjusted estimates for known confounding factors; however, in some studies we had to calculate unadjusted risk estimates using crude data available in the text.

In conclusion, our study represents an updated, comprehensive and critical meta-analysis on the role of the VDR polymorphisms on cancer risk. We provide evidence that *Fok1, Bsm1, Cdx2, Apa1* and *Taq1* are linked to cancer susceptibility for specific cancer sites: CRC, lung, ovarian, skin, multiple myeloma and brain cancer. Our meta-analysis revealed also that *Fok1*, *Bsm1* and *Apa1* polymorphisms are associated with hormone dependent cancers in some ethnic groups. The effect is more evident in Caucasian compared to other ethnicities. For Asian, the number of studies available is limited to give a firm conclusion, and published data seem not always reliable either, but these results possibly indicate that the ethnic background may be associated with hormone dependent cancers. Further studies are necessary to clarify associations in these populations.

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Data statement

Research data for this article are available and can be shared.

CRediT authorship contribution statement

Patrizia Gnagnarella: Conceptualization, Supervision, Validation, Funding acquisition, Writing - original draft. **Sara Raimondi:** Data curation, Funding acquisition, Supervision. **Valentina Aristarco:** Data curation, Funding acquisition. **Harriet Johansson:** Data curation, Writing - review & editing, Funding acquisition. **Federica Bellerba:** Formal analysis. **Federica Corso:** Formal analysis. **Simone Pietro De Angelis:** Formal analysis. **Pietro Belloni:** Formal analysis. **Saverio Caini:** Writing - review & editing. **Sara Gandini:** Conceptualization, Methodology, Supervision, Validation, Funding acquisition.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

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Patrizia Gnagnarella is a staff scientist and nutritionist at the Division of Epidemiology and Biostatistics at the European Institute of Oncology, Milan. She received her Bachelor of Science in Dietetics (2004), a MSc Degree in Health Professions (2006) and she started a PhD program in Data Science (University of Pavia) in 2019. She is involved in methodological aspects of nutritional epidemiology and in developing tools for the determination of nutritional habits and food composition databases. She is co-author of 38 publications, with h-index (Scopus) = 20.

Sara Raimondi is a staff biostatistician and epidemiologist at the Department of Experimental Oncology at the IEO. She received her MSc Degree in Biostatistics and Experimental Statistics in 2005 and a PhD in Medical Statistics in 2013. Her main research interest is molecular epidemiology and she is co-author of 104 publications, with h-index (Scopus) = 29.

Valentina Aristarco is a research assistant at Division of Cancer Prevention and Genetics at European Institute of Oncology, Milan. She received her MSc in Medical Biotechnology in 2008 and started her fellowship at EIO in 2009. Her research interest at EIO concerns the study of biomarkers linked to cancer risk and treatment response within randomized cancer prevention trial. She is co-author of 12 publications with h-index (Scopus) =7.

Harriet Johansson is a Senior Research Assistant with a MSc degree in Biology and PhD in Experimental Endocrinolgy. She works at the European Institute of Oncology, Milan. She has a long experience in the field cancer prevention and her research involves the study of biomarkers linked to cancer risk assessment and treatment safety profile and efficacy. She has developed standardized systems for collection, tracking and storage within numerous multicentric trials conducted within International Study Consortiums. She is co-author of 57 publications with H index of 27.

Federica Bellerba is a biostatistician. After a working period as a research fellow at the European Institute of Oncology in Milan, she is currently a PhD student in Computational Biology at the European School of Molecular Medicine (SEMM). Her research work is focused on meta-genomics, in particular on the study of correlations and interactions between intestinal microbiota, serum biomarkers (such as those related to inflammation) and other risk and prognostic factors of colorectal cancer.

Federica Corso graduated at University of Padua in Bioengineering. After a fellowship as Data Scientist at European Institute of Oncology, she started the PhD program in Data Analytics and Decision Sciences in collaboration with Politecnico di Milano about the analysis of real-world data in oncology.

Simone Pietro De Angelis is a biostatistician and data scientist, currently employed as a consultant in the Pharma industry. He has an MSc Degree in Biostatistics (2019) and worked at the Department of Experimental Oncology at the IEO from March 2019 to June 2020. His main research interest is drugs development, clinical trial, image processing, and data visualization.

Pietro Belloni PhD Student in Statistical Sciences at Univeristy of Padua (Italy), former Statistician Fellow at the European Institute of Oncology. Main interests are: medical statistics, machine learning for medical data and text mining.

Saverio Caini, MD, PhD, is a senior medical epidemiologist working at the Institute for Cancer Research, Prevention, and Clinical Network (ISPRO), Florence, Italy. His main research interest is the study of lifestyle-related, genetic, and environmental factors in their association with cancer risk and survival, with a particular interest in melanoma and non-melanoma skin cancer and breast cancer. He is co-author of 102 publications, with h-index (Scopus) = 24.

Sara Gandini is a biostatistician and epidemiologist Group Leader at the Department of Experimental Oncology at the IEO. She is adjunct professor in medical statistic at University “Statale di Milano” (National Academic Qualification as Associate Professor in medical statistics in 2017) and faculty member of System Medicine PhD (SEMM) University (“Statale di Milano). More than 220 publications in peer journals. H-index = 52, SCOPUS. H-index = 64, Google scholar (November 2020).