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Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk

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It was suggested that vitamin D levels influence cancer development. The vitamin D receptor (VDR) is a crucial mediator for the cellular effects of vitamin D. Results from previous studies on the association of *VDR* polymorphisms with different cancer types are somewhat contradictory, and the role of *VDR* in the etiology of cancer is still equivocal. We therefore performed a meta-analysis on the association between the two most studied *VDR* polymorphisms (*FokI* and *BsmI*) and any cancer site. Up to January 2009, we identified 67 independent studies. We used random-effects models to provide summary odds ratio (SOR) for *VDR* polymorphisms and cancer. We tested homogeneity of effects across studies and publication bias and explored between-study heterogeneity. When comparing *FokI ff* with *FF* carriers, we found a significant increase in skin cancer [SOR; 95% confidence intervals (CIs): 1.30; 1.04–1.61] and breast cancer (SOR; 95%CI: 1.14; 1.03–1.27) risk. For the same genotype comparison, we found a significantly higher risk of cancer when we pooled estimates from cancer sites possibly associated with vitamin D levels (prostate, breast, skin, ovary, non-Hodgkin lymphoma and colorectal). A significant reduction in prostate cancer risk was observed for carriers of *BsmI Bb* compared with *bb* genotype (SOR; 95%CI: 0.83; 0.69–0.99). In Caucasian populations, both *Bb* and *BB* carriers had a significant reduced risk of cancer at any site. In conclusion, this meta-analysis showed that *VDR FokI* and *BsmI* polymorphisms might modulate the risk of cancer of breast, skin and prostate and possibly affect cancer risk at any site in Caucasians.

Introduction

Biological and epidemiological data suggest that vitamin D levels may influence cancer development. The vitamin D receptor (VDR) is a crucial mediator for the cellular effects of vitamin D and additionally interacts with other cell-signaling pathways that influence cancer development (1). Genetic variations may phenotypically appear as interindividual variations in limiting rates of vitamin D synthesis in the skin, hydroxylation in the liver and in the kidney, transport, metabolism and degradation that would ultimately influence individual vitamin D status.

The VDR is an intracellular hormone receptor that specifically binds the biologically active form of vitamin D, 1,25-dihydroxyvitamin D or calcitriol and interacts with specific nucleotide sequences (response elements) of target genes to produce a variety of biologic effects. The *VDR* gene is located on chromosome 12q12–q14 and several single-nucleotide polymorphisms have been identified that may influence cancer risk. The most frequently studied single-nucleotide polymorphisms are the restriction fragment length polymorphisms *FokI* (rs2228570) and *BsmI* (rs1544410), as defined by the endonucleases *FokI* and *BsmI*, respectively. The *FokI* 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. Although no significant differences in ligand affinity, DNA binding or transactivation activity is found between these two VDR forms when studied independently (2), in transient transfection assays with a vitamin D-responsive reporter gene, the shorter *VDR* variant display higher potency than the longer one (3). It has been hypothesized that a less active VDR could be associated with either an increased susceptibility to cancer risk or to a more aggressive disease. The *BsmI* is intronic and located at the 3′ end of the gene. *BsmI* do not alter the amount, structure or function of the VDR protein produced. However, although not functional, it is strongly linked with a poly(A) microsatellite repeat in the 3′ untranslated region which may influence VDR messenger RNA stability (4–9).

The hormonal derivative of vitamin D, 1,25-dihydroxyvitamin D, has been established since the 1980s as an antiproliferative and pro-differentiation agent, and more recently as a proapoptotic agent and an inhibitor of cell migration and angiogenesis, supporting its potential in cancer prevention and cure. Numerous studies *in vitro* and *in vivo* have shown proapoptotic and anticancer effects upon binding of 1,25-dihydroxyvitamin D to the VDR for many different types of cancers (1,10). In fact *VDR* expression has been described in many types of cancer cells, including cells derived from tumors of the breast, prostate, pancreas, colon, bladder, cervix, thyroid, pituitary, skin (squamous cell carcinoma, basal cell carcinoma and melanoma), glioma, neuroblastoma, leukemia and lymphoma cells (11–14). The epidemiological literature on vitamin D and cancer has been recently reviewed (15).

Since its discovery in 1969 (16), the role of VDR in the endocrine system has been examined. VDR has been shown to be involved in insulin-like growth factor signaling, in inflammation and estrogen-related pathways, beyond the activation and regulation of vitamin D and calcium. The involvement of VDR in multiple pathways and points of convergence within these pathways indicates the potential importance of VDR in the etiology of cancer.

Association studies of several polymorphisms in the *VDR* gene have been performed to investigate their implication with different types of cancer, but the results are somewhat contradictory, possibly because single studies may have been underpowered. Some reviews and meta-analyses (17–26) were also carried out, but these latter were limited to single cancer sites.

Given the amount of accumulated data and the still equivocal role of *VDR* in the etiology of cancer in general, we decided to perform a comprehensive meta-analysis of all published studies on the association between the two most studied *VDR* polymorphisms (*FokI* and *BsmI*) and any cancer site. We provided quantitative summary risk estimates of the association for single cancer sites and for all cancers, we looked extensively at inconsistencies and variability in the estimates and identified sources of between-study heterogeneity, in order to provide some clues toward the epidemiology of *VDR* polymorphisms and cancer.

Material and methods

Literature search and data extraction

In order to identify published papers and abstracts on *VDR* polymorphisms and cancer, we performed a comprehensive and systematic bibliographic search updated to January 2009 using PubMed, Institute for Scientific Information Web of Science (Science Citation Index Expanded) and Embase. We identified the publications using the keywords 'VDR' and 'Vitamin D polymorphism' in combination with 'cancer' and 'tumor', with no search restriction. We also checked the references from retrieved articles and reviews to identify any additional relevant study.

We considered eligible for the present analysis all papers from genotype-based epidemiological studies reporting frequency of the two most studied *VDR* polymorphisms (*FokI* and *BsmI*) for cancers and controls or estimates of the association between the two *VDR* polymorphisms and cancer, with a corresponding measure of uncertainty [i.e. 95% confidence interval (CI), standard error, variance or *P*-value of the significance of the estimate]. There were 85

Abbreviations: BMI, body mass index; CI, confidence interval; H–W, Hardy–Weinberg; OR, odds ratio; SOR, summary odds ratio; VDR, vitamin D receptor.

eligible papers, including a recent pooled analysis of six independent large European and American cohort studies. By considering these six cohorts separately, the number of eligible studies was 90. Out of them, 23 were excluded because of overlap with papers based on larger samples, leaving 67 independent studies for the review and meta-analysis. Among papers on prostate cancer, whenever possible we excluded controls with benign prostatic hyperplasia since it was suggested that they could bias the estimate of *VDR* polymorphisms association with cancer (18,27,28).

When available, we extracted fully adjusted risk estimates separately for heterozygous and minor allele homozygous subjects compared with wild-type subjects. When adjusted estimates were not available, we retrieved the frequencies of *VDR FokI* and *BsmI* genotypes in cases and controls and calculated the corresponding study-specific crude odds ratio (OR), with 95% CI for cancer risk, by cancer site. Since the reference group for each polymorphism varied among the studies, we considered the homozygous genotype of the more prevalent allele (*b* for *BsmI* and *F* for *FokI*) as reference genotype in our analyses. Articles were reviewed and data were extracted and crosschecked independently by two investigators. Any disagreement was resolved by consensus among the two. For each study, we recorded the following information: study characteristics—publication year, study design, study location, exclusion of subjects among controls, adjusting or matching for confounders; exposure evaluation—laboratory methods to detect *VDR* polymorphisms, number of cases and controls genotyped for each of the polymorphisms, case and control genotype frequency, cancer site-specific reported risk estimate with 95% CIs or *P*-values and study population—total number and source of cases and controls, subtypes of cases, incident or not specified cases, mean age, mean body mass index (BMI), ethnicity, percent of males and of familial cases.

When the source of controls was not clearly defined in the paper, it was set as 'hospital' to be conservative. The ethnicity of each study population was defined as the ethnic group of 90% or more of the study subjects. When the paper did not specify the ethnicity of the study population, it was hypothesized basing on the more frequent ethnic group in the study country.

Statistical analysis

The departure of frequencies of *VDR FokI* and *BsmI* polymorphisms from expectation under Hardy–Weinberg (H–W) equilibrium was assessed by Chi-square test in controls.

We used random-effects models with maximum likelihood estimate to provide summary estimation of *VDR* polymorphisms association with cancer development. We calculated a summary risk estimate for cancer sites for which at least two published papers were found. When more than one risk estimate was provided in a single study (i.e. for different ethnic groups), the model took into account the two sources of variation (within and between studies). We performed separate pairwise comparison for heterozygous and mutant homozygous carriers and took into account the correlation between the two risk estimates by using a bivariate approach (29).

We tested homogeneity of effects across studies by the Chi-square statistic, with significance level set at 0.10, and by I^2, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance (30).

We explored between-study heterogeneity through subgroup analyses, meta-regression and sensitivity analysis valuating features of the study and the population that could influence the results (ethnicity, study design, source of controls, incident or not specified cases, deviation from H–W equilibrium, study location, mean age, mean BMI, percent of men, percent of subjects with family history of cancer, percent of postmenopausal women—only for breast cancer, inclusion of benign prostatic hyperplasia patients as controls—only for prostate cancer, risk estimate adjustments or matching). We dichotomized continuous variables using the median of the studies. Given that in the USA there is a higher use of vitamin D supplementation, we also performed meta-regression by comparing studies conducted in USA and in other countries. Publication bias was graphically represented by funnel plot and assessed both by Egger's test and Macaskill's method (31,32).

The statistical analyses were performed using SAS Software (SAS, 8.02 for Windows, Cary, NC).

Results

Out of the 67 selected studies, 22 focused on prostate cancer, 18 on breast cancer, 14 on colorectal cancer, four on skin cancer, two respectively on non-Hodgkin lymphoma, renal cell and ovary cancer and one respectively on bladder and head and neck cancer. Finally, one paper included two different studies: one on breast cancer and one on melanoma. Since all the studies presented case–control or nested case–control design, we always used OR as an estimate of the relative risk. The main characteristics of the reviewed studies are presented in Table I; study-specific ORs with 95%CI, information on adjusting or matching variables, deviation from H–W equilibrium, and the complete list of references are reported in supplementary Table I (available at *Carcinogenesis* Online).

Prostate cancer

Only one study on the association between *FokI* polymorphism and prostate cancer deviated from H–W equilibrium. Prostate cancer risk for subjects with *Ff* or *ff* genotypes was similar to that of subjects with *FF* genotype: summary odds ratios (SORs) (95%CI) were, respectively, 1.03 (0.95–1.12) and 1.03 (0.92–1.15) (Table II and Figures 1 and 2), with no evidence of heterogeneity among risk estimates, although we found evidence of publication bias by Egger's test ($P = 0.03$ and $P = 0.006$ for *Ff* and *ff* genotypes, respectively). The suggestion of publication bias was however not confirmed by the Macaskill's method.

Four of 14 studies on *BsmI* polymorphism and prostate cancer risk deviated from H–W equilibrium. SORs (95%CI) were 0.83 (0.69–0.99) and 0.92 (0.75–1.12) for *Bb* and *BB* genotypes, respectively (Table II and Figures 3 and 4), with evidence of heterogeneity only among risk estimates comparing *Bb* with *bb* carriers. However, we observed that the heterogeneity completely disappeared (Chi-square *P*-value (I^2): 0.76 (0%)) after the exclusion of one study (33) for which genotype frequency in controls deviated from the H–W equilibrium. The SORs (95%CI) after the exclusion of Habuchi *et al.* were similar to that previously calculated: 0.90 (0.82–1.00) and 0.99 (0.88–1.13) for *Bb* and *BB* genotypes, respectively. Moreover, we observed that studies that did not specify how cases were collected presented significantly lower estimates (SOR; 95%CI: 0.72; 0.25–2.07 and 0.93; 0.26–3.33 for *Bb* and *BB* genotypes, respectively) than studies including only incident cases (SOR; 95%CI: 0.91; 0.82–1.00 and 1.00; 0.88–1.14; meta-regression *P*-value: 0.04). We found no evidence of publication bias for *BsmI* polymorphism with prostate cancer risk.

No significant differences in risk estimates were found for any polymorphism by including and excluding patients with benign prostatic hyperplasia as controls.

Breast cancer

No deviation from H–W equilibrium was observed in any of the 13 independent studies on *FokI* polymorphism and breast cancer risk. SORs (95%CI) were 1.04 (0.95–1.14) and 1.14 (1.03–1.27) for *Ff* and *ff* genotypes, respectively (Table II and Figures 1 and 2), with significant heterogeneity among risk estimates only for *ff* versus *FF* comparison. By meta-regression, we could not identify any difference among risk estimates according to ethnicity, study design, source of controls, incident or not specified cases, study location, risk estimate adjustments or matching, mean age, BMI, family history of breast cancer and menopausal status.

Out of the 15 studies on *BsmI* polymorphism and breast cancer risk, five presented a deviation from the H–W equilibrium in controls. SORs (95%CI) were 0.97 (0.91–1.02) and 0.95 (0.88–1.03) for *Bb* and *BB* genotypes, respectively (Table II and Figures 3 and 4), with no evidence of heterogeneity among risk estimates.

We found no evidence of publication bias for any polymorphism with breast cancer risk.

Colorectal cancer

Three of 10 studies on *FokI* polymorphism and colorectal cancer risk presented a deviation from H–W equilibrium in controls. SORs (95%CI) were 1.05 (0.81–1.36) and 1.00 (0.76–1.31) for *Ff* and *ff* genotypes, respectively (Table II and Figures 1 and 2), with a very high heterogeneity among risk estimates. By meta-regression, we found that ORs in studies on Caucasians were significantly lower than those in studies on non-Caucasians (meta-regression *P*-value: 0.03); however, we still found heterogeneity even restricting the analysis on Caucasian studies only and the corresponding SORs (95%) were still not significant [1.04 (0.81–1.33) and 0.97 (0.74–1.28) for *Ff* and *ff*

Table I. Description of the reviewed studies on cancer and *VDR FokI* and *BsmI* polymorphisms

First author, PY	Country	Ethnicity	Study design	Source of controls	No. of cases	No. of controls	Crude/adjusted OR	*FokI*	*BsmI*
Prostate cancer									
Ingles, 1998	USA	African-American	NCC	Population	151	174	Crude		X
Correa-Cerro, 1999	France	Caucasian	CC	Population	105	132	Crude	X	
Habuchi, 2000	Japan	Asian[a]	CC	Hospital	222	128	Crude		X
Chokkalingam, 2001	China	Asian[a]	NCC	Population	242	472	Adjusted	X	X
Liu, 2003	China	Asian[a]	CC	Not specified	103	106	Crude		X
Nam, 2003	Canada	Caucasian, African-American, Asian	CC	Hospital	483	548	Adjusted		X
Suzuki, 2003	Japan	Asian[a]	CC	Hospital	81	105	Crude		X
Huang, 2004	Taiwan	Asian[a]	CC	Hospital	160	205	Adjusted		X
Oakley-Girvan, 2004	USA	African-American, Caucasian	NCC	Population	345	292	Adjusted	X	X
Tayeb, 2004	UK	Caucasian[a]	NCC	Hospital	28	56	Adjusted	X	
Yang, 2004	China	Asian[a]	CC	Not specified	80	96	Crude	X	
Hayes, 2005	Australia	Caucasian	CC	Population	862	745	Adjusted	X	X
John, 2005	USA	Caucasian	CC	Population	425	437	Adjusted	X	
Mishra, 2005	India	Caucasian[a]	CC	Hospital	128	147	Adjusted	X	
Cicek, 2006	USA	Caucasian	CC	Population[b]	439	479	Adjusted	X	X
Huang, 2006	Taiwan	Asian[a]	CC	Hospital	416	502	Adjusted	X	
Holick, 2007	USA	Caucasian	CC	Population	630	565	Adjusted	X	X
Li, 2007	USA	Caucasian[a]	NCC	Population	1066	1618	Adjusted	X	X
Mikhak, 2007	USA	Caucasian[a]	NCC	Population	684	684	Adjusted	X	X
Rukin, 2007	UK	Caucasian	CC	Hospital	430	320	Adjusted	X	
Onen, 2008	Turkey	Caucasian	CC	Hospital	133	157	Crude		X
Torkko, 2008	USA	Caucasian, Hispanic	NCC	Population	585	761	Crude	X	
22 Studies					7798	8729			
Breast cancer									
Ruggiero, 1998	Italy	Caucasian[a]	CC	Hospital	50	167	Crude		X
Curran, 1999	Australia	Caucasian[a]	CC	Not specified	135	110	Crude	X	
Hou, 2002	Taiwan	Asian[a]	CC	Hospital	34	169	Crude		X
Buyru, 2003	Turkey	Caucasian[a]	CC	Not specified	78	27	Crude		X
Guy, 2004	UK	Caucasian	CC	Population	398	427	Crude	X	X
Hefler, 2004	Germany	Caucasian	CC	Not specified	396	1936	Crude		X
Chen, 2005	USA (NHS cohort)	Caucasian	NCC	Population	1234	1676	Adjusted	X	X
VandeVord, 2006	USA	Caucasian, African-American	CC	Mixed	220	192	Adjusted		X
John, 2007	USA	Caucasian, Hispanic, African-American[c]	CC	Population	570	2058	Adjusted	X	
McCullough, 2007	USA (CPS II cohort)	Caucasian	NCC	Population	500	500	Adjusted	X	X
Trabert, 2007	USA	Caucasian, African-American	CC	Population	1621	1411	Adjusted		X
Abbas, 2008	Germany	Caucasian[a]	CC	Population	1408	2612	Adjusted	X	
Gapska, 2008	Poland	Caucasian[a]	CC	Population	1760	1510	Crude	X	X
Sinotte, 2008	Canada	Caucasian	CC	Mixed	877	1437	Adjusted	X	X
Barroso, 2008[d]	Spain	Caucasian	CC	Mixed	549	556	Adjusted	X	
McKay, 2009	Europe (EPIC cohort)	Caucasian	NCC	Population	1677	2795	Adjusted	X	X
McKay, 2009	USA (MEC cohort)	Caucasian, Hispanic, African-American, Asian, Hawaiian	NCC	Population	1598	1952	Adjusted	X	X
McKay, 2009	USA (PLCO cohort)	Caucasian	NCC	Population	1073	1100	Adjusted	X	X
McKay, 2009	USA (WHS cohort)	Caucasian	NCC	Population	685	683	Adjusted	X	X
19 Studies					14 863	21 318			
Colorectal cancer									
Speer, 2001	Hungary	Caucasian[a]	CC	Not specified	56	112	Adjusted		X
Wong, 2003	China	Asian	NCC	Population	217	890	Adjusted	X	
Murtaugh, 2006	USA	Caucasian	CC	Population	2450	2821	Adjusted	X	
Park, 2006	Korea	Asian[a]	CC	Population	190	318	Crude	X	X
Flugge, 2007	Russia	Caucasian[a]	CC	Hospital	256	256	Adjusted	X	X
Kadiyska, 2007	Bulgaria	Caucasian[a]	CC	Not specified	144	94	Adjusted		X
Yaylim-Eraltan, 2007	Turkey	Caucasian[a]	CC	Hospital	26	52	Crude	X	
Slattery, 2007	USA	Caucasian	CC	Population	2380	2990	Adjusted		X
Grunhage, 2008	Germany	Caucasian	CC	Hospital	96	220	Crude	X	
Li, 2008	China	Asian[a]	CC	Not specified	200	200	Crude	X	X
Ochs-Balcom, 2008	USA	Caucasian[a]	CC	Population	250	246	Adjusted	X	
Parisi, 2008	Spain	Caucasian[a]	CC	Hospital	170	120	Crude		X
Theodoratou, 2008	UK	Caucasian	CC	Population	3005	3072	Adjusted	X	X
Wang, 2008	China	Asian[a]	CC	Not specified	69	218	Crude	X	
14 Studies					7893[e]	9609[e]			
Skin cancer									
Hutchinson, 2000	UK	Caucasian	CC	Hospital	316	108	Crude	X	
Santonocito, 2000	Italy	Caucasian	CC	Population	101	101	Adjusted	X	X
Han, 2007	USA	Caucasian	NCC	Population	778	854	Adjusted	X	X

Table I. *Continued*

First author, PY	Country	Ethnicity	Study design	Source of controls	No. of cases	No. of controls	Crude/adjusted OR	*FokI*	*BsmI*
Li, 2008	USA	Caucasian	CC	Hospital	805	841	Adjusted	X	X
Barroso, 2008[d]	Spain	Caucasian	CC	Mixed	283	245	Adjusted	X	
Five studies					2283	2149			
Non-Hodgkin lymphoma									
Purdue, 2007	Australia	Mixed	CC	Population	561	506	Adjusted	X	X
Purdue, 2007	USA	Caucasian	CC	Population	1321	1057	Adjusted		X
Two studies					1882	1536			
Renal cell cancer									
Obara, 2007	Japan	Asian[a]	CC	Population	135	150	Adjusted		X
Karami, 2008	Eastern Europe	Caucasian	CC	Hospital	925	1192	Adjusted	X	X
Two studies					1060	1342			
Ovary cancer									
Lurie, 2007	USA	Caucasian, Asian	CC	Population	164	316	Adjusted	X	X
Clendenen, 2008	USA + Sweden	Caucasian[a]	NCC	Population	170	323	Adjusted	X	X
Two studies					334	632			
Bladder cancer									
Mittal, 2007	India	Caucasian	CC	Not specified	130	346	Crude	X	
Head and neck cancer									
Liu, 2005	USA	Caucasian	CC	Population	719	821	Adjusted	X	

CC, case–control; CPS II, Cancer Prevention Study II; EPIC, European Prospective Investigation into Cancer and Nutrition; MEC, Multiethnic Cohort; NCC, nested case–control; NHS, Nurses' Health Study; OR, odds ratio; PLCO, prostate, lung, colorectal and ovarian cancer screening trial; PY, publication year; WHS, Women's Health Study; X, odds ratios published or calculated in the correspondent article for the indicated polymorphism.

[a]No information on race in the paper. The race was hypothesized basing on the more frequent ethnicity in the study country.

[b]Controls were siblings of cases.

[c]Information on race was inferred by skin pigmentation. As reported (John, 2007), non-Hispanic Whites predominated in the light pigmentation group (65%); Hispanics and African-Americans had the highest representation in the medium (68%) and high (75%) pigmentation groups, respectively.

[d]This paper includes two independent studies: one on breast cancer and one on melanoma.

[e]Two papers (Murtaugh, 2006 and Slattery, 2007) presented overlapped subjects who were therefore counted only once to calculate the total number of cases and controls.

genotypes, respectively]. We also observed a significant difference (meta-regression *P*-value: 0.02) between risk estimates of the five studies including >50% of males (SOR; 95%CI: 0.91; 0.67–1.11 and 0.81; 0.59–1.11 for *Ff* and *ff* genotypes, respectively) compared with the three studies including at least 50% of females (SOR; 95%CI: 1.27; 0.91–1.78 and 1.64; 1.09–2.47).

Out of the eight studies on *BsmI* polymorphism and colorectal cancer risk, two presented a deviation from H–W equilibrium in controls. SORs (95%CI) were 0.63 (0.29–1.39) and 0.62 (0.28–1.36) for *Bb* and *BB* genotypes, respectively (Table II and Figures 3 and 4), again with a very high heterogeneity among risk estimates. We observed that, like for prostate cancer, the heterogeneity could be fully attributed to one study (34), which reported significantly lower estimates than all other papers. This is one of the two studies for which deviation from H–W equilibrium was observed. When we excluded it from the analysis, the heterogeneity disappeared [Chi-square *P*-value (I^2): 0.36 (0%) and 0.94 (0%) for *Bb* and *BB* genotypes, respectively] and the SORs (95%CI) became borderline protective: 0.91 (0.84–1.00) for *Bb* genotype and 0.92 (0.81–1.04) for *BB* genotype.

We found no evidence of publication bias for any polymorphism with colorectal cancer risk.

Skin cancer (including malignant melanoma)

Genotype frequencies of both *FokI* and *BsmI* polymorphisms in controls did not deviate from H–W equilibrium in any study on skin cancer. SORs (95%CI) were 1.12 (0.96–1.31) and 1.30 (1.04–1.61) for *FokI Ff* and *ff* genotypes, respectively (Table II and Figures 1 and 2), and 0.80 (0.60–1.06) and 0.87 (0.63–1.21) for *BsmI Bb* and *BB* genotypes, respectively (Table II and Figures 3 and 4). The tests for heterogeneity indicated a significant heterogeneity among risk estimates for *BsmI BB* versus *bb* analysis. The heterogeneity was reduced (although it did not completely disappear) after the exclusion of the squamous cell carcinoma risk estimate, which was in the opposite direction of all the other risk estimates (Figure 4).

We found no evidence of publication bias for any polymorphism with skin cancer risk.

Other cancer types

Six studies assessed the association of *FokI* polymorphism with other types of cancer (supplementary Table I is available at *Carcinogenesis* Online). Due to the low number of studies, we just reviewed these results, without performing a meta-analysis. While no significant association was observed with non-Hodgkin lymphoma, renal cell and ovarian cancer, a protective effect for the heterozygous *Ff* and for the variant homozygous *ff* compared with wild-type *FF* genotype was suggested in one study on bladder and one on head and neck cancer, respectively. For the study on bladder cancer, respectively, we observed a significant deviation from H–W equilibrium in controls.

Six studies evaluated the association of *BsmI* polymorphism with non-Hodgkin lymphoma, renal cell and ovary cancer. We observed a borderline increase in the risk of developing non-Hodgkin lymphoma only in one study for subjects carrying the heterozygous *Bb* genotype compared with wild-type subjects: the corresponding OR (95%CI) for the study by Purdue *et al.* was 1.31 (1.00–1.72).

All cancer sites

Pooling together all the 67 studies, we found no association between *FokI* polymorphism and cancer risk at any site. SORs (95%CI) were 1.02 (0.96–1.09) and 1.05 (0.98–1.14) for *Ff* and *ff* genotypes, respectively (Table II and Figures 1 and 2), with very high heterogeneity among risk estimates. However, when we restricted the analysis to the six cancer types (prostate, breast, skin, ovary, non-Hodgkin lymphoma and colorectal) for which association with ultraviolet radiation exposure and/or vitamin D was suggested (35–37), we found a significant increase in cancer risk for carriers of *FokI ff* compared with *FF* genotype: SOR (95%CI) was 1.08 (1.01–1.17). The corresponding SOR for heterozygous carriers was slightly higher, but still not significant (SOR; 95%CI: 1.04; 0.97–1.11). We found that studies including only incident cases reported significantly higher estimates (SOR; 95%CI: 1.06; 0.99–1.12 and 1.09; 1.02–1.17 for *Ff* and *ff* genotypes, respectively) than papers that did not specified how cases were collected (SOR; 95%CI: 0.86; 0.66–1.14 and 0.82; 0.60–1.12; meta-regression *P*-value: 0.01). Finally, by excluding gender-specific cancer sites (breast, prostate and ovary),

Table II. Study specific and summary estimates for the association of *VDR FokI* and *BsmI* polymorphisms with different types of cancer and heterogeneity estimates

VDR polymorphism	Cancer	No. of studies	Comparisons	SOR (95% CI)	*Q* test *P*-value (I^2%)
FokI	Prostate	15	*Ff* versus *FF*	1.03 (0.95–1.12)	0.21 (21)
			ff versus *FF*	1.03 (0.92–1.15)	0.30 (13)
	Breast	13	*Ff* versus *FF*	1.04 (0.95–1.14)	0.22 (19)
			ff versus *FF*	1.14 (1.03–1.27)	0.006 (50)
	Colorectal	10	*Ff* versus *FF*	1.05 (0.81–1.36)	<0.001 (72)
			ff versus *FF*	1.00 (0.76–1.31)	<0.001 (74)
	Skin	5	*Ff* versus *FF*	1.12 (0.96–1.31)	0.23 (26)
			ff versus *FF*	1.30 (1.04–1.61)	0.68 (0)
	All sites	49[a]	*Ff* versus *FF*	1.02 (0.96–1.09)	<0.001 (43)
			ff versus *FF*	1.05 (0.98–1.14)	<0.001 (51)
BsmI	Prostate	14	*Bb* versus *bb*	0.83 (0.69–0.99)	0.006 (52)
			BB versus *bb*	0.92 (0.75–1.12)	0.89 (0)
	Breast	15	*Bb* versus *bb*	0.97 (0.91–1.02)	0.17 (22)
			BB versus *bb*	0.95 (0.88–1.03)	0.37 (7)
	Colorectal	8	*Bb* versus *bb*	0.63 (0.29–1.39)	<0.001 (86)
			BB versus *bb*	0.62 (0.28–1.36)	<0.001 (93)
	Skin	3	*Bb* versus *bb*	0.80 (0.60–1.06)	0.53 (0)
			BB versus *bb*	0.87 (0.63–1.21)	0.01 (70)
	All sites	46[b]	*Bb* versus *bb*	0.86 (0.74–1.00)	<0.001 (57)
			BB versus *bb*	0.86 (0.74–1.00)	<0.001 (64)

CI, confidence interval; NHL, non-Hodgkin lymphoma.
[a]Also includes six studies on ovarian cancer (2), NHL (1), renal cell cancer (1), bladder cancer (1) and head and neck cancer (1).
[b]Also includes six studies on ovarian cancer (2), NHL (2) and renal cell cancer (2).

meta-regression suggested a significant lower risk of cancer in the eight studies including >50% of males compared with the six studies including at least 50% of females: SOR (95%CI) were, respectively, 0.94 (0.78–1.14) versus 1.13 (0.93–1.37) for *Ff* genotype and 0.84 (0.68–1.03) versus 1.55 (1.23–1.96) for *ff* genotype; meta-regression *P*-value: 0.01. This result was observed even when gender-specific cancer sites were included (meta-regression *P*-value: 0.009).

We observed a 16% reduction of cancer risk at any site for carriers of one or two copies of *BsmI B* allele: SOR (95%CI) was 0.86 (0.74–1.00) both for *Bb* and *BB* genotypes (Table II and Figures 3 and 4). The high heterogeneity among risk estimates completely disappeared when we restricted the analysis on studies with Caucasian populations [Chi-square *P*-value (I^2): 0.53 (0%) and 0.45 (1%) for *Bb* and *BB* genotypes, respectively]. In this subset of studies, both *Bb* and *BB* carriers had a significant reduced risk of cancer: 0.93 (0.89–0.98) and 0.94 (0.88–0.99), respectively. As for *FokI* polymorphism, there was a significant difference among risk estimates provided by studies including only incident cases and by the ones that did not specify how cases were collected. The SORs (95% CI) for *Bb* and *BB* genotypes were, respectively, 0.95 (0.91–0.99) and 0.96 (0.91–1.01) for studies with incident cases and 0.64 (0.32–1.27) and 0.52 (0.25–1.09) for other studies.

We found no evidence of publication bias for any polymorphism with cancer risk at any site.

Discussion

We performed a comprehensive review of the literature on the *VDR FokI* and *BsmI* polymorphisms with cancer risk. The four most studied cancer types in association with the two *VDR* polymorphisms were prostate, breast, colorectal and skin cancer.

We found a significant 30% increase in skin cancer risk and 14% increase in breast cancer risk with *FokI ff* compared with *FF* genotype, in agreement with previously published meta- and pooled analyses (25,26,38). The *f* allele results in a VDR protein that is three amino acids longer than the *F* allele (39) and functionally less effective (9,40); therefore, the less active *ff* genotype would be expected to mimic the cellular consequences of lower vitamin D status. Several studies have indeed suggested that adequate Vitamin D levels may provide protection against several chronic diseases, including cancer, and could improve cancer prognosis. Recently published data from the Nurses' Health Study and the Health Professionals Follow-Up Study supported the hypothesis that higher prediagnosis plasma levels of 25-hydroxy vitamin D, the major circulating form of vitamin D, were associated with a significant improvement in overall survival in colorectal cancer patients (41). Moreover, a meta-analysis of published randomized trials showed a significant reduction in total mortality in subjects taking Vitamin D supplementation (42). Interestingly, we found a significant higher risk of cancer for *FokI ff* compared with *FF* carriers when we pooled estimates from those cancer sites for which association with ultraviolet radiation exposure and vitamin D levels was suggested [prostate, breast, skin, ovary, non-Hodgkin lymphoma and colorectal (35–37)]. For these cancer sites, the *FokI* polymorphism may therefore play a role, although modest, in cancer development.

As in a previous published meta-analysis (22), we found no association between *FokI* polymorphism and colorectal cancer. However, we observed that carriers of *ff* genotype had a significant higher risk of colorectal cancer than carriers of *FF* genotype among study populations with higher prevalence of females. The same result was observed when we pooled estimates from all cancer sites. While this result could not be interpreted at an individual level, another recent study (43) found higher colon cancer risk for *VDR FokI* polymorphism in females than males, although the interaction with gender was not significant. The difference in circulating levels of 25-hydroxy vitamin D between men and women, with women having lower concentrations than men (44), may explain the observed differences in risk estimates found in our analysis: the lower efficiency of *FokI f* allele could in fact increase cancer risk especially at lower plasma concentrations of 25-hydroxy vitamin D levels.

A significant 17% reduction in prostate cancer risk was observed for carriers of *BsmI Bb* compared with *bb* genotype. This result was not observed in a previously published meta-analysis (18) that included a lower number of studies. A borderline significant association was found for colorectal cancer, with a 9% decrease for *Bb* compared with *bb* carriers, after exclusion of one study that was responsible for the observed heterogeneity. Finally, considering all the cancer sites together, we observed a significant 7% reduction in cancer risk for heterozygous and 6% for homozygous carriers of *BsmI B* allele in Caucasian populations. Up to date, this intronic variation has not appeared to be of significance. However, this polymorphism is in strong linkage disequilibrium with the poly(A) microsatellite located in the 3′ untranslated region (45) of the *VDR* gene, which appear to influence *VDR* messenger RNA stability and *VDR* translational activity (9). The wild-type allele *L* corresponds to the long, well-functioning form and might be the functional marker of the *b* allele, although other mechanisms may contribute too. Further research is required to determine what exactly *BsmI* is acting as a marker for. The varying degree of linkage disequilibrium between this marker allele and the functional allele might explain the variations in the strengths of associations seen across studies (9).

For both *FokI* and *BsmI* polymorphisms, we found significant differences among risk estimates calculated from studies collecting

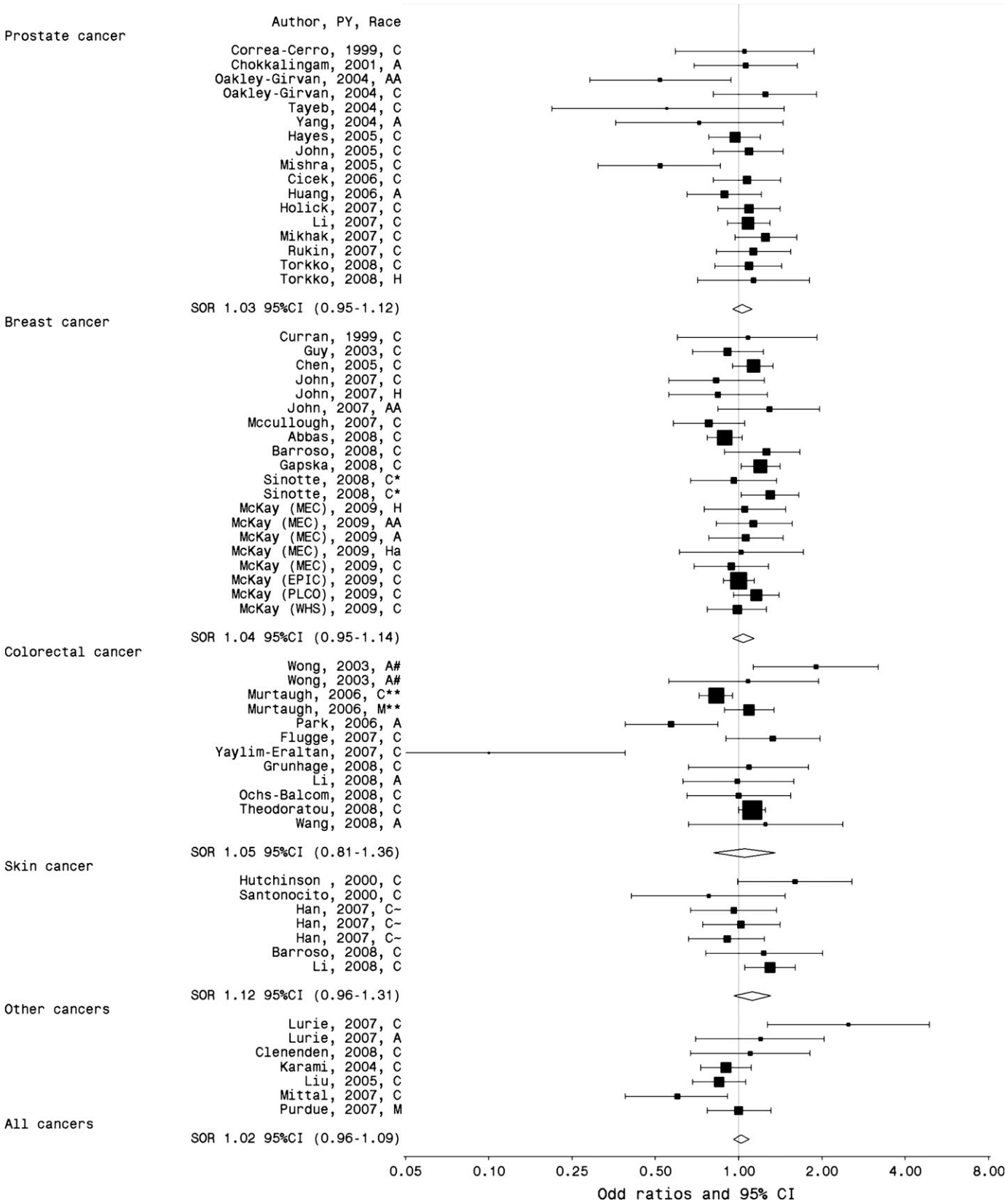

Fig. 1. Study specific and SORs with 95% Confidence Intervals for the association between cancer development and *FokI Ff* versus *FF* genotype. A, Asian; AA, African-American; C, Caucasian; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; H, Hispanic; Ha, Hawaiians; MEC, Multiethnic Cohort; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PY, publication year; WHS, Women's Health Study.
* Represents the study by Sinotte *et al.* included two independent study populations with different cases and controls; # represents the study by Wong *et al.* included two different estimates for colon and rectum cancer; ** represents the study by Murtaugh *et al.* included two different estimates for colon and rectum cancer; ~ represents the study by Han *et al.* included three different estimates for melanoma, squamous cell carcinoma and basal cell carcinoma.

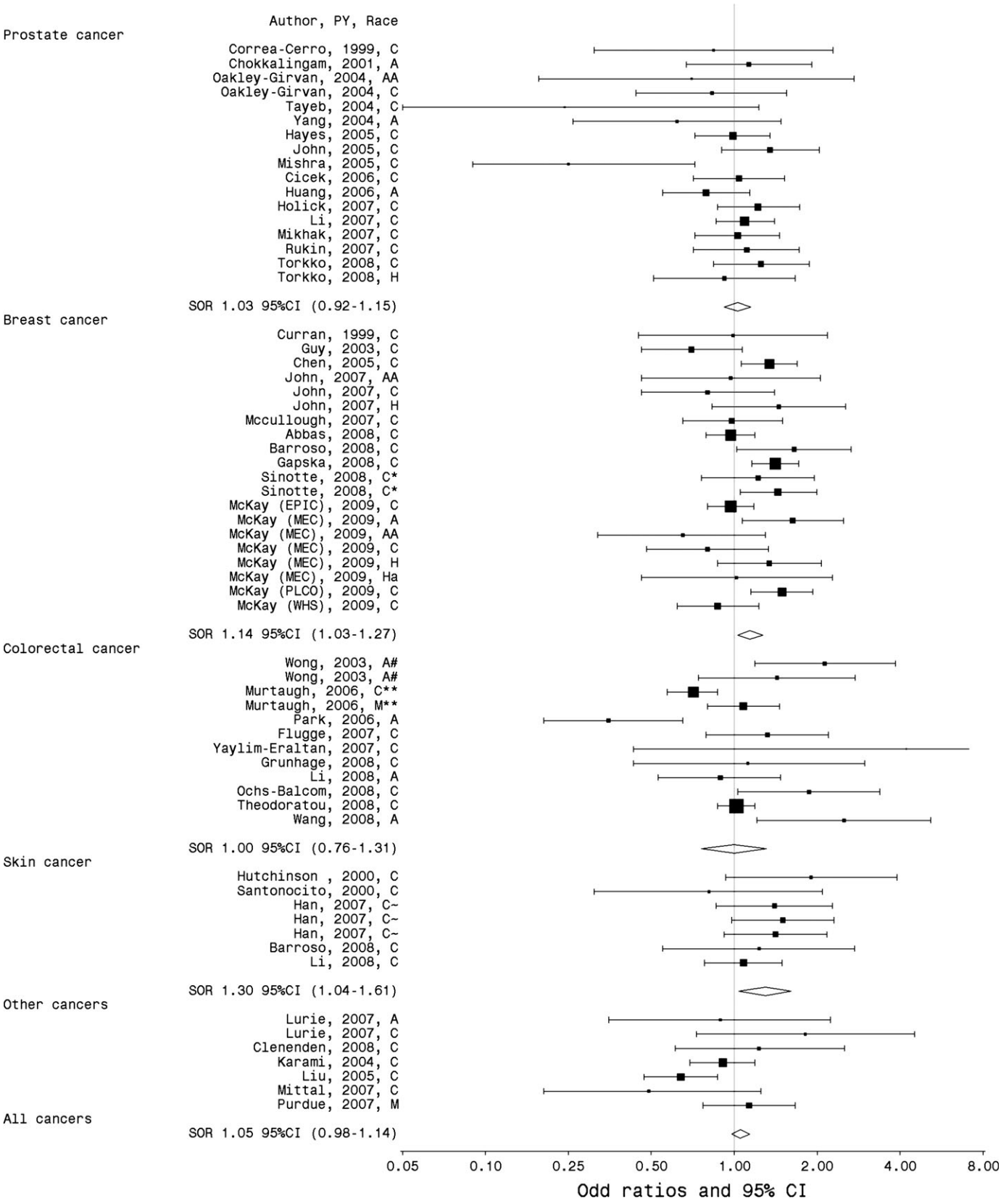

Fig. 2. Study specific and SORs with 95% Confidence Intervals for the association between cancer development and *FokI ff* versus *FF* genotype. A, Asian; AA, African-American; C, Caucasian; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; H, Hispanic; Ha, Hawaiians; MEC, Multiethnic Cohort; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PY, publication year; WHS, Women's Health Study.
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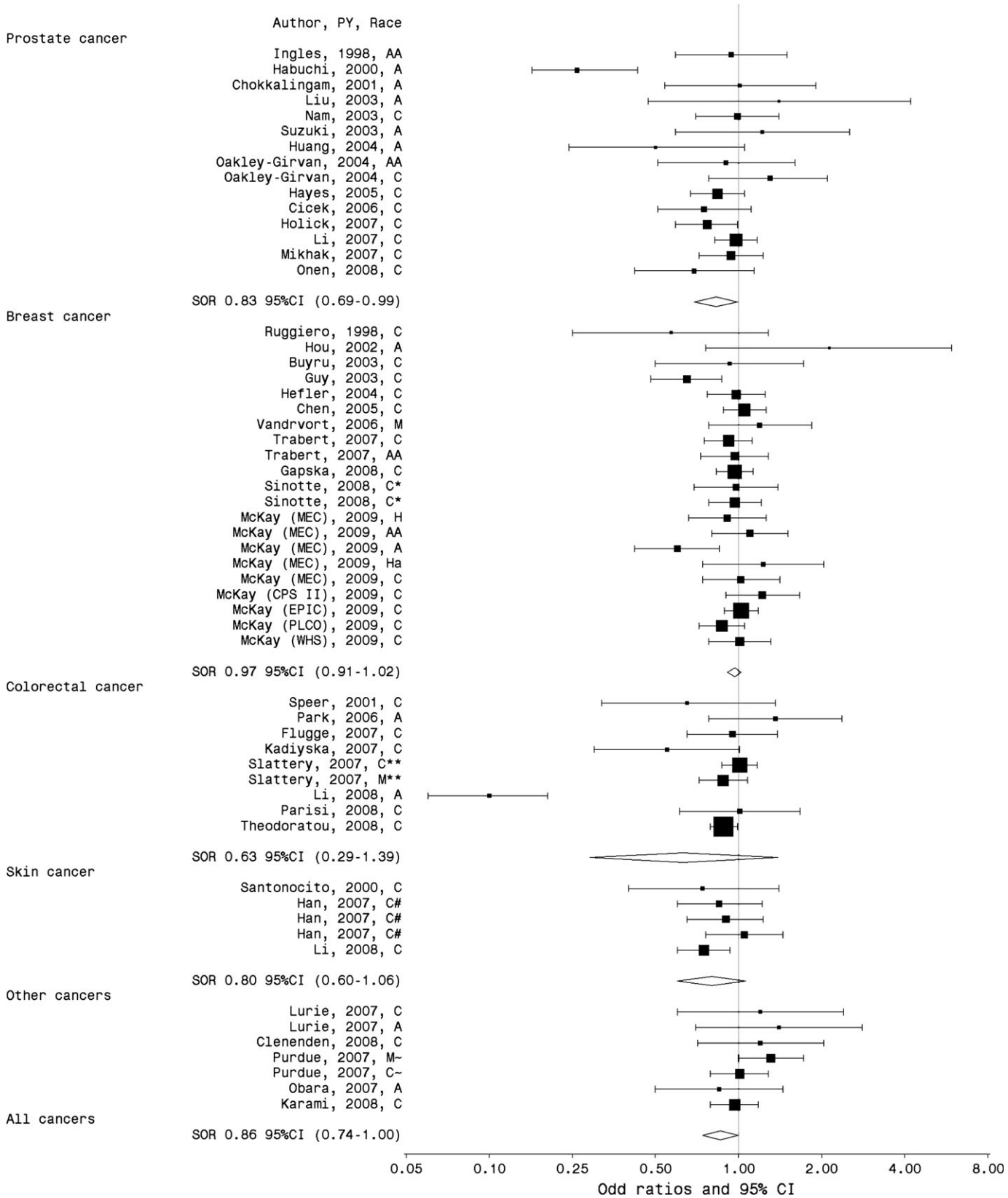

Fig. 3. Study specific and SORs with 95% confidence intervals for the association between cancer development and *BsmI Bb* versus *bb* genotype. A, Asian; AA, African-American; C, Caucasian; CI, confidence interval; CPS II, Cancer Prevention Study II; EPIC, European Prospective Investigation into Cancer and Nutrition; H, Hispanic; Ha, Hawaiians; MEC, Multiethnic Cohort; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PY, publication year; WHS, Women's Health Study. * Represents the study by Sinotte *et al.* included two independent study populations with different cases and controls; ** represents the study by Slattery *et al.* included two different estimates for colon and rectum cancer; # represents the study by Han *et al.* included three different estimates for melanoma, squamous cell carcinoma and basal cell carcinoma; ~ represents there are two independent studies published by Purdue *et al.* in 2007: one was conducted in USA and one in Australia.

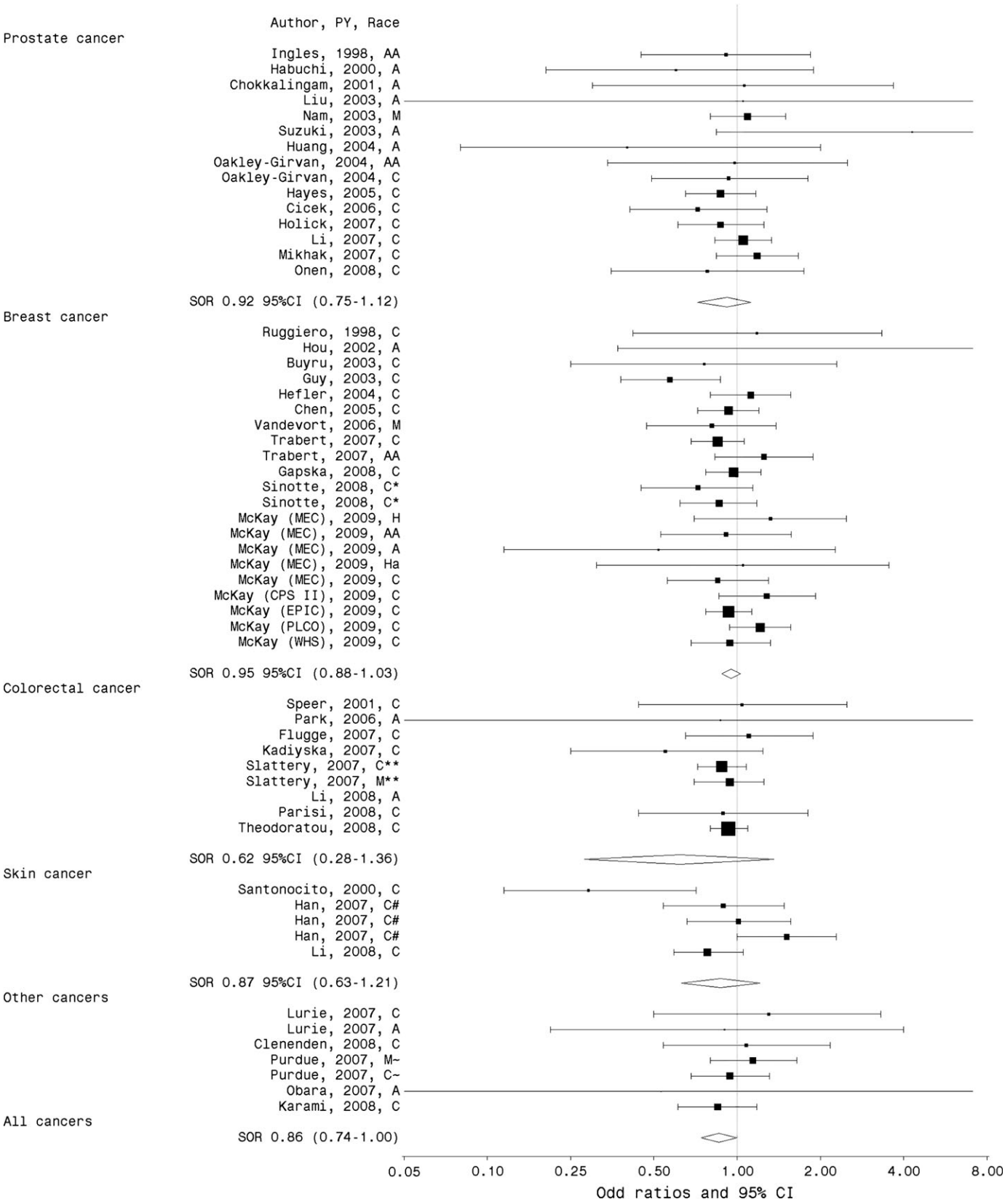

Fig. 4. Study specific and SORs with 95% confidence intervals for the association between cancer development and *BsmI BB* versus *bb* genotype. A, Asian; AA, African-American; C, Caucasian; CI, confidence interval; CPS II, Cancer Prevention Study II; EPIC, European Prospective Investigation into Cancer and Nutrition; H, Hispanic; Ha, Hawaiians; MEC, Multiethnic Cohort; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PY, publication year; WHS, Women's Health Study. * Represents the study by Sinotte *et al.* included two independent study populations with different cases and controls; ** represents the study by Slattery *et al.* included two different estimates for colon and rectum cancer; # represents the study by Han *et al.* included three different estimates for melanoma, squamous cell carcinoma and basal cell carcinoma; ~ represents there are two independent studies published by Purdue *et al.* in 2007: one was conducted in USA and one in Australia.

incident cases and those of papers that did not clearly specify how cases were recruited. These latter studies could therefore include both incident and prevalent cases. If *FokI f* allele is a risk factor both for cancer incidence and progression, then survival of patients with *FokI f* allele will be lower than that of patients with *FokI F* allele, resulting in a high number of prevalent cases with *FokI F* allele and a subsequent lower risk estimates between *FokI f* allele and cancer risk in studies including prevalent cases. Otherwise, if *BsmI B* allele reduces the risk of cancer and increase survival, then prevalent cases will have higher probability to be *BsmI B* carriers, therefore the protective effect of this allele will seem stronger in studies including prevalent cases. Out of the four studies on prostate and two on colorectal cancer that were not in H–W equilibrium for *BsmI* polymorphism, we observed that one study each for prostate and colorectal cancer provided estimates that significantly differed from the others. Deviation from H–W disequilibrium in controls is taken as an indication that the alleles are not segregating independently; there are several reasons for this, including non-random matching (which encompasses admixture), biased selection of subjects from the population, genotyping error or population stratification. We did not found any evidence of different risk estimates for studies conducted in USA compared with that carried out in other countries. National vitamin D fortification and supplementation practices are generally very different between countries. Fortification of staple foods, such as milk and margarine and spreads, plus other optional fortifications (orange juice, ready-to-eat breakfast cereals, sliced American cheese and yogurt) are mandatory in the USA, while there is no required fortification of foods in other countries.

Our study represents an updated and comprehensive review of the literature on the two most studied *VDR* polymorphisms and cancer risk at any site. Moreover, through a meta-analytic approach, we could provide powerful summary risk estimates at least for the four most studied cancer types. While previously published meta-analyses were restricted to single cancer sites, we were able to provide a complete picture of the role of *VDR* polymorphisms in cancer risk. Moreover, our meta-analysis included eight new studies and three updates of previous publications on prostate cancer compared with that published in 2006 (18); seven new studies and one update of previous publication on colorectal cancer with that published in 2008 (22); one new study and one large pooled analysis on breast cancer with that published in 2008 (25); one new study on skin cancer with those published in 2008 and 2009 (24,26). By extensive heterogeneity analysis and meta-regression on all cancer sites, we were able to highlight some factors, like ethnicity, gender, incident/prevalent cases and H–W disequilibrium, that could be responsible for the controversies of results found in the different studies. Finally, contrarily to previous meta-analyses that were performed with the DerSimonian and Laird method (25), our random-effect models with maximum likelihood estimates were able to take into account the two sources of variation (within and between studies).

One limitation of this analysis is that we did not have original data and we therefore were not able to take into account other factors, like circulating vitamin D levels, sun exposure, aspirin/NSAID use, stage disease, calcium and vitamin D intake, that could modify the risk estimates, as reported in previous publications (46–50). It is well known that dietary factors, such as calcium and vitamin D, as well as lifestyle factors, such as BMI and physical activity, may influence the *VDR* expression levels (51,52). Thus, assessment of the association among the *VDR* gene variants, diet and lifestyle factors is needed in order to determine clearly the impact of the *VDR* gene on the etiology of cancer. Another limitation is that the majority of studies in our meta-analysis included only Caucasians, limiting the generalizability of our results to other populations and restricting our ability to examine race-specific associations. Finally, it is also possible that other polymorphisms in the *VDR* gene not evaluated here may influence the risk of cancer.

In conclusion, we found a significant increase in both skin and breast cancer risk for carriers of FokI *ff* compared with *FF* genotype and a significant decrease of prostate cancer risk for *BsmI Bb* in comparison with *bb* carriers. Pooling together all cancer sites, a significant 6–7% reduction of cancer risk at any site was observed for Caucasian subjects carrying at least one copy of the *BsmI B* allele. Overall, *FokI ff* genotype seemed to increase the risk of cancer at sites probably associated with inadequate vitamin D levels.

Supplementary material

Supplementary Table I can be found at http://carcin.oxfordjournals.org/

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