Vitamin D Receptor Polymorphisms and Cancer

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Abstract

Increasing scientific evidence supports the link between vitamin D and cancer risk. The active metabolite 1,25(OH)2D exerts its activity by binding to the vitamin D receptor (VDR), an intracellular receptor that mediates transcriptional activation and repression of target genes. The binding of 1,25(OH)2D to VDR is able to regulate hundreds of different genes. VDR is active in virtually all tissues including the colon, breast, lung, ovary, bone, kidney, parathyroid gland, pancreatic b-cells, monocytes, T lymphocytes, melanocytes, keratinocytes, and also cancer cells.

The relevance of *VDR* gene restriction fragment length polymorphisms for various types of cancer has been investigated by a great number of studies.

We have carried out a systematic review of the literature to analyze the relevance of more VDR polymorphisms (*Fok1*, *Bsm1*, *Taq1*, *Apa1*, and *Cdx2*) for individual malignancies considering ethnicity as a key factor for heterogeneity.

Up to December 2018, we identified 176 independent studies with data to assess the risk of breast, prostate, colorectal, skin (melanoma and non-melanoma skin cancer), lung, ovarian, kidney, bladder, gallbladder, esophageal, thyroid, head and neck, liver and pancreatic cancer, oral squamous cell carcinoma, non-Hodgkin lymphoma, multiple myeloma and sarcoma.

Significant associations with VDR polymorphisms have been reported for prostate (*Fok1*, *Bsm1*, *Taq1*, *Apa1*, *Cdx2*), breast (*Fok1*, *Bsm1*, *Taq1*, *Apa1*, *CdX2*), colorectal (*Fok1*, *Bsm1*, *Taq1*, *Apa1*), and skin cancer (*Fok1*, *Bsm1*, *Taq1*). Very few studies reported risk estimates for the other cancer sites.

Conflicting data have been reported for most malignancies, and at present, it is still not possible to make any definitive statements about the importance of the *VDR* genotype for cancer risk. It seems probable that other factors such as ethnicity, phenotype, 25(OH)D plasma levels, and UV radiation exposure play a role as confounding factors and introduce heterogeneity.

To conclude, there is some indication that *VDR* polymorphisms may modulate the risk of some cancer sites and in future studies *VDR* genetic variation should be integrated also with assessment of vitamin D status and stratified by ethnicity.

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Keywords

VDR polymorphisms · Vitamin D · Cancer · *Fok1* · *Bsm1* · *Taq1* · *Apa1* · *Cdx2* · Breast cancer · Prostate cancer · Colon-rectum cancer · Melanoma · 25-Hydroxyvitamin D · Basal cell carcinoma · Squamous cell carcinoma · Renal cell carcinoma · Thyroid carcinoma · Esophageal adenocarcinoma · Hepatocellular carcinoma · Head and neck cancer · Non-Hodgkin lymphoma · Nasopharyngeal carcinoma · Oral squamous cell carcinoma · Ultraviolet · Risk estimates · Meta-analysis

Abbreviations

BCC	Basal cell carcinoma
BMI	Body mass index
CI	Confidence interval
CRC	Colorectal cancer
EAC	Esophageal adenocarcinoma
HCC	Hepatocellular carcinoma
HNC	Head and neck cancer
H-W	Hardy-Weinberg
MM	Malignant melanoma
NHL	Non-Hodgkin lymphoma
NMSC	Non-melanoma skin cancer
NPC	Nasopharyngeal carcinoma
OR	Odds ratio
OSCC	Oral squamous cell carcinoma
PCa	Prostate cancer
RCC	Renal cell carcinoma
RFLP	Restriction fragment length polymorphism
RR	Relative risk
SCC	Squamous cell carcinoma
SNP	Single nucleotide polymorphism
SRR	Summary relative risk
TC	Thyroid carcinoma
UV	Ultraviolet
VDR	Vitamin D receptor
vs	Versus

Introduction

Most vitamin D is derived from the action of sunlight on the skin, and this source accounts for about 80% of the total vitamin D [84]. Exogenous vitamin D comes from dietary intake through the consumption of foods that are naturally rich in or fortified with it or through supplementation [202]. The overall vitamin D reservoir is the sum of cutaneous and nutritional vitamin D.

Pre-vitamin D undergoes two hydroxylations to become biologically active [46]. First, vitamin D3 from the skin and vitamins D2 and D3 from the diet are metabolized in the liver to 25-hydroxyvitamin D (25[OH]D), which is the main circulating vitamin D metabolite measured to define the patient's vitamin D status. The conversion to its biologically active form, 1,25-hydroxyvitamin D (1,25[OH]D), is under tight hormonal control in the kidneys by the parathyroid hormone, in keeping with its important role in calcium homeostasis.

The vitamin D status varies greatly with season (the highest levels are observed in late summer and autumn) and with body mass index (BMI) (greater BMI is associated with lower 25 (OH)D).

In addition to the pivotal role of vitamin D in the maintenance of musculoskeletal health, it has also been shown to play an important role in other metabolic pathways, such as those involved in the immune response and cancer. It is emerging as a critical regulator of pathogenic processes such as pigmental disorders; cardiovascular, renal, infectious, and autoimmune diseases; as well as several types of cancers [55, 83, 147, 164–167, 184, 195].

The active metabolite 1,25(OH)2D [84] seems to play an important role in the development of cancers by regulating the expression of tumor-related genes and mediating inhibition of cell growth, adhesion, migration, and angiogenesis in vitro and in vivo [32, 41, 53, 58, 61, 80, 150, 156, 229]. It exerts its activity by binding to the vitamin D receptor (VDR), an intracellular receptor and member of the nuclear receptor family

(locus on chromosome 12q12–14) that mediates transcriptional activation and repression of target genes. The VDR controls gene expression through so-called vitamin D response elements on the DNA. The binding of 1,25(OH)2D to VDR is able to regulate hundreds of different genes [23]. VDR is active in virtually all tissues including the colon, breast, lung, ovary, bone, kidney, parathyroid gland, pancreatic b-cells, monocytes, T lymphocytes, melanocytes, keratinocytes, and also cancer cells.

Several meta-analyses of observational studies showed a reduced risk for some cancer sites associated with high vitamin D status. A meta-analysis published by Gandini et al. [64] showed a significant inverse relationship between high level of 25(OH)D levels and the risk of colorectal cancer (CRC): a SRR of 0.85 (95%CI: 0.79–0.91) for 10 ng/ml increase in serum 25-hydroxyvitamin D. This inverse association was further confirmed by another meta-analysis [207] that presents a SRR of 0.96 (95%CI: 0.94–0.97) for 100 IU/L increase of 25(OH)D.

High serum 25(OH)D levels were found to significantly decrease the risk of bladder cancer (SRR: 0.75; 95%CI: 0.65–0.87) in a meta-analysis published by Berlin [19].

A meta-analysis on lung cancer risk showed that vitamin D intake and serum 25(OH)D levels each correlated inversely with lung cancer risk [OR = 0.72 (95%CI: 0.61–0.85) and OR = 0.89 (95%CI: 0.83–0.97)]. Interestingly non-smokers had higher vitamin D levels, which correlated negatively with lung cancer risk (OR = 0.76, 95%CI: 0.65–0.88) [125]. Similar results were found for breast cancer: 25(OH)D deficiency is significantly associated with increased risk (OR = 1.91, 95%CI: 1.51–2.41), and supplemental vitamin D (OR = 0.97, 95%CI: 0.95–1.00, $P = 0.026$) was inversely associated with breast cancer risk [87].

A meta-analysis of randomized clinical trials showed that vitamin D supplementations seem to have little effect on total cancer incidence, but a significant reduction in total cancer mortality (400–833 IU per day, summary RR = 0.88, 95%CI = 0.78–0.98, $I2 = 0\%$, 3 RCTs with combined 1190 deaths) [110].

Genetic variations of VDR may phenotypically appear as interindividual rate-limiting variations of vitamin D synthesis in the skin, hydroxylation in the liver and kidney, and transportation, metabolism, and degradation that could influence individual vitamin D status. Given that single nucleotide polymorphisms (SNPs) in the VDR gene could potentially influence the binding of 1,25(OH)2D, the transcriptional activity of the receptor, and its binding to vitamin D response elements and provided the antiproliferative effects of vitamin D, VDR polymorphisms have been hypothesized to be associated with cancer risk.

The most frequently studied single nucleotide VDR polymorphisms in association with cancer risk are the restriction fragment length polymorphisms *Fok1* (rs2228570) and *Bsm1* (rs1544410) [171, 212]. More recently, other SNPs have been investigated: *Taq1* (rs731236), *Apa1* (rs7975232), and *Cdx2* (rs11568820) [185].

Materials and Methods

We performed systematic literature search of published studies evaluating the association between *VDR* gene restriction fragment length polymorphisms (RFLPs) *Fok1*, *Bsm1*, *Taq1*, *Apa1*, and *Cdx2* and 19 types of cancer, including breast (female and male), prostate, skin (melanoma and non-melanoma skin cancer), colon, ovarian, kidney, bladder, brain, esophageal, gallbladder, gastric, liver, head and neck, lung, multiple myeloma, non-Hodgkin lymphoma, pancreas, sarcoma, and thyroid and mixed cancer sites. Estimates of risk are also available for several ethnic groups (Caucasians, Asian, African, African-American, Hispanic, and others).

Data Extraction and Data Analysis

Data have been extracted retrieving the following information from each publication: authors, journal and year of publication, country of origin, ethnic group of study population, number of cases and controls for each *VDR* genotype and

by variants status and adjustments used for risk estimates.

We considered eligible for the present analysis all independent papers from genotype-based epidemiological studies reporting frequency of *VDR* polymorphisms, 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).

When available, we extracted fully adjusted relative risk (RR) estimates separately for heterozygous and minor allele homozygous subjects compared to wild-type subjects. When adjusted estimates were not available, we retrieved the frequencies of *VDR* 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 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.

We presented forest plots of risk estimates by cancer sites and ethnic groups.

When zero subjects with homozygous variants were present among controls, we imputed 0.5 in order to be able to calculate the risk estimate.

Exclusion Criteria

- Studies not independent from a study already included, because based on the same population or have in common a subgroup of population. The one with the greater sample size is preferred.
- Studies evaluating the risk of colorectal adenoma and benign prostatic hyperplasia.
- Studies that included as control group not healthy subjects (e.g., benign prostatic hyperplasia).
- Studies with too sparse data that included as control group benign prostatic hyperplasia.
- Studies with zero subjects in the wild-type category among cases or controls.
- Studies that presented no risk estimates for homozygous and heterozygous variants vs wild-type and no crude data to calculate them.
- Studies that presented risk estimates only for additive model.
- Studies for which the Minor Allele Frequency (MAF) was strongly different from HapMap MAF for the corresponding ethnic group.

Fok1 and Cancer

It has been hypothesized that a less active VDR could be associated with either an increased susceptibility to cancer risk or a more aggressive disease. 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. Although no significant differences in ligand affinity, DNA binding, or transactivation activity are found between these two VDR forms when studied independently [70], in transient transfection assays with a vitamin D-responsive reporter gene, the shorter VDR variant displays higher potency than the longer one [216].

Breast Cancer

Fok1 is the most frequently analyzed *VDR* polymorphism, and numerous studies examined its association with breast cancer risk. Between 1999 and 2018, 25 studies have been published, and they are summarized in Table 4.1 and Figs. 4.1 and 4.2. Most of them were carried out in the USA and Canada (n. 8 studies 32%) and in European countries (n. 7 studies 28%). Twelve studies (48%) were case-control studies with population controls, and 15 (60%) analyzed a Caucasian population.

We also included a study investigating the association between VDR gene polymorphism with male breast cancer risk in a Turkish population [111].

Table 4.1 Descriptive characteristics of studies grouped by cancer sites

Cancer site	Author, PY [REF]	Country	Ethnicity	Source of controls	*Apa1*	*Fok1*	*Bsm1*	Cdx2	*Taq1*
Bladder	Mittal, 2007 [140]	India	Other	Population		x			x
Bladder	Ben Fradj, 2016 [17]	Tunisia	African	Population		x			
Brain	Anic, 2012 [8]	USA	Caucasian	Population		x	x	x	x
Brain	Toptaş, 2013 [205]	Turkey	Other	Hospital		x			
Brain (pediatric)	Yilmaz, 2017 [225]	Turkey	Other	Hospital		x	x		x
Breast	Ruggiero, 1998 [180]	Italy	Caucasian	Hospital			x		
Breast	Curran, 1999 [44]	Australia	Caucasian	Hospital	x	x			x
Breast	Dunning, 1999 [51]	UK	Caucasian	Hospital					x
Breast	Hou, 2002 [88]	Taiwan	Asian	Hospital	x		x		x
Breast	Buyru, 2003 [26]	Istanbul	Other	Hospital			x		x
Breast	Guy, 2003 [75]	UK	Caucasian	Population		x	x		
Breast	Hefler, 2004 [82]	Germany	Caucasian	Hospital			x		
Breast	Sillanpaa, 2004 [190]	Finland	Caucasian	Hospital	x				x
Breast	VandeVord, 2006 [211]	USA	Mixed	Hospital			x		
Breast	John, 2007 [104]	USA	A-A, Caucasian, Hispanic	Population		x			x
Breast	Trabert, 2007 [208]	USA	A-A	Population			x		
Breast	Abbas, 2008 [1]	Germany	Caucasian	Population		x		x	x
Breast	Barroso, 2008 [15]	Spain	Caucasian	Population		x			x
Breast	Gapska, 2009 [66]	Poland	Caucasian	Population		x	x		
Breast	Sinotte, 2008 [191]	Canada	Caucasian	Hospital		x	x		
Breast	Chakraborty, 2009 [29]	India	Other	Hospital	x				x
Breast	McKay, 2009 [133]	USA	A-A, Asian, Caucasian, Hispanic, other	Population		x	x		
Breast	Anderson, 2011 [6]	Canada	Caucasian	Population	x	x	x	x	x
Breast	Dalessandri, 2012 [45]	USA	Caucasian	Population	x				
Breast	Engel, 2012 [57]	USA	Caucasian	Population	x	x			x
Breast	Huang, 2012 [90]	China	Asian	Hospital	x		x		x
Breast	Rollison, 2012 [178]	USA	Caucasian, Hispanic	Population		x	x		
Breast	Yao, 2012 [223]	USA	A-A, Caucasian	Population				x	
Breast	Akilzhanova, 2013 [3]	Kazakhstan	Other	Nr		x	x		
Breast	Fuhrman, 2013 [63]	USA	Caucasian	Population		x	x		
Breast	Mishra, 2013 [139]	USA	A-A, Hispanic	Hospital	x	x	x		x
Breast	Shahbazi, 2013 [188]	Iran	Other	Hospital		x	x		

(continued)

Table 4.1 (continued)

Cancer site	Author, PY [REF]	Country	Ethnicity	Source of controls	*Apa1*	*Fok1*	*Bsm1*	Cdx2	*Taq1*
Breast	Abd-Elsalam, 2015 [2]	Egypt	Other	Hospital	x	x	x		x
Breast	Clendenen, 2015 [40]	Sweden	Caucasian	Population		x	x	x	
Breast	Guo, 2015 [74]	China	Asian	Hospital	x		x		x
Breast	Iqbal, 2015 [100]	Pakistan	Other	Hospital				x	
Breast	Nemenqani, 2015 [149]	Saudi Arabia	Asian	Hospital		x			x
Breast	Reimers, 2015 [177]	USA	Caucasian	Population	x		x		x
Breast	Deschasaux, 2016 [49]	France	Caucasian	Population		x	x		
Breast	Amadori, 2017 [5]	Italy/Tanzania	Caucasian, African	Hospital		x		x	
Breast	Atoum, 2017 [11]	Jordan	Other	Population					x
Breast	Elzehery, 2017 [56]	Egypt	Other	Hospital			x		
Breast	Haikal, 2017 [77]	Egypt	Other	Hospital			x		
Breast	Talaneh, 2017 [201]	Iran	Other	Hospital		x	x		
Breast	Shahabi, 2018 [187]	Iran	Other	Hospital		x	x		
Breast	Shaker, 2018 [189]	Egypt	African	Hospital		x	x		
Breast	Rashid, 2015 [174]	Pakistan	Other	Hospital		x	x		
Breast (male)	Kizildag, 2011 [111]	Turkey	Other	Hospital	x	x			x
CRC	Speer, 2001 [197]	Hungary	Caucasian	Hospital			x		
CRC	Wong, 2003 [217]	Singapore	Asian	Population		x			
CRC (rectal)	Murtaugh, 2006 [146]	USA	Caucasian	Population		x			
CRC	Park, 2006 [160]	Korea	Asian	Population	x	x	x		x
CRC	Flugge, 2007 [60]	Russia	Caucasian	Hospital	x	x	x	x	x
CRC	Kadiyska, 2007 [106]	Bulgaria	Caucasian	Hospital			x		

CRC	Slattery, 2007 and Slattery 2009 [192, 193]	USA	Caucasian	Population		x	x	x	
CRC	Yaylim-Eraltan, 2007 [224]	Turkey	Other	Hospital		x			x
CRC	Grunhage, 2008 [71]	Germany	Caucasian	Hospital		x			
CRC	Li, 2009 [119]	China	Asian	Population Hospital		x	x		
CRC	Ochs-Balcom, 2008 [154]	USA	Caucasian	Population		x		x	x
CRC	Parisi, 2008 [159]	Spain	Caucasian	Population			x		
CRC	Theodoratou, 2008 [203]	UK	Caucasian	Population	x	x	x	x	
CRC	Wang, 2008 [214]	China	Asian	Hospital		x			
CRC	Jenab, 2009 [101]	Europe	Caucasian	Population		x	x		
CRC	Mahmoudi, 2010 and 2011 [130, 131]	Iran	Other	Hospital	x	x	x		x
CRC	Hughes, 2011 [95]	Czech republic	Caucasian	Hospital	x		x		x
CRC	Bentley, 2012 [18]	New Zealand	Caucasian	Population		x		x	x
CRC	Gunduz, 2012 [73]	Turkey	Other	Hospital			x		x
CRC	Rasool, 2013 and 2014 [175, 176]	India	Other	Hospital	x	x	x		
CRC	Atoum, 2014 [12]	Jordan	Other	Population					x
CRC	Laczmanska, 2014 [114]	Poland	Caucasian	Hospital	x	x	x		x
CRC	Sarkissyan, 2014 [183]	USA	Mixed	Hospital	x	x	x		x
CRC	Takeshige, 2015 [200]	Japan	Asian	Population	x	x	x		x
CRC	Alkhayal, 2016 [4]	Saudi Arabia	Other	Hospital	x	x	x		x
CRC	Cho, 2018 [36]	Korea	Asian	Hospital		x			
CRC	Moossavi, 2018 [142]	Iran	Other	Hospital		x			x
CRC	Vidigal, 2017 [212]	Brazil	Mixed	Hospital	x		x		
Esophageal	Chang, 2012 [30]	Ireland	Caucasian	Population	x	x	x		x
Esophageal	Gu, 2014 [72]	China	Asian	Hospital		x		x	
Gallbladder	Li, 2014 [120]	China	Asian	Hospital	x	x	x		x
Gastric	Cong, 2015 [42]	China	Asian	Hospital		x			
Gastric	Yin, 2017 [226]	China	Asian	Hospital		x			
Head and neck	Liu, 2005 [124]	USA	Caucasian	Population		x			x
Head and neck (Oral)	Bektas-Kayhan, 2010 [16]	Turkey	Other	Hospital					x
Head and neck (nasopharyngeal)	Huang, 2011 [93]	China	Asian	Hospital		x	x		

(continued)

Table 4.1 (continued)

Cancer site	Author, PY	Country	Ethnicity	Source of controls	*Apa1*	*Fok1*	*Bsm1*	Cdx2	*Taq1*
Head and neck	Zeljic, 2012 [230]	Serbia	Caucasian	Population	x	x	x		x
Kidney	Obara, 2007 [153]	Japan	Asian	Population	x		x		x
Kidney	Karami, 2008 [109]	Europe	Caucasian	Hospital		x	x		x
Kidney	Arjumand, 2012 [10]	India	Other	Hospital		x	x		
Kidney	Southard, 2012 [196]	Finland	Caucasian	Hospital		x			
Kidney	Yang, 2016 [222]	China	Asian	Hospital	x	x	x	x	x
Liver	Falleti, 2010 [59]	Italy	Caucasian	Hospital	x	x	x		x
Liver	Hung, 2014 [96]	Taiwan	Asian	Hospital	x		x		x
Liver	Peng, 2014 [162]	China	Asian	Hospital		x			
Lung (SCLC)	Dogan, 2009 [50]	Turkey	Other	Hospital			x		x
Lung	Kaabachi, 2014 [105]	Tunisia	African	Hospital	x	x	x		x
Lung (NSCLC)	Wu, 2016 [218]	China	Asian	Hospital	x	x	x		x
Lung	Gromowski, 2017 [69]	Poland	Caucasian	Hospital	x	x	x	x	x
Multiple myeloma	Shafia, 2013 [186]	India	Other	Hospital	x	x	x		
Multiple myeloma	Chen, 2017 [34]	China	Asian	Hospital	x	x			
Non-Hodgkin lymphoma	Purdue, 2007 [170]	Australia	Caucasian	Population		x	x		
Non-Hodgkin lymphoma	Purdue, 2007 [169]	USA	Caucasian	Population			x		x
Non-Hodgkin lymphoma	Smedby, 2011 [194]	Sweden	Caucasian	Population			x		x
Ovary	Lurie, 2007 [127]	USA	Asian, Caucasian	Population	x		x	x	x
Ovary	Clendenen, 2008 [39]	USA + Sweden	Caucasian	Population	x	x	x		x
Ovary	Tworoger, 2009 [209]	USA	Caucasian	Population		x	x	x	
Ovary	Lurie, 2011 [128]	USA + Europe	Caucasian	Population		x			
Ovary	Grant, 2013 [68]	USA	A-A, Caucasian	Population		x	x		x
Ovary	Mohapatra, 2013 [141]	India	Other	Population		x			
Ovary	Mostowska, 2016 [144]	Poland	Caucasian	Hospital		x	x		
Pancreas	Li, 2015 [121]	China	Asian	Hospital		x	x		
Prostate	Ingles, 1998 [98]	USA	A-A	Population			x		
Prostate	Ma, 1998 [129]	USA	Caucasian	Population					x
Prostate	Correa-Cerro, 1999 [43]	France	Caucasian	Population		x			x
Prostate	Blazer, 2000 [22]	USA	A-A, Caucasian	Population					x
Prostate	Habuchi, 2000 [76]	Japan	Asian	Hospital	x		x		x
Prostate	Chokkalingam, 2001 [37]	China	Asian	Population		x	x		

Prostate	Medeiros, 2002 [134]	Portugal	Caucasian	Hospital					x
Prostate	Liu, 2003 [123]	China	Asian	Hospital			x		
Prostate	Nam, 2003 [148]	Canada	A-A, Asian, Caucasian	Hospital			x		
Prostate	Suzuki, 2003 [198]	Japan	Asian	Hospital	x		x		x
Prostate	Huang, 2004 [91]	Taiwan	Asian	Hospital	x		x		x
Prostate	Maistro, 2004 [132]	Brazil	Mixed	Hospital	x				x
Prostate	Oakley-Girvan, 2004 [152]	USA	A-A, Caucasian	Population	x	x	x		x
Prostate	Yang, 2004 [221]	China	Asian	Hospital		x			
Prostate	Hayes, 2005 [81]	Australia	Caucasian	Population		x	x		
Prostate	John, 2005 [103]	USA	Caucasian	Population				x	x
Prostate	Mishra, 2005 [138]	India	Other	Hospital		x			
Prostate	Andersson, 2006 [7]	Sweden	Caucasian	Population					x
Prostate	Chaimuangraj, 2006 [28]	Thailand	Asian	Hospital			x		x
Prostate	Cicek, 2006 [38]	USA	Caucasian	Population	x	x	x	x	x
Prostate	Huang, 2006 [92]	Taiwan	Asian	Hospital		x			
Prostate	Holick, 2007 [85]	USA	Caucasian	Population		x	x		x
Prostate	Li, 2007 [117]	USA	Caucasian	Population		x	x		
Prostate	Mikhak, 2007 [137]	USA	Caucasian	Population		x	x	x	
Prostate	Onen, 2008 [155]	Turkey	Other	Hospital	x		x		x
Prostate	Torkko, 2008 [206]	USA	Caucasian, Hispanic	Population		x		x	
Prostate	Bai, 2009 [14]	China	Asian	Population	x	x	x		x
Prostate	Holt, 2009 [86]	USA	A-A, Caucasian	Population		x	x		x
Prostate	Szendroi, 2011 [199]	Hungary	Caucasian	Hospital			x		
Prostate	Rowland, 2013 [179]	USA	A-A, Caucasian	Population		x		x	
Prostate	Hu, 2014 [89]	China	Asian	Hospital					x
Prostate	Yousaf, 2014 [227]	Pakistan	Other	Hospital	x	x			x
Prostate	Atoum, 2015 [13]	Jordan	Other	Population		x			
Prostate	Gilbert, 2015 [67]	UK	Caucasian	Hospital	x	x	x	x	x
Prostate	Jingwi, 2015 [102]	USA	A-A	Hospital	x				x
Prostate	Deschasaux, 2016 [48]	France	Caucasian	Population		x	x	x	
Prostate	Nunes, 2016 [151]	Brazil	Mixed	Hospital	x	x	x		

(continued)

Table 4.1 (continued)

Cancer site	Author, PY	Country	Ethnicity	Source of controls	*Apa1*	*Fok1*	*Bsm1*	Cdx2	*Taq1*
Prostate	El Ezzi, 2017 [54]	Lebanon	Caucasian	Hospital	x	x	x		x
Prostate	Kambale, 2017 [107]	India	Other	Hospital	x	x			x
Prostate	Braczkowski, 2018 [24]	Poland	Caucasian	Hospital		x	x		x
Sarcoma sarcoma)	Ruza, 2003 [181]	Spain	Caucasian	Population	x	x			x
Skin (melanoma)	Hutchinson, 2000	UK	Caucasian	Hospital					x
Skin (melanoma, BCC, SCC)	Han, 2007 [79]	USA	Caucasian	Population		x	x	x	
Skin (melanoma)	Santonocito, 2007 [182]	ITALIA	Caucasian	Population		x	x		
Skin (melanoma)	Gapska, 2009 ([65], [66])	Poland	Caucasian	Population		x	x		x
Skin (melanoma)	Li, 2008 [117]	USA	Caucasian	Hospital		x	x		
Skin (melanoma)	Randerson-Moor, 2009 [173]	UK	Caucasian	Population	x	x	x	x	x
Skin (BCC)	Lesiak, 2011 [116]	Poland	Caucasian	Hospital	x	x	x		x
Skin (BCC, SCC)	Köstner, 2012 [113]	Germany	Caucasian	Hospital	x				x
Skin (melanoma)	Pena-Chilet, 2013 [161]	Spain	Caucasian	Hospital		x			x
Skin (melanoma)	Zeljic, 2014 [231]	Serbia	Caucasian	Hospital	x	x			x
Skin (NMSC)	Burns, 2017 [25]	USA	Caucasian	Hospital	x		x		x
Skin (melanoma)	Cauci, 2017 [27]	Italy	Caucasian	Hospital		x	x		
Solid pediatric tumor	Bienertova-Vasku, 2016 [21]	Czech Republic	Caucasian	Population		x	x	x	x
Tobacco-related	Deschasaux, 2015 [47]	France	Caucasian	Population		x	x	x	
Thyroid (follicular, papillary)	Penna-Martinez, 2009 [163]	Germany	Caucasian	Population	x	x	x		x
Thyroid (papillary)	Beysel, 2018 [20]	Turkey	Other	Hospital	x	x	x		x

A-A: African-American

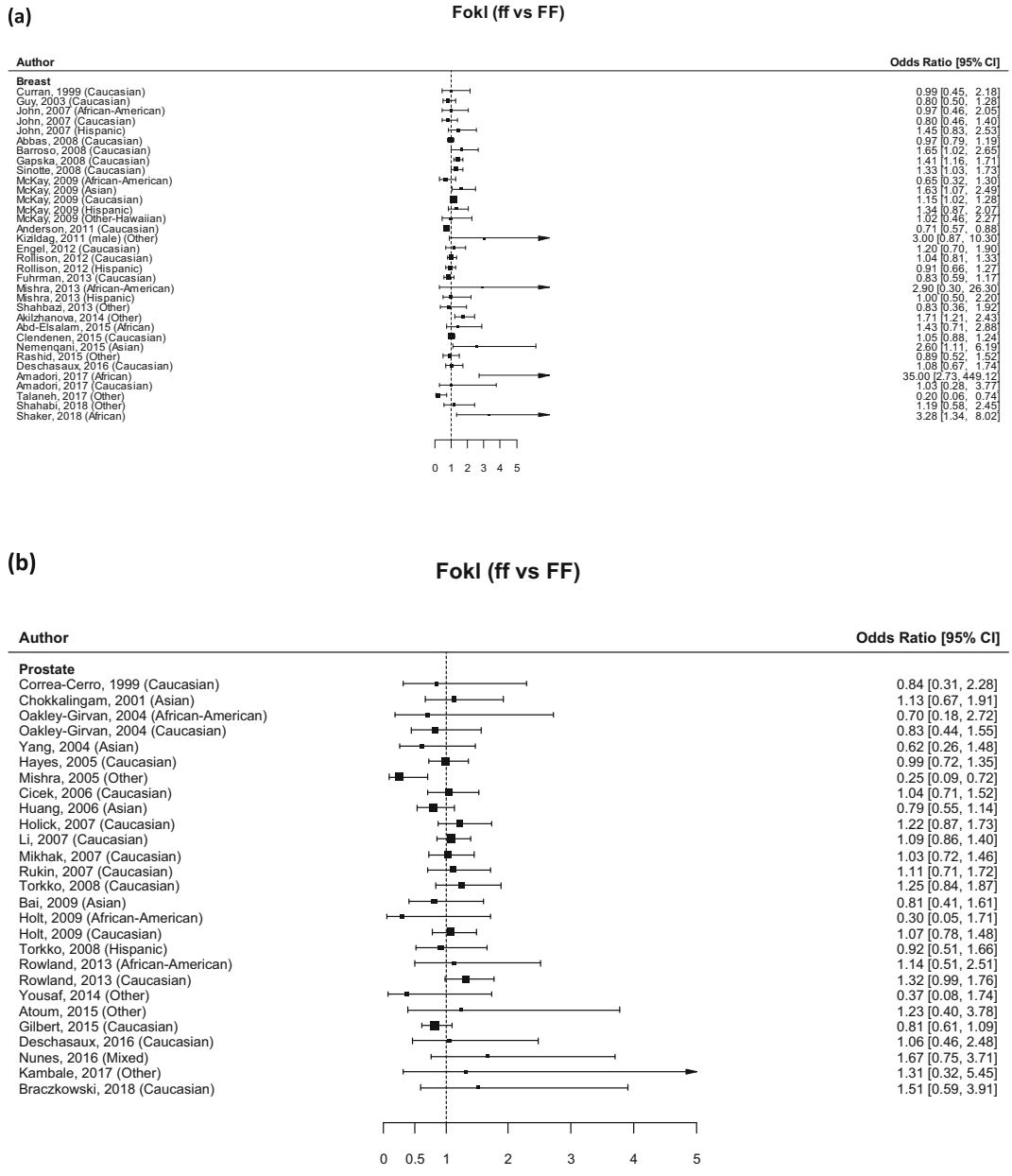
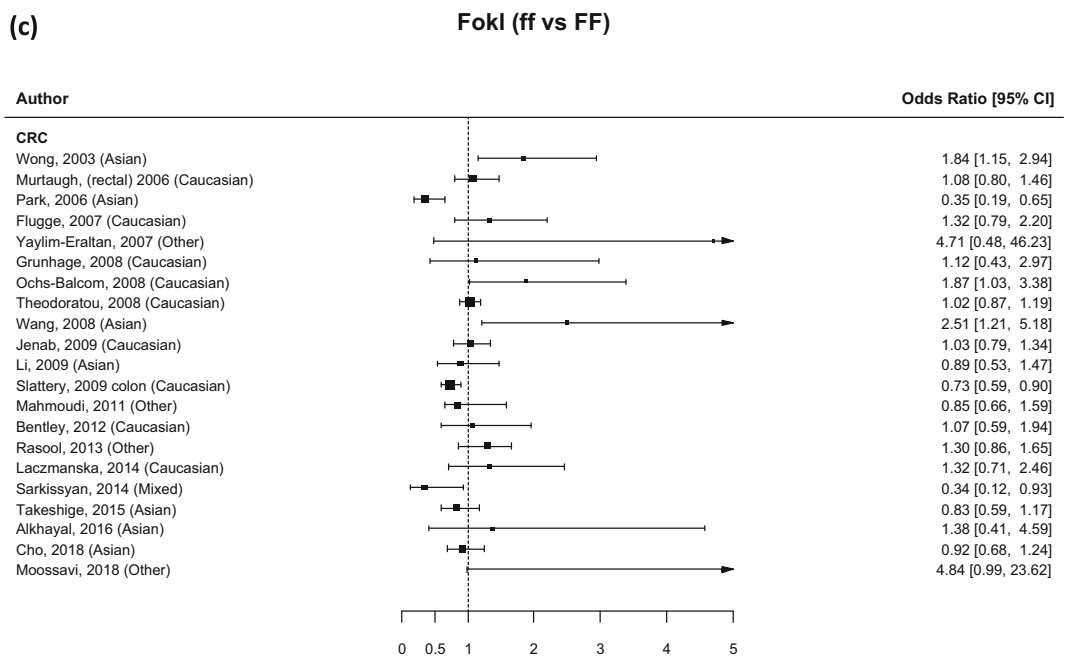
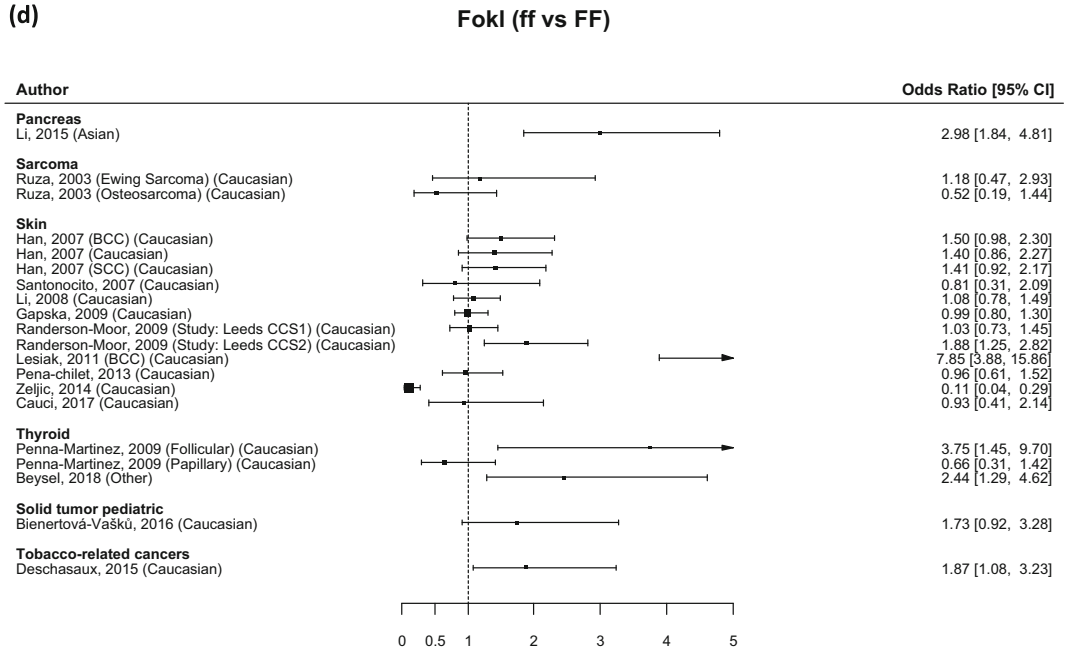


Fig. 4.1 Forest plot for the association between *Fok1 ff* and *FF* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the pancreas, skin, and thyroid, sarcoma, pediatric solid tumors, and tobacco-related cancers; (**e**) cancers of the kidney, liver, lung, and ovary, multiple myeloma, and non-Hodgkin lymphoma; (**f**) cancers of the bladder, brain, esophagus, gallbladder, and head and neck and gastric cancer





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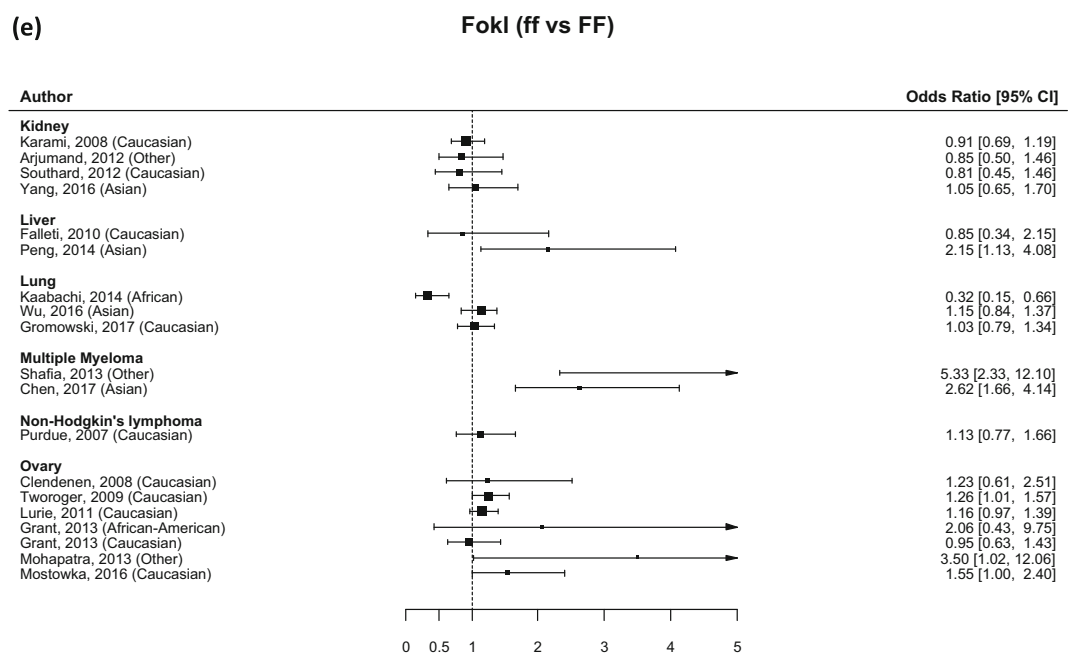


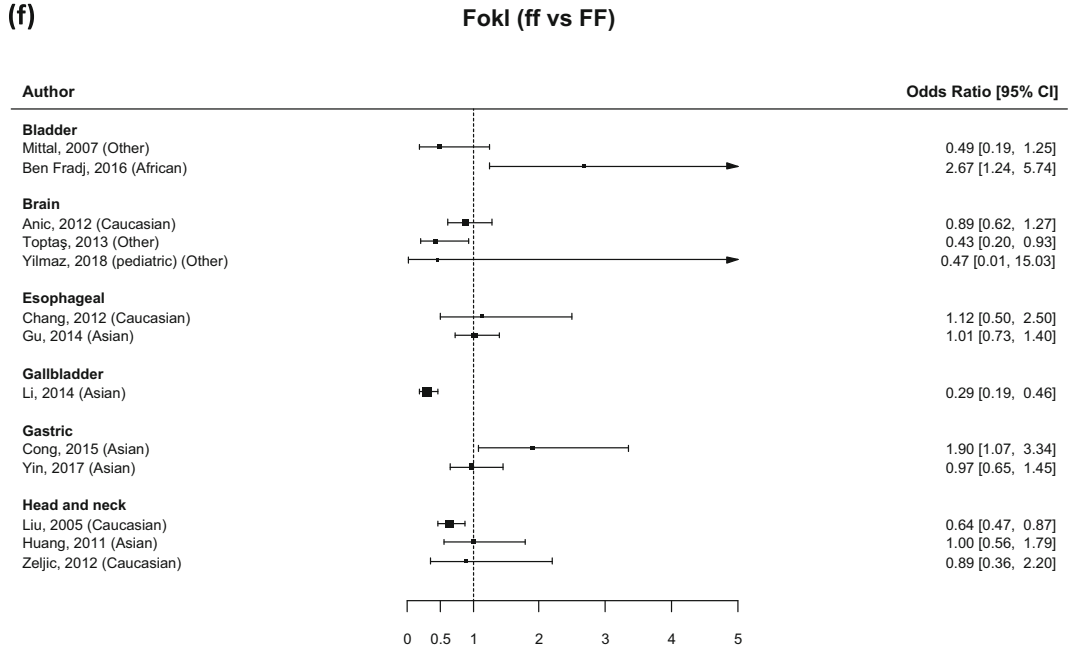


Fig. 4.1 (continued)

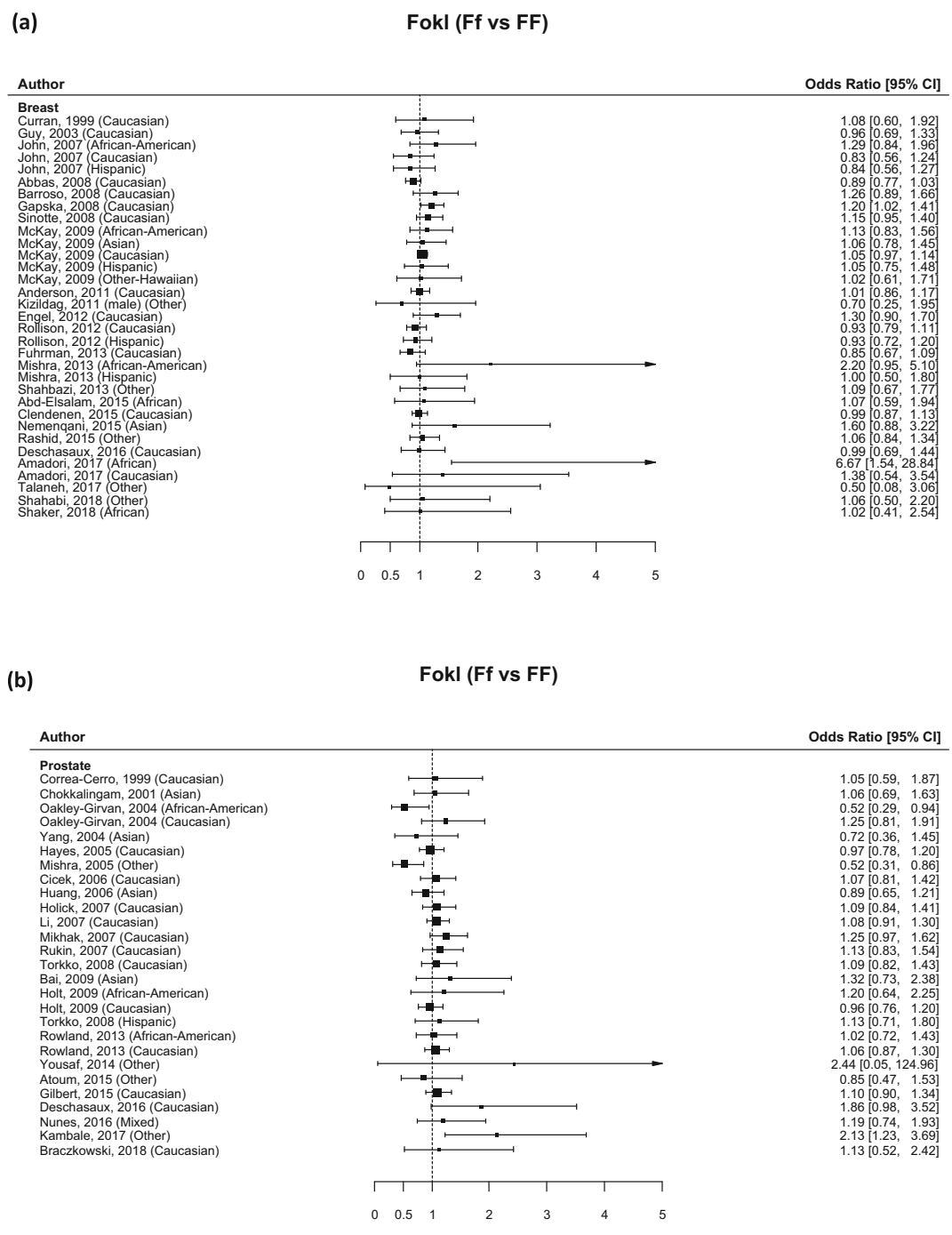
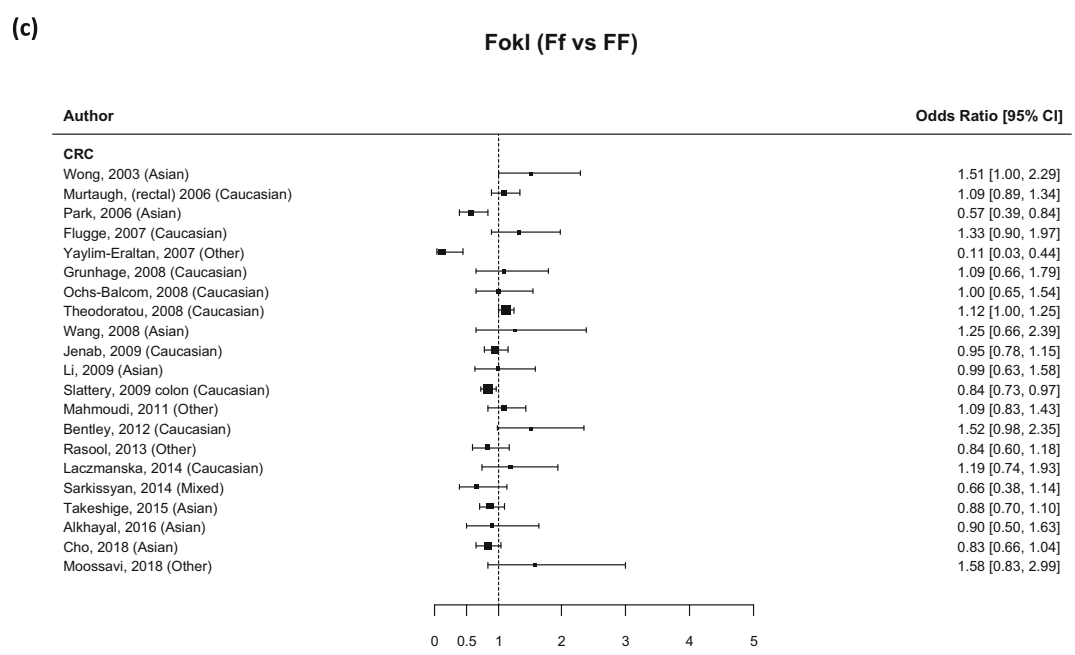


Fig. 4.2 Forest plot for the association between *Fok1 Ff* and *FF* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the pancreas, skin, and thyroid, sarcoma, pediatric solid tumors, and tobacco-related cancers; (**e**) cancers of the kidney, liver, lung, and ovary, multiple myeloma, and non-Hodgkin lymphoma; (**f**) cancers of the bladder, brain, esophagus, gallbladder, and head and neck and gastric cancer



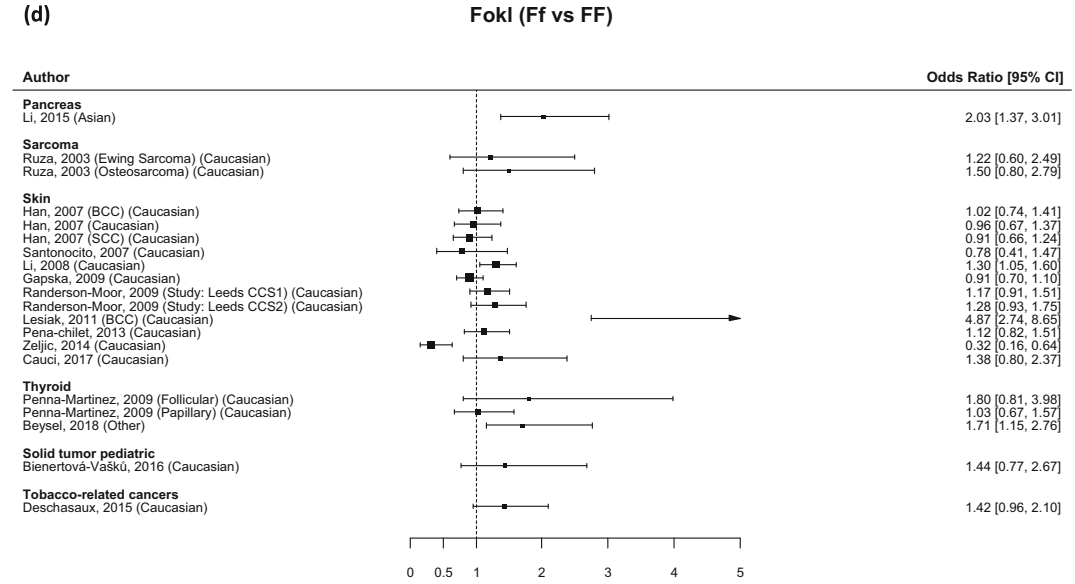
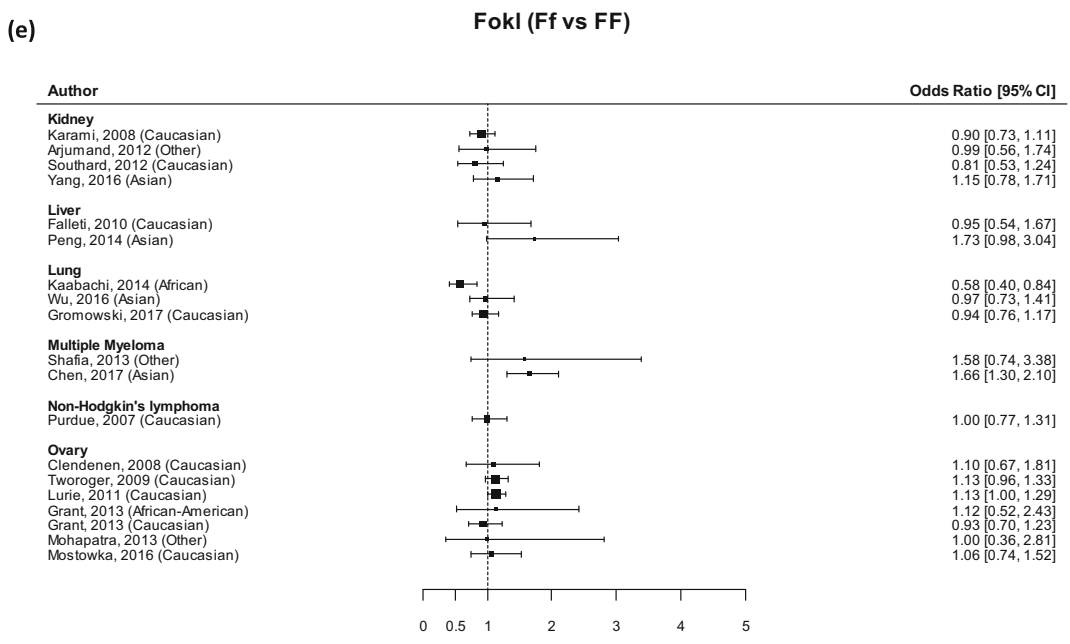


Fig. 4.2 (continued)



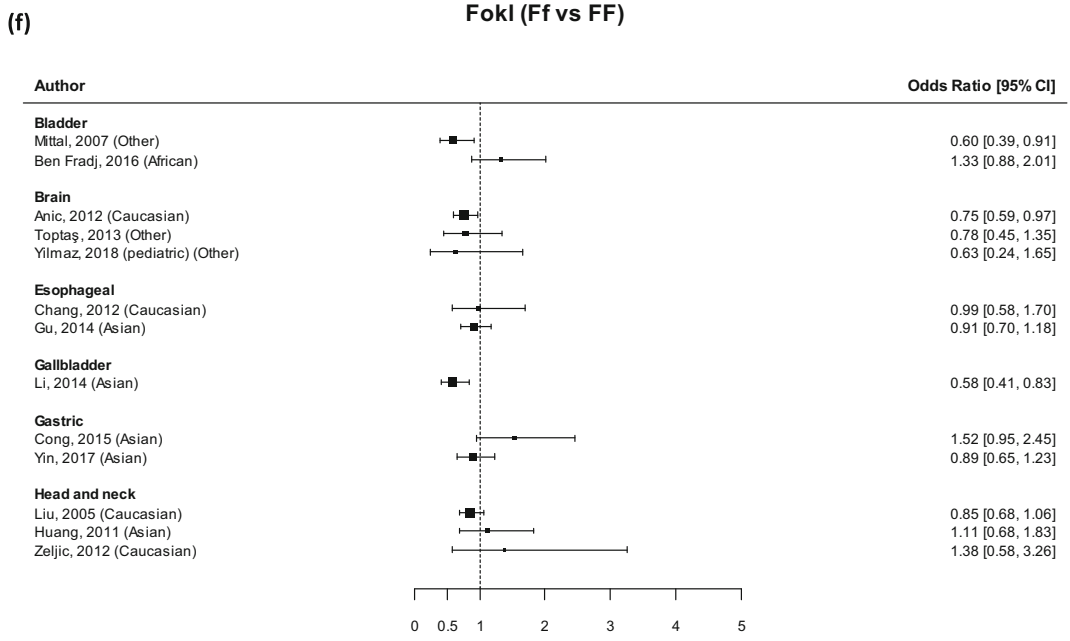


Fig. 4.2 (continued)

Only two studies [6, 201] found the *Fok1 ff* genotype significantly inversely associated with breast cancer risk (OR = 0.71; 95%CI: 0.57–0.88 and OR = 0.20; 95%CI: 0.06–0.74, respectively). It is unclear the reason for this association. Anderson analyzed a big sample size and the estimates were adjusted for age. However this study presents a significant departure from Hardy-Weinberg equilibrium for this polymorphism. In the most recent study conducted in Iran [201], the authors suggested that the observed discrepancies could be attributed to the small number of participants, races, and risk factors not considered in the analysis (analyses not adjusted).

On the other hand, eight studies reported a significant positive association [3, 5, 15, 65, 133, 149, 189, 191] between *Fok1 ff* genotype and breast cancer risk. The biggest study, Gapska [65], found a 41% significant increased risk (OR = 1.41; 95%CI: 1.16–1.71) in a Caucasian population (Poland) including 1736 cases and 1484 controls. Another big study was performed in Canada: Sinotte [191] found a significant higher breast cancer risk (OR = 1.33, 95% CI = 1.03–1.73), and this association was also observed for women without family history of breast cancer in first-degree relatives.

McKay [133] found a significant increase in breast cancer risk associated with the *ff* genotype in Japanese (OR = 1.63; 95%CI: 1.07–2.49) and Caucasian (OR = 1.15; 95%CI: 1.02-1.28) women in a multiethnic cohort study conducted in USA.

The remaining studies found no significant association (Figs. 4.1 and 4.2).

Analyzing *Fok1 Ff* genotype, only two studies found a significant increased risk of breast cancer: Gapska [65] (OR = 1.20; 95%CI: 1.02–1.41) and Amadori [5] (OR = 6.67; 95%CI: 1.54–28.84).

Amadori conducted the study on a mix population (indigenous black Tanzanian and Caucasian Italian population), but they found an effect only in the African population, and this result could also be given by the relatively limited sample size (18 cases and 50 controls). Finally, Gapska identified an association between the *Fok1* polymorphisms and early-onset breast cancer risk in a Polish population [65].

In conclusion, the weight of the evidence tends to indicate an association of breast cancer with *Fok1 ff* genotype. The most recent meta-analysis published by Iqbal [99] showed that the *Fok1-f* allele was associated with breast cancer risk with a recessive model, but the SOR was not statistically significant (*Fok1 ff* + F*f* vs *FF*; SOR = 0.25, 95%CI: 0.896–1.759). The authors explained the discrepancies may be due in part to variation in linkage disequilibrium between these functional and marker alleles. Further studies are necessary to clarify these observations.

Prostate Cancer

Twenty-three eligible studies have been published between 1999 and 2018 (Table 4.1, Figs. 4.1 and 4.2) analyzing the association between *Fok1* polymorphism of the *VDR* gene and prostate cancer risk. They are carried out mainly in the USA (eight studies), and the remaining 15 in China (three), France (two), India (two), the UK, Australia, Poland, Brazil, Jordan, Pakistan, Lebanon, and Taiwan. Fourteen (61%) were case-control studies with population controls, and 14 (61%) analyzed a Caucasian population.

There was no strong evidence of altered risk of developing prostate cancer analyzing the *ff* genotype. Two big studies with more than 1000 cases [117, 179] were from the USA. The *Fok1* was not directly associated with prostate cancer risk. An increased risk was associated with the less functional *Fok1 ff* genotype only in the presence of low 25(OH)D status [117] and only among Caucasian and for advanced disease [179].

Two studies carried out in India [107, 138] found an association with prostate cancer risk. Mishra found the Fok1 *ff* and *Ff* genotype significantly inversely associated with prostate cancer risk (OR = 0.25; 95%CI: 0.09–0.72 and OR = 0.52; 95%CI: 0.31–0.86, respectively). This was the first report from an Indian population, suggesting that the *f* allele could be protective in nature and hence less aggressive

[219]. The most recent study [107] found an opposite effect only for the *Ff* genotype (OR = 2.13; 95%CI: 1.23–3.69). On the contrary, *Ff* genotype was associated with a reduced risk of prostate cancer in the study by Oakley-Girvan in the USA; however, this association was found only in the group of African-Americans [152].

The other studies failed in finding any significant association. Two recent meta-analyses have been published on prostate cancer [108, 136]. In the overall analysis, both studies found that *Fok1* polymorphism was not significantly associated with the susceptibility to prostate cancer, but they found a significant association in the subgroup analysis for Caucasians and in the subgroup of population-based controls.

The most recent study, published in Poland [24], indicated a lack of relationship between prostate cancer and the *Fok1 VDR* gene polymorphisms, but these results could also be given by the relatively limited sample size.

In conclusion, there is no evidence of an association between the *VDR* gene *Fok1* polymorphism and prostate cancer risk, and further studies are necessary to clarify possible interactions with other factors.

Colorectal Cancer

Twenty-one studies presented data on *Fok1* and colorectal cancer (CRC). Six studies were performed in Asian countries (two in China, two in Korea, one in Singapore, and one in Japan), nine studies analyzed a Caucasian population, and the reaming six studies were performed on other populations [4, 131, 142, 175, 183, 224] (Table 4.1, Figs. 4.1 and 4.2).

One big study conducted in the USA suggested a significant 27% decreased risk of CRC for *ff* genotype [193]: OR = 0.73 (95%CI: 0.59, 0.90). Accordingly, there are two other small studies published by Sarkissyan [183] and Park [160] suggesting a protective role of 65–66% for CRC, respectively.

Contrasting results were published by three studies [154, 214, 217] reporting a significant increased risk for CRC for *ff* variant versus *FF*. Two studies were performed in Singapore and China [214, 217]: OR = 1.84 (95%CI: 1.15, 2.94) and OR = 2.51 (95%CI: 1.21, 5.18), respectively. The third study was published in the USA by Ochs-Balcom [154], OR = 1.87 (95%CI: 1.03, 3.38), but the sample size is limited (250 cases and 246 controls). All the others suggest no effect or increased risk.

For heterozygous genotype, three estimates indicated a significant protective effect for *Ff* vs *FF* ranging from 89% (OR = 0.11: 95%CI: 0.03, 0.44) in the very small study from Turkey [224] to 43% in a study from Korea [160] (OR = 0.57: 95%CI: 0.39, 0.84). The big study conducted in the USA [193] suggested a more modest significant decreased risk of 16% [193] OR = 0.84 (95%CI: 0.73, 0.97). Only two studies indicated an increased risk for the heterozygous genotype, *Ff* vs *FF*: a very big study conducted in the UK [203] suggested a borderline significant increased risk: OR = 1.12 (95%CI: 1.00, 1.25). They also found a statistically significant interaction of *Fok1* with vitamin D and calcium dietary intake. Individuals homozygous for the variant and who had a high dietary intake of vitamin D or calcium had a higher risk compared with those homozygous for the wild-type with a high dietary intake of vitamin D and calcium. The other study published by Wong [217] indicated an increased risk of 51% in an Asian population (Singapore).

The most recent meta-analyses published in 2018 included 29 studies finding a borderline significant association comparing *F* allele versus *f* in a mixed model (OR = 1.029, 95%CI: 0.999, 1.059) considering this polymorphism a risk factor for CRC.

Skin Cancer

Nine studies were found on *Fok1* and skin cancer, and all were performed on Caucasian populations (Table 4.1, Figs. 4.1 and 4.2). Three estimates were reported for basal cell carcinoma or squamous cell carcinoma [79, 116] and eight estimates on melanoma. Seven studies were from Europe and two from the USA (Table 4.1, Figs. 4.1 and 4.2).

Three studies indicate positive associations between *ff* and *FF* for skin cancer (Fig. 4.1). Only one study reported an 88% significant increased risk for melanoma in a second Leeds case-control study [173], and one study published in Serbia [231] reported a contrasting result. They found a significant protective effect for the *ff* and for *Ff* variants vs *FF* (OR = 0.11; 95%CI: 0.04, 0.29 and OR = 0.32; 95%CI: 0.16, 0.64, respectively), but these results may be due to the small sample size of the study [231].

A study performed in a Polish population presented a significant and very-high-risk estimate for *ff* variant (OR = 7.85; 95%CI: 3.88, 15.86) but also for *Ff* vs FF (OR = 4.87; 95% CI: 2.74, 8.65) for basal cell carcinoma [116], but the sample size of the study is quite small (100 cases), and there is evidence of significant departure from Hardy-Weinberg equilibrium.

The most recent meta-analysis published in 2015 [115] revealed no association between melanoma and the *Fok1 F* allele in all study subjects (OR = 1.016, 95%CI = 0.869–1.189, p = 0.839). They also did not find association with melanoma susceptibility also comparing recessive and dominant models versus homozygote genotype [115], while the previous meta-analysis published by Zhao [232] found that *Fok1* polymorphism was associated with an overall significant increased risk of skin cancer (*Ff* vs *FF*: OR = 1.20, 95% CI = 1.01–1.44; *ff* vs *FF*: OR = 1.41, 95%CI =1.08–1.84; *Ff* + *ff* vs *FF*: OR = 1.26, 95%CI =1.04–1.53) including melanoma and non-melanoma skin cancer.

Ovarian Cancer

Six studies evaluated the association with ovarian cancer (Table 4.1, Figs. 4.1 and 4.2). Three studies reported positive risk estimates for *FF* genotype. A pooled analysis [209] of the New England Case-Control study and a nested case-control study of three prospective cohort studies (the Nurses' Health Study, NHSII, and the Women's Health Study) observed a significant positive association between the number of *Fok1 f* alleles and ovarian cancer risks (p-trend = 0.03). The odds ratio for the *ff* versus *FF* genotype was 1.26 (95%CI: 1.01, 1.57).

Two other small studies found positive association between *ff* and *FF* genotype. Mohapatra [141] and Mostowska [144] found an increased risk. The Indian study [141] showed that the *ff* genotype was associated with a threefold increase in ovarian cancer risk, and the authors also found that vitamin D deficiency and *VDR* gene *Fok1* polymorphism acted non-synergistically (p value <0.4).

Only one study, Lurie [128], found a borderline increased risk for the *Ff* heterozygous genotype (OR = 1.13; 95%CI: 1.00, 1.29) in a pooled analysis of five population-based case-control studies within the Ovarian Cancer Association Consortium.

Two recent meta-analyses were published in 2018 analyzing the effect of the *Fok1* polymorphism on ovarian cancer susceptibility [31, 122]. Li suggested that the recessive model of the *Fok1* polymorphism (*ff* vs *Ff/FF*; OR = 1.15, 95%CI: 1.05–1.18; p = 0.000, I^2 = 67.9%) in Caucasian population (*ff* vs *Ff/FF*; OR = 1.12, 95%CI: 1.05–1.19; p = 0.000, I^2 = 73.2%) predicted the risk of ovarian cancer [122]. The other meta-analysis showed a fixed-effect odds ratio of 1.14 (95%CI 1.05–1.23) under a dominant model. They found also that the fixed-effect odds ratios were 1.12 (95%CI 1.03–1.21) and 1.49 (95%CI 1.06–2.09) in Caucasian and Asian populations, respectively.

Other Cancer Sites

Thirty-two publications for the other cancer sites are available for 15 cancer sites (Table 4.1, Figs. 4.1 and 4.2), and 2 studies were performed on different sites, Deschasaux [47] on tobacco-related cancers (2015) and Bienertová-Vašků [21] on pediatric solid tumors (2016).

Ten studies presented a significant increased risk for *ff* genotype and gastric [42], multiple myeloma [34, 186], liver [162], thyroid [20, 163], bladder [17], pancreas [121], and brain [205] cancers. The increased risk range from an 87% [47] on different cancer sites to a

fivefold increased risk reported by Shafia [186] in a small study (75 cases and 150 controls) conducted in India. Chen [34], Li [121], and Beysel [20] reported a statistical increased risk also for the *Ff* genotype versus *FF* and multiple myeloma, pancreas, and thyroid cancers, respectively, not found by the other studies.

Only three studies found a significant protective effect for *ff* and *Ff* genotype for gallbladder cancer for head and neck cancer, for brain cancer and for lung cancer (Figs. 4.1 and 4.2). Kabaki et al. reported a protective role also for the *Ff* variant vs *FF*. The other reports did not show significant associations.

Bsm1 and Cancer

Bsm1 is located at the 3′ end of the VDR gene. Since it is intronic, it apparently does not alter the amino acid sequence of the translated VDR protein [143]; however, in Caucasians, it is in strong linkage disequilibrium with the *poly(A)* microsatellite located in the 3′ untranslated region which appears to influence *VDR* messenger RNA stability and *VDR* translational activity [210] and thus affect local VDR protein levels. Some degree of coupling with *poly(A)* microsatellite was observed even in non-Caucasian populations, but the strength of the linkage disequilibrium varied by ethnicity [97]. A study of 599 healthy men reported that those with the *bb* genotype at the *Bsm1* locus had, on average, 2.3 pg/mL lower levels of $1,25(OH)_2D_3$ compared with *BB* carriers [129], supporting the hypothesis that *Bsm1* polymorphism may be a mediator for the cellular effects of vitamin D.

Breast Cancer

With respect to breast cancer risk, 28 studies were published in 10 years, from 1998 to 2018: 9 from the USA or Canada, 9 from Asia, 6 from Europe, 4 from Egypt, 1 from Kazakhstan, and 1 from Turkey (Table 4.1; Figs. 4.3 and 4.4). Seventeen studies (61%) were hospital-based, nine (32%) were population-based, and two (7%) included mixed controls (both hospital and healthy subjects), and one was not reported (Table 4.1).

The biggest study is reported by McKay et al. in 2009 [133] and pooled data from six smaller cohort studies carried out in the USA and Europe, including 6473 cases and 8397 controls. The authors indicated no significant association overall between *Bsm1* polymorphism and breast cancer; however, they found a significant 58% risk reduction in the Asian subgroup (Japanese American) (OR = 0.60; 95%CI: 0.42–0.85) for heterozygous *Bb* genotype versus *bb*. In the same study in a subgroup analysis, they found a statistically significant lower risk of advanced breast cancer (OR = 0.74; 95%CI: 0.60–0.92) in women of all races with the *Bsm1 BB* genotype.

Summary estimates obtained in our previous meta-analysis [172] suggested no association between breast cancer and *Bsm1* polymorphism, with very similar estimates for heterozygous and *BB* homozygous subjects: summary odds ratio were indeed SOR = 0.99 (95%CI: 0.93–1.05) and SOR = 0.98 (95%CI: 0.91–1.05) for *Bb* and *BB* genotypes, respectively, compared with *bb* genotype.

After that meta-analysis, 12 new studies were published, most of all in Egypt (four) and Medium-Oriental areas (four from Kazakhstan, Pakistan, and Iran), with contrasting results. One small study conducted in Egypt [2] on 130 cases and 100 controls reported a protective effect of the *B* allele on breast cancer risk, with a significant risk reduction of 44% and 60%, respectively, for *Bb* and *BB* genotypes versus *bb*. Similar results for *BB* genotype were found in further studies conducted in Kazakhstan [3], Pakistan [174], and Iran [187], where a 32%, 33%, and 47% significant reduction of breast cancer risk were found, respectively. On the other side, other two small Egyptian studies [56, 189] found a risk effect of *B* allele on breast cancer, with ORs = 9.71 (95%CI: 2.61–36.11) and OR = 2.51 (95%CI: 1.32–4.77) for *Bb* genotype, respectively, but only Shaker found a significant increased risk for *BB* genotype OR = 2.38 (95% CI: 1.23–4.57). In the same direction, one study on Caucasian subjects from the USA [177] found a borderline significant increase of breast cancer

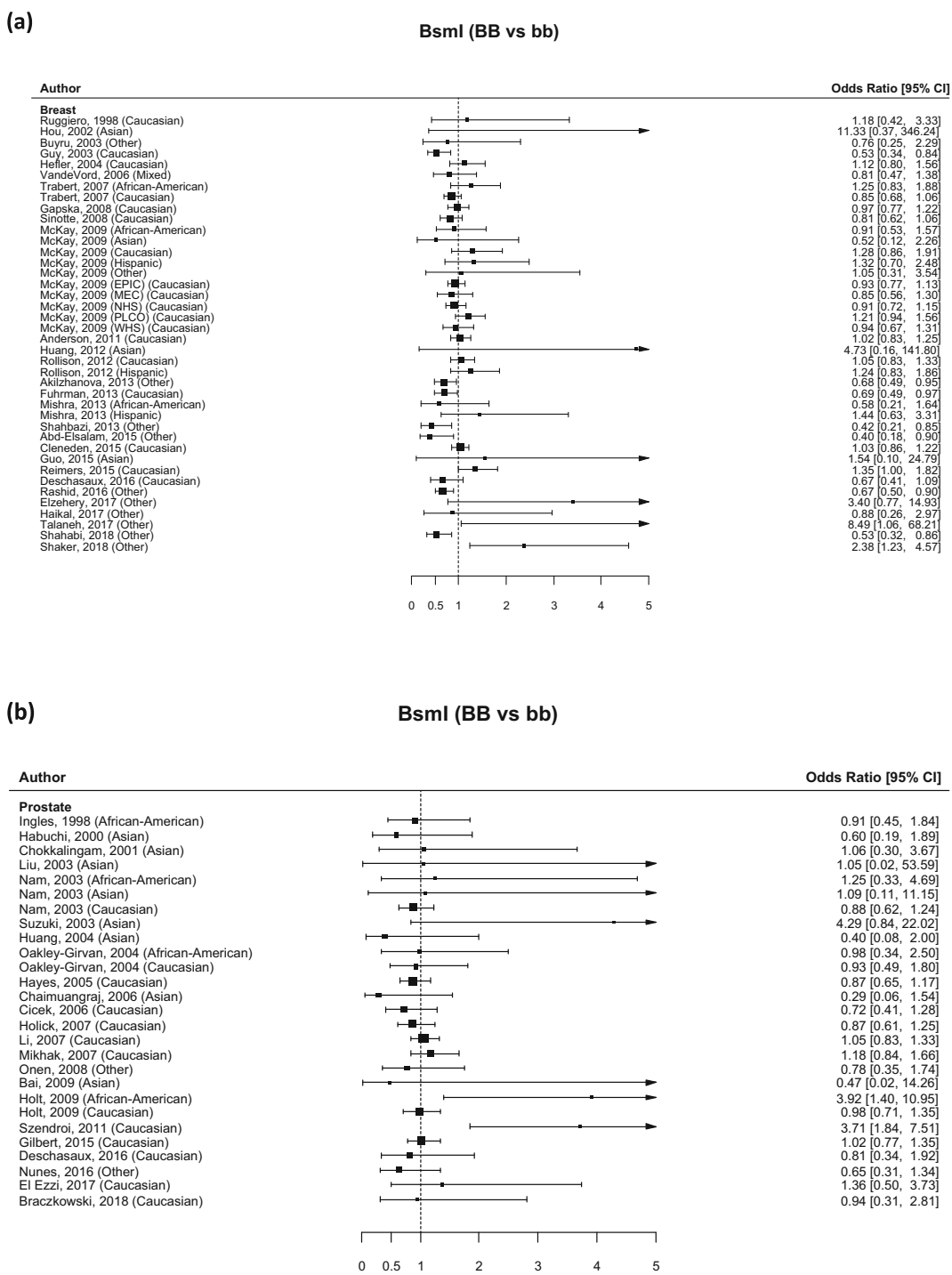
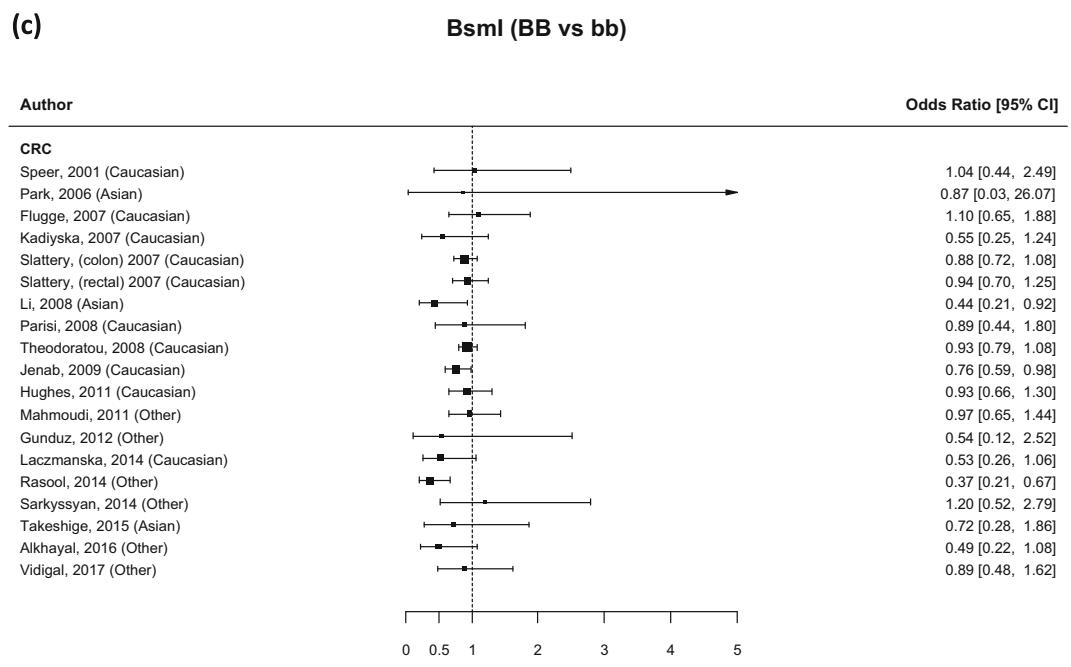
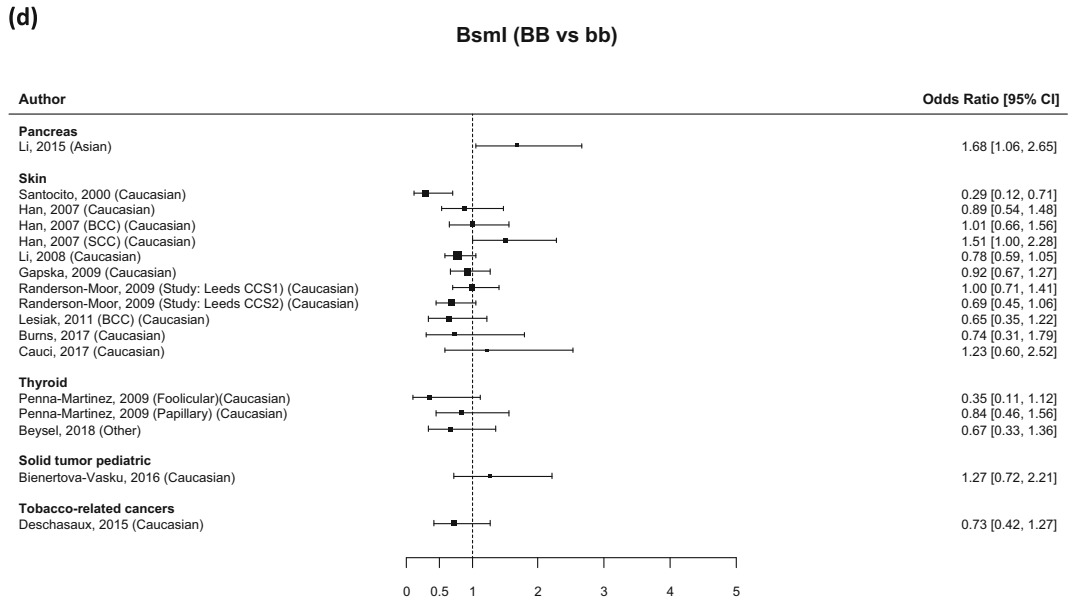


Fig. 4.3 Forest plot for the association between *Bsm1 BB* and *bb* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the pancreas, skin, and thyroid, pediatric solid tumors, and tobacco-related cancers; (**e**) cancers of the lung and ovary, multiple myeloma, and non-Hodgkin lymphoma; (**f**) cancers of the brain, esophagus, gallbladder, head and neck, kidney, and liver





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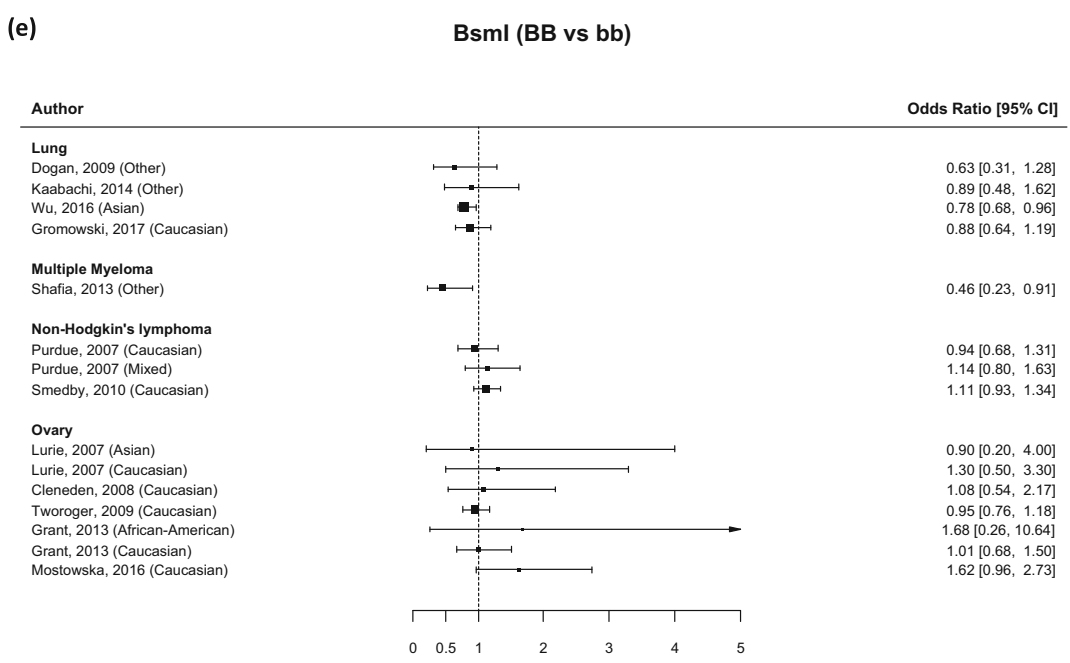

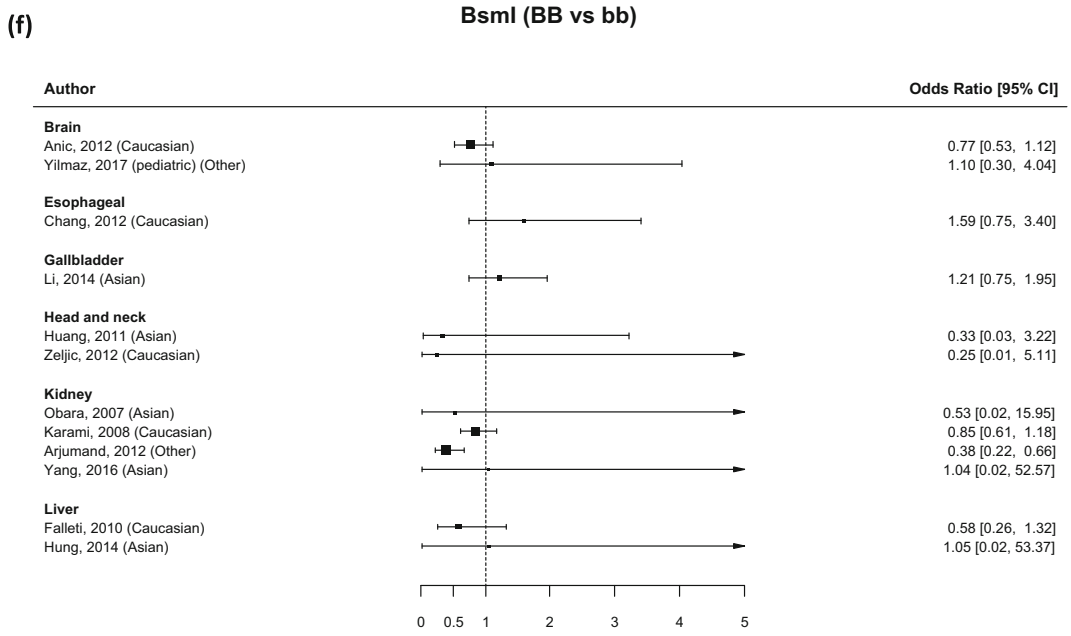

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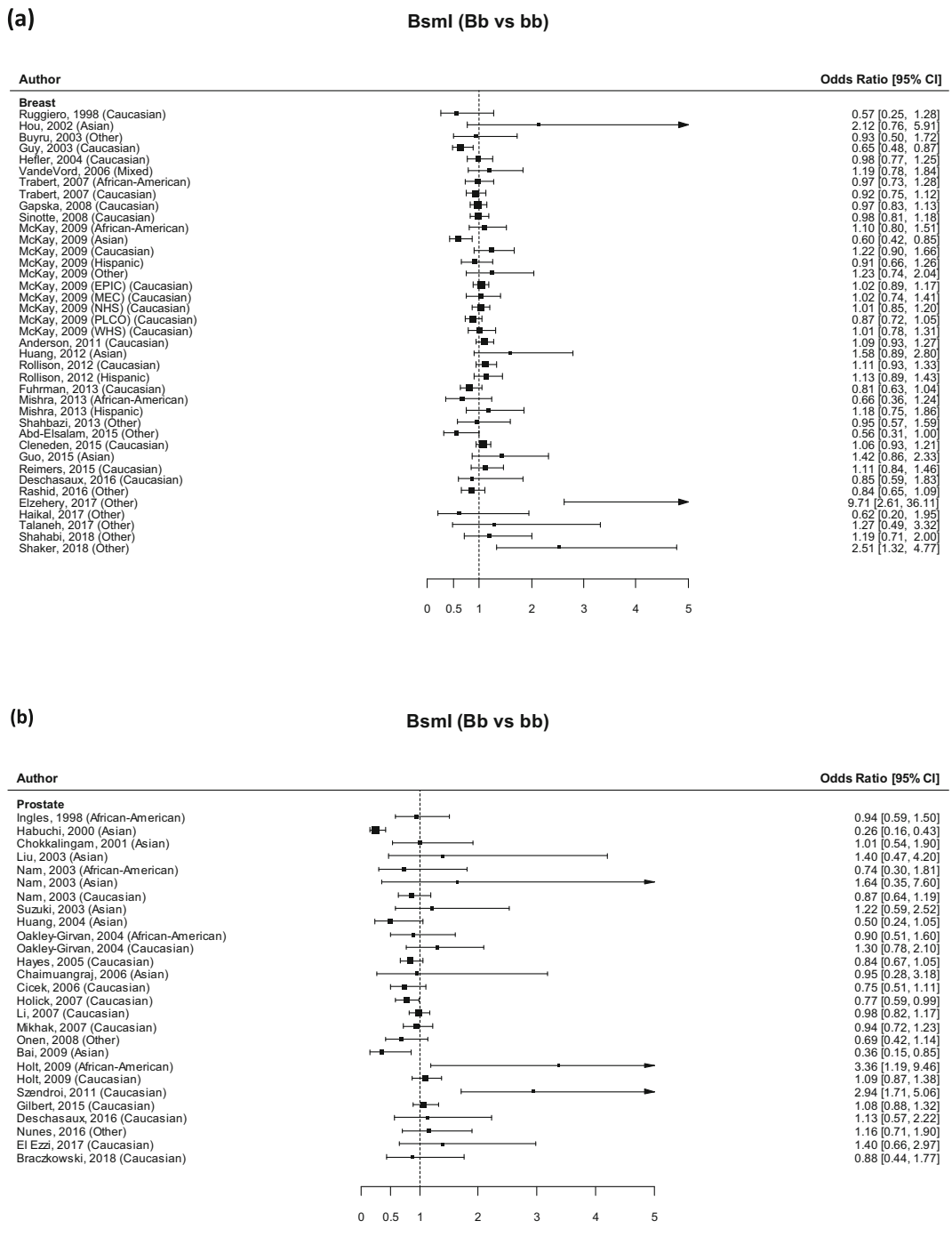
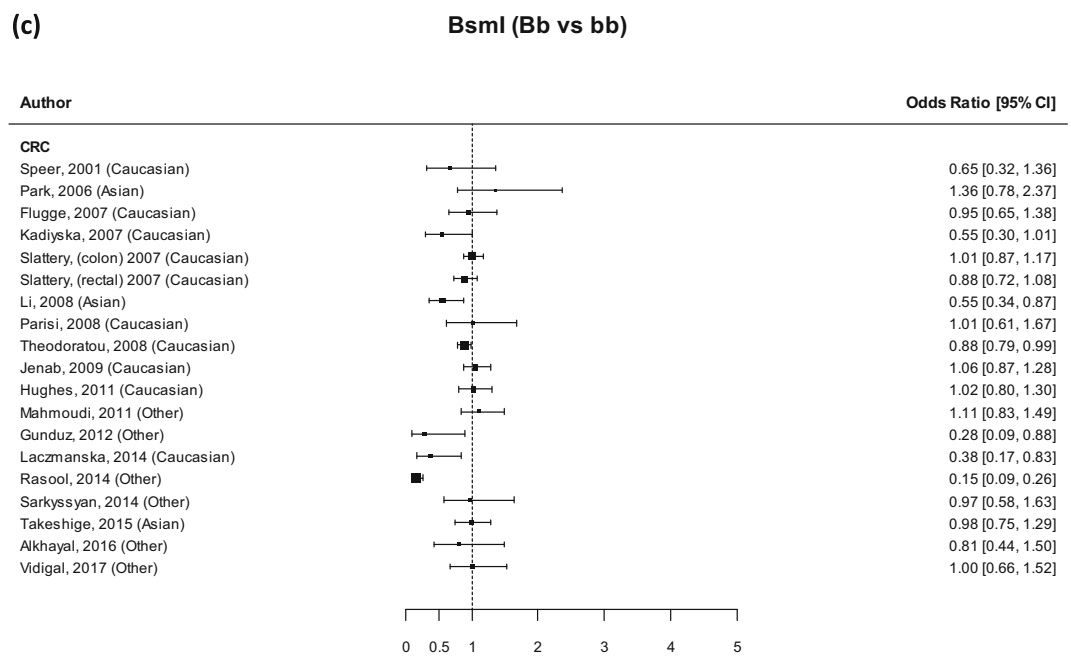


Fig. 4.4 Forest plot for the association between *Bsm1 Bb* and *bb* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the pancreas, skin, and thyroid, pediatric solid tumors, and tobacco-related cancers; (**e**) cancers of the lung and ovary, multiple myeloma, and non-Hodgkin lymphoma; (**f**) cancers of the brain, esophagus, gallbladder, head and neck, kidney, and liver



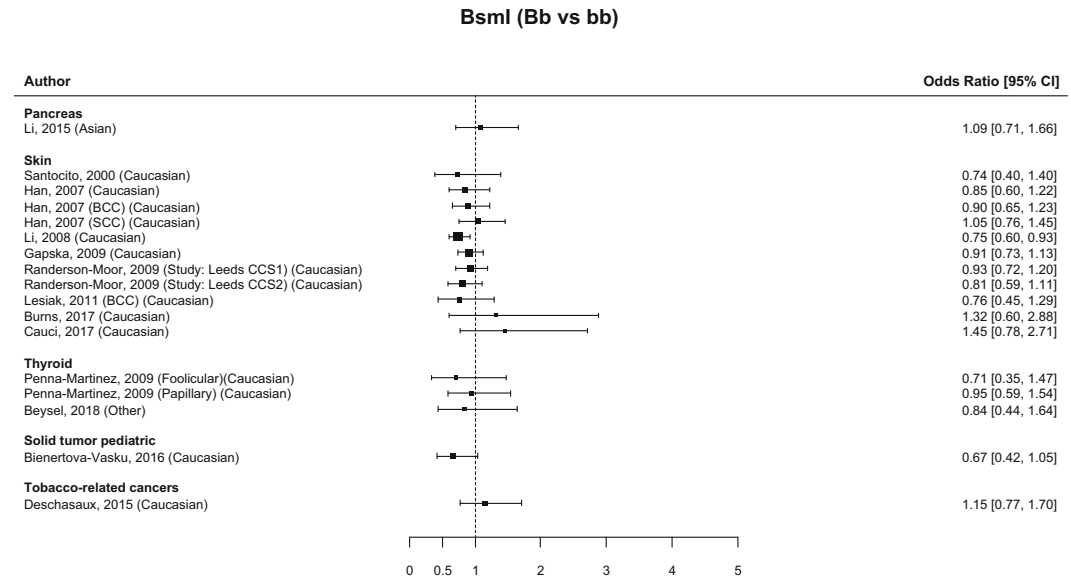
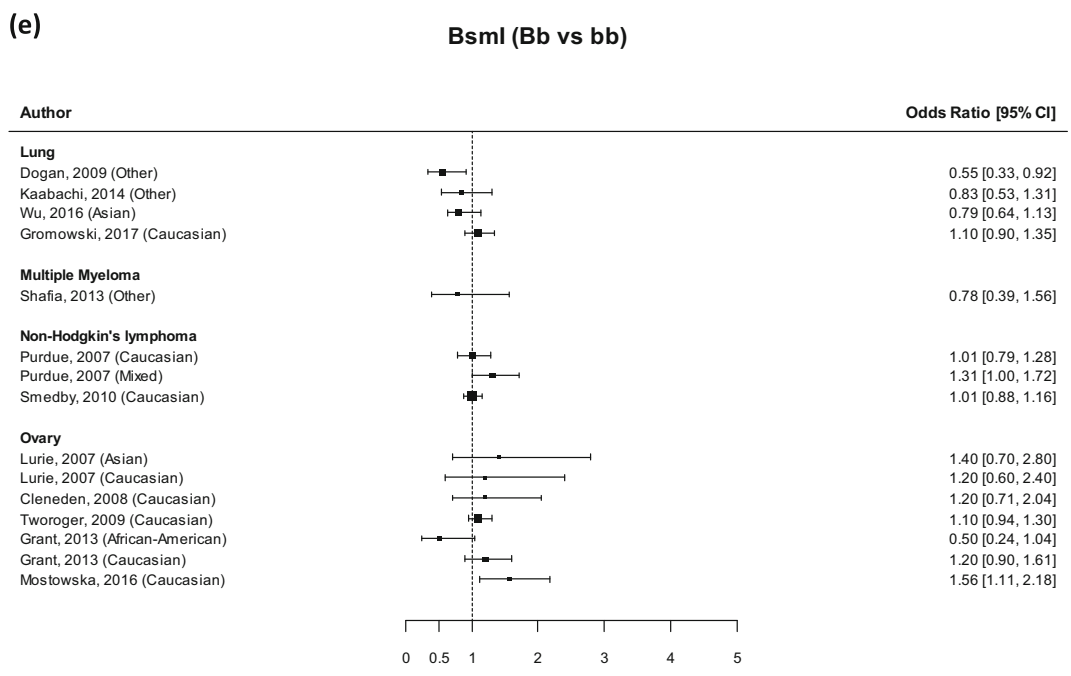


Fig. 4.4 (continued)



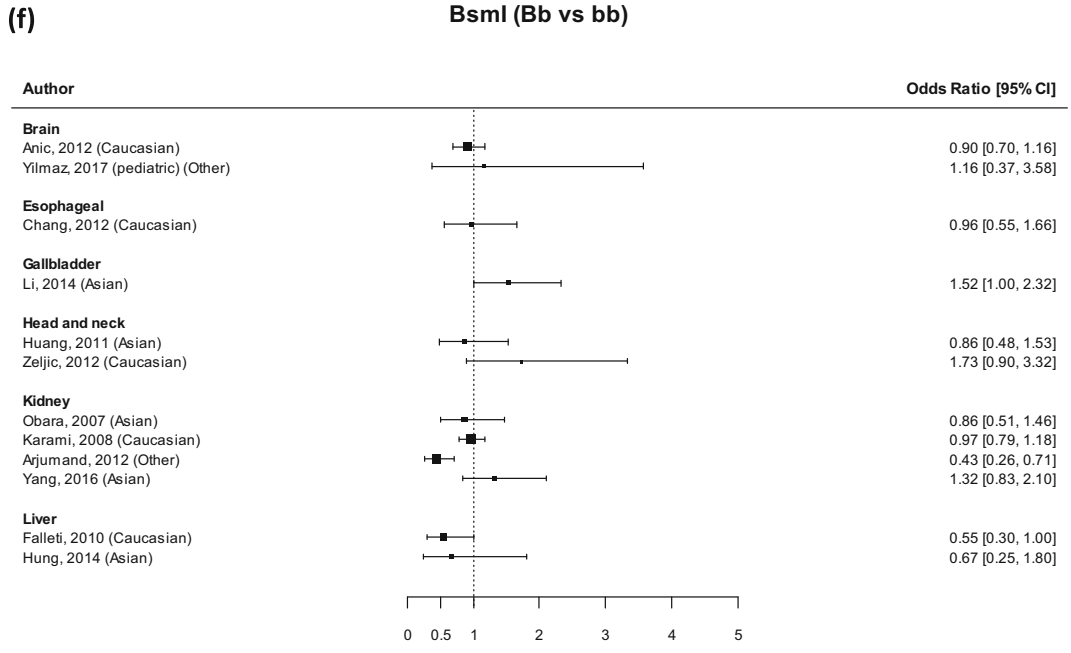


Fig. 4.4 (continued)

risk for *BB* compared to *bb* genotype. Other studies did not report significant association between breast cancer risk and *Bsm1* polymorphism (Figs. 4.3 and 4.4).

In conclusion, while on average it seems that no association existed between breast cancer risk and *Bsm1* polymorphism, recent studies provided very heterogeneous estimates even in populations of similar ethnic group, and this may be warranted to be investigated in future studies and possibly in subgroup analyses.

Prostate Cancer

With respect to prostate cancer, 23 studies published between 1988 and 2018 were found: 8 from the USA or Canada, 7 from Asia, 4 from Europe, and 1 each from Australia, Brazil, Lebanon, and Turkey (Table 4.1; Figs. 4.3 and 4.4). Fourteen studies (52%) were hospital-based; others are population-based (Table 4.1).

In a previous meta-analysis published in 2014 [172], SORs were 0.86 (95%CI: 0.69–1.08) and 0.95 (95%CI: 0.85–1.07) for *Bb* and *BB* genotypes, respectively, compared with *bb* genotype.

Generally, the results of studies on *Bsm1* and prostate cancer are controversial. Heterozygous *Bb* risk estimates give us an indication of protective effect compared to *bb* in earlier studies, while in recent ones, the ORs were usually above 1.00 [48, 54, 67, 151], although results were not significant. The biggest study (the Physicians' Health Study, with 1066 cases) [117] indicated no significant association.

Hayes [81], Cicek [38], Holick [84], Onen [155], Deschasaux [48], Nunes [151], and Braczkowski [24] showed a non-significant decreased risk of *BB* for developing prostate cancer as compared to *bb* genotypes. Only two studyies conducted in Hungary [199] and USA [86] suggested a significant almost 3-fold increased risk of prostate cancer for both *BB* and *Bb* vs wild-type *bb* genotype.

In conclusion, the studies included in this review seem to be not able to demonstrate a strong association between the VDR gene Bsm1 polymorphism and prostate cancer risk.

Colorectal Cancer

Eighteen studies presented data on *Bsm1* and colorectal cancer. Eight were from Europe, six from Asia, and two from the USA, one was from Turkey, and one was from Brazil (Table 3; Figs. 4.3 and 4.4). The two biggest studies with more than 1000 subjects were conducted in the USA [192] and Europe [101]. Twelve studies (67%) were hospital-based, while the remaining were population-based.

Our previous meta-analysis [172] suggested a significant risk reduction of colorectal cancer for carriers of *BB* genotype compared to carriers of *bb* genotype (SOR = 0.89; 95%CI: 0.80–0.98), with no evidence of between-study heterogeneity ($I^2 = 0\%$). This result was mainly due to the big study conducted in Europe, a nested case-control study within the European Prospective Investigation into Cancer and Nutrition [101], which indeed suggested a reduction of 24% for colon cancer risk for carriers of *BB* genotype.

Five studies on different ethnic groups were published after the above-cited meta-analysis, and all of them confirmed a trend of colorectal cancer reduction for *BB* genotype carriers, with significant results obtained in the study by Rasool et al. [176]: OR = 0.37 (95%CI: 0.21–0.67).

A trend of colorectal cancer risk reduction was also suggested for *Bb* genotype compared to *bb* genotype carriers. SOR (95%CI) from the published meta-analysis [172] was 0.88 (95%CI: 0.77–1.01); in line with this result, the five recently published studies reported inverse association with colorectal cancer risk, with significant risk reduction of 62% and 85%, respectively, observed in the study by Laczmanska et al. [114] and Rasool et al. [176].

In conclusion, publications up to now are suggestive of a protective effect of the *Bsm1* both *BB* and *B*b variant allele on colorectal cancer risk.

Skin Cancer

In eight studies, seven estimates were retrieved on *Bsm1* and melanoma and four estimates on non-melanoma skin cancer (NMSC). Five studies were from Europe and 4 from the USA (Table 4.1; Figs. 4.3 and 4.4). Half of the studies were hospital-based and half population-based (table).

Our previous meta-analysis [172] reported a significant protective effect of *Bb* genotype (SOR = 0.86; 95%CI: 0.76–0.98) and borderline protective effect of *BB* genotype (SOR = 0.87; 95%CI: 0.70–1.08) compared to *bb* genotype on overall skin cancer risk.

Only one study [78] reported data for squamous cell carcinoma (SCC), and the *BB* genotype was significantly associated with increased cancer risk (OR = 1.51, 95%CI: 1.00–2.28).

Recently, 2 small studies were published: 1 from Italy [27] included 120 melanoma cases and the second one from the USA [25] 97 NMSC cases. No association was found between *Bsm1* polymorphism and skin cancer, with ORs surprisingly above 1.00 for carriers of *B* allele.

The relative low number of studies on the association between melanoma and NMSC with *Bsm1* polymorphism makes it difficult to reach a firm conclusion, although most of the published studies and our previous meta-analysis seem to suggest a protective effect of the *B* allele on skin cancer risk.

Ovarian Cancer

Five studies evaluated the association with ovarian cancer: three were from the USA, one was mixed (the USA and Sweden), and one was from Poland (Table 4.1; Figs. 4.3 and 4.4). All except one were population-based studies.

Our previous meta-analysis [172] found no association of *Bsm1* polymorphism with ovarian cancer for carriers of neither one (SOR = 1.15; 95%CI: 0.96–1.37) or two (SOR = 1.01; 95%CI: 0.79–1.29) *B* alleles. In a pooled analysis [209] of 3 cohort studies and 1 nested case-control study summarizing 1473 ovarian cases, *Bsm1* was not found significantly associated with ovarian cancer risk.

A recently published update of a previously published study in Poland [144] suggested a significant 56% higher risk of ovarian cancer for carriers of *Bb* compared to *bb* genotype.

In summary, although no significant association was found for *Bsm1* and ovarian cancer, it seems that, contrary to other cancer sites, *B* allele confers a possible higher risk of cancer compared to *b* allele.

Renal Cancer

Four studies were published on the association between *Bsm1* polymorphism and renal cancer. Two were from Asia, one was from Eastern Europe, and one was from India (Table 4.1). Two (50%) were hospital-based and two (50%) population-based studies.

Due to the low number of studies and investigated cases, no significant association was suggested, although a trend toward a protective effect of the *B* allele was apparent, especially for Asian studies [135, 157], in line with results for other cancer sites.

Lung Cancer

Four studies investigated *Bsm1* polymorphism in relation to lung cancer. They were conducted in different countries, China, Turkey, Poland, and Tunisia, and they all were hospital-based studies (Table 4.1).

Three of the four studies were published after our meta-analysis published in 2014 [172]. Almost all the risk estimates were under 1.00, with significant lung cancer risk reduction suggested for carriers of the *Bb* genotype in one study [50], SOR = 0.55 (95%CI: 0.33–0.92), and for carriers of the *BB* genotype in another study [218]: SOR = 0.78 (95%CI: 0.68–0.96).

Other Cancer Sites

Other cancer sites (Table 4.1; Figs. 4.3 and 4.4) were rarely investigated: non-Hodgkin lymphoma (three studies), brain cancer (two studies), hepatocellular carcinoma (two studies), thyroid carcinoma (two studies), multiple myeloma, esophageal adenocarcinoma, gallbladder cancer, nasopharyngeal carcinoma, oral squamous cell carcinoma, pediatric solid tumors, and tobacco-related cancers (Table 4.1).

As for *Bb* genotype, a 52% and 31% borderline significant higher risk of Gallbladder cancer, Non-Hodgkin lymphoma and liver cancer were found, respectively, in studies conducted in China [119], Australia [170] and Italy [59]. Otherwise for *BB* genotype, a 54% significant lower risk of multiple myeloma was found in a study conducted in India [186], while a 68% higher risk of pancreatic cancer was suggested by a Chinese study [121].

No other significant association was found for other cancer sites.

Taq1 and Cancer

The *Taq1* polymorphism is a synonymous SNP, near the 3′ terminus of the *VDR* gene, and does not determine any structural modification of the receptor. *Taq1* is in linkage disequilibrium with two other common *VDR* SNPs, *Bsm1* and *Apa1*, both located in the 3′-UTR region of the gene, thus outside the coding regions. The 3′UTR is known to be involved in regulation of gene expression, possibly through the control of mRNA stability, thus affecting gene transcription, translation, or RNA processing [52, 216]. Thus *Taq1* may act as an indirect marker [112] through its association with other variants (*Bsm1* and *Apa1*).

Breast Cancer

All but two [65, 177] of nineteen studies reported in the literature between 1999 and 2017 confirmed no significant association for *Taq1* polymorphism and breast cancer risk, including also a study investigating the association between VDR gene polymorphism and male breast cancer risk in a Turkish population [111] (Table 2; Figs. 4.3a and 4.8a). Three estimates were reported for Asians, two for African-Americans, twelve in Caucasian and 7 in other ethnicity groups. Among these studies, several were big population-based case-control studies (Abbas [1] with 1408 cases and Anderson [6] with 1546 cases). Overall, estimates are very heterogeneous, some showed a generally not significant trend to increased risk, while others [2, 15, 26, 44, 74] showed a trend to a risk reduction in homozygote and heterozygote subjects versus wild type. Only two studies, Reimers [177] and Gapska [65] presented significant increase risk for *tt* vs *TT* (OR=1.32 95%CI: 1.01, 1.73 and 1.29 95%CI: 1.03- 1.63, respectively).

The most recent meta-analyses reported no significant association [126].

Prostate Cancer

Some studies, reported more estimates for different. Twenty-three studies have been published in 20 years (1998–2018) reporting on *Taq1* SNP and prostate cancer risk (Table 4.1; Figs. 4.5 and 4.6). We obteined 12 estimates for Caucasian, 4 for African-American, 6 for Asian, and 6 for other ethnicity groups. The prevalence of the *t* allele was in average 30% but 17% in control subjects.

In a meta-analysis, the role of *Taq1* polymorphism in prostate cancer was investigated in 17 studies [185]. Overall more than 8800 subjects were included, and no significant association between the *Taq1* polymorphism and prostate cancer risk was observed.

A trend for a protective role for the *Taq1* polymorphism was observed for both homozygous and heterozygous genotype (*tt* and *Tt* vs *TT*, respectively) showing SORs lower than 1.00, although a statistical significance was not reached (SOR = 0.94; 95%CI: 0.78–1.12 and SOR = 0.95; 95%CI: 0.80–1.12 for *tt* and *Tt* vs *TT*, respectively).

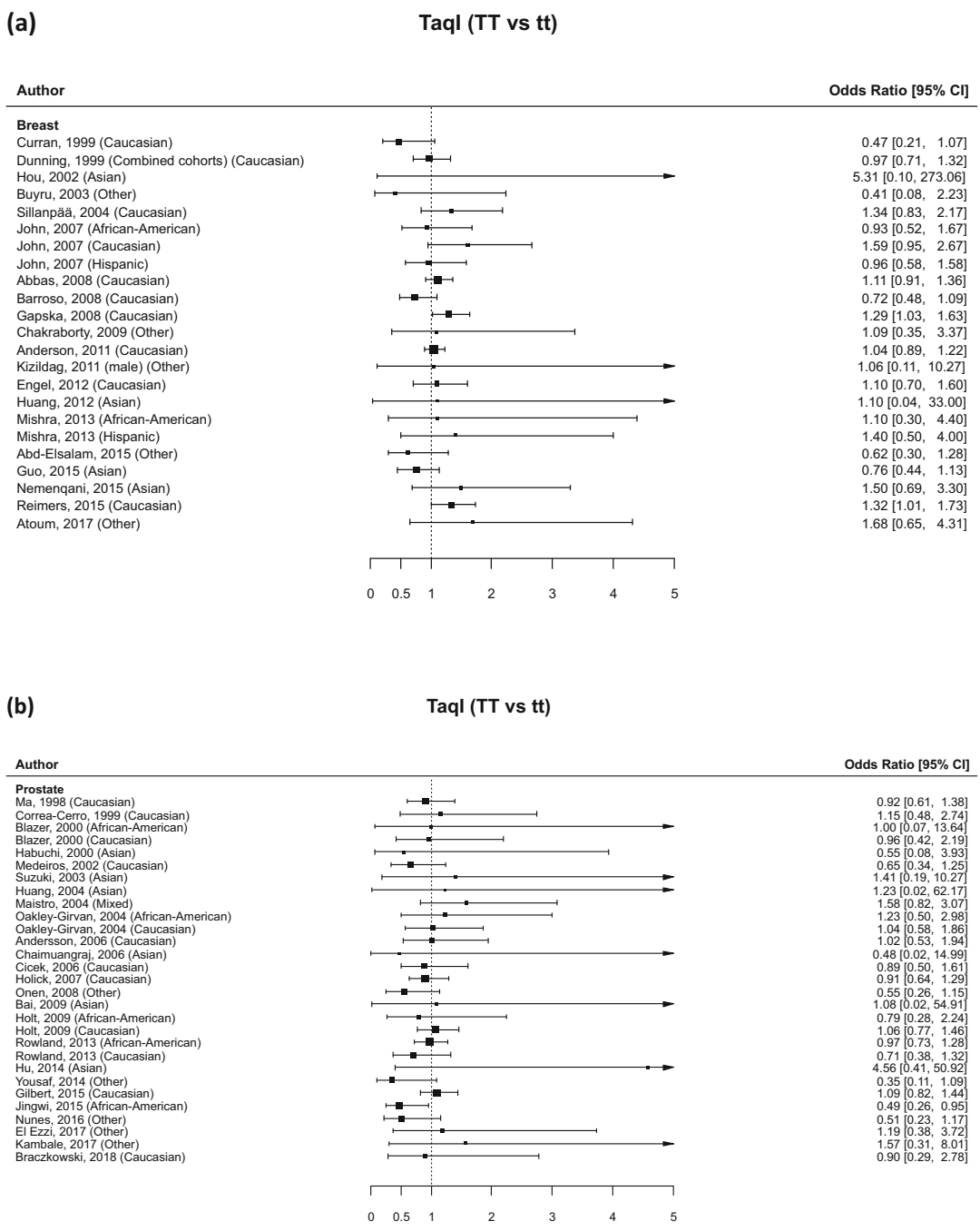
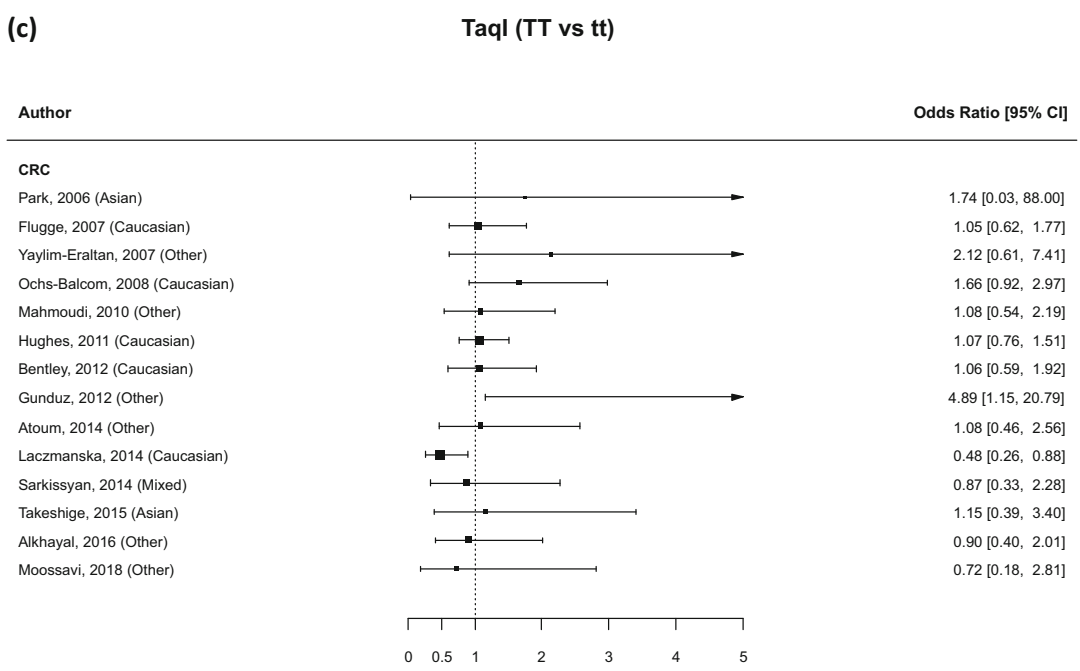


Fig. 4.5 Forest plot for the association between *Taq1 TT* and *tt* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the skin and thyroid, sarcoma, and pediatric solid tumors; (**e**) cancer of the kidney, liver, lung, non-hodggkin's lymphoma, ovary; (**f**) cancers of the bladder, brain, esophagus, gallbladder, head and neck cancer

A statistically not significant trend for an inverse association for the *tt* genotype was observed in several studies. One case-control study in African-Americans reported a statistically significant reduction in risk for *tt* carriers versus *TT* [102] (OR = 0.49 95%CI: 0.26, 0.95).



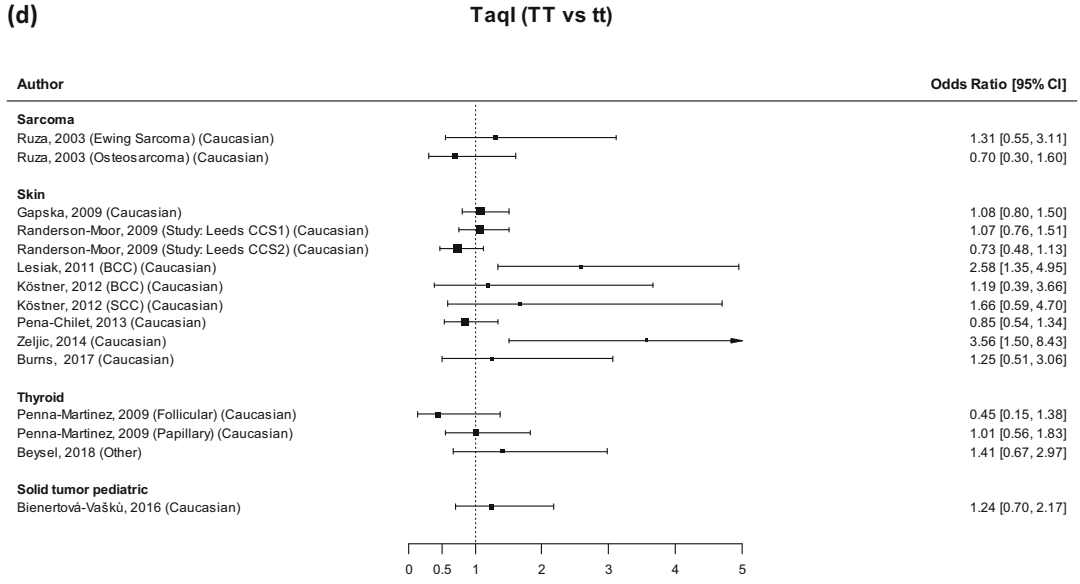
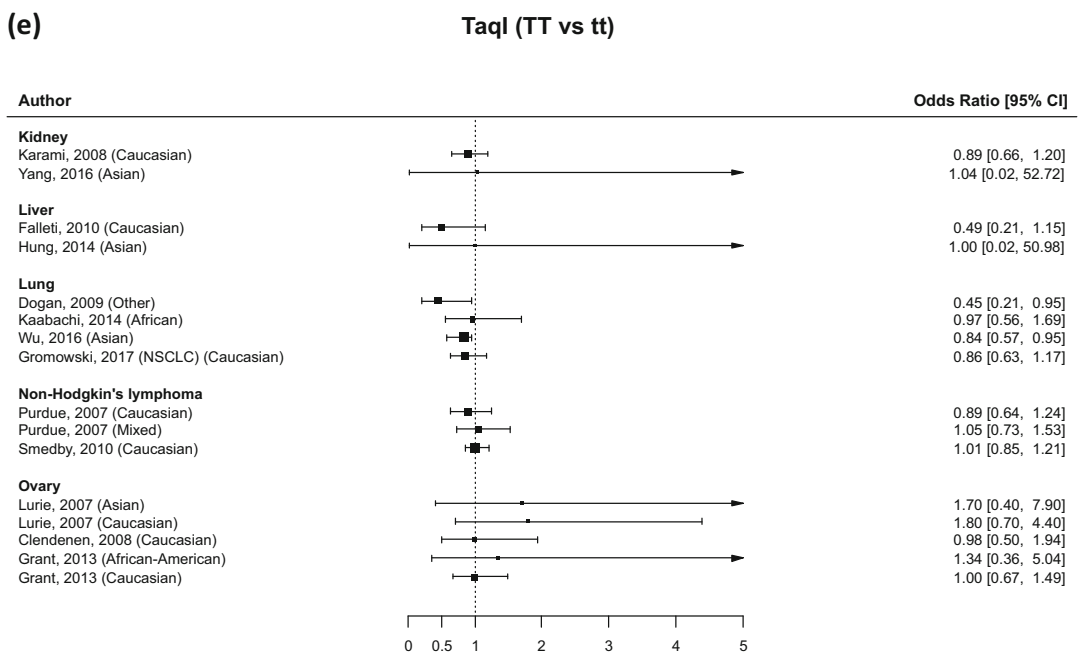


Fig. 4.5 (continued)

Similarly the analysis for heterozygous (*Tt* versus *TT*) showed a trend toward a protective effect of this SNP, with three studies that reached a statistical significance reduction of risk: Correa-Cerro [43] (OR = 0.50 95%CI: 0.27, 0.92), Holick [85] (OR = 0.73 95%CI: 0.56, 0.95), and Kambale [107] (OR = 0.29 95%CI: 0.16, 0.50).

The *t* allele was also found to be protective in a meta-analysis published in 2014 [220]. A more recent meta-analysis confirmed this association particularly in Asian populations and suggested that PCa patients carrying the *t* allele or *tt* genotype were less likely to progress to advanced stage [35].



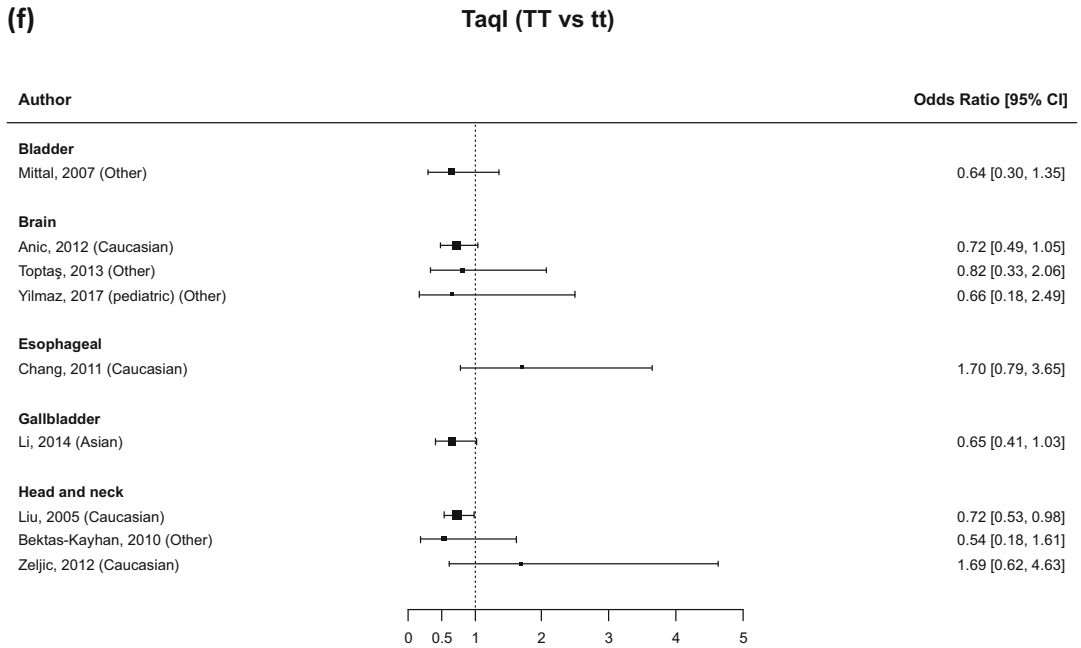


Fig. 4.5 (continued)

Colorectal Cancer

Colorectal cancer risk and *Taq1* were analyzed in 14 studies published between 2006 and 2018 (Table 4.1; Figs. 4.5 and 4.6). A consistent detrimental trend was observed among all the studies for the *tt* compared to the *TT*, less evident in the heterozygous condition.

In a recent meta-analysis [185], eight studies with data on CRC and *Taq1* were included. The

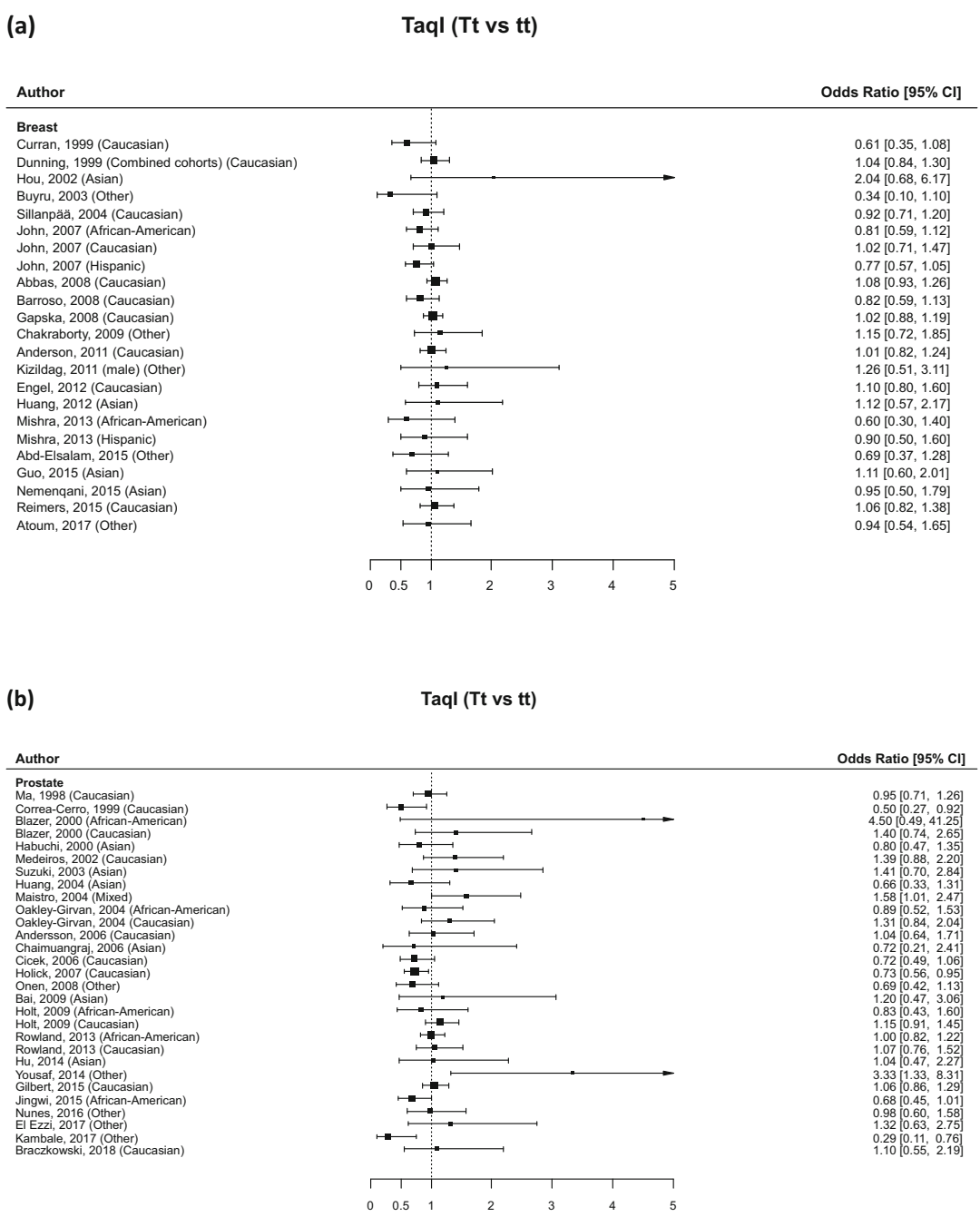
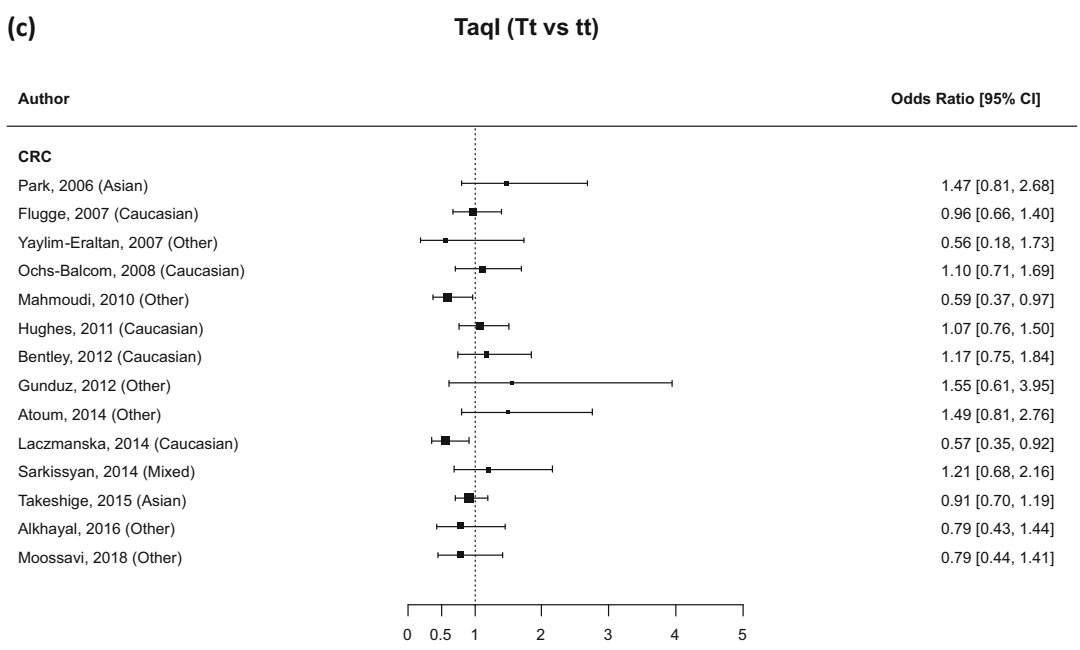


Fig. 4.6 Forest plot for the association between *Taq1 Tt* and *tt* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the sarcoma, skin, thyroid and pediatric solid tumors; (**e**) cancers of the kidney, liver, lung, non-Hodgkin lymphom and ovary; (**f**) cancers of the bladder, brain, esophagus, gallbladder, head and neck cancer

Taq1 tt genotype showed an increased risk for CRC (SOR = 1.43, 95%CI: 1.30–1.58), but the data lost significance in Caucasians (SOR = 1.21, 95%CI: 0.89–1.64).

The study by Gunduz [73, 204] showed the greatest increase in risk, almost fivefold, for colorectal cancer in subjects with *Taq1 tt* (OR = 4.90; 95%CI: 1.15, 20.79). The *t* allele frequency was highly different between cases and controls in that



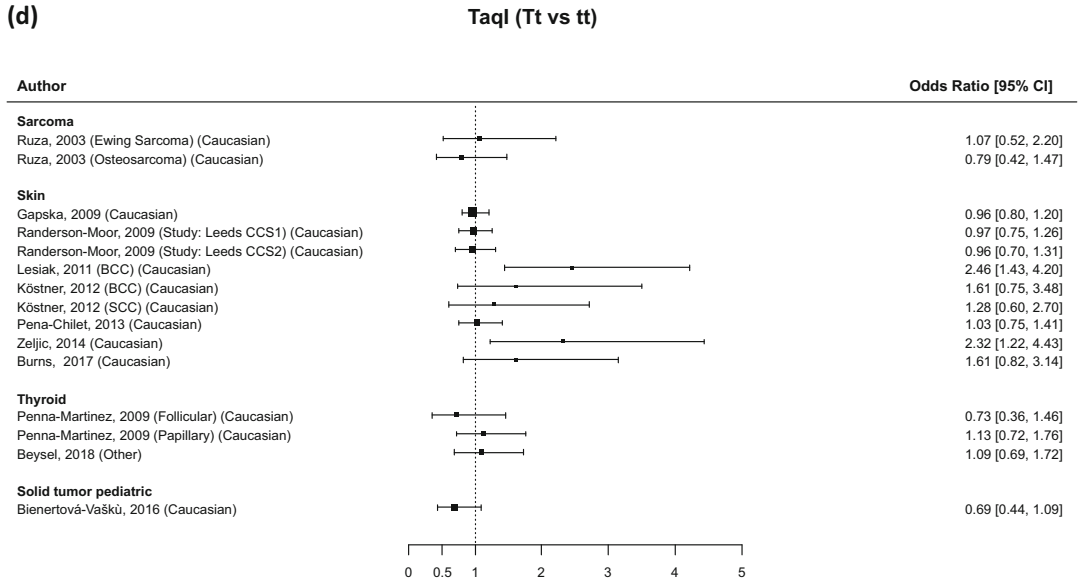
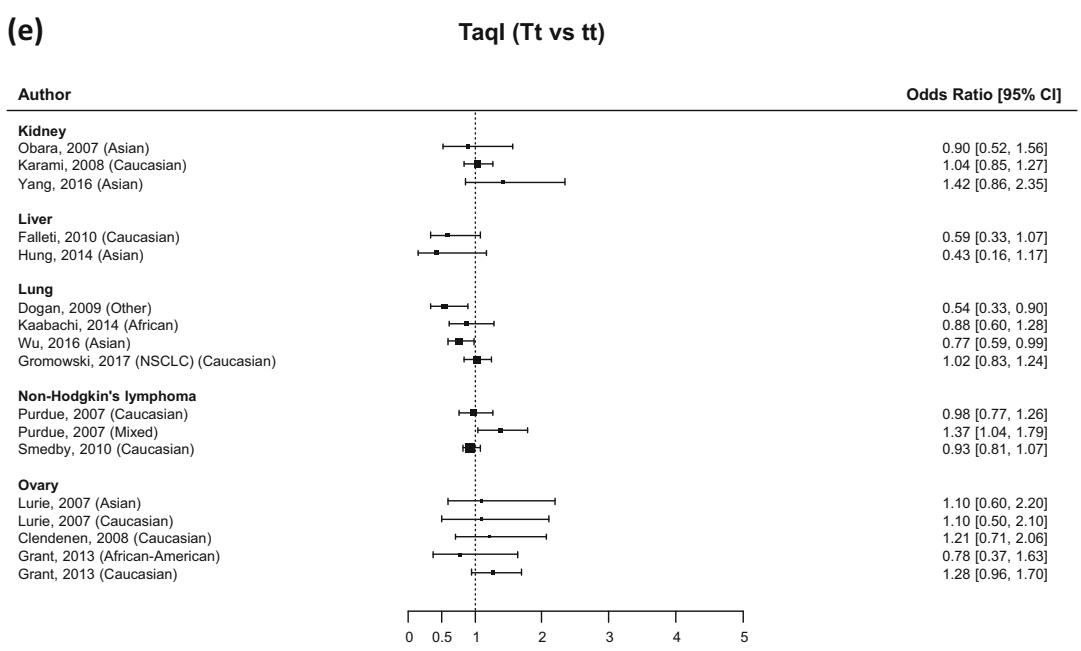


Fig. 4.6 (continued)

study (44% in cases and 27% in controls), and this might in part explain the different results in that study. In the heterozygote subjects, the risk was increased by 55% (OR = 1.55 95%CI: 0.61, 3.95) in the study published by Gunduz, but it did not reach a statistical significance for any of the other studies. The only study the presented significant inverse associations, for both tt and *Tt*, compared to the *TT* group, was the one carried out in Poland [114].



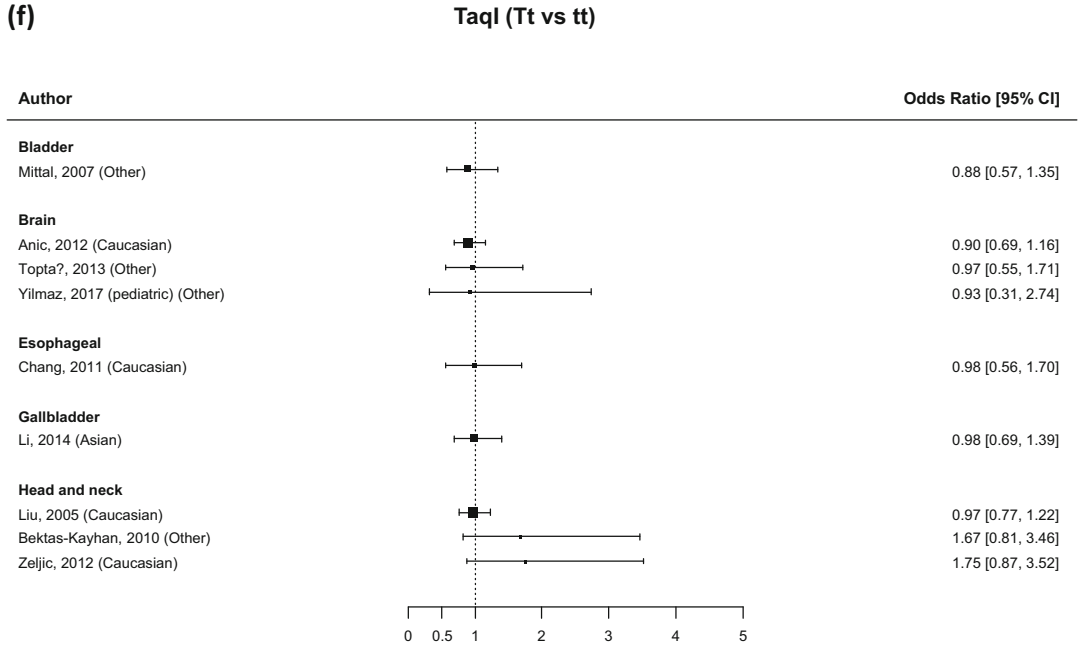


Fig. 4.6 (continued)

Skin Cancer

Seven studies have been conducted to investigate the role of VDR *Taq1* SNP and melanoma between 2009 and 2017 (Table 4.1; Figs. 4.5 and 4.6). The majority of the papers, including melanoma and non-melanoma skin cancer, showed a non-significant increased risk for *tt* vs *TT*.

Only two studies found significant associations. Lesiak [116] presented estimates for BCC and found that subjects having *Taq1 tt* genotypes were associated with an increased risk for developing BCC more than twice and half compared to the *TT* genotype (OR = 2.59; 95% CI: 1.35, 4.95).

Zeljic et al. [231] presented results of a study carried out in Serbia and found a significant increased risk of melanoma for *tt* vs *TT* OR = 3.56 (95%CI: 1.50, 8.43) and for *Tt* vs *TT* OR = 2.32 (95%CI: 1.22, 4.43).

However, the meta-analysis by Serrano [185] did not show a significant association between *Taq1* VDR polymorphisms and skin cancer risk (SOR = 1.01; 95%CI: 0.71–1.45 and SOR = 1.0; 95%CI: 0.82–1.45 for tt and Tt vs TT, respectively). After that publication, only one study, carried out in the USA [25], has been published indicating a non-significant increased risk.

Lung Cancer

Four studies published estimates on *Taq1* and lung cancer. They were carried in Turkey, Tunis, Poland, and China. The Turkish [50] and Chinese studies presented significantly inverse association for both *tt* and *Tt* versus *TT*. Furthermore Dogan [50] observed that *tt* homozygous men among the patients who smoked were less likely to develop lung cancer compared to *TT* (for smokers: OR = 0.25, 95%CI: 0.09–0.75, $P = 0.012$).

In a recent meta-analysis, the *tt* genotype was found inversely associated with lung cancer risk compared with the *Taq1 Tt* + *TT* genotype (OR = 0.70, 95%CI = 0.55–0.90) [228].

Other Cancers

Several other cancers were investigated, such as bone cancer, brain cancer, esophageal adenocarcinoma, hepatocellular carcinoma, head and neck cancer, non-Hodgkin lymphoma, oral SCC, renal cell carcinoma, and thyroid carcinoma, with a total of 30 studies included. None of these studies reached significant associations of *Taq1* polymorphism and cancer risk (Table 4.1; Figs. 4.5 and 4.6).

The meta-analysis by Serrano [185] found a borderline significant risk reduction for "other cancer" for the heterozygous *tt* genotype compared with *TT* genotype (SOR = 0.88, 95%CI: 0.78–1.00).

Apa1 and Cancer

Apa1 polymorphism is located near the 3′ UTR of VDR gene similar to *Taq1* and *Bsm1* and does not alter the protein's amino acid sequence. The functional significance of the VDR *Apa1* polymorphism remains unknown.

Breast Cancer

Fourteen epidemiologic studies, counting for more than 5000 subjects, have investigated the association between *Apa1* and breast cancer risk (including also male breast cancer) (Table 4.1). Some studies suggested an increased risk of breast cancer and others a reduction (Table 4.1; Figs. 4.7 and 4.8).

A statistically significant increased risk was found by Curran et al. [44] carried out in Australia with 2.5-fold risk increment for aa compared to *AA* (OR = 2.53; 95%CI 1.20, 5.39), and similar results were achieved in one study [2]. Four studies presented significant decreased

risk of breast cancer for the *Aa* versus *AA* from 30% to 72% [74, 88, 90, 190]. Only one study conducted in the USA found a statistical increased risk for the *Aa* versus *AA* genotype [45]. Other studies reported that the *Apa1* polymorphism was not associated with breast cancer risk.

Prostate Cancer

With respect to *Apa1* polymorphism, 15 studies have been published between 2000 and 2017, and 4 studies found statistically significant association with prostate cancer risk (Table 4.1; Figs. 4.7 and 4.8). Two studies [91, 107] conducted in India and Taiwan suggested a significant decreased risk of prostate cancer for both *aa* and *Aa* vs wild-type *AA* genotype, whereas one study [155] conducted in Turkey presented an increased risk for both. Contrasting results were published by Yousaf [227] conducted in Pakistan with a significant decreased risk for *aa* vs *AA* and a significant decreased risk for *Aa* vs *AA*.

In the most recent meta-analysis [215] including 6427 cases and 6039 controls from 16 case-control studies, Wang suggested that these polymorphisms did not increase the risk of prostate risk in genetic models, which was consistent with our previous meta-analysis [185].

Colorectal Cancer

Eleven studies including subjects from different ethnicities, conducted from 2006 to 2017, have focused on the association between *Apa1* and colorectal cancer with no consistent results (Table 4.1; Figs. 4.7 and 4.8). In six studies, *Apa1* variant was not associated with risk of colorectal cancer. Four studies in different ethnicities suggested that the *Apa1 aa/Aa* polymorphism genotypes may increase [130, 212] or decrease [114, 160, 176] the risk respect to AA genotype. The recent meta-analysis by Pan et al. did not found any association with cancer risk [158].

Skin Cancer

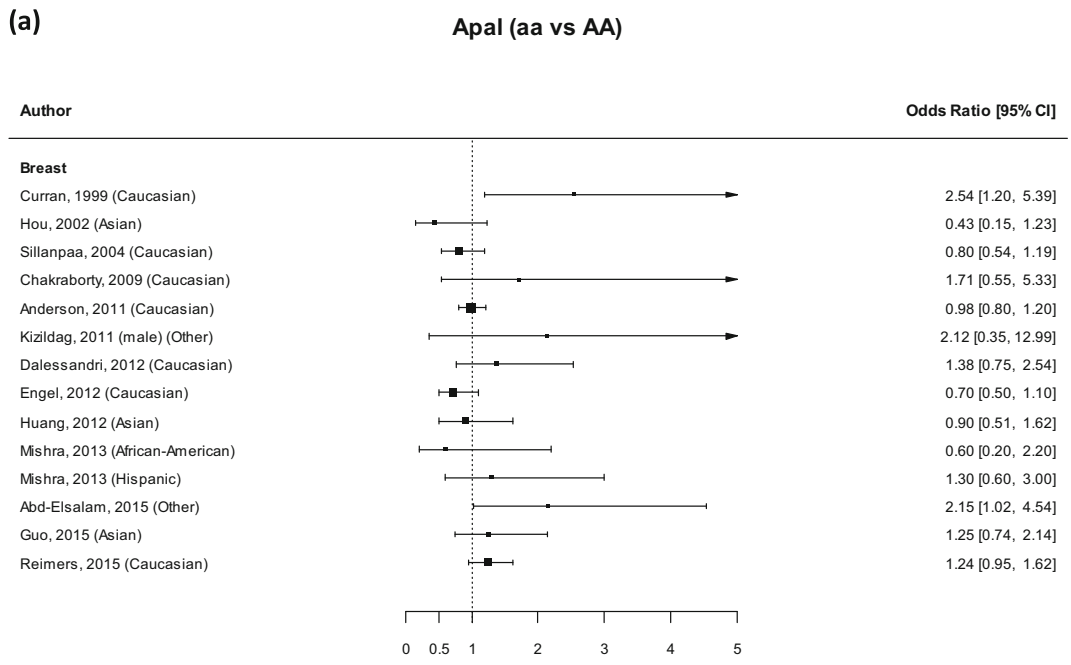
Only a few epidemiological studies have addressed the relationship between *Apa1* polymorphism and risk of melanoma and NMSC [25, 113, 116, 173, 231]. All these studies were conducted in Caucasian populations (Table 4.1; Figs. 4.7 and 4.8). A recent meta-analysis from Von Schuckmann et al. [213] showed a decreased basal cell carcinoma risk in *Apa1* recessive genotype *AA* (SOR = 0.74; 95%CI: 0.56–0.098).

Other Cancers

Nineteen studies were included, investigating different cancer sites, such as esophageal adenocarcinoma, gallbladder cancer, hepatocellular carcinoma, lung cancer, multiple myeloma, oral cancer, ovary cancer, renal cell carcinoma, and thyroid carcinoma.

Regarding lung cancer risk, *Apa1* was investigated in 2 meta-analyses [33, 62] including 5 studies involving 602 patients and 662 healthy controls (examining Asian and Turkish population). No statistically significant association with lung cancer risk was found. Kaabachi et al. [105] found an increased significant association for *aa* and *Aa* versus *AA* genotypes (OR = 2.64; 95%CI: 1.37–5.07 and OR = 2.30; 95%CI: 1.22–4.35, respectively). But in the most recent Polish case-control study [69], *Apa1* was not related to lung cancer risk.

Three studies evaluated the association between *Apa1* and ovarian cancer with null results [39, 67, 128] in Caucasians and a significant increase risk in African American [67] for *aa* vs *AA* genotype. Other studies included esophageal adenocarcinoma, hepatocellular carcinoma, oral squamous cell carcinoma, thyroid cancer, and sarcoma. Interesting results were reported by Zeljic et al. [230] for oral squamous cell carcinoma (110 cases and 122 controls): they found a significant increased risk for *Apa1 aa* vs *AA* (OR = 2.06, 95%CI: 1.04, 4.09) and for *Aa* vs *AA* (OR = 2.44, 95%CI: 1.31, 4.54). Penna-



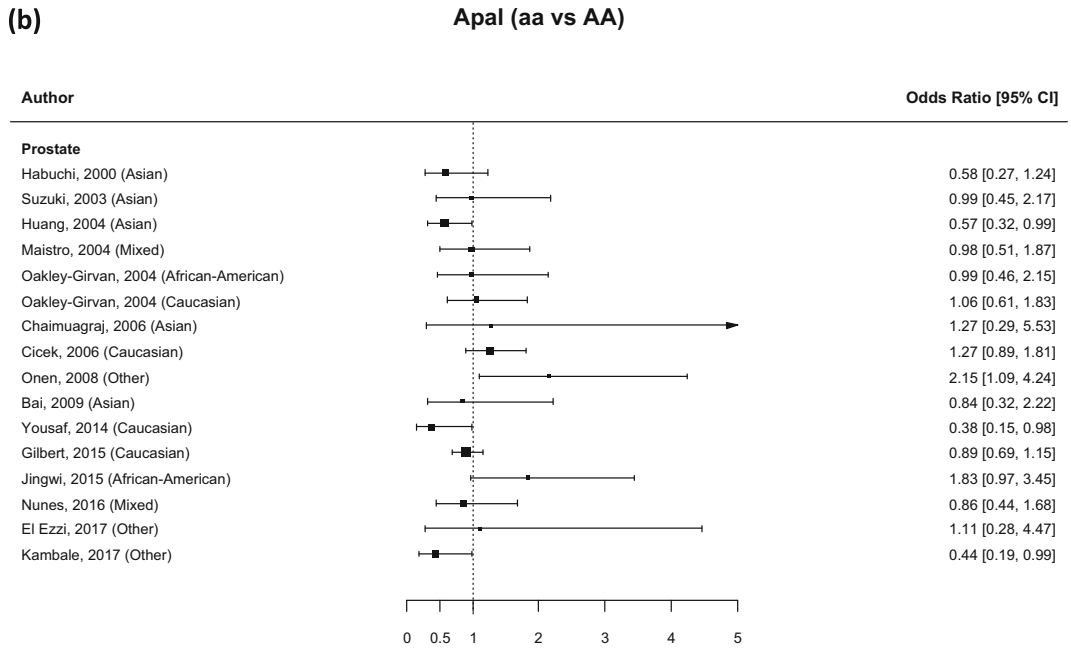
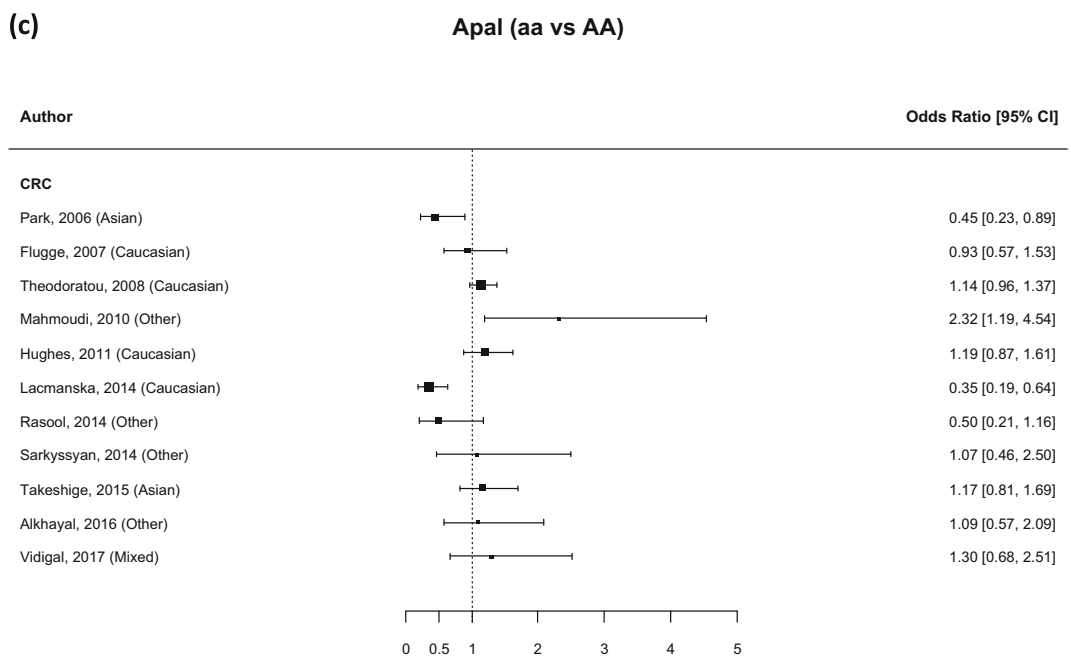
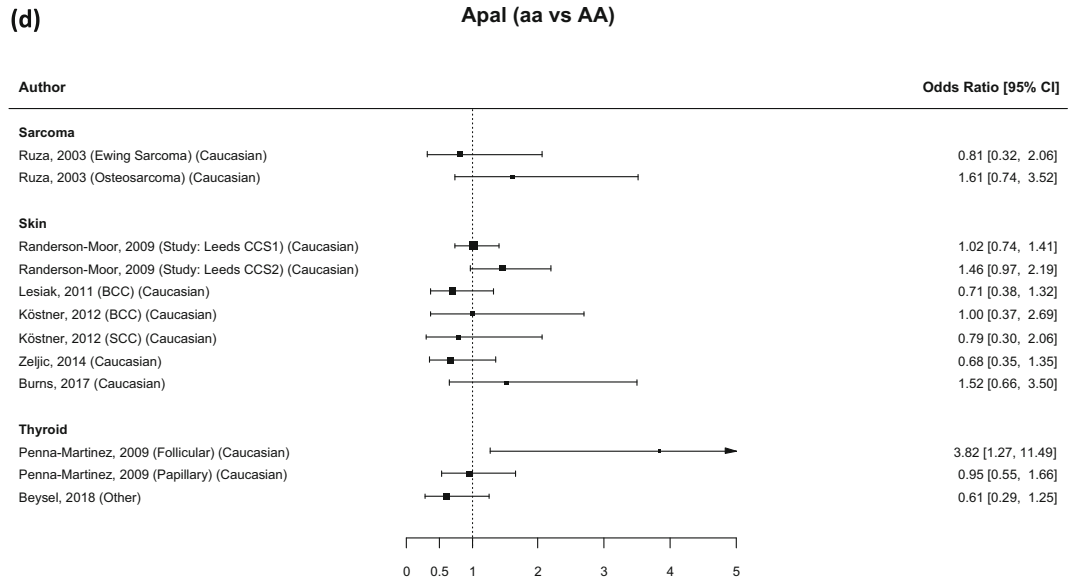


Fig. 4.7 Forest plot for the association between *Apa1 aa* and *AA* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the skin and thyroid, sarcoma, and pediatric solid tumors; (**e**) cancers of the lung and ovary and multiple myeloma; (**f**) cancers of the esophagus, gallbladder, head and neck, kidney, and liver





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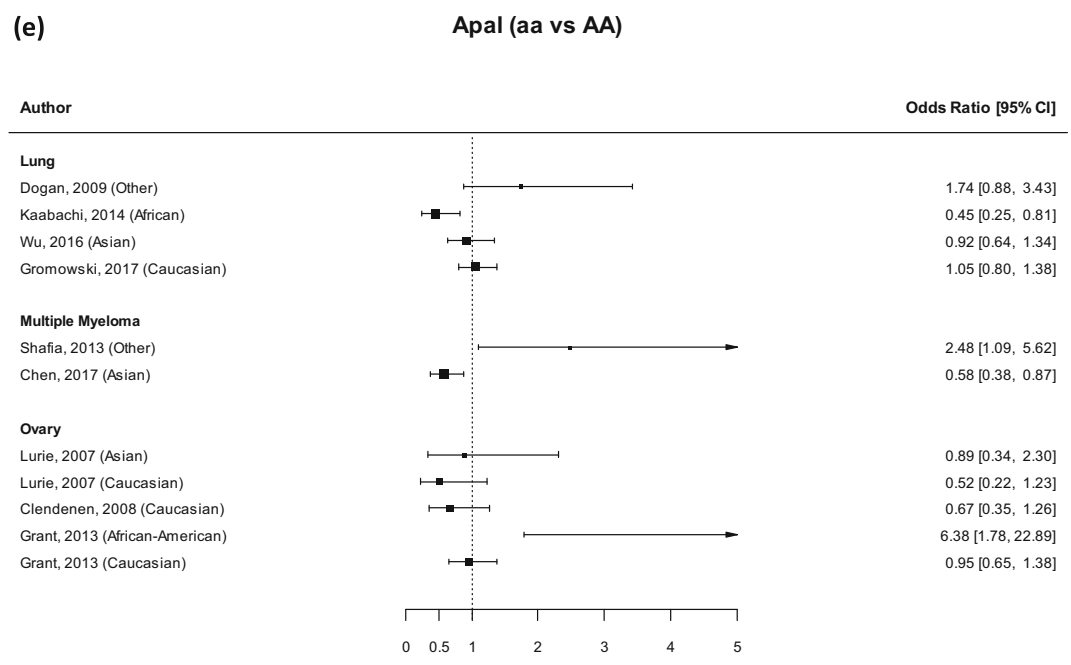

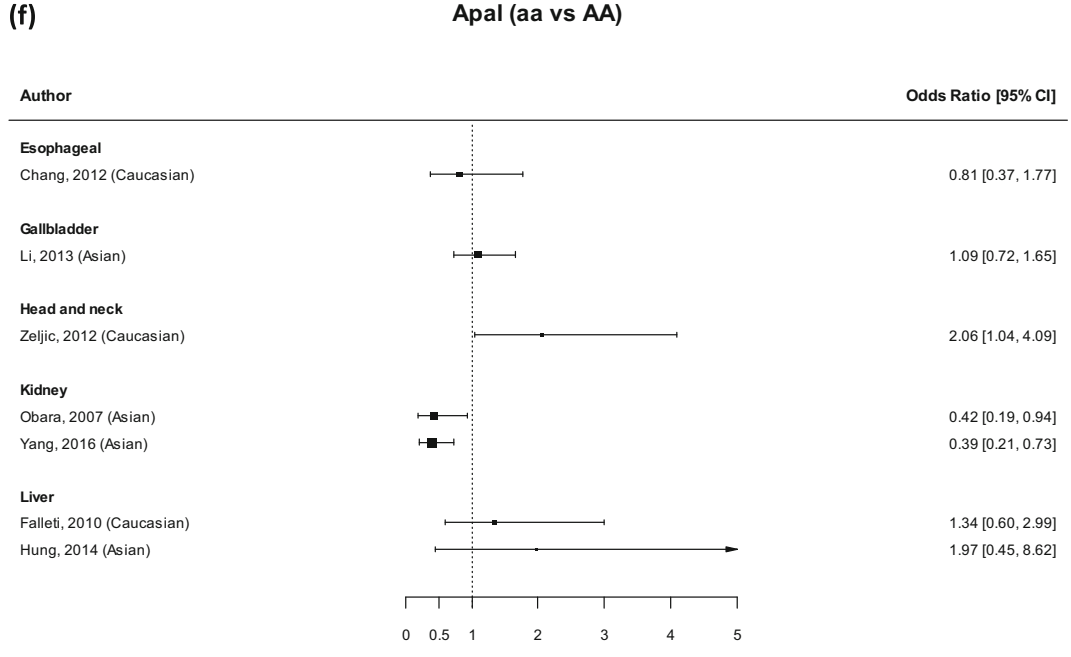

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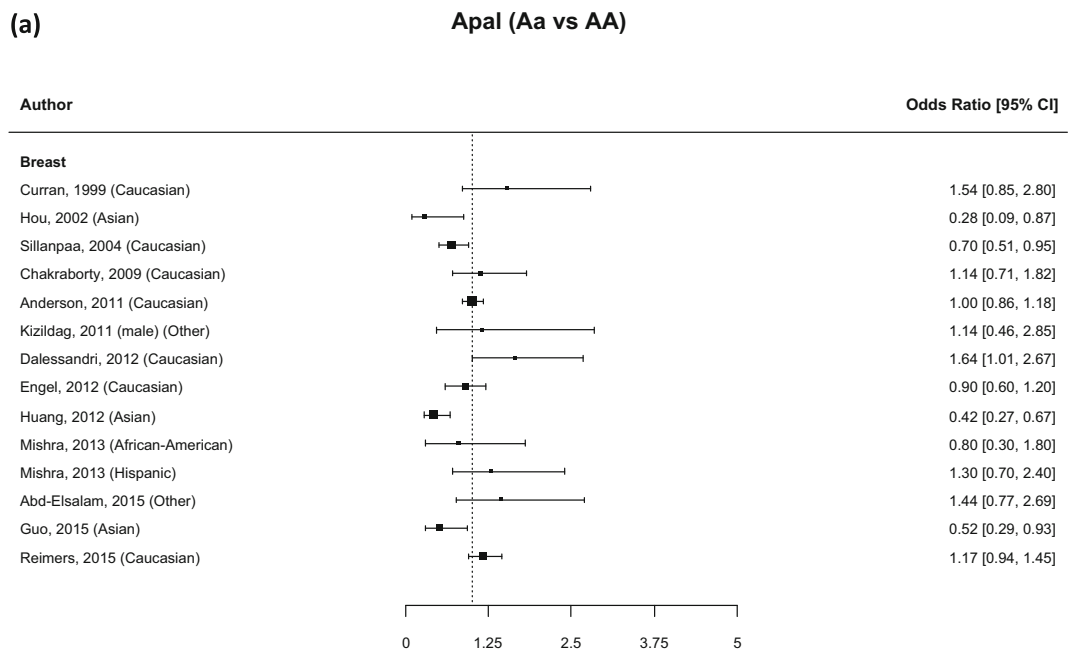


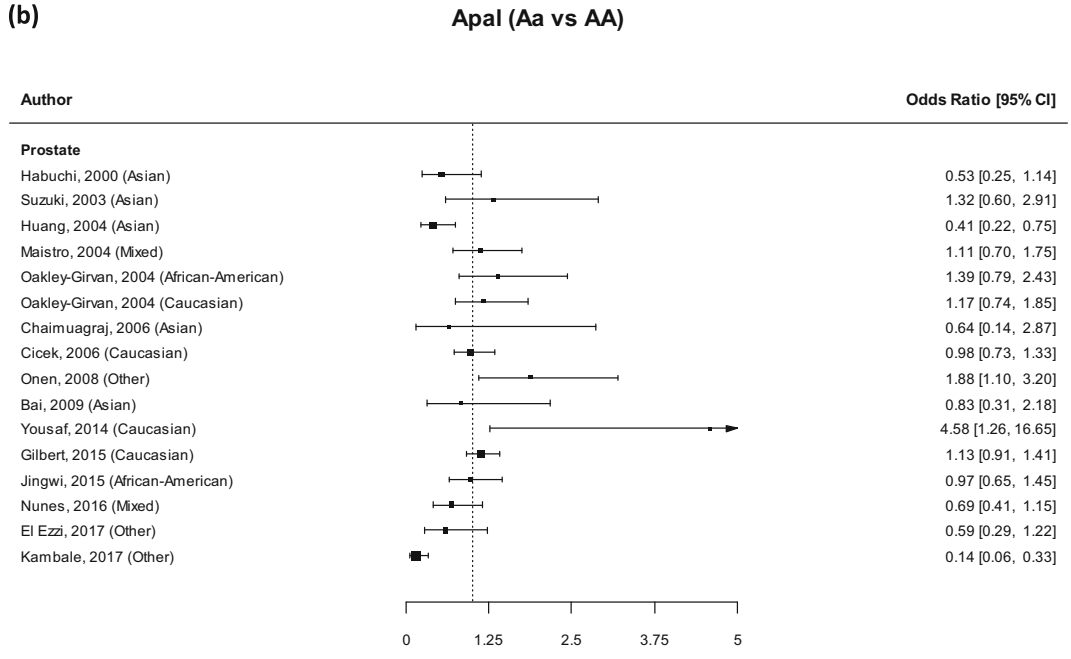
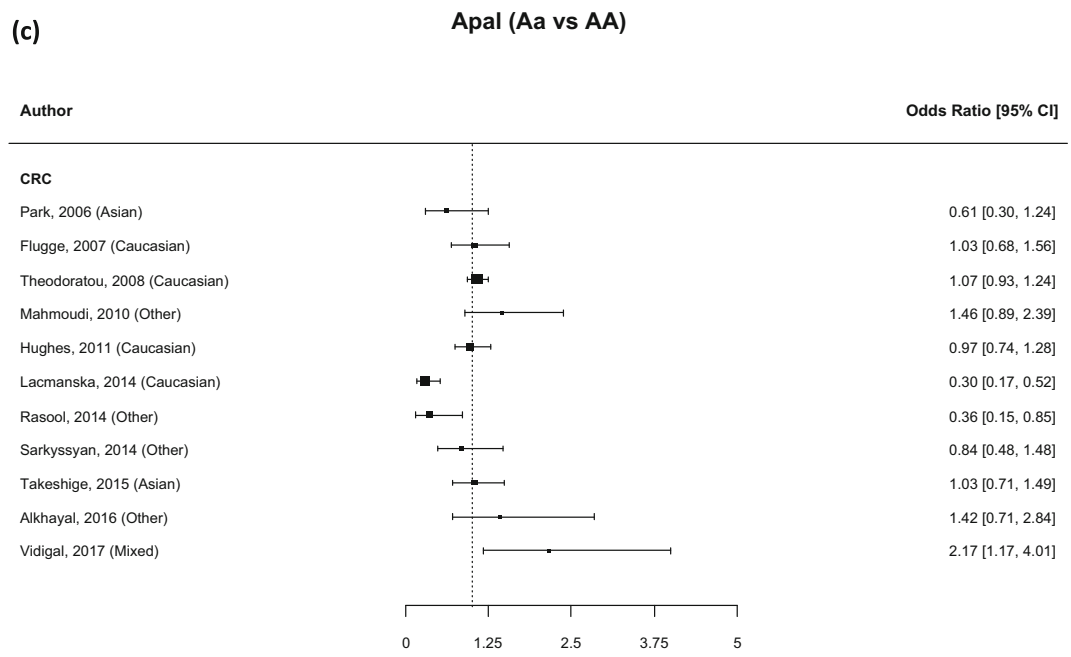
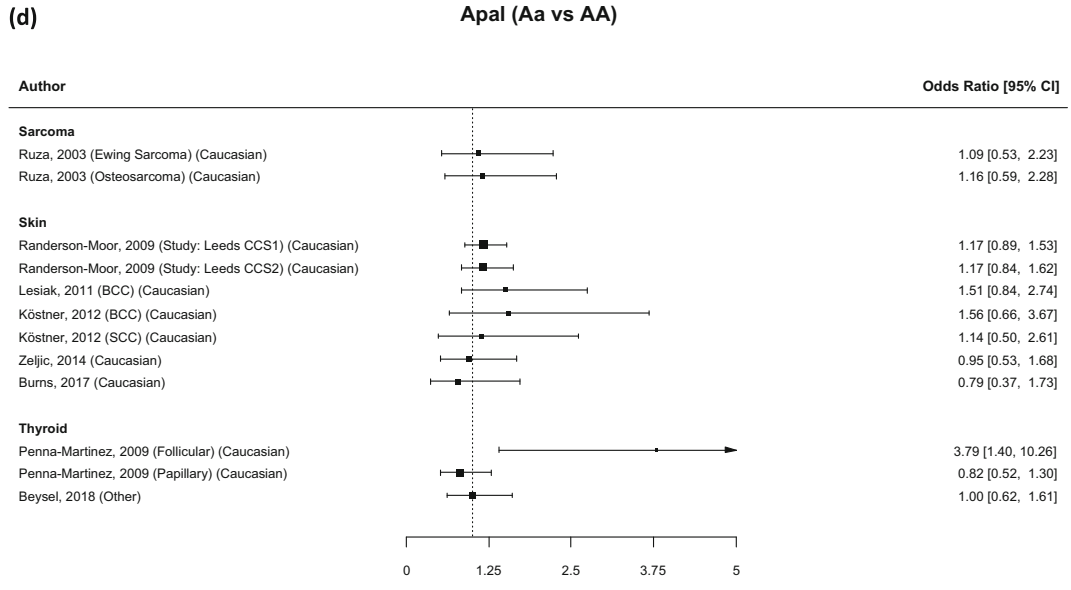


Fig. 4.8 Forest plot for the association between *Apa1 Aa* and *AA* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the skin and thyroid, sarcoma, and pediatric solid tumors; (**e**) cancers of the lung and ovary and multiple myeloma; (**f**) cancers of the esophagus, gallbladder, head and neck, kidney, and liver





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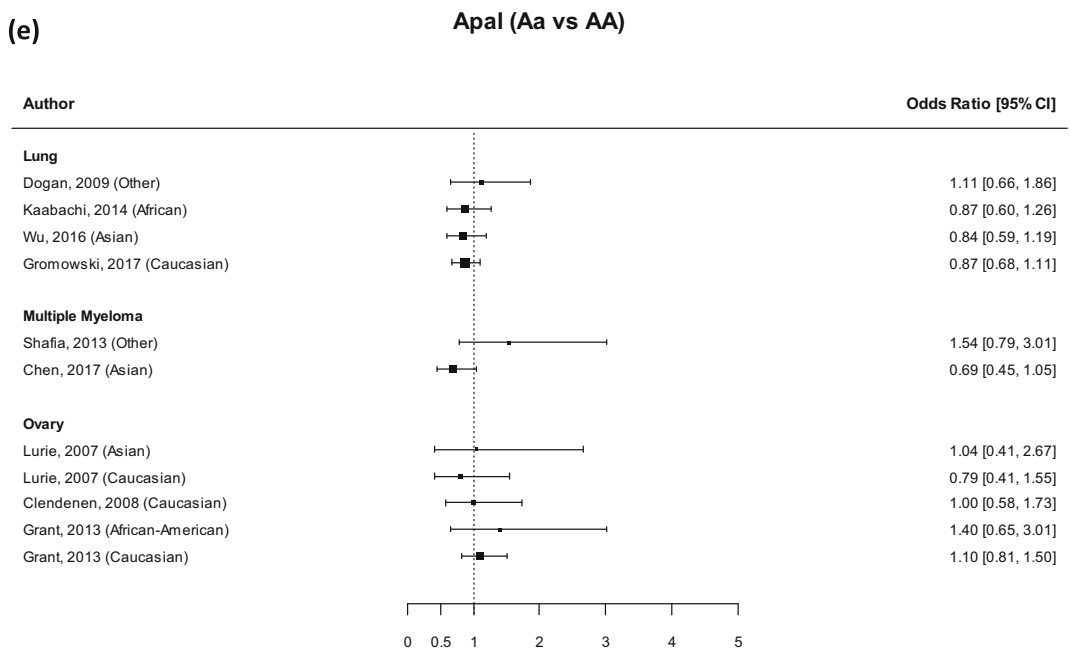


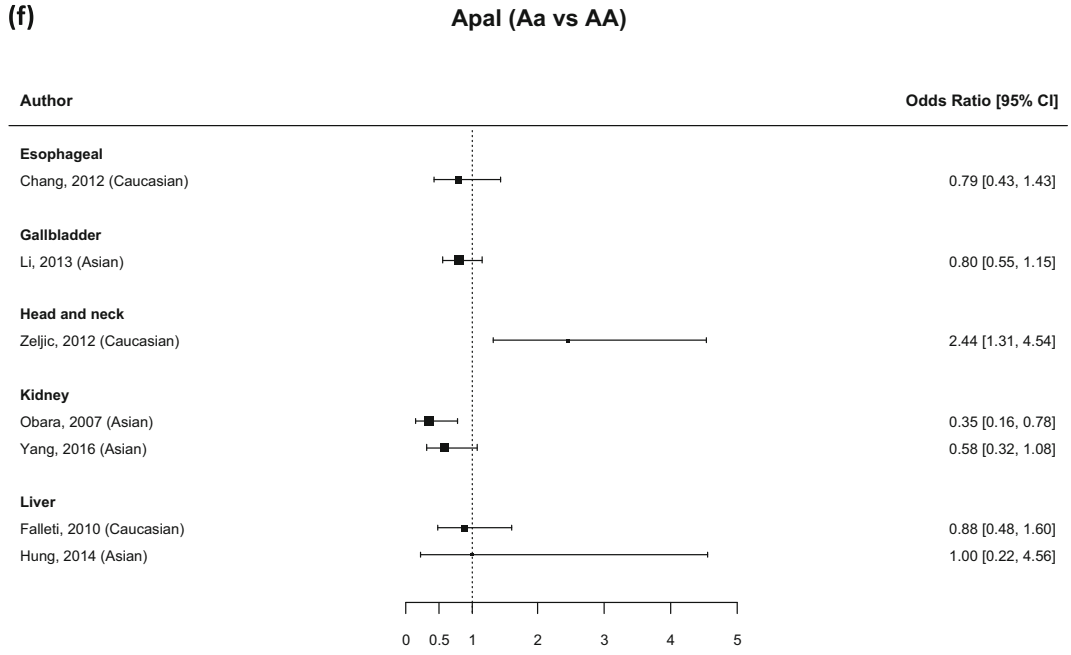


Fig. 4.8 (continued)

Martinez [163], analyzing the thyroid follicular and papillary carcinoma, showed no correlation between *Apa1* and cancer risk for the papillary carcinoma, whereas an almost fourfold increased risk was observed for the follicular type for *aa* vs *AA* (OR = 3.82, 95%CI: 1.27, 11.49) and for *Aa* vs *AA* (OR = 3.79, 95%CI: 1.40, 10.26). A subsequent study in a Turkish [20] population did not reveal any effect of *Apa1* on papillary carcinoma.

For renal cell carcinoma, we found two papers, both showing a risk reduction for *aa* and Aa vs *AA*. Other studies reported not association for the *Apa1* polymorphism and cancer risk.

Cdx2 and Cancer

Cdx2, located in the 5′ region of the VDR, has been suggested to modulate promoter activity [9].

Since 2005 28 studies included *Cdx2*, 7 in prostate cancer, 6 in breast cancer, 5 in colorectal and 2 in skin cancer, and 9 in other cancer sites. The studies were conducted mainly in North America and Europe, three were in China, one was in Pakistan, and one was in New Zealand (Table 4.1; Figs. 4.9 and 4.10).

Data were summarized in a previous meta-analysis published by Serrano et al. in 2016 [185] that estimated a modest but significant increased risk for all cancer sites: SOR = 1.12 (95%CI: 1.00–1.25) for *gg* versus the *GG* genotype and 1.03 (95%CI: 0.96–1.10) for *Gg* versus the *GG* genotype (Table 4.1; Figs. 4.9 and 4.10).

Breast Cancer

For breast cancer Anderson [6] had the largest series with 1546 cases and 1627 controls. Subjects with gg have a significant 50% increased risk for breast cancer (OR = 1.49, 95%CI: 1.05–2.11), but in the same cohort, the *Gg* is suggested to have a protective effect with a 17% significant risk reduction (OR = 0.83, 95%CI: 0.72–0.97). Pooling estimates, Serrano found a non-significant increased risk for carriers of *gg* genotype (Summary OR = 1.22, 95%CI: 0.70–2.12) and a non-significant reduction in breast cancer for carriers of heterozygous *Gg* genotype (summary OR = 0.97, 95%CI: 0.70–1.36) [185]. In a meta-analysis published by Zhou et al., *Cdx2* might be associated with the risk of breast cancer in African-Americans [233], consistent with the data reported by Huang et al. [94].

The three more recent studies (Clendenen et al. [40] carried out in Sweden, Iqbal et al. [100] carried out in Pakistan, Amadori et al. [5] that presented data for *Cdx2* only for Italian subjects) do not suggest any significant associations.

Prostate Cancer

Five of the seven studies [38, 86, 103, 137, 206] were included in a recent meta-analysis [185]. *Cdx2* was found to be not associated with prostate cancer: SOR was 1.09 (95%CI: 0.73–1.64) and 1.01 (95%CI: 0.83–1.22) for *gg* and *Gg* versus the *GG* genotype, respectively. Results of the two recent studies (Gilbert et al. [67] that presented the results of the ProtecT studies carried out in the UK and Deschasaux et al. [48] that presented the results of the SU. VI. MAX nested case-control study carried out in France) also do not support an association.

Colorectal Cancer

In all studies but one [18] for CRC published since 2007, a consistent trend toward an increased risk is observed for subjects carrying gg genotype [60, 154, 193, 203]; however, the SORs obtained in the meta-analysis by Serrano et al. [185] do not confirm a significant increased risk: 1.24 (95%CI: 0.94–1.63) and 1.09 (95%CI: 0.96–1.24) for *gg* and *Gg* versus the *GG* genotype, respectively.

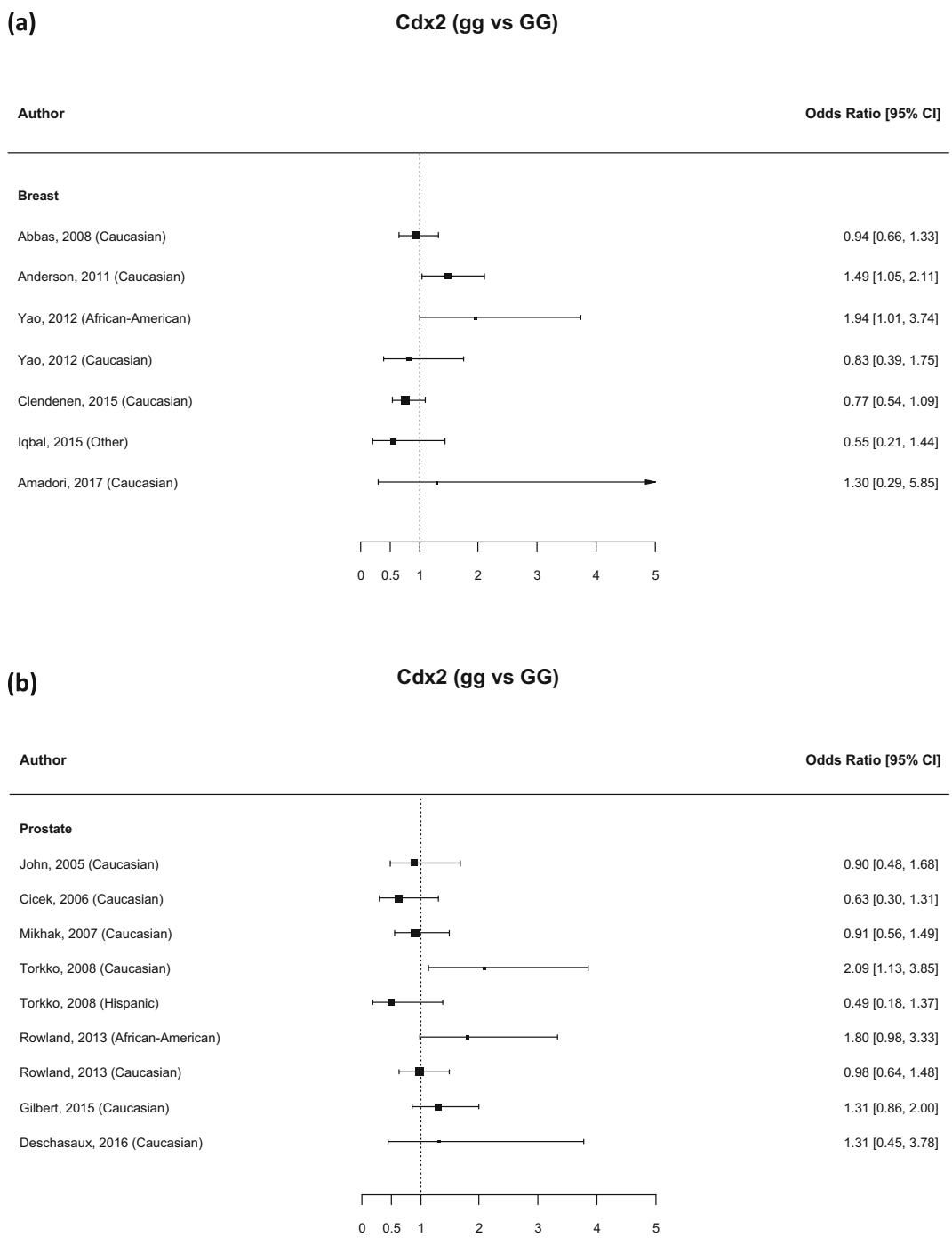
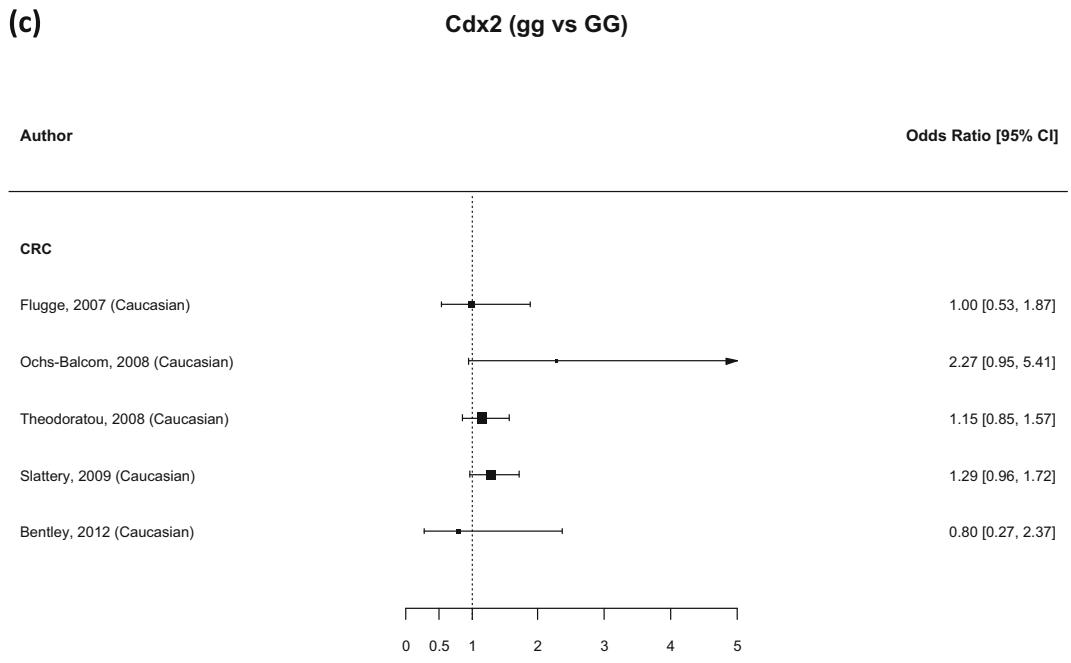


Fig. 4.9 Forest plot for the association between *Cdx2 gg* and *GG* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the skin, pediatric solid tumors, and tobacco-related cancers; (**e**) cancers of the brain, esophagus, kidney, lung, and ovary



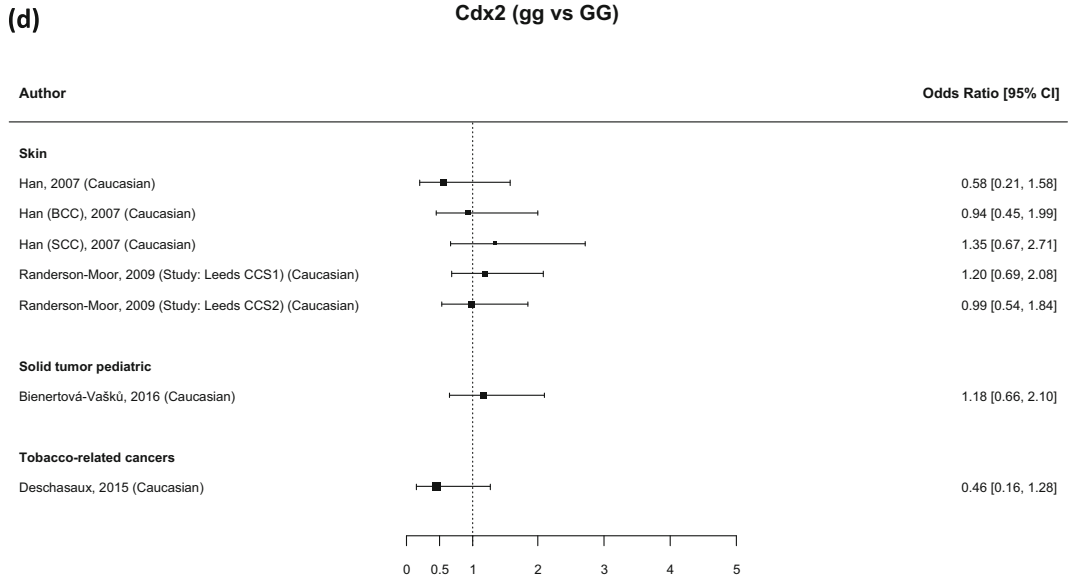


Fig. 4.9 (continued)

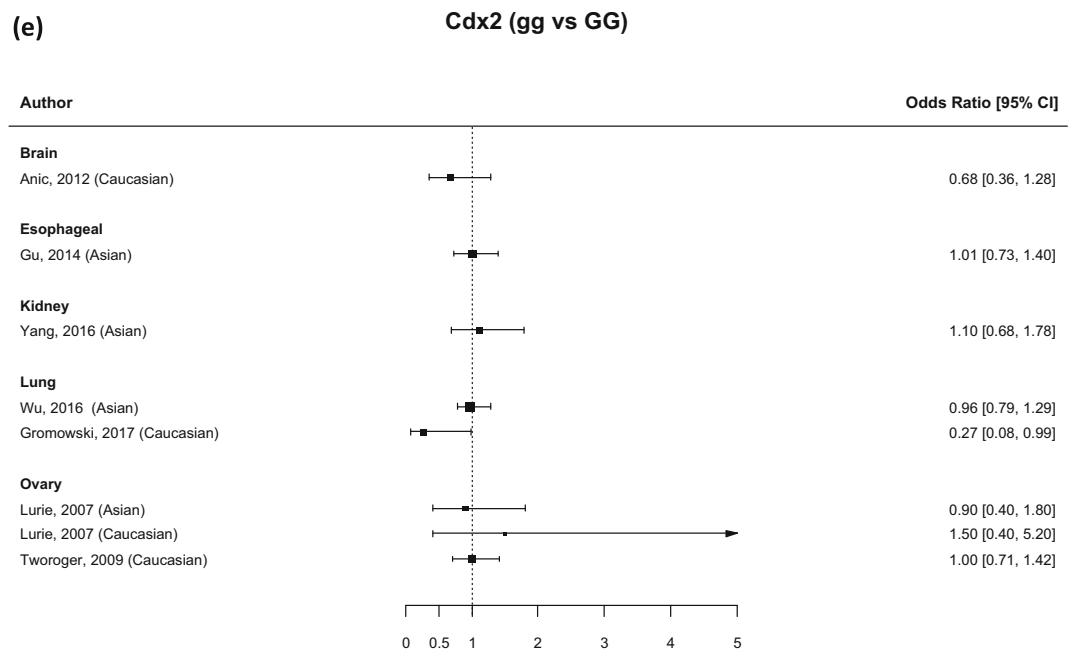


Fig. 4.9 (continued)

Other Cancers

Several studies presented risk estimates for other cancer sites: skin cancer [79, 173], ovarian cancer [127, 209], brain cancer [8] and esophageal cancer [72], renal cell cancer [222], lung cancer [69, 218], all solid pediatric tumor together [21], and all tobacco-related cancers [47]. None of them found significant association except for Gromowski et al. [69] who observed a significant inverse association with lung cancer of *gg* genotype vs *GG* (SOR = 0.27, 95%CI: 0.08–0.99) (Table 4.1; Figs. 4.9 and 4.10).

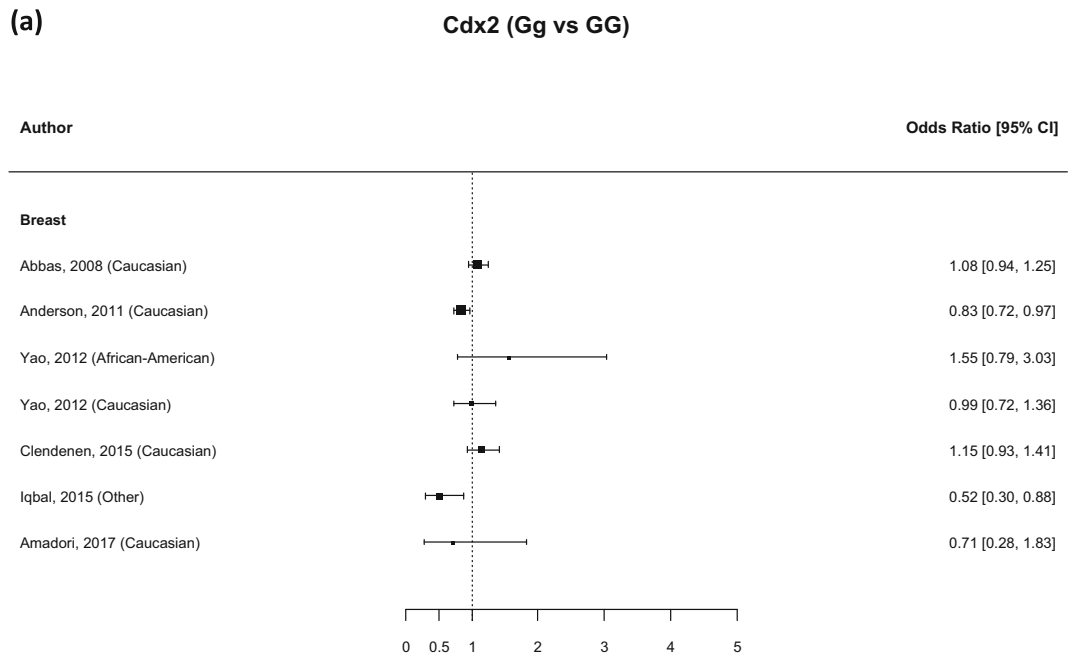
Conclusions and Discussion

Over the last 30 years, an increasing number of studies have examined the association of VDR polymorphisms and cancer. We performed a comprehensive review of the literature on the *VDR Fok1*, *Bsm1*, *Taq1*, *Apa1*, and *Cdx2* polymorphisms and cancer risk. We identified 176 independent studies published up to 2018 with data to calculate cancer risk estimates for 19 cancer sites. The four most studied cancer types were prostate, breast, colorectal, and skin cancer.

We found some significant associations with VDR polymorphisms for all genotypes with prostate, breast, and colon-rectum cancer, even if the associations are sometime heterogeneous. VDR *Fok1* polymorphisms might modulate the risk of cancer of breast and possibly affect cancer risk at any site. *Bsm1 B* allele was suggested to reduce cancer risk at most sites, especially colon-rectal and skin. Some opposite effect of *B* allele was suggested for ovarian and bladder cancer and for non-Hodgkin lymphoma, which could be spurious results due to the small number of studies and included subjects. For some cancer sites, especially breast cancer, opposite risk estimates were obtained in some studies, possibly suggesting different effect of *B* allele in sub-populations and/or interaction with other genetic and host factors. This would be warranted to be further investigated in future studies.

For skin cancer significant associations with VDR polymorphisms have been reported for *Fok1*, *Bsm1*, and *Taq1*.

No significant association has been reported for esophageal cancer, non-Hodgkin lymphoma,



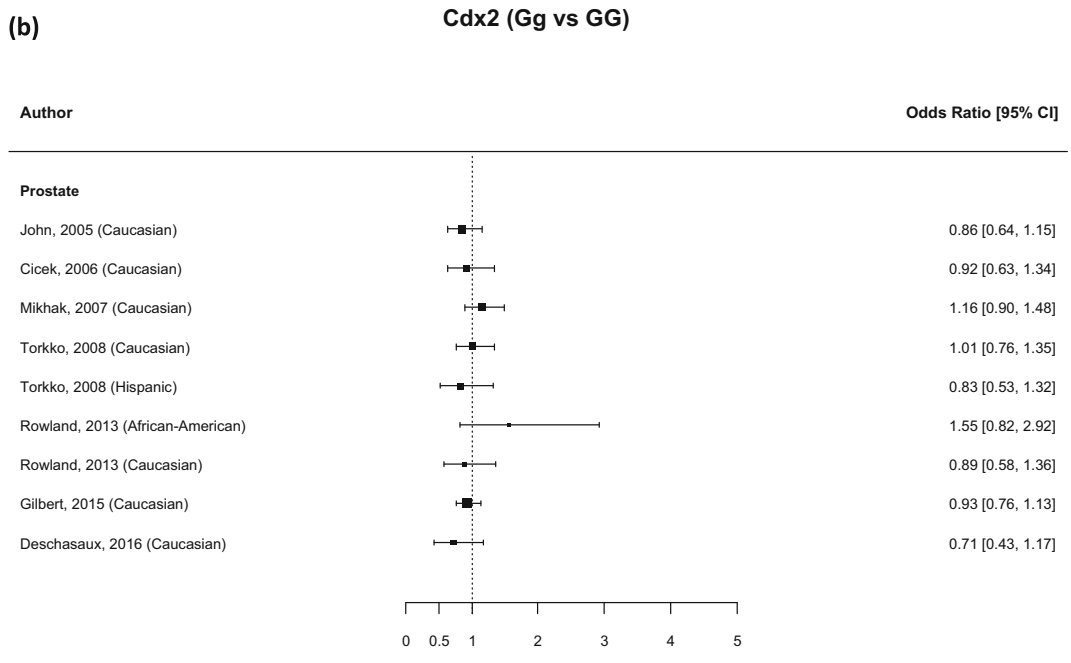
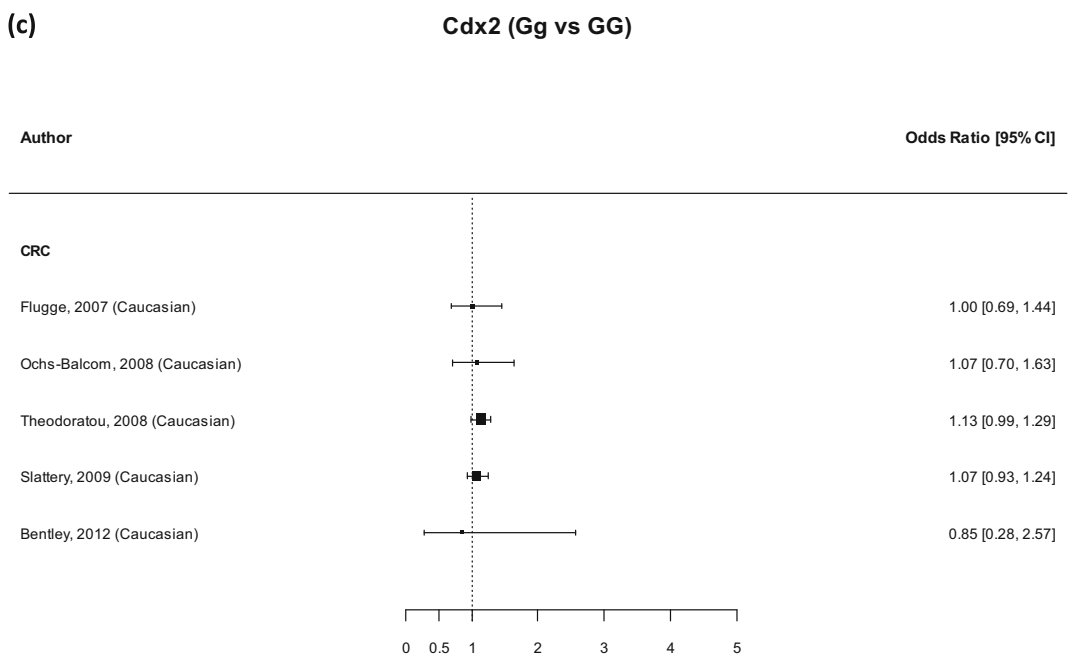


Fig. 4.10 Forest plot for the association between *Cdx2 Gg* and *GG* genotype for (**a**) breast cancer; (**b**) prostate cancer; (**c**) colorectal cancer; (**d**) cancers of the skin, pediatric solid tumors, and tobacco-related cancers; (**e**) cancers of the brain, esophagus, kidney, lung, and ovary



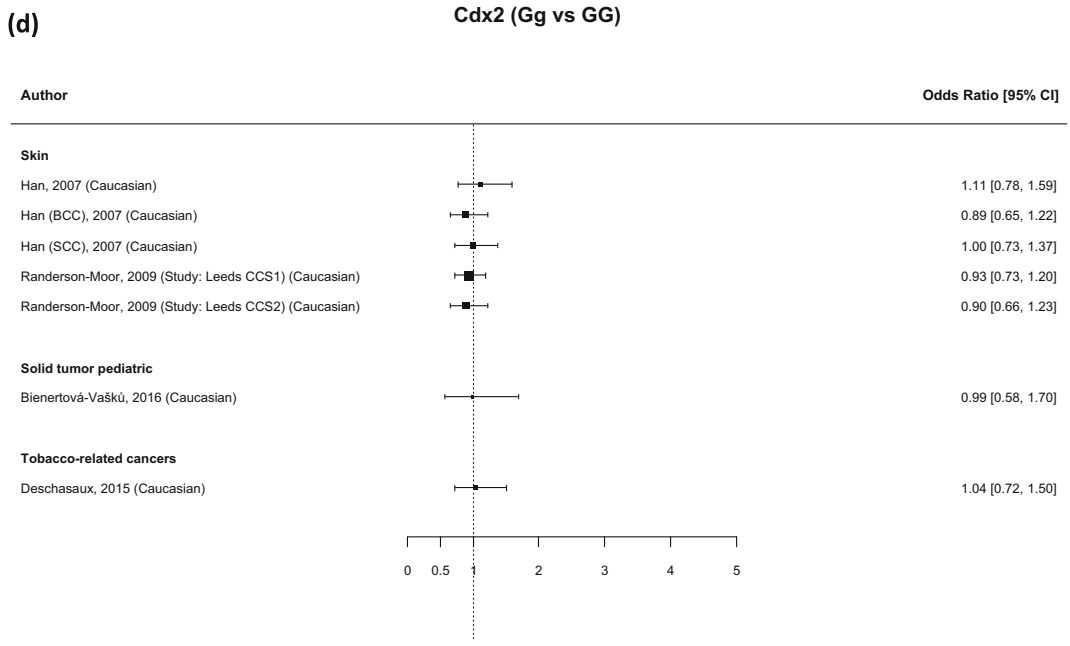


Fig. 4.10 (continued)

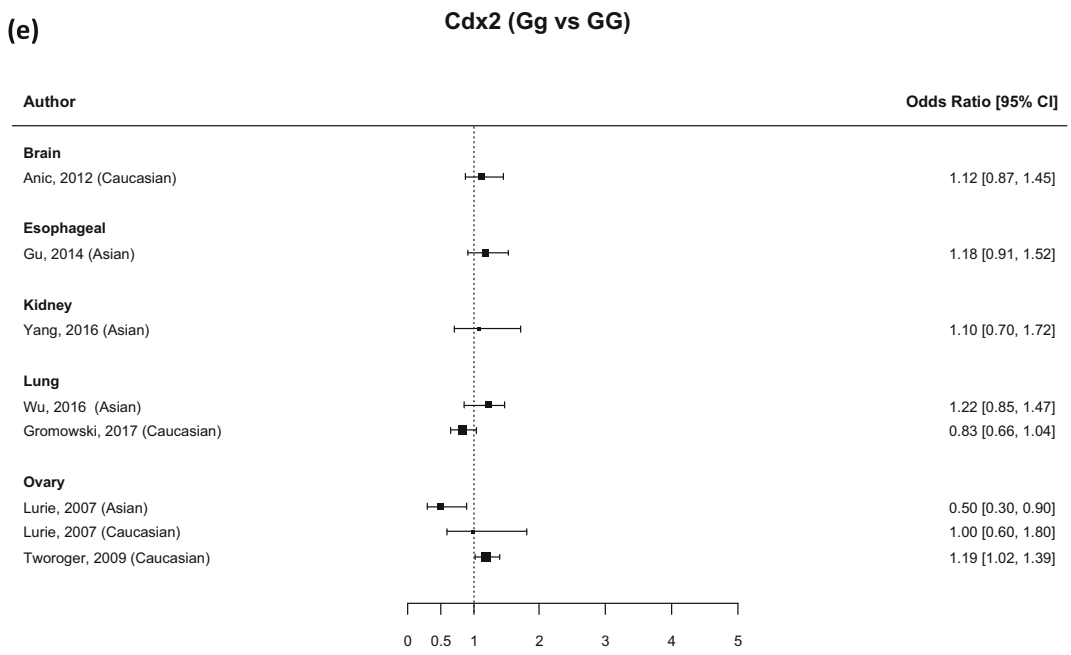


Fig. 4.10 (continued)

sarcoma, pediatric solid tumor, and tobacco-related cancers.

In a previous meta-analysis [171], we found that VDR Fok1 and *Bsm1* polymorphisms might modulate the risk of cancer of the breast, skin, and prostate and possibly affect cancer risk at any site in Caucasians. We found a significant 30% increase in skin cancer risk and 14% increase in breast cancer risk with *Fok1 ff* compared to *FF* genotype. We found a significant 17% reduction in prostate cancer risk with *Bsm1 Bb* compared to *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.

The more recent meta-analysis published by Xu et al. [220] indicated that *b* allele of *Bsm1* polymorphism was a risk factor for cancer susceptibility. Moreover, *f* allele of *Fok1* polymorphism was a risk factor for ovarian and skin cancer and a protective factor for glioma. Furthermore, *t* allele of *Taq1* polymorphism was found to be positively associated with oral, breast, and basal cell cancer and inversely with prostate cancer. Finally, *a* allele of *Apa1* polymorphism was a risk factor for basal cell cancer in Asian population.

In 2015, another meta-analysis evaluated the associations between VDR gene polymorphisms (*Cdx-2*, *Fok1*, *Bsm1*, *Apa1*, and *Taq1*) and female reproductive cancers (breast, ovarian, cervical, endometrial, uterine, and vaginal cancers) [145]. Up to April 2014, the authors evaluated the risks for reproductive cancers under the heterozygous, homozygous, dominant, and recessive models with fixed or random effects models. They indicated that the *Fok1* polymorphism was related to increased risks for breast and ovarian cancers, whereas the *Bsm1* polymorphism was associated with a decreased risk for developing these cancers.

A meta-analysis published by Serrano et al. in 2016 [185] assessed the association of *Taq1*, *Apa1*, and *Cdx2* SNPs with the risk of cancer and estimated a modest but significant increased risk for any cancer site for *Cdx2*: summary OR = 1.12 (95%CI: 1.00–1.25) for *gg* versus the *GG* genotype and 1.03 (95%CI: 0.96–1.10) for *Gg* versus the *GG* genotype.

Two meta-analyses were recently published [35, 228]. Yu found the *tt* genotype of *Taq1* inversely associated with lung cancer risk compared with the *Taq1 Tt* + *TT* genotype

(OR = 0.70, 95%CI = 0.55–0.90) [228], while Chen [35] confirmed the association in particular in Asian population and suggested that PCa patients carrying the *t* allele or *tt* genotype were less likely to progress to advanced stage.

There are several potential explanations for contrasting results and inconsistencies in findings for these common SNPs. Design issue or small sample size may limit the generalizability of the results. It is well established that *VDR* genotypes vary widely by ethnicity and it is needed to evaluate these associations among ethnic subgroups to evaluate differences in allele frequency [168, 207]. We considered the deviation from H-W disequilibrium in controls as an indication that the alleles remain constant and are not segregating independently. There are several reasons for heterogeneity, including non-random matching (which encompasses admixture), biased selection of subjects from the population, genotyping error, population stratification, and adjustment for confounders. Sun exposure and dietary consumption are potential modification of the genotype-cancer associations.

To conclude, there is some indication that *VDR* polymorphisms may modulate the risk of some cancer sites and in future studies *VDR* genetic variation should be integrated also with prediagnostic biomarkers of vitamin D status.

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