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Review

The Relevance of Vitamin D Receptor (VDR) Gene Polymorphisms for Cancer: A Review of the Literature

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Abstract. *Background: In recent years, the relevance of vitamin D receptor (VDR) gene restriction fragment length polymorphisms for various types of cancer has been investigated by a great number of studies. It has been hypothesized that VDR polymorphisms may influence both the risk of cancer occurrence and prognosis. However, studies investigating the associations between specific VDR polymorphisms and cancer often show controversial results. We have now performed a systematic review of the literature to analyse the relevance of VDR polymorphisms for individual malignancies, including cancer of the skin, prostate, breast, colon, ovary, kidney and bladder. Materials and Methods: An analysis of studies evaluating the association between vitamin D receptor gene polymorphisms Fok1, Bsm1, Taq1, Apa1, and Cdx2, poly (A) and Bgl1 as well as some haplotype combinations and cancer risk has been performed. Data were extracted from PubMed using the key words VDR polymorphism in combination with breast cancer, prostate cancer, skin cancer, colorectal cancer, ovarian cancer, renal cell carcinoma or bladder cancer. Results: This analysis was performed with the intent of giving an up-to-date overview of all data concerning the relevance of VDR polymorphisms for cancer. Obviously, at present it is still not possible to make any definitive statements about the importance of the VDR genotype for cancer occurrence. It seems probable that interactions with other factors such as calcium and vitamin D intake,* 25(OH)D *plasma levels and UV radiation exposure play a decisive role in cancer occurrence and should not be underestimated. Other risk factors such as obesity, smoking status, parity status, energy intake and others are also frequently mentioned as being more or less important for carcinogenesis depending on the VDR genotype. Moreover, it is often noticed that the same VDR polymorphism has a different effect depending on the type of cancer, or may be only decisive for more or less aggressive staging of the tumour. Conclusion: Significant associations with VDR polymorphisms have been reported in cancer of the breast (Fok1, Bsm1, Taq1, Apa1, poly (A)), prostate (Fok1, Bsm1, Taq1, poly (A)), skin (Fok1, Bsm1, A-1210), colorectum (Fok1, Bsm1), ovary (Fok1, Apa1) and bladder (Fok1), and in renal cell carcinoma (Taq1, Apa1). However, conflicting data have been reported for most malignancies. After careful evaluation of the actual literature, it can be summarized that data indicating an association of VDR polymorphisms and cancer risk are strongest for breast cancer (Bsm1, Fok1), prostate cancer (Fok1) and malignant melanoma (MM) (Fok1). Data indicating an association of VDR polymorphisms and cancer prognosis are strongest for prostate cancer (Fok1), breast cancer (Bsm1, Taq1), MM (Bsm1) and renal cell carcinoma (Taq1).*

Abbreviations: BCC: Basal cell carcinoma; BMI: body mass index; BMD: bone mineral density; BPH: benign prostate hyperplasia; CCS: case–control study; CI: confidence interval; CM: cutaneous melanoma; COS: case only study; *CYP24A1*: gene encoding for vitamin D deactivating enzyme 24-hydroxylase; *CYP27B1*: gene encoding for vitamin D activating enzyme 1-α-hydroxylase; ER: oestrogen receptor; FCCS: family-based case–control study; HCCS: hospital based case–control study; LD: linkage disequilibrium; MM: malignant melanoma; NCCS: nested case–control study; NSAID: nonsteroidal anti-inflammatory drugs. OR: odds ratio; *P*: percentile; exceeding probability; PC: prostate cancer; PCCS: population-based case–control study; RCC: renal cell carcinoma; RFLP: restriction fragment length polymorphism; SCC: squamous cell carcinoma; SNP: single nucleotide polymorphism; SRD5A2: 5α-reductase type II (enzyme that converts testosterone to dihydrotestosterone in the prostate); TNM classification: tumour staging classification (International Union Against Cancer); UVR: ultraviolet radiation; VDR: vitamin D receptor; VNTR: variable number of tandem repeats.

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The vitamin D endocrine system regulates a broad variety of independent biological processes including bone metabolism, innate immune response, cell proliferation and differentiation (1). Epidemiological and laboratory investigations have convincingly shown that vitamin D deficiency is associated with several common diseases, including rickets and other bone diseases, diabetes, cardiovascular diseases, autoimmune diseases, tuberculosis and cancer (1-3).

1,25-Dihydroxyvitamin D_3 ($1,25(OH)_2D_3$, calcitriol), the biologically most active naturally occurring metabolite of vitamin D, has been shown to regulate the growth and differentiation of various cell types, including cancer cells (4-7). Furthermore, there is recent evidence of regulatory effects on cell death, tumour invasion and angiogenesis in cancer (8-12). In agreement with these findings, the importance of the vitamin D endocrine system for cancer is now increasingly being recognized (8, 13-15).

There are two principal enzymes involved in the formation of circulating $1,25(OH)_2D_3$ from dietary absorbed or skin-synthesized vitamin D: the hepatic microsomal or mitochondrial vitamin D 25-hydroxylase (CYP27A1) and the renal mitochondrial enzyme 1α-hydroxylase (CYP27B1) for vitamin D and $25(OH)D_3$, respectively (16, 17). These hydroxylases belong to a class of proteins known as cytochrome P450 mixed function monooxidases. In recent years, extrarenal activity of $25(OH)D_3$-1α-hydroxylase (CYP27B1) has been reported in various cell types including macrophages, keratinocytes, prostate and colon cancer cells (18-20). It was shown that $1,25(OH)_2D_3$ is produced locally in many tissues.

The potent seco-steroid hormone $1,25(OH)_2D_3$ acts *via* binding to a corresponding intranuclear receptor (VDR), present in target tissues (21, 22). VDR belongs to the superfamily of transacting transcriptional regulatory factors, which includes the steroid and thyroid hormone receptors as well as the retinoid-X receptors and retinoic acid receptors (23, 24). VDR is encoded by a large gene (>100 kb) located on the chromosome 12q12-14 (21, 25). The *VDR* gene encompasses two promoter regions, eight protein-coding exons (namely 2-9) and six untranslated exons (1a-1f) (21). It has an extensive promoter region capable of generating multiple tissue-specific transcripts.

It has been demonstrated that VDR requires heterodimerization with auxiliary proteins for effective DNA interaction (24-27). These auxiliary proteins have been identified as the retinoid-X receptors (RXR)-α, -ß, and -γ (24, 26, 27). Vitamin D response elements have been identified in numerous genes involved in cellular growth, differentiation, apoptosis, invasion and metastasis of tumour cells: *i.e.* cell cycle regulators such as the human *p21/WAF1, cyclin A* and *cyclin E*, human *nm23.H1* human *c-fms, c-fos, c-jun* and *c-myc*, human *retinoblastoma*, murine *fibronectin*, human *plasminogen activator inhibitor 2*, human *laminin* and *laminin receptor (α6)*, and chicken *β3-integrin* gene (28-32). Therefore, it can be assumed that VDR-mediated signalling pathways and *VDR* gene polymorphisms may be of importance for cancer.

Polymorphisms, defined as mutations with an allele frequency of at least 1% in a given population, are subtle DNA sequence variations which occur often in the population and can have modest but real biological effects. Because of their abundance in the human genome as well as their high frequencies in the human population, they have often been studied with the aim of explaining variations in the risk for common diseases (33). According to Shastry (34) and Li *et al.* (33), humans carry a huge number of polymorphisms which may lead to different cellular effects due to various mechanisms such as enhanced/reduced transcription, altered posttranscriptional or posttranslational activity or changes in the tertiary structure of the gene product (34, 33).

To date, more than sixty *V*DR polymorphisms have been discovered that are located in the promoter, in and around exons 2-9 and in the 3'UTR region (3, 35). The analysis of the importance of these *VDR* polymorphisms for various diseases has proven difficult. As a result, only few polymorphisms of this large gene have been studied. Most of them are restriction fragment length polymorphisms (RFLP) with an unknown functional effect. In some cases, it has been indicated that they may be linked to truly functional polymorphisms elsewhere in the *VDR* gene (or in a nearby gene), which explains some of the associations observed (3).

From a historic point of view, the first studies of *VDR* polymorphisms have been performed using parameters of bone metabolism as endpoints, especially in osteoporosis (36, 3). Studies analysing associations of *VDR* gene polymorphisms with other diseases including various types of cancer and immune system related disorders were later reported in the literature (37, 38).

VDR gene variants that are frequently studied include a 5' Fok1 site in exon 2 that alters the start codon (38), changes in intron 8 that generate Bsm1 and Apa1 restriction enzyme sites, and a similar change in exon 9 (codon 352) that generates a Taq1 restriction enzyme site and a poly (A) microsatellite in the 3' flanking region (39).

Besides these frequently studied variants, this meta-analysis also investigates other polymorphisms which are still less often studied including A1012G (A to G substitution) (40), Cdx2 (41-45) and various resulting *VDR* genotype combinations.

There is still controversy about the importance of *VDR* polymorphisms for individual malignancies. Some studies reported conflicting results and others only found associations between *VDR* polymorphisms and cancer when other risk factors such as UVB exposure (46, 47), oral

vitamin D and calcium intake (48), or the plasma level of $25(OH)D_2$ (49) were present. Therefore, we have now performed a systematic review of the literature to analyse the relevance of *VDR* polymorphisms for individual malignancies, including cancer of the skin, prostate, breast, colon, ovary, bladder and renal cell carcinoma. A meta-analysis of studies evaluating the association between *VDR* polymorphisms Fok1, Bsm1, Taq1, Apa1, Cdx2, poly (A), Bgl1, as well as some haplotype combinations and cancer risk has been performed. Data were extracted from Pubmed using the key words: *VDR* polymorphism in combination with breast cancer, prostate cancer, skin cancer, colorectal cancer, ovarian cancer, renal cell carcinoma or bladder cancer.

VDR Polymorphisms

The first techniques used to analyse the presence of *VDR* polymorphisms were rather insensitive. By screening with different restriction enzymes, only limited areas in the *VDR* gene could be analysed for variances in the DNA sequence. Examples of *VDR* gene variants that were detected using the conventional restriction enzyme approach are the Apa1 (50), Bsm1 (51) and Taq1 (52) *VDR* gene polymorphism discovered in the 3' end of the *VDR* gene. The VDR gene Taq1 polymorphism (rs731236) is an RFLP at codon 352 in exon 9 of the *VDR* gene. Depending on the presence or absence of a Taq1 restriction site in each allele, products are digested into two fragments of 495 and 245 bp (T allele: absence of the restriction site) or three fragments of 290, 245 and 205 bp (t allele: presence of the restriction site). Individuals are generally classified as TT, Tt or tt. The TT genotype has been shown to be associated with lower circulating levels of active vitamin D_3 (52-54). The Apa1 (rs 7975232) and the Bsm1 (rs 1544410) polymorphisms are RFLPs in intron 8 at the 3' end of the *VDR* gene. In general, the majority of polymorphisms in the *VDR* gene are found to be in regulatory areas such as the 5' promoter area and the 3' UTR region rather than in coding exons (35). The Apa1 and the Bsm1 polymorphisms of the *VDR* gene are considered to be silent single nucleotide polymorphisms (SNPs). These polymorphisms do not change the amino acid sequence of the encoded protein. However, they may affect gene expression through regulation of mRNA stability (55). Of particular interest is a thymine/cytosine (T/C) polymorphism (Fok1: rs 10735810) located at the first potential start site (36, 56) which can be detected by RFLP using the Fok1 restriction enzyme (57). It alters an ACG codon that is located ten base pairs upstream from the translation start codon and results in the generation of an additional start codon. If the initiating translation starts from this alternative site (thymine variant), it results in the generation of a longer VDR protein of 427 amino acids. This polymorphism is referred to as the f allele (56). However, the f allele exerts less transcriptional activity (58), with the F variant being 1.7-fold more active (57, 59, 60). To date, the Fok1 polymorphism is the only known *VDR* gene polymorphism that results in the generation of an altered protein.

A *VDR* polymorphism that was found through sequence analysis of a targeted area is the Cdx2 polymorphism (rs 11568820) (42). It is a guanine (G) to adenine (A) sequence variation in the promoter area (1e promoter) of the *VDR* gene, more specifically in a binding site for an intestinal-specific transcription factor which is called Cdx2 (41). It was first found among Japanese women, but it has since been shown to be present also among Caucasians as well as other race groups (43). The A allele has been demonstrated to be more active by binding the Cdx2 transcription factor more strongly and by having greater transcriptional activity (42). It has been assumed that in consequence, the A allele may result in a higher *VDR* expression in the intestine and therefore in an increased bone mineral density (BMD) through a better intestinal absorption of calcium (42, 43, 3). The poly (A) polymorphism of the *VDR* gene is characterized by a variable number of tandem repeats (VNTR) in the 3'UTR region (39). It can be distinguished as bi-allelic, therefore individuels can be classified as having alleles with short (S, with <18 As) or long (L, with >18 As) poly (A) stretches. The S allele is considered to be the more active VDR allele (58).

Finally, there are two other still rarely analysed, *VDR* polymorphisms, the A-1012G polymorphism and the Tru 91 polymorphism. The A-1012G polymorphism is characterized by an adenine (A) to guanine (G) substitution which is located 1012 bp close to the exon 1a transcription start site. It was found by screening of single-stranded conformational polymorphism in the *VDR* promoter region (40). The *VDR* polymorphism Tru91 is a G (U allele) to A (u allele) polymorphism in the *VDR* intron 8 region, which was reported by Gong *et al*. (61).

Linkage Disequilibrium (LD)

Linkage disequilibrium (LD) describes the co-occurrence of alleles of adjacent polymorphisms with each other (62). As a result, the presence of a polymorphism predicts the presence of another polymorphism that is linked to it, because very little recombination has occurred between them during evolution. When there are many LDs in a certain area, there will be only a limited number of haplotypes in that area. Haplotypes can be defined as blocks of linked alleles of adjacent polymorphisms (3, 63). The haplotype block size can vary between 5 to >50 kb, with an average of 10-20 kb (62-64, 3). This means that frequent haplotypes can be found that comprise the polymorphisms in such areas and as a consequence, relatively few polymorphisms are enough to

cover the variance in a certain area. In general, the LD and haplotype structure of the *VDR* gene is important for association analyses to see whether and to what extent a certain polymorphism contributes to the risk of disease *e.g.* of cancer occurrence. This means that if a certain polymorphism has been found to be associated with a higher risk of cancer incidence, it must be taken into consideration that this association might also be explained by one or more other alleles that are linked to that allele within the haplotype because of LD and haplotype combination. With reference to the extent of LD across the *VDR* gene, a strong LD has been noticed at the 3' end of the gene for the Bsm1, Apa1 and Taq1 RFLPs (51, 52, 65, 66). This leads to the assumption that with reference to these three polymorphisms, there may be similar results concerning cancer risk. The most frequent haplotypes were found to be haplotype 1 (baT: 48%) and haplotype 2 (BAt: 40%) (2). In the BAt allele, the restriction sites for Bsm1 and Apa1 are absent but the restriction site for Taq1 is present, whereas the opposite is true for the baT allele (Bsm1 and Apa1 are present but Taq1 is absent). Another LD has been observed between the Bsm1 RFLP and the poly (A) polymorphism: the two common haplotypes are bL and BS. Haplotype 1 (baT) is linked to the long poly (A) stretch (L) whereas haplotype 2 (BAt) is linked to the short poly (A) stretch (S) (52, 66, 2). According to Kibel *et al.*, the Taq1 RFLP is also in strong LD with the poly (A) microsatellite (67). This same LD (Taq1/poly (A)) has been also reported by Blazer *et al.* (68) ($p<0.0001$), with Caucasians demonstrating stronger LD than blacks (D=0.24 *versus* D=0.18). As noticed in several studies, the Fok1 polymorphism is in no LD with any of the other *VDR* polymorphisms and, consequently, can be considered as an independent marker in the *VDR* gene (3, 57).

Ethnic Variation in *VDR* Gene Polymorphisms

Several large studies reported ethnic variation in the occurrence of *VDR* gene polymorphisms (3, 69). In a recent analysis by Uitterlinden *et al.*, the f allele of Fok1 occurs less frequently in Africans as compared to Caucasians and Asians, whereas the frequency of the Bsm1 B allele is much lower in the Asian population compared to other populations (3, 69) (Fok1 f: Caucasians 34%, Asians 51%, Africans 24%; Bsm1 B allele: Caucasians 42%, Asians 7%, Africans 36%). On the other hand, the Cdx2 A allele has been reported to be much more common in the African population than in Caucasians and Asians (Cdx2 A allele: Caucasians 19%, Asians 43%, Africans 74%) (43). Moreover, the Apa1 A allele has been noticed at a higher frequency in the Asian population (Apa1 A allele: Caucasians 44%, Asians 74%, Africans 31%). Due to LD, the Taq1 and poly (A) polymorphism occur at similar ratio, with the lowest percentage in Asians (Taq1 T allele: Caucasians 43%, Asians 8%, Africans 31%; poly (A) S allele: Caucasians 41%, Asians 12%, Africans 29%). As to the most common haplotypes 1 and 2, haplotype 1 (baT) is most frequent in the Asian population, whereas Caucasians are demonstrated to have mostly haplotype 2 (BAt). Nevertheless, despite all these ethnic differences in the occurrence of *VDR* gene polymorphisms, the functional effect of a certain polymorphism will most likely not differ between ethnic groups, most importantly because the physiological role of the vitamin D endocrine system is considered to be the same in all ethnic groups.

Vitamin D and Breast Cancer

Breast cancer is a common disease with major public health implications. In various observational studies, high vitamin D intake and high serum concentrations of vitamin D metabolites have been associated with reduced risk for developing breast cancer (70-72). There are laboratory data that support the hypothesis that the anticarcinogenic effects of vitamin D could be mediated *via* the oestrogen pathway by down-regulation of the oestrogen receptor (ER) and thus attenuating oestrogenic bioresponses such as cell growth (73, 74). Therefore, further epidemiological studies assessing the association of vitamin D and breast cancer risk should take the receptor status of the tumour and other gene variants of oestrogen metabolism into account. However, more studies on certain polymorphisms and haplotypes in the *VDR*, especially functional studies with respect to impact on VDR activity and concentration are needed.

Vitamin D and Prostate Cancer

Prostate cancer has a high incidence as well as a high mortality, which make it an important worldwide health issue. Its aetiology is complex, including many risk factors such as age, hormonal status, ethnic origin and family history of prostate cancer. Moreover, recent studies reported a significant north-south trend of prostate cancer mortality rates in the USA, with higher mortality rates being found in the northern USA, possibly implicating the lack of active vitamin D (75, 76). In the clinical setting of prostate cancer, active vitamin D compounds may retard the progression of indolent prostate cancer to more active disease (75, 77). Indeed, it has been shown that oral administration of active vitamin D metabolites delays the recurrence of prostate cancer following primary therapy (78). This indicates that active vitamin D metabolites can be effective in slowing the progression of prostate cancer. Finally, since the vitamin D pathway includes the VDR and since genetic predisposition is seen as a major risk factor, there are many studies suggesting an association between *VDR* polymorphisms and the development of prostate cancer.

Vitamin D and Skin Cancer

Skin cancer is a very common neoplasm in Caucasians. There are three main types of skin cancer: the most common is basal cell carcinoma (BCC), followed by squamous cell carcinoma (SCC) and malignant melanoma (MM). Ultraviolet radiation (UVR) is known to have strong carcinogenic effects on skin tissue which makes it a strong risk factor for non melanoma skin cancer (79, 80). Although it is obvious that the relationship between UVR and skin cancer is more complex than for other types of cancer, there is evidence of a protective effect of vitamin D. Sunlight causes DNA damage but also induces production of vitamin D whose metabolite $1,25(OH)_2D_3$ has anti-proliferation and pro-differentiation effects in both melanocytes and cutaneous melanoma (CM) cells, mediated through the VDR. MM cells have been demonstrated to express the VDR, and the anti-proliferation and pro-differentiation effects of $1,25(OH)_2D_3$ have been shown in cultured melanocytes, MM cells and MM xenografts (81). Moreover, $1,25(OH)_2D_3$ has been shown to exert an inhibitory effect on the spread of MM cells and it has been noticed that MM patients have low serum levels of $1,25(OH)_2D_3$. In addition to these findings, *VDR* polymorphisms have been shown to be associated with both the occurrence and outcome of MM (81). Therefore, further work is required to study the influence of the vitamin D endocrine system, including the effects of *VDR* polymorphisms, on incidence and outcome of skin cancer.

Vitamin D and Colon Cancer

Colorectal cancer aetiology includes many modifiable risk factors, including components of energy balance and dietary patterns such as sucrose to fibre ratio and glycemic index (82). Additional factors that have to be considered are diet, lifestyle, body mass index, physical activity and calcium intake. As the VDR is present in colon cancer cells, functional *VDR* gene polymorphisms may also play a decisive role in carcinogenesis through modulation of cell growth, protection from oxidative stress, cell–cell matrix effects and insulin/insulin-like growth factor pathways.

Vitamin D and Ovarian Cancer

Ovarian cancer is a fatal gynaecological malignancy, especially because of its late clinical manifestation and the lack of screening methods for early detection. There are several risk factors that are considered to be associated with ovarian cancer such as gravidity, family history of ovarian cancer, tubar legation, use of contraceptive steroids, premenopausal status and the use of menopausal oestrogens in combination with progesterone. Epidemiological and laboratory studies have shown that the vitamin D endocrine system may be involved in ovarian carcinogenesis. The presence of VDR in normal ovarian epithelium, in human ovarian tumours and in human ovarian cancer cell lines has been demonstrated (83-85). VDR is necessary for full ovarian function through direct effects on oestrogen biosynthesis and regulation of aromatase gene expression (86). Moreover, VDR and its ligands regulate fundamental processes of cellular proliferation, differentiation and apoptosis which may influence ovarian cancer development. Additionally, it may also antagonize androgen, which has been suggested to play an important role in ovarian carcinogenesis (87, 88), by inhibiting the androgen receptor expression which was found in the majority of ovarian tumours (84). Interestingly, in contrast to the observed down-regulation in colon and breast tumours, *VDR* has been found to be up-regulated in ovarian tumours when compared with non-matched normal ovarian tissue (85, 89). With regard to ethnical differences, substantial racial variation has been observed in the incidence of ovarian cancer, with highest rates in Caucasian women and lowest rates among Asian women (90). This fact might be partially explained by differences in variant allele frequencies, the association of *VDR* polymorphisms with ovarian cancer risk being generally inconsistent among ethnic groups (86).

Vitamin D and Renal Cell Carcinoma

VDR polymorphisms in renal cell carcinoma (RCC) have been mostly analysed in Japanese patients. Biological and epidemiological data suggest that $1,25(OH)_2D_3$ levels may influence the development of RCC. Serum levels of $1,25(OH)_2D_3$ are reported to be significantly lower in Japanese patients with RCC compared to those in healthy people (91, 92). Moreover, serum levels of $1,25(OH)_2D_3$ were significantly lower in RCC patients with T3 and T4 disease (tumour invasive from outside the kidney) compared to those with T1 and T2 disease (tumour located inside the kidney) and it has been demonstrated that serum levels of $1,25(OH)_2D_3$ were significantly lower in RCC patients with rapid-growth tumour compared to those with slow-growth tumour (92). In addition, $1,25(OH)_2D_3$ has been reported to be effective as an antitumour treatment for murine RCC (93). However, currently, there is still a scarcity of data regarding the association of *VDR* genotype with RCC patients.

Vitamin D and Bladder Cancer

Bladder cancer is a complex and multifactorial disease and a very common genitourinary malignancy (90). Similar to other solid tumours, bladder cancer develops through a series of genetic changes such as chromosomal alterations and loss of cell cycle regulation that lead to tumour progression (94).

Moreover, the human bladder is a potential target for VDR ligands and has a similar *VDR* expression to that of the prostate, which is a well-characterized VDR ligand-sensitive tissue. *VDR* has been confirmed to be also expressed in bladder cancer cells (95). Bladder cancer is considered to be a polygenic disease. Therefore it was necessary to include various gene polymorphisms such as the *VDR* polymorphisms in the search for candidate genes which might be useful for screening and risk evaluation of bladder cancer.

Materials and Methods

We performed a meta-analysis of published studies evaluating the association between *VDR* gene RFLPs Fok1, Bsm1, Taq1, Apa1, Cdx2, poly (A), Bgl1 and some genotype combinations and various types of cancer, including breast, prostate, skin, colon, ovarian, renal cell and bladder cancer. Sources were PubMed (last search update was May 2008) using the key word *VDR* polymorphism in combination with breast cancer, prostate cancer, skin cancer, colorectal cancer, ovarian cancer, renal cell carcinoma and bladder cancer. References of review articles of *VDR* polymorphisms in association with cancer were also screened. In general, cases with cancer were eligible for the analysis even if they had a first-degree relative with cancer. In terms of prostate cancer, disease-free controls were accepted regardless of whether they had benign prostate hyperplasia.

Data Extraction

Data have been extracted taking the following information from each report: authors, journal and year of publication, country of origin, racial descent of study population, number of cases and controls for each *VDR* genotype. The studies were heterogeneous in terms of number of cases and controls, racial composition and analysed polymorphisms.

Results

Fok1 polymorphism and cancer.

Fok1 and breast cancer. Analysing the relevance of the *VDR* Fok1 polymorphism for breast cancer risk, most studies reported no association (48, 96-100, 44, 46). Most of these studies were case–control studies with a great number of cases (mostly Caucasian women). Abbas *et al*. found neither a direct association between Fok1 and breast cancer occurrence, nor any interaction between *VDR* genotypes or haplotypes and serum levels of 25(OH)D (44). Guy *et al*. reported that there was no association when individual *VDR* polymorphisms were analysed in isolation, but the Fok1 polymorphism modulated the increased risk of another *VDR* genotype (bb/LL genotype: Bsm1 b allele, poly (A) L allele) in such a way that possession of one or more F alleles together with the bb/LL genotype resulted in increased breast cancer risk (97). Interestingly, a significantly increased risk of breast cancer was observed in one large study (1234 cases, 1676 controls) among carriers of the ff genotype of Fok1 (multivariate OR=1.34) compared with those with the FF genotype (101). In that study, the Fok1 association did not vary significantly with menopausal status, oestrogen, and progesterone receptor status of the tumours, or plasma levels of 25(OH)D or $1,25(OH)_2D_3$. In conclusion, even if there is a clear tendency for a lack of association of the Fok1 polymorphism with breast cancer risk, further studies still seem to be necessary to clarify these observations. The references analysing Fok1 polymorphism and breast cancer are summarized in Table I.

Fok1 and prostate cancer. According to a meta-analysis performed by Ntais *et al*. there is no evidence of an association of the ff genotype with the risk of prostate cancer relative to the FF genotype (37). The reports studied by this meta-analysis are of Correa-Cerro *et al*. (102), Luscombe *et al*. (103) and Chokkalingam *et al*. (104). In detail, the prevalence of the f allele was 36% and 46% in controls of European and Asian descent, respectively (37). The respective prevalence rates of F/f heterozygosity (ff homozygosity) were 44% (14%) and 51% (21%). The mentioned meta-analysis included 514 prostate cancer cases and 545 control cases with genotype data of Fok1. Other studies analysing putative associations between Fok1 and prostate cancer also failed in finding any significant association (105-109). Mikhak *et al*. found no association between the analysed SNPs (Cdx2, Fok1, Bsm1) and susceptibility to prostate cancer but also analysed the associated haplotypes (108). Interestingly, haplotype 2 (Afb: Cdx2 A, Fok1 f, Bsm1 b) and haplotype 3 (AFB: Cdx2 A, Fok1 F, Bsm1 B) were associated with reduced risk of aggressive PC (high stage or Gleason sum ≥7; p=0.02), as compared to the most common haplotype (AFb) (108). Although another study (110) found no association between Fok1 and prostate cancer risk in Caucasian American men, a significant increase in risk was found for African–Americans (Fok1 FF genotype: OR=1.9). Moreover, it has been noticed that the FF genotype is more prevalent in African–Americans than in US Caucasians. On the other hand, in other studies, the Fok1 ff genotype has been reported to be increased (not significantly) in the case group (OR=2.33) (106) and to be associated with an increased prostate cancer risk (OR=2.91) (45). Relative to all other Fok1 and Taq1 combinations, this study revealed that the genotype combinations FF/TT (OR=0.35, p=0.026) are associated with reduced prostate cancer risk (45).

A very recent study tested the interactions of polymorphisms of the *VDR* and *SRD5A2*, a gene which

Table I. *Fok1 polymorphism and cancer.*

Reference	Polymorphism	Study type	Study population	Cases/Controls
Breast cancer				
Abbas *et al*. (44)	Fok1, Taq1, Cdx2, VDR-5132	PCCS	German	1408/2612
Bretherton-Watt *et al*. (96)	Fok1, Bsm1, poly (A)	CCS	Caucasian	181/241
Chen *et al*. (101)	Fok1	CCS	USA	1234/1676
Curran *et al*. (99)	Fok1, Taq1, Apa1	CCS	Australian	135/110
Guy *et al*. (98)	Fok1, Bsm1	CCS	Caucasian	313/410
Guy *et al*. (97)	Fok1, Bsm1, poly (A)	CCS	Caucasian	398/427
Ingles *et al*. (100)	Fok1, Bsm1, poly (A)	CCS	Latina	143/300
John *et al*. (46)	Fok1, Taq1, Bgl1	CCS	Hispanic, Non-Hispanic	814/910
McCullough *et al*. (48)	Fok1, Bsm1, Taq1, Apa1, poly (A)	NCCS	Caucasian	500/500
Prostate cancer				
Bodiwala *et al*. (45)	Fok1, Taq1	CCS	UK	368/243
Cheteri *et al*. (107)	Fok1, Bsm1, poly (A)	PCCS	USA	552/521
Chokkalingam *et al*. (104)	Fok,1 Bsm1	PCCS	Chinese	191/304
Cicek *et al*. (113)	Fok1, Bsm1, Taq1, Apa1, poly (A), Cdx2	FCCS	USA	918
Holick *et al*. (109)	Fok1, Bsm1, Taq1	PCCS	USA	630/565
John *et al*. (47)	Fok1, Taq1, Cdx2, Bgl1	PCCS	USA	450/455
Li *et al*. (114)	Fok1	NCCS	USA	1066/1618
Luscombe *et al*. (103)	Fok1, Taq1	CCS	UK	210/155
Mikhak *et al*. (108)	Fok1, Bsm1, Cdx2	NCCS	USA	649/649
Oakley-Girvan *et al*. (110)	Fok1, Bsm1, Taq1, Apa1, poly (A)	CCS	USA	African–American: 113/121, Caucasian: 232/171
Tayeb *et al*. (106)	Fok1, Taq1	CCS	UK	28/56
Torkko *et al*. (111)	Fok1, Cdx2	CCS	USA	Non-Hispanic Caucasian: 932, Hispanic Caucasian: 414
Xu *et al*. (112)	Fok1	COS	Caucasian	191
Yang *et al*. (105)	Fok1	CCS	Chinese	80/96
Skin cancer				
Han *et al*. (118)	Fok1, Bsm1, Cdx2	NCCS	USA	219 MM, 286 SCC, 300 BCC/873
Hutchinson *et al*. (81)	Fok1, Taq1	HCCS	UK	316 MM/108
Li *et al*. (115)	Fok1, Taq1	HCCS	USA, Non-Hispanic Caucasian	602/603
Li *et al*. (117)	Fok1, Bsm1, Taq1	HCCS	USA, Non-Hispanic Caucasian	805/841
Santonocito *et al*. (116)	Fok1, Bsm1, A-1012G	CCS	Italian	101 MM/101
Colon cancer				
Ingles *et al*. (123)	Fok1, Bsm1	CCS	USA	373/394
Murtaugh *et al*. (82)	Fok1	CCS	USA	1698 colon /1861, 752 rectal/960
Peters *et al*. (120)	Fok1	CCS	USA	239/228
Slattery *et al*. (119)	Fok1, Bsm1, Taq1, poly (A)	PCCS	USA	250/364
Slattery *et al*. (137)	Fok1, Bsm1, poly (A)	PCCS	USA	1174 colon/1174, 785 rectal/1000
Sweeney *et al*. (125)	Fok1, Bsm1, poly (A)	CCS	USA	1811 colon/1451, 905 rectal/679
Wong *et al*. (122)	Fok1	CCS	USA, Singapore Chinese	217/890
Yalim-Eraltan *et al*. (124)	Fok1, Taq1	CCS	Turkish	26/52
Ovarian cancer				
Clendenen *et al*. (126)	Fok1, Bsm1, Taq1, Apa1	CCS	Caucasian	170/323
Lurie *et al*. (86)	Fok1, Bsm1, Taq1, Apa1, Cdx2	CCS	Caucasian, Japanese	313/574 (Caucasian: 72/148, Japanese: 94/173)
Bladder and renal cancer				
Mittal *et al*. (127)	Fok1, Taq1	CCS	Indian	130/346

CCS: Case–control study, PCCS: population-based case–control study, FCCS: family-based case–control study, NCCS: nested case–control study, HCCS: hospital-based case–control study, COS: case only study.

codes for the enzyme 5α-reductase type II that converts testosterone to dihydrotestosterone in the prostate, and their association with prostate cancer (111). The polymorphisms analysed in that study included the *SRD5A2* gene polymorphisms V89L and A49T as well as the Fok1 and Cdx2 polymorphisms of the *VDR* gene. As to the Fok1 polymorphisms, the interaction terms for Fok1 and V89L in the logistic model were significant (p=0.02) and, when stratified by V89L genotype, the Fok1 polymorphism (ff/Ff *versus* FF) was significantly associated with prostate cancer in non-Hispanic white men with the V89L VV genotype (Fok1 OR=1.53, 95%, CI: 1.06-2.23). This result indicates that the *VDR* Fok1 ff/Ff genotype interacts with the *SRD5A2* V89L VV genotype in non-Hispanic white men to increase their risk for prostate cancer.

Xu *et al*. reported that individuals with the ff genotype had a lower mean percentage of Gleason grade 4/5 cancer (30.3%) than those with the FF or Ff genotypes (42.8% and 43.8%, respectively; p=0.015 by t-test for ff *versus* FF + Ff) (112). They concluded that the ff genotype may be associated with more aggressive prostate tumours. A similar conclusion was achieved by Cicek *et al*. showing that the Fok1 FF genotype was inversely associated with prostate cancer among men with less advanced disease (Gleason score <7 and tumour stage <T2c) (OR=0.56, 95%, CI: 0.31-1.01; p=0.05) (113). In some studies, the *VDR* genotype polymorphism was only associated with cancer risk when seen in conjunction with other factors such as sun exposure. John *et al*. associated reduced risk of advanced prostate cancer with high sun exposure (OR=0.51) and high occupational outdoor activity (OR=0.73) (47). They found significant risk reductions with the high-activity alleles Fok1 FF and Ff in the presence of high sun exposure. The findings of that study support the hypothesis that sun exposure and *VDR* polymorphisms together play important roles in the aetiology of prostate cancer. A follow-up study (114) analysed putative associations of prediagnostic plasma levels of 25(OH)D and $1,25(OH)_2D_3$ with total and aggressive disease, as well as exploring whether relations between vitamin D metabolites and prostate cancer were modified by the functional *VDR* Fok1 polymorphism using conditional logistic regression. It was noticed that a large proportion of the US men had suboptimal vitamin D status (especially during the winter/spring season). Men whose levels for both 25(OH)D and $1,25(OH)_2D_3$ were below (*versus* above) the median had a significantly increased risk of aggressive prostate cancer (OR=2.1, 95% CI: 1.2-3.4), although the interaction between the two vitamin D metabolites was not statistically significant (p interaction=0.23). Referring to the Fok1 *VDR* gene polymorphism, a significant interaction was observed between Fok1 and circulating 25(OH)D levels (p interaction <0.05). Compared to those with plasma 25(OH)D levels greater than the median and the Fok1 FF or Ff genotype, men who had low 25(OH)D levels and the less functional Fok1 ff genotype had increased risks of total (OR=1.9, 95%, CI: 1.1-3.3) and aggressive prostate cancer (OR=2.5, 95%, CI: 1.1-5.8). Among men with plasma 25(OH)D levels above the median, the ff genotype was no longer associated with risk. In contradiction to this, among men with the ff genotype, a high plasma 25(OH)D level (> *versus* < median) was related to significantly (60%) lower risk of total and aggressive prostate cancer. In conclusion, an interaction was found between the Fok1 polymorphism and vitamin D status (measured by plasma 25(OH)D) which modifies prostate cancer risk, the ff genotype being more susceptible to prostate cancer in the presence of low 25(OH)D status.

Fok1 and skin cancer. Hutchinson *et al*. found an association of *VDR* Fok1 polymorphisms with an altered risk for MM (p=0.014) (81). Using the Breslow thickness as outcome measure, variant alleles could be associated with increased Breslow thickness including the tt/ff genotype (Taq1 t and Fok1 f) which was found to be associated with tumours thicker than 3.5 mm (OR=31.5, p=0.001). Examining the relationship between the Fok1 polymorphism and CM, the Ff genotype was associated with increased CM risk (OR=1.32) and the Ff + ff genotypes with a borderline significantly higher risk (OR=1.26) compared to the FF genotype (115).

The suggestion that the f allele may be a risk allele for skin cancer was not confirmed by several other recent studies (116: MM, 117: CM, 118: MM, BCC, SCC). Santonocito *et al*. found no association between the Fok1 genotype frequency and MM along with Breslow thickness (116). Li *et al*. stated that the Fok1 polymorphism is not an independent risk factor but interacts with skin colour (p=0.029), moles (p=0.017) and number of first-degree relatives with any cancer (p=0.013) in modifying melanoma risk (117). Associations of haplotype combinations including Fok1, Taq1 and Bsm1 polymorphisms with melanoma risk and their interaction with known risk factors were also analysed by Li *et al*. (117). Only the combined genotypes TT/Bb + BB/Ff + ff (adjusted OR=2.35) were associated with increased risk when compared to TT/bb/Ff + ff genotypes. On the other hand, the haplotype combinations tBF (adjusted OR=0.52) and tBf (adjusted OR=0.51) were associated with a 50% risk reduction when compared to Tbf. Furthermore, the combined genotypes Tt + tt/Bb + BB/Ff + ff (adjusted OR=0.69) and Tt + tt/Bb + BB/FF (adjusted OR=0.58) were associated with risk reduction for MM. In conclusion, *VDR* polymorphisms may directly affect or modify the risk associated with known melanoma risk factors.

Fok1 and colon cancer. Analysing a putative association of the *VDR* polymorphism Fok1 and colorectal cancer risk, results of recent studies are controversial (see Table I). Two studies did not find a significant association of the Fok1 variant and colon cancer risk (119-120). However, in one of these studies, an inverse association of serum 25(OH)D levels with colorectal adenoma was observed (120). It was shown that with each 10 ng/ml increase of serum 25(OH)D, the risk of colorectal adenoma decreased by 26% (OR=0.74, 95% CI: 0.60-0.92). This was considered as evidence for a weak association between calcium intake and colorectal adenoma (OR=0.97 per each 100 mg calcium intake). However, the effect of vitamin D and calcium was not modified by the Fok1 polymorphism in this study. Slattery *et al*. analysed associations between BMI, energy intake, energy expenditure, *VDR* Fok1 genotype and colorectal cancer (121). The ff genotype was observed to be associated with >2-fold greater risk of colon cancer for obese people (OR=2.62, 95% , CI: 1.15-5.99; *p* interaction=0.12) and with >3-fold greater risk of colon cancer in people who were not physically active (OR=3.46, 95% CI: 1.58-7.58; *p* interaction=0.05). In that study, a significant interaction could be stated between Fok1 polymorphism and energy intake (*p* interaction=0.01 for colon cancer and *p* interaction=0.04 for rectal cancer) modifying together colorectal cancer risk. Another study (122), which was limited to a Singapore Chinese population, also associated the Fok1 variant with increased cancer risk. In this study, the Ff genotype was associated with a 51% increase in risk of colorectal cancer and the ff genotype with an 84% increase in risk. Furthermore, the effect of the *VDR* genotype on risk seemed to be modified by dietary calcium and fat intake, the ff genotype having a 2.5-fold increased risk among those with either low calcium or low fat intake. The fact of a relation between the Fok1 polymorphism and adenoma risk among those with low dietary vitamin D intake as well as with low dietary calcium intake was reported in 2001 (123). In that study, adenoma risk was not significantly related to Fok1 polymorphism, but compared to the FF genotype, the Ff and ff genotypes were associated with lower risk of large adenomas (OR=0.79 and OR=0.32, respectively). Murtaugh *et al*. observed that the lowest colon cancer risk was associated with Ff/ff genotypes and a low sucrose-to-fibre ratio, whereas rectal cancer risk was increased by red meat consumption and FF genotype (82). In a small Turkish study, the frequencies of the FF, Ff and ff genotypes in colorectal cancer patients were 73.1% , 11.5% and 15.4% whereas the control group had frequencies of 38.5% , 59.6% , and 1.9% , respectively (124). A study estimating haplotypes with regard to colon and rectal cancer associated the common haplotype bLF (Bsm1 b, poly (A) L and Fok1 F) (OR=1.15) and the less frequent haplotype BLF (OR=2.4) with an increased risk of colon cancer, whereas no case–control differences were noticed with regard to rectal cancer (125).

The number of individuals with TT/Ff or Tt/Ff genotype in colorectal cancer patients was very low compared with all other genotypes (OR=0.112, 95% , CI: 0.03-0.42) (125). These data suggest that *VDR* Tt/Ff or TT/Ff genotype may protect against colorectal carcinogenesis. However, further studies are necessary to confirm these findings.

Fok1 and ovarian cancer. Ovarian cancer has just recently been analysed with respect to an association between cancer susceptibility and *VDR* polymorphism. Lurie *et al*. reported a 2.5-fold increased risk of ovarian carcinoma for Caucasian heterozygous carriers of the Fok1 f allele (OR=2.5) compared to homozygous carrier of the common allele F (86). However this association was not observed in other ethnic groups. Moreover, this result was not confirmed by another recent study which examined mostly Caucasian women (126).

Fok1 and bladder cancer. With regard to bladder cancer and VDR polymorphisms, there are still very few data published. An Indian study reported a significant difference in genotype frequencies of *VDR* Fok1 polymorphisms between patients and controls (p=0.033) (127). The genotype FF had a 2-fold increased risk of bladder cancer (OR=2.042). It has also been investigated whether *VDR* polymorphisms were associated with particular clinical/pathological characteristics of the patients as well as with smoking status but no significant association was observed. Analysing the relationship between haplotypes including the Fok1 and Taq1 *VDR* polymorphisms, it has been noticed that the genotype combinations FT and ft are associated with lower risk of developing bladder cancer than those with other haplotypes. In conclusion, these data suggest that there may be an association between *VDR* Fok1 polymorphism and risk of bladder cancer.

Summary: Fok1 and cancer (Table I). Fok1 is the *VDR* polymorphism which has been most frequently analysed with the aim of finding an association with various types of cancer. To date, results are controversial. Overall, there are a great number of studies which report a significant association between the Fok1 polymorphism and the risk of various types of cancer (breast cancer (101), prostate cancer (112-114), MM (117), ovarian cancer (86)) and even a larger group which did not observe any significant associations (breast cancer (44, 46, 48, 96-100), prostate cancer (102-109), MM (116), MM, BCC, SCC (118)).

These discrepancies may be due to various reasons such as a limited number of cases, or the analysis of different ethnic groups. An example is the significant increase of prostate cancer risk which was found for African–Americans with the ff genotype but not for US Caucasians with the same genotype (110). Moreover, some studies indicate that the

Fok1 polymorphism cannot be regarded as an independent prognostic factor. In a huge US study, the Fok1 polymorphism interacted with the vitamin D status (measured by plasma 25(OH)D) and modified prostate cancer risk in such a way that those with the ff genotype are more susceptible to prostate cancer in the presence of low 25(OH)D status (114). In other studies, *VDR* Fok1 polymorphism is only associated with cancer risk when seen in conjunction with other factors such as sun exposure or high occupational outdoor activity (47).

Similar associations can made for skin cancer, where the Fok1 polymorphism seems to interact with MM risk factors such as skin colour and moles in modifying melanoma risk (115). With regard to colon cancer occurrence, there is a relationship between *VDR* genotype and factors related to energy balance such as obesity and high energy intake in modifying colorectal cancer risk (121).

Interestingly, even though some studies were unable to demonstrate any importance of Fok1 polymorphism as an independent cancer risk factor, an association with cancer risk was demonstrated when the Fok1 polymorphism was analysed together with other *VDR* polymorphisms in haplotype combinations. In several types of cancer, various haplotypes containing the Fok1 polymorphism were associated with increased or reduced cancer risk, whereas the Fok1 polymorphism as independent factor showed no significant association (45, 97, 117, 125, 127).

Concerning the importance of the *VDR* Fok1 polymorphism for cancer prognosis, it can be stated that some studies report an association of the ff genotype with more aggressive tumour behaviour (prostate cancer (112, 113, 117)). However, these findings are too preliminary to allow definite conclusions.

In conclusion, it can be suggested that the importance of Fok1 polymorphisms for cancer risk and prognosis may strongly depend on additional factors including *VDR* haplotype combinations, other genetic factors (*SRD5A2* polymorphism, *CYP27B1* polymorphism), 25(OH)D serum level, calcium intake, sun exposure, adiposity, smoking and other cancer-specific risk factors.

Bsm1 Polymorphism and Cancer

Bsm1 and breast cancer. With respect to breast cancer risk, a strong tendency for an association between the bb genotype and increased breast cancer risk has been reported. A great number of studies support this statement (96-98, 128, 129). Trabert *et al*. reported a 1.5-fold increased risk of breast cancer for postmenopausal carriers of the bb genotype among Caucasians (OR=1.53) but not among African–American women. The association between the Bsm1 genotype and breast cancer risk was modified by smoking status, whereas it did not significantly vary with oral contraceptive use, hormone replacement therapy, or body mass index. Similar results were achieved by Guy *et al*., who reported a 1.8-fold increased risk among Caucasian women with the bb genotype (OR=1.79) (98). Moreover, over 70% of seven commonly used breast cancer cell lines were found to have the high-risk bb genotype. In 2004, Guy *et al*. reported a nearly 2-fold increased risk for the bb genotype (OR=1.92) (97). Another study (96) reported that the Bsm1 polymorphism is in LD with the poly (A) sequence in the 3' untranslated region and also observed a significant association between the bb genotype and breast cancer risk (OR=2.32). No statistically different distribution of the Bsm1 polymorphism distribution in the case and control group was observed by Ruggiero *et al*. (129), but the metastatic cancer group showed a >2-fold higher prevalence of the bb genotype (14/38, 37%) than did the control group, and the percentage of the BB women with metastases was half in the control group (2/38, 5%). Women who were homozygous bb appeared to have almost a four-fold higher risk of developing metastases than BB women. These with 25(OH)D levels <50 nM and the bb Bsm1 *VDR* genotype were 6.82 times more likely to have breast cancer than those with levels of 25(OH)D >50 nM and either BB or Bb genotype (49). However, another study found no significant association between the Bsm1 polymorphism and breast cancer risk (130), but this study included only a limited number of cases (*i.e*. 78) of Turkish origin. In contrast to the results achieved by the previously mentioned studies, three other studies referring to Caucasian women (48), Taiwanese women (131) and Latinas (100) associated the BB genotype with increased breast cancer risk. Ingles *et al*. reported that compared to the bb genotype, the Bb and BB genotypes had a 1.6-fold and 2.2-fold increased breast cancer risk, respectively (OR=1.6, OR=2.2, respectively) (100). In the study of Hou *et al*. (131), the Bsm1 B allele was associated with increased breast cancer risk. Moreover, when the allelic frequencies of Bsm1 polymorphism were compared among the three populations, a significant difference was observed (p=0.0084). McCullough *et al*. did not associate the Bsm1 polymorphism directly with breast cancer risk (48). Women with the bb genotype who consumed more than the median intake of total calcium (≥902 mg/day) were observed to have lower odds of breast cancer compared to women with the Bb or BB genotype and less than the median calcium intake (OR=0.61, p interaction=0.01).

Bsm1 and prostate cancer. The meta-analysis published by Ntais *et al*. showed no evidence that the B allele modified the risk of prostate cancer (37). No clear effect was seen for the BB genotype compared to the bb genotype. 987 patients with prostate cancer and 1504 controls with genotype data of Bsm1 were included. The prevalence of the B allele in those of the control group was 41% (European descent) and 14% (Asian descent). The overall prevalence of BB homozygosity (Bb heterozygosity) was 15% (51%) in European controls and 3% (22%) in Asian controls.

In one study, heterozygosity or homozygosity for the absence of the Bsm1 restriction site was associated with strongly reduced risk of prostate cancer (OR=3.31, $p<0.0001$) as well as with 50% reduced risk of benign prostate hyperplasia (BPH) (OR=2.07, $p<0.005$) when compared to the male controls (132). The authors concluded that the Bsm1 polymorphism in the *VDR* gene plays a significant role in protecting against prostate cancer and BPH. However, because the strength of the linkage disequilibrium between the three polymorphisms Bsm1, Apa1, Taq1 varies among ethnic groups, they deemed that additional studies are necessary to support this statement.

The results of other studies concerning Bsm1 and prostate cancer are controversial. Some studies found no association between Bsm1 and prostate cancer risk (109, 110, 133, 134). The study of Chaimuangraj *et al*. analysed a Taiwanese population (134) and the study of Liu *et al*. referred exclusively to a Northern Chinese Han population (133). They suggested that one reason for the racial difference in prostate cancer risk might be due to variations in the distribution of Bsm1 in different ethnic populations. As mentioned before, Mikhak *et al*. were unable to demonstrate a general association between the studied SNPs and all prostate cancer subtypes but they did find associations of haplotype 2 (Afb) with Cdx2 A, Fok1 f, and Bsm1 b alleles and of haplotype 3 (AFB) with Cdx2 A, Fok1 F and Bsm1 B alleles compared to the most common haplotype (AFb) with reduced risk of aggressive prostate cancer (high stage or Gleason sum ≥7, $p=0.02$) (108). In another study analysing a Taiwanese population, the control group was found to have a significantly higher frequency of the Bsm1 BB and Bb genotypes (15.6%) as compared to prostate cancer patients (8.1%) (135). BB and Bb genotypes were associated with a 2-fold decreased risk (OR=0.50, $p=0.045$) for developing prostate cancer as compared to bb genotypes. Moreover, the associations were stronger in advanced stages (T3/T4/N1/M1) and in poorly differentiated disease (Gleason score ≥7) (BB *versus* bb: OR=0.25, $p=0.024$ and Bb *versus* bb: OR=0.25, $p=0.026$). Another study, analysing a US Caucasian population (107) reported that polymorphisms in the *VDR* gene were not strong predictors of prostate cancer risk. In that study, only a modest increase in risk (OR=1.49, $p=0.04$) was associated with the bb genotype as compared to the BB genotype. In contrat to this study, a study analysing an African–American population reported an association of the b allele with a 2-fold decrease in risk of advanced prostate cancer (77). However, this association was confined to haplotypes carrying a long (L) allele of the poly (A) microsatellite (BL haplotype: increased risk; bL haplotype: reduced risk) and was not associated with the BS or bs haplotypes. In conclusion, none of the studies included in this meta-analysis were able to demonstrate a strong association between the *VDR* gene Bsm1 polymorphism and prostate cancer risk, except the study of Huang *et al*. (135) which was, however, limited to a Taiwanese population.

Bsm1 and skin cancer. Analysing the putative relevance of the Bsm1 polymorphism for skin cancer risk, interesting findings are reported in the literature. Significant associations were found between the Bsm1 bb genotype frequency and the tumour thickness (Breslow) of MM ($p=0.001$) (116). This result was confirmed by multivariate logistic regression analysis. Analysing SCC, the BB genotype was significantly associated with increased cancer risk (OR=1.51) (118). Moreover, an interaction between the Bsm1 polymorphism and total vitamin D intake was observed in SCC patients, with >2-fold higher risk seen in women with the BB genotype and high vitamin D intake (OR=2.38, p interaction=0.08) (118).

Bsm1 and colorectal cancer. Most of the studies investigating the Bsm1 *VDR* gene polymorphisms in patients suffering from colorectal cancer associated the BB genotype with reduced risk of colon cancer (119, 136). In the study of Slattery *et al*. (119), a 50% colon cancer risk reduction (OR=0.5) was observed for the BB genotype. The study of Kim *et al*. (136) reported an OR of 0.77 for BB, which indicates a 23% reduction in the risk of colon cancer. In this study however, the risk of colorectal cancer was lowest in patients with the BB genotype and the lowest vitamin D (OR=0.24) and calcium ingestion. This surprising result is in conflict with the generally accepted fact that higher ingestion of calcium and vitamin D may be associated with a reduced risk of colorectal cancer, as shown in a study of Slattery *et al*. (137). High levels of calcium intake were associated with reduced risk of rectal cancer in women (OR=0.39) but not in men (OR=1.02). Furthermore, other positive effects on cancer risk were reported in this study for patients with high levels of vitamin D (OR=0.52), consumption of low-fat dairy products (OR=0.61) and high levels of sunshine exposure (OR=0.62 for men diagnosed when <60 years). Interestingly, a 40% rectal cancer risk reduction for persons with low calcium intake was found in one study in the BB genotype group (137). With regard to colon cancer, high levels of dietary intake of calcium, vitamin D and low-fat dairy products showed a protective effect for the BB genotype. In a study published in 2004 by Slattery *et al*. (137), the BB genotype was associated with a higher risk for colon cancer in obese individuals (OR=3.50). However, it was suggested that the energy intake is more important for the occurrence of colon cancer than Bsm1 genotype. In 2006, a Bulgarian study (138) reported a 1.8-fold increased risk for colorectal carcinoma among bb carriers (OR=1.8). A previously mentioned study reported an association between the haplotypes bLF and BLF and increased colon cancer risk (125). However, no association was found analysing the Bsm1 polymorphism alone because both alleles (b and B) were associated with increased risk depending on the haplotype combination.

Bsm1 and ovarian cancer. Bsm1 B allele carriers among Caucasian and Japanese women were found to be at higher risk of developing ovarian cancer, but this association was not statistically significant (86). Moreover, the distribution of the Bsm1 polymorphism alleles did not match the Hardy-Weinberg equilibrium, because the B allele was strongly underrepresented in Japanese and other Asian women (p=0.001). In a more recent analysis, Clendenen *et al.* (126) found no association between the Bsm1 RFLP and epithelial ovarian cancer occurrence.

Bsm1 and RCC. The only study analysing the importance of the Bsm1 polymorphism for RCC did not find any statistically significant association between any Bsm1 variants and renal cell carcinoma risk (139). However, further studies are required to confirm these data.

Summary: Bsm1 and cancer (Table II). The importance of the *VDR* Bsm1 polymorphism seems to vary among the studied types of tumours. Numerous studies did associate the Bsm1 polymorphism with cancer risk (breast cancer (49, 96-98, 100, 128, 129, 131), prostate cancer (107, 132, 135), ovarian cancer (86), MM (116), colon cancer (119, 137), colorectal cancer (136, 138)) but other studies report no association with cancer risk (breast cancer (130), prostate cancer (109, 110, 133, 134), ovarian cancer (126), RCC (139)).

There is strong evidence that the Bsm1 bb genotype is associated with increased breast cancer risk (96-98, 128, 129). However, this association may be influenced by other risk factors such as smoking status (128). Concerning the importance of the Bsm1 polymorphism for cancer prognosis, one study reported that women who were homozygous bb appeared to have almost a four-fold higher risk of developing metastases than did BB women (129). Since this study was limited to a small number of cases (88 cases/167 controls) but nevertheless achieved a highly statistically significant result, the coherence between the bb genotype and worse prognosis should also be analysed by other larger studies.

Moreover, the influence of the Bsm1 polymorphism varies among different ethnic groups. A huge US study observed that the bb genotype was associated with increased risk of breast cancer for postmenopausal carriers of the bb genotype among Caucasians but not among African–American women (128). The racial difference in cancer risk might be due to variations in the distribution of the Bsm1 polymorphism in different ethnic populations (134).

In contrast to the clear association of the bb genotype with increased breast cancer risk, none of the studies which analysed the Bsm1 polymorphism with regard to prostate cancer risk were able to demonstrate a similar strong association (37).

With regard to colorectal cancer, the BB genotype was mostly associated with a reduced risk of colon cancer (119, 136). Interestingly, vitamin D and calcium intake seem to influence the colorectal cancer risk. But the results are controversial. Whereas one study observed that the risk of colorectal cancer was lowest in patients with the BB genotype and the lowest vitamin D and calcium intake (136), Slattery *et al.* (137) claimed that higher intake of calcium and vitamin D may be associated with a reduced risk of colorectal cancer. Moreover, in one huge US study (2306 cases/2749 controls) high levels of calcium intake were associated with reduced risk of rectal cancer in women but not in men (137). Therefore, when analysing the *VDR* genotype, differences in gender should be taken into consideration.

As for skin cancer, ovarian cancer and RCC, results are still limited to smaller studies. The Bsm1 bb genotype was observed to be associated with thicker tumour thickness (Breslow) and therefore with worse prognosis in MM (116), whereas the BB genotype, especially together with high vitamin D intake, seems to be associated with increased SCC risk (118). As for ovarian and RCC, there was no significant association.

Another aspect that should be kept in mind is the strong LD between the three RFLPs Bsm1, Apa1 and Taq1 [frequent haplotypes: haplotype 1 (baT 48%) and haplotype 2 (BAt: 40%)] which may lead to a mutual influence in terms of occurrence and prognosis of cancer.

Taq1 Polymorphism and Cancer

Taq1 and breast cancer. Most studies published in the literature report no significant association between the Taq1 SNP and susceptibility to breast cancer (46, 48, 130, 131, 140-142). However, Sillanpää *et al.* (142) observed a tendency towards a decreasing risk of breast cancer for genotypes containing the T allele (Tt and TT) (OR=0.68). Unfortunately, the potential impact of the Taq1 polymorphism could not be assessed properly because the distribution of Taq1 alleles in the controls was not in Hardy-Weinberg equilibrium (p=0.01).

Several studies analysed the interaction of the Taq1 polymorphism with other risk factors such as calcium intake. It was reported that women with the TT genotype who consumed more than 902 mg total calcium a day (corresponds to the medium intake) had lower odds of breast cancer compared to women with the tt or Tt genotype and less than the median calcium intake (48). In conclusion, these findings support the concept that dietary factors may influence the association of *VDR* genotypes with cancer risk. Interestingly, a case–control study which analysed Australian women found a trend for the Taq1 RFLP to be associated with an approximately 1.5-fold increased breast cancer risk (99). In a very recent study, the Taq1 RFLP was associated with a significantly increased risk for ER-positive tumours (OR=1.18) comparing t allele carriers with non-carriers but not for ER-negative tumours (OR=0.88, p for interaction=0.04) (44).

Table II. *Bsm1 polymorphism and cancer.*

Reference	Polymorphism	Study type	Study population	Cases/Controls
Breast cancer				
Bretherton-Watt *et al*. (96)	Bsm1, Fok1, poly (A)	CCS	Caucasian	181/241
Buyru *et al*. (130)	Bsm1, Taq1	CCS	Turkish	78/27
Guy *et al*. (98)	Bsm1, Fok1	CCS	Caucasian	313/410
Guy *et al*. (97)	Bsm1, Fok1, poly (A)	CCS	Caucasian	398/427
Hou *et al*. (131)	Bsm1, Taq1, Apa1, Taq1	CCS	Taiwanese	80/169
Ingles *et al*. (100)	Bsm1, Fok1, poly (A)	CCS	Latinas	143/300
Lowe *et al*. (49)	Bsm1	CCS	Caucasian	179/179
McCullough *et al*. (48)	Bsm1, Fok1, Taq1, Apa1, Taq1, poly (A)	NCCS	Caucasian	500/500
Ruggiero *et al*. (129)	Bsm1	CCS	Italian	88/167
Trabert *et al*. (128)	Bsm1, poly (A)	PCCS	Caucasian, African–American	1631/1435
Prostate cancer				
Chaimuangraj *et al*. (134)	Bsm1, Taq1, Apa1, Taq1	CCS	Asians	28/30;, 44 BPH
Cheteri *et al*. (107)	Bsm1, Taq1, poly (A)	PCCS	USA	559/523
Chokkalingam *et al*. (104)	Bsm1, Fok1	CCS	Chinese	191/304
Habuchi *et al*. (132)	Bsm1, Taq1, Apa1, Taq1	CCS	Asian	222/337
Holick *et al*. (109)	Bsm1, Fok1, Taq1	PCCS	USA	630/565
Huang *et al*. (135)	Bsm1, Taq1, Apa1, Taq1	CCS	Taiwanese	160/205
Ingles *et al*. (77)	Bsm1, poly (A)	CCS	USA	151/174
Liu *et al*. (133)	Bsm1	CCS	Chinese	103/106
Ma *et al*. (54)	Bsm1, Taq1	CCS	USA	372/591
Mikhak *et al*. (128)	Bsm1, Fok1, Cdx2	NCCS	USA	619/619
Nam *et al*. (157)	Bsm1	CCS	Canadian	483/548
Oakley-Girvan *et al*. (110)	Bsm1, Fok1, Taq1, Apa1, poly (A)	CCS	USA	African–Americans: 113/121; Caucasian: 232/171
Suzuki *et al*. (146)	Bsm1, Taq1, Apa1	CCS	Japanese	81/105
Skin cancer				
Han *et al*. (118)	Bsm1, Fok1, Cdx2	NCCS	USA	219 MM, 286 SCC, 300 BCC/873
Li *et al*. (117)	Bsm1, Fok1, Taq1	HCCS	USA, Non-Hispanic Caucasian	805/841
Santonocito *et al*. (116)	Bsm1, Fok1, A-1012G	CCS	Italian	101 MM/101
Colon cancer				
Kadiyska *et al*. (138)	Bsm1	CCS	Bulgarian	140/94
Kim *et al*. (136)	Bsm1	HCCS	USA	393/406
Slattery *et al*. (119)	Bsm1, Fok1, Taq1, poly (A)	PCCS	USA	250/364
Slattery *et al*. (137)	Bsm1, poly (A)	CCS	USA	2306/2749
Slattery *et al*. (121)	Bsm1, Fok1, poly (A)	PCCS	USA	1174 colon/1174, 785 rectal/1000
Sweeney *et al*. (125)	Bsm1, Fok1, poly (A)	CCS	USA	1811 colon/1451, 905 rectal/679
Ovarian cancer				
Clendenen *et al*. (126)	Bsm1, Fok1, Taq1, Apa1	CCS	Caucasian	170/323
Lurie *et al*. (86)	Bsm1, Fok1, Taq1, Apa1, Cdx2	CCS	Hawai: Caucasian, Japanese	313/574 (Caucasian: 72/148; Japanese: 94/173)
Bladder and renal cancer				
Obara *et al*. (139)	Bsm1, Taq1, Apa1	CCS	Japanese	135/150

CCS: Case–control study, PCCS: population-based case–control study, NCCS: nested case–control study, HCCS: hospital-based case–control study.

Haplotype analysis revealed that the haplotype FtCA (Fok1 F, Taq1 t, VDR-5132 C, Cdx2 A) was associated with a significantly greater breast cancer risk compared to the most frequent haplotype FTCG (OR=1.43). Finally, in another study (141) patients without the Taq1 RFLP (TT genotype) showed a significant increased risk for lymph node metastasis (OR=1.8). On the other hand, among patients with the tt genotype, a tendency toward increased survival was noticed among ER-positive, tamoxifen-treated patients. The authors concluded that the *VDR* gene may

influence tumour progression and tamoxifen treatment response in early-onset breast carcinomas (141).

Taq1 and prostate cancer. Inherited polymorphisms in the 3' untranslated region of the *VDR* gene including the Taq1 SNP have been associated with the risk and progression of prostate cancer in some populations. According to the meta-analysis performed by Ntais *et al*. (37), the frequency of the t allele is higher among controls of European (40%) and African descent (37%) than among controls of Asian descent (14%). Overall the prevalence of tt homozygosity (T/t heterozygosity) was 17% (48%), 18% (39%) and 3% (18%) in controls of European, African and Asian descent, respectively. Most of the studies in the meta-analysis did not associate the Taq1 SNP with prostate cancer risk (45, 54, 67, 68, 89, 103, 109, 110, 132, 134, 135, 143-148). In the study of Ma *et al*. (54) neither the Taq1 T nor the poly (A) L allele were statistically significantly associated with more advanced disease (Taq1: OR=2.5, poly (A): OR=2.8). Because exposure to UVR may influence the impact of *VDR* polymorphisms, Bodiwala *et al*. studied associations of variants with prostate cancer risk in men divided into low (<median) and high (>median) cumulative UVR exposure/year (45). The group found no association for the Taq1 genotype. However, the genotype combinations GG/TT (Cdx2 GG, Taq1 TT) (p=0.022, OR=0.30) and FF/TT (Fok1 FF, Taq1 TT) (p=0.026, OR=0.35) were associated with reduced prostate cancer. Interestingly, some studies associated the Taq1 RFLP with prostate cancer risk (102, 106, 149, 150). Taylor *et al*. demonstrated a higher percentage of the homozygous tt genotype in the Caucasian control group (22%), whereas this genotype was present only in 8% of the prostate cancer patients (p<0.01) (149). A similar, but statistically less significant trend was found among the small number of blacks included in that study (13% for controls, 8% for cases). Race-adjusted combined analysis suggested that men with the tt genotype have only a risk of 30% for developing prostate cancer with required prostatectomy compared to men with the TT or Tt genotype (OR=0.34, p<0.01). These results were confirmed by Tayeb *et al*. (106). In that study, 89% of the case group had a TT genotype, whereas only 57% of the control group had this genotype (OR=5.16). Another study (150) also showed an association of the T allele with prostate cancer risk (OR=1.87, p=0.035). This association was confirmed by using logistic regression analysis (OR=2.11, p=0.015) and was strongest in men >66 years (OR=2.36). This was confirmed by analysing prostate cancer patients with a poor prognosis, demonstrating that they less frequently have the TT genotype (p=0.03) (151). Contrary to this result, an association was shown between prostate cancer risk and the Tt genotype (OR=0.5, p=0.026) which was even stronger for patients ≤70 years (OR=0.31, p=0.001) (102). The risk alleles in that study were the S allele (poly (A)) and the t allele (Taq1). In the study of Onsory *et al*. (152) the odds ratio of the Taq1 tt genotype with regard to prostate cancer risk was 0.43 (95% CI: 0.13-1.39) and for the Tt genotype 0.65 (95%; CI: 0.36-1.16), which indicates a reduced risk of prostate cancer for these two genotypes.

Taq1 and skin cancer. There are still few data concerning the effect of the Taq1 polymorphism on skin cancer occurrence and outcome. Hutchinson *et al*. did not demonstrate a correlation between the Taq1 polymorphism and altered susceptibility for MM (81). However, homozygosity for variant alleles at the Taq1 and Fok1 restriction sites were significantly associated with higher Breslow thickness (OR=31.5). A more recent study suggested that the Taq1 t allele may be associated with a reduced risk for MM (115). The Tt genotype and the Tt/tt genotypes were associated with a 30% reduced melanoma risk (OR=0.70) as compared with the TT genotype (115). Moreover, the Taq1 polymorphism has been shown to be an independent risk factor for melanoma by multivariate analysis (117).

Taq1 and colon cancer. Analysing colon cancer risk, it has been shown that the Taq1 tt variant, which is in LD with the poly (A) SS and Bsm1 BB RFLPs, is associated with reduced risk of colon cancer (OR=0.5) (119). However, further studies are required to confirm this result. In a Turkish study, colorectal cancer patients with the TT genotype had lower serum 25(OH)D levels as compared to patients with Tt/tt genotypes (p=0.016) (124). Moreover, the frequency of individuals with TT/Ff or Tt/Ff genotype in colorectal cancer patients was very low compared with all other genotypes (OR=0.112), which leads to the conclusion that the *VDR* genotypes Tt/Ff and TT/Ff may protect against colorectal carcinogenesis.

Taq1 and ovarian cancer. Lurie *et al*. reported a strong LD (Taq1, Apa1, Bsm1) among Caucasian and Japanese women (86). However, this LD was weaker among other ethnic groups. The Taq1 t allele was observed to be more frequent among Caucasian and Japanese women with ovarian cancer, but this association was statistically not significant. In a more recent investigation no association of the Taq1 variant with susceptibility for ovarian cancer was found (126).

Taq1 and RCC. In a Japanese study, the TT genotype was statistically 2.5-fold more frequent among RCC patients than in the control group (OR=2.54) (153). Moreover, the occurrence of the genotype TT was noticed to be significantly higher in patients with rapid-growth type (92.1%) compared to patients with slow-growth type (73.4%) (OR=4.22, p=0.0175). In conclusion, it was suggested that the TT genotype plays an important role in

determining the risk of developing more aggressive RCC in Japanese. However, in a recent study (139), also analysing a Japanese population, no statistically significant difference was found. In summary, further studies are needed to draw a definite conclusion about the importance of Taq1 polymorphisms for risk of RCC.

Taq1 and bladder cancer. Analysing the Taq1 polymorphism in bladder cancer, there was no significant difference in genotype distribution or allelic frequencies in patients with bladder cancer compared to healthy individuals. However, present data are still very limited.

Summary: Taq1 and cancer (Table III). In the majority of studies, there was no association of the *VDR* Taq1 polymorphism with cancer occurrence (breast cancer (46, 130, 131, 140, 142), prostate cancer (45, 54, 67, 68, 89, 103, 109, 110, 132, 134, 135, 143-148), MM (81), ovarian cancer (126), RCC (139)). However, associations with cancer risk and prognosis have been reported (breast cancer (44, 48, 99, 141), prostate cancer (102, 106, 149, 150, 152), MM (115), colorectal cancer (119, 124), ovarian cancer (86), RCC (153)).

The Taq1 polymorphism was shown to be influenced by dietary factors such as calcium intake (breast cancer (48)). Women with the tt genotype who consumed more than 902 mg total calcium a day had lower odds of breast cancer (48). Moreover, the *VDR* Taq1 polymorphism was mentioned several times in conjunction with cancer prognosis (breast cancer (44, 141), RCC (153)). For breast cancer, the Taq1 t allele was associated with ER-positive tumours (44) and the tt genotype with an increased survival in ER-positive, tamoxifen-treated patients (141). The protective role of the t allele can be stressed by its association with reduced risk of MM (115, 117) and colon cancer (119). On the other hand, the TT genotype was associated with increased risk of lymph node metastasis in patients with breast cancer (141) and in patients with rapid-growth type of RCC (153). Furthermore, there is a tendency for the Taq1 T allele to be associated with increased prostate cancer risk (106, 149, 150). A possible explanation might be that the T allele was associated with lower circulating levels of active vitamin D (52, 54, 124).

In conclusion, the *VDR* Taq1 RFLP appears to be associated with cancer risk and prognosis, with the T allele as risk allele and the t allele as protective allele.

Apa1 Polymorphism and Cancer

Apa1 and breast cancer. The Apa1 polymorphism was analysed in only a few studies with regard to breast cancer occurrence and outcome. Curran *et al*. observed that the Aa and aa genotypes were significantly associated with increased breast cancer risk (OR=1.56, p=0.016) (99). However, conflicting results were reported in a Taiwanese study (131), showing a trend for increasing breast cancer risk for the AA genotype, while the Aa genotype tended to be associated with reduced risk (OR for Aa genotype=0.333, OR for aa genotype=0.515). Furthermore, a statistically significant difference in the Apa1 genotype distribution between cases and controls was observed by a Finnish study (142). The AA genotype was more common in women with breast cancer, whereas the lowest risk of breast cancer was seen in women with the aa genotype (OR=0.03) (142). Moreover, women with the Apa1 a allele showed a decreased risk for breast cancer (OR=0.73) compared to the AA genotype, especially when they had a positive family history of breast cancer (OR=0.14) (142).

Apa1 and prostate cancer. Only a few studies have examined the possible association of the Apa1 RFLP with prostate cancer risk. But all of these studies found no association between the Apa1 polymorphism and prostate cancer risk (110, 132, 134, 135, 147). However, a recent study by Cicek *et al*. (113) analysed the possible association of the *VDR* gene polymorphisms Fok1, Bsm1, Apa1, Taq1, and the poly (A) microsatellite with prostate cancer risk. A weak inverse association with disease (OR=0.64, 95% CI: 0.39-1.03, p=0.06) was shown for patients carrying one or two copies of the Apa1 A allele (113). This association was strengthened in Caucasian men with more advanced disease (OR=0.44, 95% CI: 0.21-0.93, p=0.03). Moreover, the haplotype FBAt (Fok1 F, Bsm1 B, Apa1 A, Taq1 t) was associated with a 50% prostate cancer risk reduction (OR=0.48, p=0.002) whereas the fbaT haplotype (Fok1 f, Bsm1 b, Apa1 a, Taq1 T) was associated with a 40% risk reduction (OR=0.60, p=0.03) (113). Interestingly, these risk reductions were even stronger among men with more advanced disease. For men with the genotype FBAt, the OR was 0.31 (p=0.0008), while for men with the genotype fbaT, the OR was 0.32 (95% CI: 0.16-0.64, p=0.001).

Apa1 and ovarian cancer. It has been shown that heterozygous and homozygous Apa1 A allele carriers among Caucasian women (72 cases and 148 controls) have a nearly 3-fold higher ovarian carcinoma risk than homozygous carrier of the Apa1 a allele (OR=2.8 for Aa and OR=3.4 for AA) (86). Moreover, the bb/Aa/TT and BB/AA/tt genotypes with the Apa1 A allele have also been shown to be associated with a higher ovarian carcinoma risk as compared to the most common bb/aa/TT genotype (86). This association has also been reported among Japanese women. In contrary to these significant results, another recent study in Caucasian women did not confirm this association (126).

Apa1 and RCC. A Chinese study analysed the association between Apa1 polymorphism and RCC (139). The authors observed significant differences in the presence of the Apa1

Table III. *Taq1 polymorphism and cancer.*

Reference	Polymorphism	Study type	Study population	Cases/Controls
Breast cancer				
Abbas *et al*. (44)	Taq1, Fok1, Cdx2, VDR-5132	PCCS	German	1408/2612
Buyru *et al*. (130)	Taq1, Bsm1	CCS	Turkish	78/27
Curran *et al*. (99)	Taq1, Fok1, Apa1	CCS	Australian	135/110
Dunning *et al*. (140)	Taq1	CCS	Caucasian	951/627
Hou *et al*. (131)	Taq1, Bsm1, Apa1	CCS	Taiwanese	80/169
John *et al*. (46)	Taq1, Fok1, Bgl1	CCS	Hispanic, Non-Hispanic	814/910
Lundin *et al*. (141)	Taq1	CCS	Swedish	111/130
McCullough *et al*. (48)	Taq1, Fok1, Bsm1, Apa1, poly (A)	NCCS	Caucasian	500/500
Sillanpää *et al*. (142)	Taq1, Apa1	CCS	Finnish	483/482
Prostate cancer				
Andersson *et al*. (89)	Taq1	CCS	Swedish	137/176
Blazer *et al*. (68)	Taq1, poly (A)	CCS	USA	Whites: 70/169, Blacks: 7/14
Bodiwala *et al*. (45)	Taq1, Fok1	CCS	UK	368/243
Chaimuangraj *et al*. (134)	Taq1, Bsm1, Apa1	CCS	Asian	72/30
Correa-Cerro *et al*. (102)	Taq1, Fok1, poly (A)	CCS	European	132/105
Furuya *et al*. (145)	Taq1	CCS	Asian	66/60
Gsur *et al*. (143)	Taq1	CCS	European	190/190
Habuchi *et al*. (132)	Taq1, Bsm1, Apa1	CCS	Asian	222/337
Hamasaki *et al*. (158)	Taq1	CCS	Asian	115/133
Holick *et al*. (109)	Taq1, Fok1, Bsm1	PCCS	USA	630/565
Huang *et al*. (135)	Taq1, Bsm1, Apa1	CCS	Taiwanese	160/205
Kibel *et al*. (67)	Taq1, poly (A)	CCS	USA	41/41
Luscombe *et al*. (103)	Taq1, Fok1	CCS	UK	210/155
Ma *et al*. (54)	Taq1, Bsm1	NCCS	USA	372/591
Maestro *et al*. (147)	Taq1, Apa1	CCS	European	165/200
Medeiros *et al*. (150)	Taq1	CCS	Southern European	163/211
Oakley-Girvan *et al*. (110)	Taq1, Fok1, Bsm1, Apa1, poly (A)	CCS	USA	African–Americans: 113/121; Caucasian: 232/171
Onsory *et al*. (152)	Taq1	CCS	Indian	100/100
Patino-Garcia *et al*. (151)	Taq1	CCS	Mexican	48/68
Suzuki *et al*. (146)	Taq1, Bsm1, Apa1	CCS	Asian	81/105
Tayeb *et al*. (148)	Taq1	COS	UK	400
Tayeb *et al*. (106)	Taq1, Fok1	CCS	UK	28/56
Taylor *et al*. (149)	Taq1	CCS	USA	Whites: 94/157, Blacks: 14/14
Watanabe *et al*. (144)	Taq1, poly (A)	CCS	Asian	100/202
Skin cancer				
Hutchinson *et al*. (81)	Taq1, Fok1	HCCS	UK	316 MM/108
Li *et al*. (115)	Taq1, Fok1	HCCS	USA, Non-Hispanic Caucasian	602/603 805/841
Li *et al*. (117)	Taq1, Fok1, Bsm1	HCCS	USA, Non-Hispanic Caucasian	
Colon cancer				
SlatterSlattery *et al*. (119)	Taq1, Fok1, Bsm1, poly (A)	PCCS	USA	250/364
Yalim-Eraltan *et al*. (124)	Taq1, Fok1	CCS	Turkish	26/52
Ovarian cancer				
Clendenen *et al*. (126)	Taq1, Fok1, Bsm1, Apa1	CCS	Caucasian	170/323
Lurie *et al*. (86)	Taq1, Fok1, Bsm1, Apa1, Cdx2	CCS	Hawai: Caucasian, Japanese	313/574 (Caucasian: 72/148, Japanese: 94/173)
Bladder and renal cancer				
Ikuyama *et al*. (153)	Taq1	CCS	Japanese	102/204
Obara *et al*. (139)	Taq1, Bsm1, Apa1	CCS	Japanese	135/150
Mittal *et al*. (127)	Taq1, Fok1	CCS	Indian	130/346

CCS: Case–control study, PCCS: population-based case–control study, NCCS: nested case–control study, HCCS: hospital-based case–control study.

Table IV. *Apa1 polymorphism and cancer.*

Reference	Polymorphism	Study type	Study population	Cases/Controls
Breast cancer				
Curran *et al*. (99)	Apa1, Fok1, Taq1	CCS	Australian	135/110
Hou *et al*. (131)	Apa1, Bsm1, Taq1	CCS	Taiwanese	80/169
Sillanpää *et al*. (142)	Apa1, Taq1	CCS	Finnish	483/482
Prostate cancer				
Chaimuangraj *et al*. (134)	Apa1, Bsm1, Taq1	CCS	Asian	72/30
Cicek *et al*. (113)	Apa1, Fok1, Bsm1, Taq1, poly (A), Cdx2	FCCS	USA	439/479
Habuchi *et al*. (132)	Apa1, Bsm1, Taq1	CCS	Asian	222/337
Huang *et al*. (135)	Apa1, Bsm1, Taq1	CCS	Taiwanese	160/205
Maestro *et al*. (147)	Apa1, Taq1	CCS	European	165/200
Oakley-Girvan *et al*. (110)	Apa1, Taq1, Fok1, Bsm1, poly (A)	CCS	USA	African–American: 113/121, Caucasian: 232/171
Ovarian cancer				
Clendenen *et al*. (126)	Apa1, Fok1, Bsm1, Taq1	CCS	Caucasian	170/323
Lurie *et al*. (86)	Apa1, Fok1, Bsm1, Taq1, Cdx2	CCS	Caucasian, Japanese	313/574 (Caucasian: 72/148, Japanese: 94/173)
Bladder and renal cancer				
Obara *et al*. (139)	Apa1, Bsm1, Taq1	CCS	Japanese	135/150

CCS: Case–control study, FCCS: family-based case–control study.

genotype between the RCC cases and controls (p=0.032). The AA genotype was significantly more frequent in cases than in controls (OR=2.5, p=0.012; 17% in cases, 7.3% in controls). More than half of the patients (52, 2%) with the AA genotype but only 6.3% of the patients with other genotypes had distant or lymph node metastasis. Furthermore, multivariate regression analysis including factors of the TNM classification, histopathological grade and Apa1 polymorphism showed that the AA genotype was an independent prognostic factor for cause-specific survival (OR=3.3, p=0.038). In conclusion, the AA genotype may be a risk factor for incidence and poor prognosis for RCC in Japanese patients. In other populations, there are no data about Apa1 polymorphism and RCC reported in the literature.

Summary: Apa1 and cancer (Table IV). The Apa1 polymorphism has been analysed only by few, in general small, studies which were frequently limited to only one racial group. However, in contrast to all other polymorphisms, in most cases an association with cancer risk was reported (breast cancer (99, 131, 142), prostate cancer (113), ovarian cancer (86), RCC (139)). Yet other studies found no association, especially studies analysing the Apa1 polymorphism in prostate cancer patients (prostate cancer (110, 132, 134, 135, 147), ovarian cancer (126)).

As a trend, absence of the Apa1 restriction site (A allele) seems to be associated more frequently with increased cancer risk (breast cancer (131, 142), ovarian cancer (86), RCC (139)), while the Apa1 a allele seems to be associated with reduced cancer risk (breast cancer (131, 142)). However, there are still discrepancies and other studies reported an association between the a allele and increased cancer risk (breast cancer (99)), or between the A allele and reduced cancer risk (prostate cancer (113)). Concerning the importance of the Apa1 polymorphism as a prognostic factor, the recent study of Cicek *et al*. (113) stressed the importance of the A allele as prognostic factor for reduced risk of advanced prostate cancer, and a Japanese study (139) claimed the AA genotype to be an independent prognostic factor for cause-specific survival in Japanese individuals.

In conclusion, there seem to be a trend for the A allele to be the risk allele but the results are still controversial. Additionally, the Apa1 polymorphism might be less important for prostate cancer risk but further studies are required.

Poly (A) Polymorphism and Cancer

Poly (A) and breast cancer. Results concerning poly (A) polymorphisms and breast cancer risk are still controversial. Ingles *et al*. reported a higher risk for breast cancer to be associated with an increasing number of the short poly (A) allele (S) (OR=1.5 for SL genotype and OR=3.2 for SS genotype) compared to the LL genotype (100). Moreover, a recent Swedish study also observed that women carrying two short poly (A) alleles (SS genotype) had an increased breast

cancer risk (OR=1.26; 95% CI: 1.04-1.51) (154). On the other hand, homozygosity for the long poly (A) allele (L allele) was associated with a more advanced clinical stage at diagnosis. Interestingly, there was a statistically significant interaction between *VDR* genotype and parity, such that women with two short alleles had a halved risk for breast cancer (154), irrespective of parity, compared with nulliparous women with two long alleles. Two other studies (96, 97) which examined Caucasian women reported an association between the poly (A) polymorphism and increased breast cancer risk (Guy *et al.*: OR=1.94 for LL *versus* SS). It has been suggested that the L poly (A) variant may be associated with increased breast cancer risk because the poly (A) polymorphism is in LD with the Bsm1 polymorphism (96). The Bsm1 SNP was significantly associated with increased breast cancer risk. Conflicting results were reported in a recent study by McCullough *et al.* (48). No association of incident breast cancer with the poly (A) variant was found. However, the poly (A) LL variant was associated with lower risk in women who consumed high levels of calcium (>902 mg/day) (48). Another recent study (128), which examined Caucasian women and African–American women, was also unable to detect any significant association between the poly (A) genotype and breast cancer risk in both racial group. Interestingly, the association between the poly (A) genotype and breast cancer risk was noticed to be altered by smoking status but not by oral contraceptive use, hormone replacement therapy, nor body mass index (128).

Poly (A) and prostate cancer. According to the previously mentioned meta-analysis reported by Ntais *et al.*, which included 540 patients with prostate cancer and 870 controls with genotype data of the poly (A) polymorphism, the prevalence of the S allele was 41% , 27% and 12% in controls of European, African and Asian descent, respectively (37). The respective prevalence rates of L/S heterozygosity were 46% , 25% and 18% .

It has been demonstrated that the poly (A) microsatellite is in strong LD with the Taq1 *VDR* gene polymorphism ($p<0.0001$) (67, 68). Caucasians show a stronger LD than blacks (D=0.24 *versus* D=0.18). This fact indicates that both polymorphic markers identify the same vitamin D receptor genotype in the majority of cases. Correa-Cerro *et al.* noticed that the short poly (A) alleles (S alleles) and the Taq1 t alleles were in LD with the polymorphisms near the 3' end of the gene ($p<0.0001$) (102).

Most of the reports which examined the poly (A) polymorphism in reference to prostate cancer did not find any significant association (67, 68, 107, 110, 144). Although the studies of Kibel *et al.* (67) and Watanabe *et al.* (144) did not find any association between the poly (A) polymorphism and prostate cancer, these two studies are good examples pointing out the ethnic variation concerning allelic distribution. In a European population, the allelic distribution was LL/LS in 80% of the controls and 84.2% of the cases, and SS in 20% of the controls and 15.8% of the cases (67). In Japanese, the frequency of the SS genotype was only 2% in cases and 3% in controls (LL in controls/cases: 79.2%/80% and LS in controls/cases: 17.8%/18%) (144).

Blazer *et al.* reported an overall lack of association between the Taq1 genotype, the poly (A) genotype and prostate cancer (OR=1.4, 95% CI: 0.7-2.8 and OR=1.2, 95% CI: 0.6-2.5, respectively) (68). A statistically significant association between these polymorphisms and advanced disease was not be found (OR=2.5, 95% CI: 0.3-21.7; OR=2.8, 95% CI: 0.3-23.8, respectively). In conflict with the previously mentioned studies, Ingles *et al.* reported a 4-fold (adjusted OR of 4.61, 95% CI: 1.34-15.82) increased risk of prostate cancer for individuals carrying at least one long *VDR* poly (A) allele (A18 to A22) *versus* these carrying two short poly (A) alleles (A14 to A17) (39). The L allele was more strongly associated with advanced disease than with localized disease. In 1998, Ingles *et al.* published a report examining the haplotype Bsm1/poly (A) in African–Americans (77). It was shown that the haplotype BL was associated with an increased risk of cancer and the haplotype bL with a reduced risk, whereas neither BS nor bS haplotypes were associated with prostate cancer risk in this population. Andersson *et al.* reported a >4-fold increased risk among individuals with short repeats (155). The poly (A) genotype SL was demonstrated to be associated with prostate cancer (OR=0.44, 95% CI: 0.198-0.966, $p=0.041$) by logistic regression (102). Moreover, in a Caucasian population, patients >70 years old and patients with a Gleason score ≥6 had even lower ORs. The S allele was considered to be the risk allele.

Poly (A) and colon cancer. The short poly (A) variant (S allele) has mostly been found to be associated with reduced cancer risk (119, 121). The risk reduction was 50% for colon cancer (OR=0.5) and 29% for colorectal cancer in men (OR=0.71) (121). On examination of calcium intake as an additional factor in relation to the *VDR* genotype, the SS genotype has been shown to be associated with a significant 40% risk reduction of rectal cancer when calcium intake was low (p interaction=0.01 for calcium interaction). On the other hand, for colon cancer, high levels of dietary intake of calcium, vitamin D, and low-fat dairy products reduced risk of cancer for the SS genotype, although the p for interaction was not statistically significant. In general, obese individuals with the SS genotype had a greater risk of colon cancer (OR=3.5), though the association between energy intake and colon cancer appears to be driven more by energy intake than by the poly (A) *VDR* genotype.

In the haplotype examination, the haplotypes bLF and BLF, which both contain the long poly (A) allele (L variant), were associated with increased colon cancer risk. Therefore, it has been concluded that the short allele (S) may be associated with reduced colon cancer risk (125).

Table V. *Poly (A) polymorphism and cancer.*

Reference	Polymorphism	Study type	Study population	Cases/Controls
Breast cancer				
Bretherton-Watt *et al*. (96)	poly (A), Bsm1, Fok1	CCS	Caucasian	181/241
Guy *et al*. (97)	poly (A), Bsm1, Fok1	CCS	Caucasian	398/427
Ingles *et al*. (100)	poly (A), Bsm1, Fok1	CCS	Latina	143/300
McCullough *et al*. (48)	poly (A), Bsm1, Fok1, Taq1, Apa1	NCCS	Caucasian	500/500
Trabert *et al*. (128)	poly (A), Bsm1	PCCS	Caucasian, African–American	1631/1435
Wedrén *et al*. (154)	poly (A)	PCCS	Swedish	1502/1510
Prostate cancer				
Blazer *et al*. (68)	poly (A), Taq1	CCS	USA	Whites: 70/169, Blacks: 7/14
Cheteri *et al*. (107)	poly (A), Bsm1, Fok1, Taq1, Apa1	PCCS	USA	543/510
Correa-Cerro *et al*. (102)	poly (A), Fok1, Taq1	CCS	European	132/105
Ingles *et al*. (39)	poly (A)	CCS	Caucasian	57/ 169
Ingles *et al*. (77)	poly (A), Bsm1	CCS	African–American	151/174
Kibel *et al*. (67)	poly (A), Taq1	CCS	USA	41/41
Oakley-Girvan *et al*. (110)	poly (A), Bsm1, Fok1, Taq1, Apa1	CCS	USA	African–American: 113/121, Caucasian: 232/171
Watanabe *et al*. (144)	poly (A), Taq1	CCS	Asian	100/202
Colon cancer				
Slattery *et al*. (119)	poly(A), Bsm1, Fok1, Taq1	PCCS	USA	250/364
Slattery *et al*. (137)	poly(A), Bsm1	CCS	USA	2306/2749
Slattery *et al*. (121)	poly(A), Bsm1, Fok1	PCCS	USA	1174 colon/1174, 785 rectal/1000
Sweeney *et al*. (125)	poly(A), Bsm1, Fok1	CCS	USA	1811 colon/1451, 905 rectal/679

CCS: Case–control study, PCCS: population-based case–control study, NCCS: nested case–control study.

Summary: Poly (A) and cancer (Table V). Results on the *VDR* poly (A) polymorphism are very controversial, even among large studies. Associations with cancer risk are reported by various studies (breast cancer (48, 96, 97, 100, 154), prostate cancer (39, 102, 155), colorectal cancer (119, 121, 125); nevertheless, other studies did not find any significant association (breast cancer (128), prostate cancer (67, 68, 107, 110, 144)).

In four studies, the homozygous poly (A) SS genotype was reported to be associated with an increased cancer risk (breast cancer (100, 154), prostate cancer (155), colorectal cancer (121)), whereas, especially for colorectal and colon cancer, the short poly (A) allele (S allele) was reported to be associated with reduced cancer risk (119, 121, 125). This might lead to the conclusion that other risk factors must be taken into consideration as possible reasons for obtaining these controversial results. Wedrén *et al*. (154) mentioned parity as a factor which may interact with the *VDR* genotype. Other influencing factors might be different racial groups, limited number of cases, calcium intake (48), or smoking status (128). Another important fact is the strong LD of the poly (A) polymorphism with the Bsm1 polymorphism (96), as well as with the Taq1 polymorphism (67, 68, 102). Interestingly, the strength of the LD seems to vary among ethnic groups. For example, Caucasians show a stronger LD between the poly (A) polymorphism and the Taq1 polymorphism than blacks. Moreover, it has been demonstrated that the allelic distribution in general varies among different ethnic groups which may lead to controversial results in different populations (37, 67, 144). As example, the poly (A) S allele was present in 41% , 27% and 12% in controls of European, African and Asian descent, respectively. These data might, at least in part, explain the discrepancies among different studies.

Cdx2 Polymorphism and Cancer

Cdx2 and breast cancer. Only few studies which analyse the relevance of the potentially functional Cdx2 polymorphisms for breast cancer risk have been published so far. Abbas *et al*. found no overall association between the Cdx2 variant and breast cancer risk (44).

Cdx2 and prostate cancer. A nested case–control study (108) found no association of the Cdx2 polymorphism with susceptibility to prostate cancer. But carriers of the Cdx2 A allele who were deficient in plasma 25(OH)D (≤15 ng/ml) compared to non-carriers with normal 25(OH)D, had a lower

risk of total and poorly differentiated PCs (Gleason sum ≥7) (*p* for interaction=0.02 and 0.04, respectively) (108). Plasma $1,25(OH)_2D_3$ deficiency (≤26 pg/ml) was associated with a 3-fold risk of poorly differentiated PC (*p* for interaction=0.01) when comparing carriers of the Cdx2 A allele to non-carriers with normal levels of $1,25(OH)_2D_3$ (108).

A controversial result was reported by a very recent study analysing the interactions of the *VDR* polymorphisms Cdx2 and Fok1 and polymorphisms of other genes such as *SRD5A2* (V89L, A49T) and their associations with prostate cancer (111). They found a significant interaction (p=0.03) in the logistic model for Cdx2 and V89L VV genotype in non-Hispanic white men. However, the Cdx2 polymorphism (GG *versus* AG/AA) was significantly associated with prostate cancer only in men with the V89L VV genotype (Cdx2: OR=3.16, 95% CI: 1.39-7.19; *p* for interaction=0.02). In conclusion, with regard to this study, the Cdx2 GG genotype may interact with the *SRD5A2* V89L VV genotype in Hispanic-Causasian men, resulting in an increased risk of prostate cancer.

Cdx2 and skin cancer. No association between the Cdx2 polymorphism and risk for any type of skin cancer was observed in a recent investigation by Han *et al*. (118).

Cdx2 and colon cancer. A recent study which analysed the association between the Cdx2 polymorphism and both colon and rectal cancer showed that the Cdx2 polymorphism was not independently associated with either colon or rectal cancer, nor did it modify associations of dietary calcium, vitamin D, or fat with colon or rectal cancer. Considering haplotype variants, the bLFA haplotype, being more common in African–Americans, was shown to be associated with an increased risk of colon cancer (OR=2.4) and the BSfG haplotype was associated with an 1.61-fold increased risk of rectal but not colon cancer. The BSFA haplotype was associated with a significantly reduced risk of rectal (OR=0.71) but not colon cancer (Slattery *et al*., 2007).

Cdx2 and ovarian cancer. Among Japanese women (94 cases/173 controls) ovarian cancer risk was significantly reduced (OR=0.5) for Cdx2 A allele heterozygotes (GA genotype) compared with homozygous G allele (GG genotype) carriers (86).

Summary: Cdx2 and cancer (Table VI). Data on the *VDR* Cdx2 polymorphism and cancer are still very limited. The polymorphism has been investigated in different kinds of tumours, but mostly no association with cancer risk has been seen (breast cancer (44), prostate cancer (108), MM, BCC and SCC (118), colorectal cancer (156)). Only few studies report an association of this polymorphism with cancer risk (prostate cancer (111), ovarian cancer (86)). The Cdx2 A allele heterozygotes (AG genotype) were associated with a reduced risk of ovarian cancer; but this study was limited to a small Japanese population (86). Other cancer risk factors mentioned in relation to the Cdx2 polymorphism are plasma $1,25(OH)_2D_3$ deficiency (≤26 pg/ml) (108) and interaction with the *SRD5A2* V89L VV genotype (111).

In conclusion, the importance of the Cdx2 polymorphism with regard to cancer occurrence is still rarely analysed and more studies are required for more reliable information.

A-1012G, Bgl1, *VDR*-5132 and Tru91 Polymorphisms and Cancer

A-1012G and skin cancer (Table VI). The A-1012G polymorphism was shown to be strongly associated with MM risk (40). With GG as reference, the A allele was more than 2-fold more frequent in MM patients (OR=2.5) and when there was homozygosity for this allele (AA genotype), the risk increased more than 3-fold (OR=3.3). Additionally, the A allele was related to a higher Breslow thickness group (p=0.04) and the development of metastasis (p=0.008). The probability of metastasis at five years was, according to Kaplan-Meier analysis, 21% for the AA variant and 9% for the AG variant when compared to the GG genotype. The effect on metastasis was independent of tumour thickness, and the A-1012G polymorphism was considered to have predictive potential, additional to Breslow thickness. Finally, an interaction between the A-1012G and Fok1 polymorphism (p=0.025) was noticed which enhanced the effect of the A allele of the A-1012G polymorphism on metastasis, increasing the probability of metastasis for the AAff genotype at 5 years up to 57%. Interestingly, a recent study did not find any association between the A-1012 G polymorphism and MM (116).

Bgl1 and breast cancer (Table VI). A recent population-based case–control study which examined various racial groups such as Hispanic, African–American and non-Hispanic Caucasians found no association between Bgl1 polymorphism and localized breast cancer (46). High sun exposure index was associated with reduced risk of advanced breast cancer risk among women with light constitutive skin pigmentation (OR=0.53), but not among women with medium or dark pigmentation. This association was not alternated by the *VDR* genotype.

VDR-5132 and breast cancer (Table VI). Abbas *et al*. reported no significant association between the potentially functional variant *VDR* -5132 and overall breast cancer risk (44).

Tru91 and colon cancer (Table VI). A Chinese study reported that the frequencies of U and u alleles were 89.3% and 10.7%, respectively (61). In this study, the Uu and uu genotypes were associated with a reduced risk for colon adenoma (OR=0.71).

Table VI. *Other polymorphisms and cancer.*

Reference	Polymorphism	Study type	Study population	Cases/Controls
Breast cancer				
Abbas *et al*. (44)	Cdx2, VDR-5132, Fok1, Taq1,	PCCS	German	1408/2612
John *et al*. (46)	Bgl1, Fok1, Taq1	CCS	Hispanic, Non-Hispanic	814/910
Prostate cancer				
Mikhak *et al*. (108)	Cdx2, Fok1, Bsm1	NCCS	USA	681/681
Torkko *et al*. (111)	Cdx2, Fok1	CCS	USA	Non-Hispanic Caucasian: 932, Hispanic Caucasian: 414
Skin cancer				
Halsall *et al*. (40)	A-1012G	CCS	UK	91 MM/80
Han *et al*. (118)	Cdx2, Fok1, Bsm1	NCCS	USA	219 MM, 286 SCC, 300 BCC/873
Santonocito *et al*. (116)	A-1012G, Fok1, Bsm1	CCS	Italian	101 MM/101
Colon cancer				
Gong *et al*. (61)	Tru91	CCS	Asian	171/220
Slattery *et al*. (156)	Cdx2	CCS	USA	1574 colon/1970, 791 recta/999
Ovarian cancer				
Lurie *et al*. (86)	Cdx2, Fok1, Bsm1, Taq1, Apa1	CCS	Caucasian, Japanese	313/574 (Caucasian: 72/148, Japanese: 94/173)

CCS: Case–control study, PCCS: population-based case–control study, NCCS: nested case–control study.

The inverse association was more pronounced for multiple adenomas and adenomas that were larger, had moderate or greater dysplasia, or were sessile (OR=0.51, OR=0.37, OR=0.68 and OR=0.36, respectively). In combined analyses, inverse associations were more obvious among those with at least one u allele, of young age (OR=0.60), women (OR=0.38), without smoking history (OR=0.39) and non-steroidal antiflammatory drug (NSAID) intake (OR=0.38). However, there was no evidence for interactions with calcium or vitamin D intake. In conclusion, it can be suggested that the Tru91 polymorphism may be associated with lower risk for colorectal adenoma, particularly in interaction with various risk factors, except with calcium or vitamin D (61).

Other *VDR* Polymorphisms and Cancer

Recently, Holick *et al*. published a report on the analysis of 22 different polymorphisms across the entire *VDR* gene and prostate cancer risk (109). In this study, haplotypes of *VDR* were not associated with prostate cancer risk except for two variants located in intron 2 (rs 2107301) and intron 3 (rs 2238135). Homozygotes at these two *VDR* loci were associated with a 2- to 2.5-fold higher risk of prostate cancer (OR=1.95, p=0.007 and OR=2.47, p=0.002, respectively). This effect was not modified by age at diagnosis, prostate cancer aggressiveness, first degree family history of cancer or vitamin D intake. However, as mentioned in the study, the association between these two variants and prostate cancer was neither be confirmed by other studies (Moon *et al*., 2006), nor by the Cancer Genetics Markers of Susceptibility (http://cgems.cancer.gov/) which included 1,188 prostate cancer cases.

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