Association of vitamin D receptor gene polymorphisms with risk of cutaneous melanoma. A meta-analysis based on 40 case-control studies

Zależność między polimorfizmami genu kodującego receptor witaminy D i ryzykiem wystąpienia czerniaka skóry – metaanaliza 40 badań kliniczno-kontrolnych

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ABSTRACT

Introduction. Previous studies on the association of vitamin D receptor (VDR) gene polymorphisms with cutaneous melanoma risk reported conflicting results.

Objective. To obtain a more precise assessment of the associations, we performed a meta-analysis of previously published studies.

Material and methods. We searched for eligible studies in the PubMed, Embase, and CNKI databases. A total of 40 case-control studies with 1,144 cases and 2,925 controls were included.

Results. The pooled analyses suggested a significant association between the FokI C>T and BsmI G>A polymorphisms of the VDR gene and susceptibility to melanoma. However, we found that the VDR TaqI T>C, EcoRV A>G, ApaI G>T, and Cdx2 G>A polymorphisms were not associated with melanoma risk.

Conclusions. The meta-analysis suggests that VDR FokI C>T and BsmI G>A polymorphisms are significantly associated with melanoma risk, while TaqI T>C, EcoRV A>G, ApaI G>T, and Cdx2 G>A polymorphisms are not associated with melanoma risk.

STRESZCZENIE

Wprowadzenie. Dotychczasowe badania analizujące związek między polimorfizmami genu kodującego receptor witaminy D (VDR) a ryzykiem rozwoju czerniaka skóry przyniosły sprzeczne wyniki.

Cel pracy. W celu uzyskania bardziej precyzyjnego obrazu tych zależności przeprowadzono metaanalizę opublikowanych do tej pory badań.

Materiał i metody. Publikacje kwalifikujące się do metaanalizy wyszukano w bazach PubMed, Embase i CNKI. Zakwalifikowano łącznie 40 badań kliniczno-kontrolnych obejmujących 1144 pacjentów i 2925 osób w grupach kontrolnych.

Wyniki. Przeprowadzona metaanaliza wykazała istotną zależność między polimorfizmami FokI C>T i BsmI G>A genu VDR a podatnością na czerniaka. Nie stwierdzono jednak związku między ryzykiem zachorowania na czerniaka a polimorfizmami TaqI T>C, EcoRV A>G, ApaI G>T i Cdx2 G>A genu VDR.

Wnioski. Metaanaliza wykazała istotną zależność między polimorfizmami FokI C>T i BsmI G>A genu VDR a ryzykiem wystąpienia czerniaka oraz brak takiej zależności w przypadku polimorfizmów TaqI T>C, EcoRV A>G, ApaI G>T i Cdx2 G>A.

Key words: cutaneous melanoma, vitamin D receptor, polymorphism, meta-analysis.

Słowa kluczowe: czerniak skóry, receptor witaminy D, polimorfizm, metaanaliza.

INTRODUCTION

Melanoma is a malignant skin cancer originating from the unregulated growth of melanocytes, which is responsible for over 70% of skin cancer deaths [1, 2]. Melanoma is a heterogeneous disease with different genetic alterations, and the modifications within the tumors and metastases make it difficult to target [3, 4]. The most dangerous aspect of melanoma is its ability, in later stages, to metastasize to other parts of the body [5]. In 2011, an estimated 166 900 new cases of melanoma will be diagnosed in developed countries [6].

In malignant melanoma, a number of mechanisms leading to neoplasia have been described [7]. Melanomas that occur in humans are usually deregulated in the RAS pathway, either by mutations or upregulation of surface receptors genes such as c-KIT and EGFR or by mutations in intracellular signaling genes such as NRAS, BRAF, and NF-1, which leads to elevated levels of activated ERK [8]. In addition to gene deletion and mutational alteration of protein activity, epigenetic alterations in DNA and histones have recently become a part of melanoma genetic aberrations [9]. Evidence is rapidly accumulating that low to moderate risk genes such as FTO, XRCC1, MC1R, MITF, ASIP, MTAP, PAX3, IL-10, IL-1β, TNF-α, IRF4, and VDR may play a central role in the pathobiology of melanoma [10–12].

There is evidence that vitamin D receptor (VDR) gene polymorphic variants such as FokI (rs10735810), BsmI (rs1544410), ApaI (rs7975232) and TaqI (rs731236) may contribute to the risk of melanoma in certain populations [13–15]. For example, the study by Zeljic *et al.* suggested that VDR polymorphisms might affect the melanoma risk in a Serbian population [16]. Vitamin D modulates immune cells' activity through binding to the VDR, triggering innate and adaptive immune responses [17]. VDR is a ligand-dependent nuclear transcription factor, which plays an important role in maintaining calcium metabolism, and regulating cell proliferation and differentiation [18]. The VDR gene is situated at chromosome 12q13.11, which spans ~100 kb and has five promoters, eight coding exons, and six untranslated exons [15].

Although several epidemiological studies have assessed the association between the VDR gene polymorphisms and the risk of melanoma [11, 13, 15], the results are to some extent divergent and inconclusive, which may be due to limitations in individual studies. To gain better insight into the impact of VDR gene polymorphisms on the risk of melanoma, a meta-analysis with subgroup analysis from all published case-control studies was performed. Recently, increasing evidence has been accumulated to support the hypothesis that common genetic variations of the VDR gene may be of importance in determining an individual's sensitivity to develop melanoma.

MATERIAL AND METHODS

Study identification and selection

This meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria. Two investigators independently searched the databases MEDLINE (PubMed), Google Scholar, Web of Science (Thomson-Reuters), Chinese National Knowledge Infrastructure (CNKI), the Chinese Wanfang Database, and the Chinese VIP Database for eligible articles examining the association of BsmI, TaqI, FokI, and ApaI polymorphisms of the VDR gene with risk of melanoma published up to March 10, 2018. The following terms were used: ("melanoma" OR "cutaneous melanoma" OR "skin cancer"') AND ("vitamin D receptor" OR "VDR" OR "calcitriol receptor" OR "nuclear receptor subfamily 1" OR "NR1I1")

AND ("BsmI" OR "rs1544410" OR "+63980 G > A") AND ("TaqI" OR "rs731236" OR "+65058 T>C") AND ("FokI" OR "rs2228570" OR "+30920 C>T") AND ("ApaI" OR "rs7975232" OR "+64978 C>A") AND ("polymorphism", OR "mutation" OR "variant" OR "gene" OR "genotype" OR "SNP" OR "allele"). In addition, hand searching of the references of eligible studies, reviews and related meta-analyses, and the abstracts presented at relevant conferences was performed to identify potentially relevant studies. If there were multiple reports of the same study or overlapping data, only the study with the largest sample sizes or the most recent one should be in the final analysis.

Inclusion and exclusion criteria

Studies were selected according to the following inclusion criteria: (1) full-text published studies up to March 10, 2018; (2) a case-control design or cohort design; (3) the study goal was to evaluate the association of VDR FokI C>T, BsmI G>A, TaqI T>C, EcoRV A>G, ApaI G>T and Cdx2 G>A polymorphisms with risk of melanoma; (4) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). The exclusion criteria were as follows: (1) studies with only case group (no control population), case reports, commentaries, and reviews; (2) studies without detailed genotype frequencies, which were unable to calculate OR.

Data extraction

Information was carefully extracted from all the eligible studies independently by two investigators using a pre-designed form according to the selection criteria listed above. For each study the following information was extracted: name of first author, publication year, country where the study was conducted, racial descent (categorized as Asian, Caucasian, or mixed descent), polymorphisms, genotypic testing method, number of cases and controls, genotype frequency of cases and controls, minor allele frequencies (MAFs) in control subjects, and result of Hardy-Weinberg equilibrium test in control subjects. Disagreements were resolved in consultation with the third reviewer.

Statistical analysis

The strength of associations was assessed using ORs and 95% CIs. The significance of the pooled effect size was determined by *Z*-tests, and $p < 0.05$ was considered statistically significant. The pooled ORs were calculated in five genetic models, including: allele model (B vs. A), homozygote model (BB vs. AA), heterozygote model (AB vs. AA), dominant model (BB + AB vs. AA), and recessive model (BB vs. AA + AB); A represents the major allele and B represents the minor allele. All ORs for the five genetic models will be compared with each other, and the genetic model with the greatest OR and statistically significant result will be the inheritance model that is most likely to contribute to the risk of melanoma. Between-study heterogeneity was calculated through Cochran's χ^2-based Q-statistic test. Moreover, the I^2 statistic (ranging from 0 to 100%) was then used to quantitatively evaluate heterogeneity, with I^2 = 0–25% indicating no heterogeneity, I^2 = 25–50% indicating moderate heterogeneity, and I^2 > 50% indicating large heterogeneity [19]. The *p*-value of < 0.05 for the Q-test indicated a lack of heterogeneity among studies, so that the pooled OR estimate of each study was calculated by the fixed-effects model (the Mantel–Haenszel method); otherwise the random effects model (the DerSimonian-Laird method) was used [20, 21]. Furthermore, to explore the source of between-study heterogeneity, subgroup analyses were performed. One-way sensitivity analyses were performed to survey the stability of the results; namely, a single study in the meta-analysis was omitted each time to reflect the influence of the individual data set to the pooled OR. Publication bias was assessed by visually examining the asymmetry of a funnel plot in which the log estimates were plotted against their standard errors. Furthermore, we also employed an Egger regression test in our analysis to calculate two-tailed *p*-values for quantifying publication bias [22, 23]. A Hardy-Weinberg equilibrium (HWE) test of the VDR gene polymorphisms in healthy subjects was examined using the χ^2 test. If the *p*-value > 0.05, the genotype distribution of the control group conformed to the HWE. All the statistical analyses were performed by comprehensive meta-analysis (CMA) version 2.0 software (Biostat, USA). All *p*-values were two sided and values less than 0.05 were considered significant.

RESULTS

Eligible studies

By searching online databases and references and related articles, 348 records were retrieved, among which 62 irrelevant papers were excluded due to duplication. After screening the titles and abstracts of the 286 articles, 138 articles were excluded because of obvious irrelevance. After systematically reading the full texts, we excluded another 126 articles. Finally, 40 eligible studies in twelve publications were included in the current meta-analysis. The study selection process is presented in detail in figure 1. There were eleven studies for FokI C>T polymorphism (4,581 cases and 4,226 controls) [16, 24–33], eight studies for TaqI T>C polymorphism (4,141 cases and 3,132 controls) [4, 16, 24, 29–31, 33, 34], eight studies for EcoRV A>G polymorphism (3,608 cases and 2,560

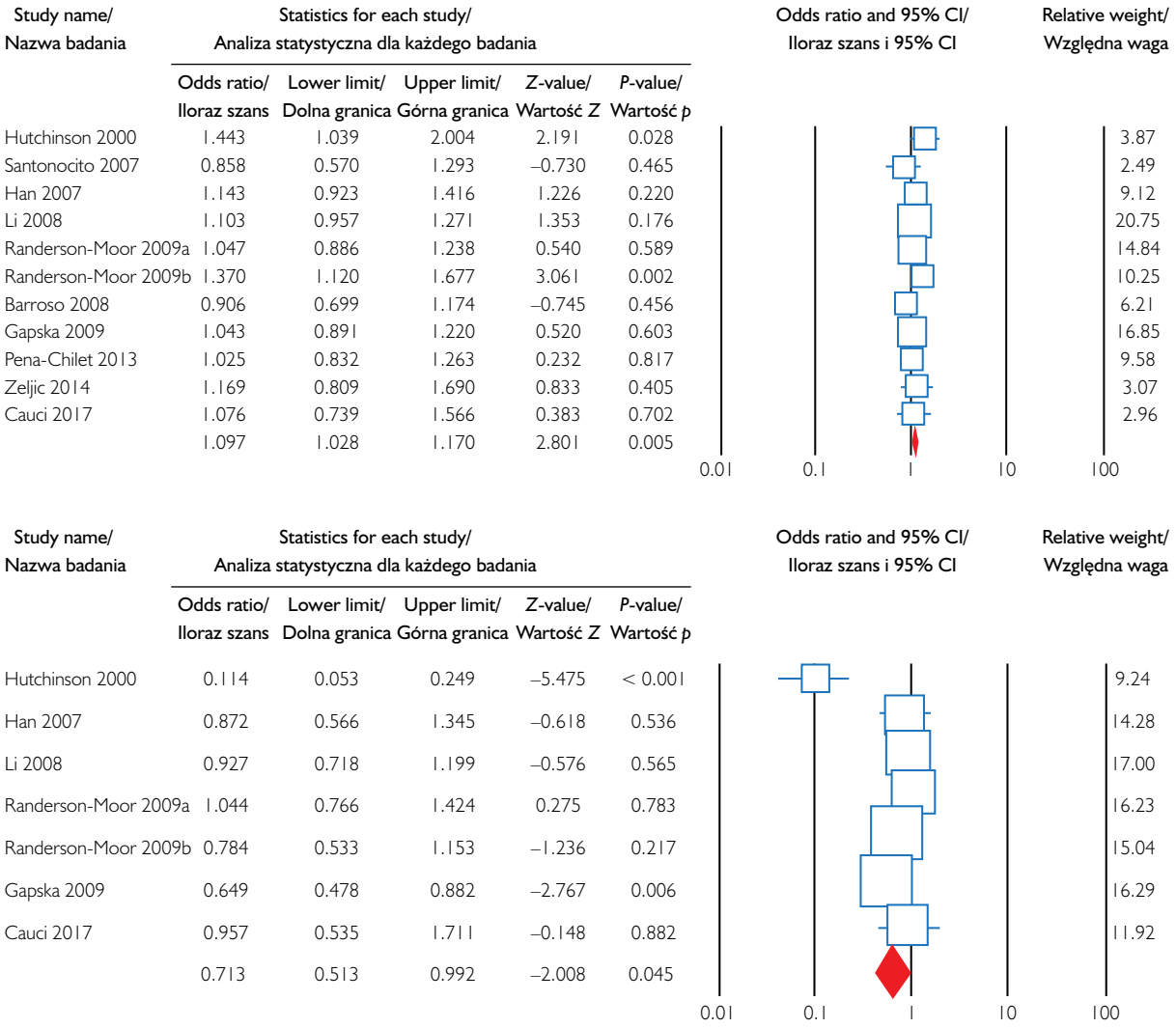

Figure 1. Forest plot of VDR polymorphisms and melanoma. **A** – FokI C>T polymorphism under allele model (T vs. C), **B** – BsmI G>A polymorphism under recessive model (AA vs. AG + GG)

Rycina 1. Wykres drzewkowy zależności między polimorfizmami genu VDR a czerniakiem. **A** – Polimorfizm FokI C>T w modelu alleli (T *vs* C), **B** – polimorfizm BsmI G>A w modelu recesywnym (AA *vs* AG + GG)

controls) [16, 26, 30, 32, 33, 35, 36], seven studies for BsmI G>A polymorphism (3,550 cases and 3,444 controls) [24, 25, 28–30, 37], three studies for ApaI G>T polymorphism (1,444 cases and 1,084 controls) [16, 30], and three studies for Cdx2 G>A polymorphism (1,546 cases and 1,835 controls) [28, 30]. All of the included studies were performed in Caucasian populations. The countries of these studies included the UK, Italy, the USA, Spain, Australia, and Serbia. Genotyping methods used in the studies included PCR-RFLP, real-time PCR, TaqMan, and sequencing. Other basic information, including the first author's name, year of publication, ethnicity of the study population, number of cases and controls, source of controls, and genotyping methods are listed in table 1. All of the studies indicated that the distribution of genotypes in the controls was consistent with HWE, except one case-control study for ApaI G>T (table 1).

Meta-analysis results

The overall analyses suggested significant associations between the FokI C>T polymorphism and melanoma susceptibility in allele (T vs. C: OR = 1.097, 95% CI: 1.028–1.170; p = 0.005, fig. 1 A) and heterozygote (TC vs. CC: OR = 1.159, 95% CI: 1.054–1.275; p = 0.002) models, and clear evidence of associations was found between the BsmI G>A polymorphism and risk of melanoma in all genetic models (A vs. G: OR = 0.891, 95% CI: 0.829–0.958; p = 0.002; AA vs. GG: OR = 0.834, 95% CI: 0.717–0.971; p = 0.019; AG vs. GG: OR = 0.857, 95% CI: 0.768–0.956; p = 0.006; AA + AG vs. GG: OR = 0.570, 95% CI: 0.349–0.931; p = 0.027 and AA vs. AG + GG: OR = 0.713, 95% CI: 0.513–0.992; p = 0.045, fig. 1 B). However, no evidence of associations was detected between melanoma and three VDR polymorphisms

Table 1. Characteristics of studies included in the meta-analysis

Tabela 1. Charakterystyka badań włączonych do metaanalizy

First author/ Pierwszy autor	Country (ethnicity)/Kraj (pochodzenie etniczne)	SOC	Genotyping technique/ Technika genotypowania	Case/control / Pacjenci/ osoby z grupy kontrolnej	Cases/Pacjenci					Controls/Osoby z grupy kontrolnej					MAFs	HWE
					Genotypes/Genotypy			Genotypes/ Genotypy		Genotypes/Genotypy			Genotypes/ Genotypy			
FokI C>T (rs2228570)					CC	TC	TT	C	T	CC	TC	TT	C	T		
Hutchinson 2000	UK (Caucasians)/ UK (kaukaskie)	HB	PCR-RFLP	316/108	105	142	46	380	252	52	44	12	148	68	0.314	0.563
Santonocito 2007	Italy (Caucasians)/Włochy (kaukaskie)	PB	PCR-RFLP	101/101	47	41	13	135	67	41	46	14	128	74	0.366	0.869
Han 2007	USA (Caucasians)/ USA (kaukaskie)	PB	TaqMan	219/873	77	101	37	260	178	325	418	111	1092	654	0.374	0.193
Li 2008	USA (Caucasians)/ USA (kaukaskie)	HB	PCR-RFLP	805/841	287	427	91	1001	609	344	396	101	1082	598	0.355	0.424
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	1028/402	381	489	158	1251	805	161	176	65	498	306	0.380	0.151
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	299/560	96	139	64	331	267	225	255	80	705	415	0.370	0.058
Barroso 2008	Spain (Caucasians)/ Hiszpania (kaukaskie)	HB	TaqMan	283/245	135	121	27	391	175	110	108	27	328	162	0.330	0.949
Gapska 2009	Australia (Caucasians)/ Australia (kaukaskie)	HB	TaqMan	763/540	240	377	144	859	667	252	357	143	619	461	0.427	0.408
Pena-Chilet 2013	Spain (Caucasians)/ Hiszpania (kaukaskie)	HB	AS-PCR	530/314	217	225	58	698	362	140	130	39	417	211	0.336	0.308
Zeljic 2014	Serbia (Caucasians)/ Serbia (kaukaskie)	NA	TaqMan	117/122	40	60	17	139	95	46	62	14	154	90	0.368	0.312
Cauci 2017	Italy (Caucasians)/ Włochy (kaukaskie)	NA	PCR-RFLP	120/120	47	60	13	154	86	54	50	16	158	82	0.341	0.418
TaqI T>C (rs731236)					TT	CT	CC	T	C	TT	CT	CC	T	C		
Hutchinson 2000	UK (Caucasians)/ UK (kaukaskie)	HB	PCR-RFLP	316/108	94	127	40	381	251	39	41	13	138	78	0.360	0.674
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	1028/402	369	484	175	1223	833	144	194	64	482	322	0.400	0.920

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First author/ Pierwszy autor	Country (ethnicity)/Kraj (pochodzenie etniczne)	SOC	Genotyping technique/ Technika genotypowania	Case/control / Pacjenci/ osoby z grupy kontrolnej	Cases/Pacjenci					Controls/Osoby z grupy kontrolnej					MAFs	HWE
					Genotypes/Genotypy			Genotypes/ Genotypy		Genotypes/Genotypy			Genotypes/ Genotypy			
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	299/560	107	150	42	364	234	187	273	100	647	473	0.422	0.983
Barroso 2008	Spain (Caucasians)/ Hiszpania (kaukaskie)	HB	TaqMan	283/245	98	137	48	333	233	91	117	37	299	191	0.389	0.951
Li 2008	USA (Caucasians)/ USA (kaukaskie)	HB	PCR-RFLP	805/841	330	355	120	1015	595	269	422	150	960	722	0.429	0.485
Gapska 2009	Australia (Caucasians)/ Australia (kaukaskie)	HB	TaqMan	763/540	315	351	94	985	541	324	350	88	708	372	0.345	0.656
Pena-Chilet 2013	Spain (Caucasians)/ Hiszpania (kaukaskie)	HB	AS-PCR	530/314	186	248	64	660	400	109	141	44	384	244	0.389	0.884
Zeljic 2014	Serbia (Caucasians)/ Serbia (kaukaskie)	NA	TaqMan	117/122	33	62	22	128	106	59	48	15	166	78	0.319	0.291
EcoRV A>G (rs4516035)					**AA**	**GA**	**GG**	**A**	**G**	**AA**	**GA**	**GG**	**A**	**G**		
Halsall 2009	USA (Caucasians)/ USA (kaukaskie)	NA	PCR-RFLP	174/80	50	88	38	186	162	34	46	10	101	59	0.366	0.340
Povey 2007	UK (Caucasians)/ UK (kaukaskie)	PB	PCR-RFLP	596/441	196	297	103	689	503	130	195	86	488	394	0.446	0.416
Santonocito 2007	Italy (Caucasians)/ Włochy (kaukaskie)	PB	PCR-RFLP	101/101	35	51	15	121	81	43	45	13	131	71	0.351	0.819
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	1028/402	337	509	182	1183	873	137	188	77	462	342	0.425	0.384
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	299/560	87	151	61	325	273	198	261	101	657	463	0.413	0.355
Gapska 2009	Australia (Caucasians)/ Australia (kaukaskie)	HB	TaqMan	763/540	237	370	154	846	680	216	392	147	589	491	0.454	0.195
Pena-Chilet 2013	Spain (Caucasians)/ Hiszpania (kaukaskie)	HB	AS-PCR	530/314	183	228	94	623	437	106	149	45	378	250	0.398	0.530
Zeljic 2014	Serbia (Caucasians)/ Serbia (kaukaskie)	NA	TaqMan	117/122	24	66	27	114	120	37	51	34	125	119	0.487	0.071

Table 1. Characteristics of studies included in the meta-analysis

Tabela 1. Charakterystyka badań włączonych do metaanalizy

First author/ Pierwszy autor	Country (ethnicity)/Kraj (pochodzenie etniczne)	SOC	Genotyping technique/ Technika genotypowania	Case/control / Pacjenci/ osoby z grupy kontrolnej	Cases/Pacjenci					Controls/Osoby z grupy kontrolnej					MAFs	HWE
					Genotypes/Genotypy			Genotypes/ Genotypy		Genotypes/Genotypy			Genotypes/ Genotypy			
BsmI G>A (rs1544410)					**GG**	**AG**	**AA**	**G**	**A**	**GG**	**AG**	**AA**	**G**	**A**		
Hutchinson 2000	UK (Caucasians)/ UK (kaukaskie)	HB	PCR-RFLP	316/108	37	54	10	400	232	26	51	24	110	106	0.490	0.917
Han 2007	USA (Caucasians)/ USA (kaukaskie)	PB	TaqMan	219/873	85	94	29	278	160	312	398	130	1062	684	0.391	0.868
Li 2008	USA (Caucasians)/ USA (kaukaskie)	HB	PCR-RFLP	805/841	305	366	134	976	634	265	427	149	957	725	0.431	0.308
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	1028/402	356	497	175	1209	847	134	202	66	470	334	0.415	0.488
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	299/560	110	145	44	365	233	175	284	101	634	486	0.433	0.444
Gapska 2009	Australia (Caucasians)/ Australia (kaukaskie)	HB	TaqMan	763/540	327	340	96	994	532	308	352	98	690	390	0.361	0.869
Cauci 2017	Italy (Caucasians)/ Włochy (kaukaskie)	NA	PCR-RFLP	120/120	26	64	30	116	124	33	56	31	122	118	0.491	0.466
ApaI G>T (rs7975232)					**GG**	**TG**	**TT**	**G**	**T**	**GG**	**TG**	**TT**	**G**	**T**		
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	1028/402	283	524	221	1090	966	120	190	92	430	374	0.465	0.314
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	299/560	80	151	68	312	286	175	283	102	633	487	0.434	0.504
Zeljic 2014	Serbia (Caucasians)/ Serbia (kaukaskie)	NA	TaqMan	117/122	55	41	21	151	83	52	41	29	145	99	0.405	≤ 0.001
Cdx2 G>A (rs11568820)					**GG**	**AG**	**AA**	**G**	**A**	**GG**	**AG**	**AA**	**G**	**A**		
Han 2007	USA (Caucasians)/ USA (kaukaskie)	PB	TaqMan	219/873	132	68	5	355	83	548	269	36	1397	349	0.199	0.681
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	1028/402	648	324	56	1620	436	250	134	18	634	170	0.211	0.993
Randerson-Moor 2009	UK (Caucasians)/ UK (kaukaskie)	PB	AS-PCR	299/560	193	89	17	475	123	350	179	31	879	241	0.215	0.204

SOC – source of control, HB – hospital based, PB – population based, NA – not applicable, PCR-RFLP – polymerase chain reaction – restriction fragment length polymorphism, AS-PCR – allele-specific PCR, MAF – minor allele frequency, HWE – Hardy-Weinberg equilibrium.

SOC – pochodzenie grupy kontrolnej, HB – szpitalne, PB – populacyjne, NA – nie dotyczy, PCR-RFLP – reakcja łańcuchowa polimerazy – polimorfizm długości fragmentów restrykcyjnych, AS-PCR – reakcja PCR swoista dla allela, MAF – częstość rzadszego allela, HWE – równowaga Hardy'ego-Weinberga.

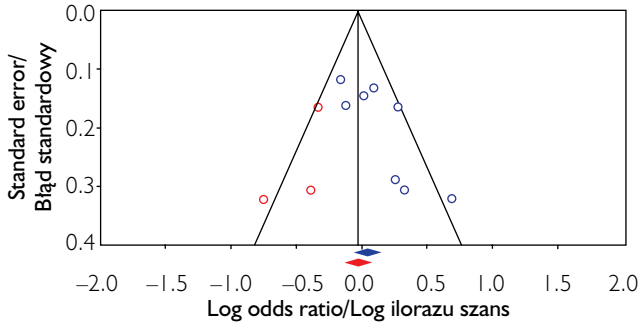

Figure 2. Funnel plot for publication bias in the meta-analysis of the VDR EcoRV A>G polymorphism and melanoma risk under heterozygote model (GA vs. AA)

Rycina 2. Wykres lejkowy dla stronniczości publikacji w metaanalizie polimorfizmu EcoRV A>G genu VDR i ryzyka rozwoju czerniaka w modelu heterozygot (GA *vs* AA)

(TaqI T>C, EcoRV A>G, and ApaI G>T) and melanoma susceptibility.

The studies were further stratified on the basis of genotyping method. When stratifying by genotyping technique, significantly increased associations between FokI C>T polymorphism and melanoma risk were found in the PCR-RFLP group under the heterozygote model (TC vs. CC: OR = 1.282, 95% CI: 1.079–1.522, $p = 0.005$) and the dominant model (TT + TC vs. CC: OR = 1.217, 95% CI: 1.033–1.433, $p = 0.019$); and in the AS-PCR group under the heterozygote model (TC vs. CC: OR = 1.127, 95% CI: 1.010–1.258, $p = 0.032$), but not in the TaqMan group. Moreover, there was a significant association between BsmI G>A polymorphism and melanoma in the PCR-RFLP group only under the heterozygote model (CA vs. AA: OR = 0.794, 95% CI: 0.654–0.964, $p = 0.020$). Meanwhile, no significantly increased risk of melanoma with other polymorphisms was found in the subgroup analyses by genotyping method (data not shown).

Evaluation of heterogeneity and sensitivity analysis

The Q-test and I^2 statistic were employed to assess heterogeneity among the selected studies. However, heterogeneity was not found in the VDR polymorphisms. Therefore, a fixed effects model was applied to synthesize the data (table 1). Sensitivity analyses were performed to evaluate the robustness of the association results or the influence of each individual study on the pooled OR by sequential removal of individual studies. The results suggested that no individual study significantly affected the pooled OR, suggesting that the overall results of our meta-analysis were stable and credible to some extent.

Publication bias

Publication bias in the literature was qualitatively assessed by Begg's funnel plot and quantitatively assessed by Egger's test. Neither Begg's funnel plot nor Egger's test detected obvious evidence of publication bias in the overall and subgroup analyses for FokI C>T, BsmI G>A, ApaI G>T, and Cdx2 G>A polymorphisms in all genetic models (table 2). However, the shapes of the funnel plots displayed some asymmetry for TaqI T>C under the heterozygote model (CT vs. TT) and for EcoRV A>G under the homozygote (GG vs. AA) and the heterozygote (GA vs. AA) models, suggesting the presence of publication bias. Thus, Egger's test was used to provide statistical evidence of funnel plot symmetry. The statistical results still show evidence of publication bias in these studies for TaqI T>C under the heterozygote model (PBeggs = 0.035, PEggers = 0.030) and for EcoRV A>G under the homozygote (PBeggs = 0.107, PEggers = 0.048) and the heterozygote (PBeggs = 0.035, PEggers = 0.031, fig. 2) models. To adjust for this bias, the trim-and-fill method developed by Duval and Tweedie was used to both identify and correct for funnel plot asymmetry arising from publication bias. Statistically similar data were obtained after trimming, indicating that our results were statistically reliable.

Minor allele frequencies (MAFs)

The minor allele frequencies (MAFs) of the VDR polymorphisms in the healthy subjects are presented in table 1. The allele and genotype distributions of VDR gene polymorphisms exhibited ethnic variations. The FokI T, TaqI C, EcoRV G, BsmI A, ApaI T, and Cdx2 A frequencies were 37.05% (31.40–42.70%), 37.40% (31.90–42.90%), 41.90% (35.10–48.70%), 42.90% (36.10–49.10%), 43.50% (40.50–46.50%), and 20.70% (19.90–21.50%), respectively.

DISCUSSION

Several studies have examined associations between VDR polymorphisms and melanoma risk, but the results were controversial. Meta-analysis has been recognized as an important tool to more precisely de-

Table 2. Summary risk estimates for association of VDR gene polymorphisms with cutaneous melanoma

Tabela 2. Zestawienie szacowanego ryzyka dla zależności między polimorfizmami genu VDR a czerniakiem skóry

Subgroup/Podgrupa	Genetic model/ Model genetyczny	Type of model/Rodzaj modelu	Heterogeneity/ Niejednorodność		Odds ratio/ Iloraz szans			Publication bias/ Stronniczości publikacji		
			I^2 (%)	P_H	OR	95% CI	*Z* test	P_{OR}	P_{Beggs}	P_{Eggers}
FokI C>T (rs2228570)	T vs. C	Fixed/Efektów stałych	17.99	0.272	1.097	1.028–1.170	2.801	0.005	0.755	0.950
	TT vs. CC	Fixed/Efektów stałych	35.04	0.118	1.109	0.969–1.269	1.503	0.133	0.755	0.721
	TC vs. CC	Fixed/Efektów stałych	4.88	0.397	1.159	1.054–1.275	3.044	0.002	0.436	0.652
	TT + TC vs. CC	Random/Efektów losowych	91.76	0.00	0.987	0.700–1.393	–0.072	0.943	0.212	0.547
	TT vs. TC + CC	Random/Efektów losowych	55.63	0.013	1.005	0.820–1.230	0.044	0.965	0.876	0.366
BsmI G>A (rs1544410)	A vs. G	Fixed/Efektów stałych	40.94	0.118	0.891	0.829–0.958	–3.107	0.002	1.000	0.623
	AA vs. GG	Fixed/Efektów stałych	31.41	0.188	0.834	0.717–0.971	–2.343	0.019	0.763	0.389
	AG vs. GG	Fixed/Efektów stałych	0.00	0.507	0.857	0.768–0.956	–2.755	0.006	1.000	0.393
	AA + AG vs. GG	Random/Efektów losowych	94.67	≤ 0.001	0.570	0.349–0.931	–2.247	0.027	0.763	0.560
	AA vs. AG + GG	Random/Efektów losowych	80.36	≤ 0.001	0.713	0.513–0.992	–2.008	0.045	0.763	0.548
TaqI T>C (rs731236)	C vs. T	Random/Efektów losowych	70.22	0.001	1.105	0.888–1.161	0.222	0.825	0.063	0.023
	CC vs. TT	Random/Efektów losowych	59.11	0.017	0.995	0.781–1.267	–0.044	0.965	0.175	0.072
	CT vs. TT	Random/Efektów losowych	66.56	0.004	1.030	0.851–1.246	0.301	0.764	0.035	0.030
	CC + CT vs. TT	Random/Efektów losowych	90.85	≤ 0.001	0.832	0.587–1.179	–1.035	0.301	0.536	0.382
	CC vs. CT + TT	Fixed/Efektów stałych	20.83	0.264	0.887	0.776–1.014	–1.758	0.079	0.173	0.118
EcoRV A>G (rs4516035)	G vs. A	Random/Efektów losowych	25.87	0.222	1.028	0.954–1.107	0.724	0.469	0.107	0.085
	GG vs. AA	Fixed/Efektów stałych	32.12	0.171	1.059	0.912–1.230	0.754	0.451	0.107	0.048
	GA vs. AA	Fixed/Efektów stałych	38.62	0.122	1.052	0.936–1.182	0.845	0.398	0.035	0.031
	GG + GA vs. AA	Random/Efektów losowych	80.77	≤ 0.001	1.056	0.766–1.455	0.30	0.741	0.901	0.218
	GG vs. GA + AA	Random/Efektów losowych	52.59	0.039	0.971	0.790–1.195	–0.274	0.784	0.179	0.119
ApaI G>T (rs7975232)	T vs. G	Fixed/Efektów stałych	45.25	0.161	1.052	0.933–1.185	0.828	0.408	1.000	0.603
	TT vs. GG	Fixed/Efektów stałych	49.47	0.138	1.097	0.866–1.390	0.766	0.444	1.000	0.693
	TG vs. GG	Fixed/Efektów stałych	0.00	0.934	1.153	0.947–1.404	1.418	0.156	0.296	0.171
	TT + TG vs. GG	Fixed/Efektów stałych	0.00	0.385	1.129	0.939–1.359	1.291	0.197	1.000	0.510
	TT vs. TG+GG	Fixed/Efektów stałych	50.32	0.134	1.017	0.829–1.247	0.157	0.875	1.000	0.779
Cdx2 G>A (rs11568820)	A vs. G	Fixed/Efektów stałych	0.00	0.893	0.968	0.847–1.107	–0.472	0.637	0.296	0.119
	AA vs. GG	Fixed/Efektów stałych	0.00	0.427	0.998	0.684–1.455	–0.013	0.990	0.296	0.082
	AG vs. GG	Fixed/Efektów stałych	0.00	0.784	0.952	0.806–1.125	–0.574	0.566	1.000	0.673
	AA + AG vs. GG	Fixed/Efektów stałych	0.00	0.961	0.941	0.803–1.103	–0.748	0.455	1.000	0.332
	AA vs. AG + GG	Fixed/Efektów stałych	6.92	0.341	1.013	0.698–1.471	0.068	0.946	0.296	0.051

fine the effect of genetic polymorphism on the risk of diseases. The present meta-analysis was carried out by critically reviewing 40 relevant and new recently published studies on VDR polymorphisms with melanoma risk. Therefore, it can provide more information.

Our meta-analysis showed that VDR FokI C>T and BsmI G>A polymorphism was associated with risk of melanoma. However, the analysis indicated that VDR TaqI T>C, EcoRV A>G, ApaI G>T, and Cdx2 G>A polymorphisms were not associated with risk of melanomas. In a meta-analysis, Iqbal *et al.* found that VDR BsmI, ApaI, and FokI polymorphisms may be risk factor for breast cancer [38]. The findings of *Liu et al.* suggest a significant association between TaqI and prostate cancer risk, but BsmI was not associated with prostate cancer [39]. Ou *et al.* reported that the ApaI, BsmI, and FokI polymorphisms were associated with the risk of renal cell carcinoma in Asians [40]. However, Sheng *et al.* reported that TaqI polymorphisms were significantly associated with susceptibility to colorectal cancer [41]. It is clear that different types of cancer have distinct initiation and progression mechanisms, in which VDR gene polymorphisms play critical roles. According to the results, the exact mechanism for association between VDR polymorphisms and melanoma was not clear, and the carcinogenetic mechanism may also differ by VDR polymorphisms may exert varying effects in melanoma susceptibility. The discrepancy between previous results and the present findings may be attributed to the fact that the polymorphisms of the same gene may exert different genetic effects on different cancers. The inconsistent outcome for the effects of VDR polymorphisms on melanoma susceptibility is partly caused by genetic diversity in different ethnicities. Moreover, reasons for the conflicting results where VDR polymorphisms play different roles in melanoma susceptibility may be genetic heterogeneity in different populations and clinical heterogeneity in different studies. Potentially, differences in patient populations including gender difference and lifestyle might cause different results.

Heterogeneity plays an important role when performing a meta-analysis, and finding the source of heterogeneity is very important for the final result of the meta-analysis [42–46]. It is known that different factors, such as population stratification, source of controls, year of publication, sample size, diversity in design, genotyping methods, measurement errors, deviation from Hardy–Weinberg equilibrium, and other covariates, may contribute to common sources of heterogeneity [44, 47, 48]. In order to control heterogeneity between studies, we have applied inclusion criteria, but obvious between-study heterogeneity still existed in the overall population. Unluckily, the heterogeneity was not eliminated effectively, indicating that all the above factors should be taken into consideration.

Several potential limitations of the present meta-analysis should be acknowledged. First, limited studies have assessed the association of VDR polymorphisms with risk of melanoma in Asians. Therefore, we would refrain from generalizing these findings across populations. Studies with a larger sample size from other ethnicities should be performed in the future. In addition, few studies have been performed on TaqI T>C and EcoRV A>G polymorphisms with the risk of melanoma. Second, the sample size of the VDR ApaI G>T and Cdx2 G>A polymorphisms involved was not large enough. Therefore, they do not have adequate power to detect the possible association for these polymorphisms. Third, the current meta-analysis only included studies published in English or Chinese, and therefore some eligible studies written in other languages were not included. Thus, selection bias might have occurred at the beginning. Fourth, all the studies were conducted in Caucasians; therefore, the findings of the meta-analysis at present should be limited to Caucasians. Moreover, publication bias existed in the meta-analysis for TaqI T>C (the heterozygote model) and EcoRV A>G (the homozygote and heterozygote models) polymorphisms. For example, studies may not have been published if they reported a significant association between VDR polymorphism and risk of melanoma. The publication bias could cause the negative results. Fifth, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for adjustment by other co-variants, including environmental factors and other lifestyle. Thus, more individual data required to draw a more precise conclusion. Finally, gene-gene, gene-environment or even the different polymorphism loci of the VDR gene interactions were not estimated in the current meta-analysis due to the insufficient data.

Despite these limitations, the current meta-analysis also had some advantages. First, we performed the most comprehensive and up-to-date meta-analysis with more VDR polymorphisms and articles than before, to better understand the association of VDR polymorphisms and melanoma susceptibility. Second, although possible publication bias was suggested between TaqI T>C and EcoRV A>G polymorphisms and risk of melanoma, adjusting for possible publication bias using the Duval and Tweedie nonparametric "trim and fill" method showed that the results did not change, indicating that the whole pooled results should be unbiased.

CONCLUSIONS

The present study suggests a significant risk of melanoma associated with VDR FokI C>T and BsmI G>A polymorphisms, but not with TaqI T>C, EcoRV A>G, ApaI G>T, Cdx2 G>A polymorphisms. According to current findings, the exact mechanism for association between VDR polymorphisms and melanoma was not clear, and VDR polymorphisms may exert varying effects in the carcinogenetic mechanism of melanoma. Considering the limitations mentioned above, further studies with a larger sample size and population-based studies, especially among Asians, are warranted to further confirm our findings and to explore the potential gene-gene and gene-environment interactions between the VDR gene polymorphisms and melanoma susceptibility.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

References
Piśmiennictwo

1. **Apalla Z., Lallas A., Sotiriou E., Lazaridou E., Ioannides D.:** Epidemiological trends in skin cancer. Dermatol Pract Concept 2017, 7, 1-6.
2. **Lomas A., Leonardi-Bee J., Bath-Hextall F.:** A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012, 166, 1069-1080.
3. **Bertolotto C.:** Melanoma: from melanocyte to genetic alterations and clinical options. Scientifica 2013, 2013, 635203.
4. **Sun X., Yu Q.:** Intra-tumor heterogeneity of cancer cells and its implications for cancer treatment. Acta Pharmacol Sin 2015, 36, 1219-1227.
5. **Kee J.Y., Han Y.H., Kim D.S., Mun J.G., Park S.H., So H.S., et al.:** beta-Lapachone suppresses the lung metastasis of melanoma via the MAPK signaling pathway. PLoS One 2017, 12, e0176937.
6. **Woodman S.E., Lazar A.J., Aldape K.D., Davies M.A.:** New strategies in melanoma: molecular testing in advanced disease. Clin Cancer Res 2012, 18, 1195-1200.
7. **Bastian B.C.:** The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol 2014, 9, 239-271.
8. **Karachaliou N., Pilotto S., Teixidó C., Viteri S., Gonzalez-Cao M., Riso A., et al.:** Melanoma: oncogenic drivers and the immune system. Ann Transl Med 2015, 3, 265.
9. **Sarkar D., Leung E.Y., Baguley B.C., Finlay G.J., Askarian-Amiri M.E.:** Epigenetic regulation in human melanoma: past and future. Epigenetics 2015, 10, 103-121.
10. **Potrony M., Badenas C., Aguilera P., Puig-Butille J.A., Carrera C., Malvehy J., et al.:** Update in genetic susceptibility in melanoma. Ann Transl Med 2015, 3, 210.
11. **Zhao J., Huang X., Yang M., Li M., Zheng J.:** Association between the FTOrs8050136 polymorphism and cancer risk: a meta-analysis. Famil Cancer 2016, 15, 145-153.
12. **Jiang H., Xu W., Zhang F., Wei L., Wang Y., Wang Y., et al.:** Quantitative assessment of the association between XRCC1 Arg-399Gln and Arg194Trp polymorphisms and risk of cutaneous melanoma. Melanoma Res 2016, 26, 290-299.
13. **Lee Y.H., Gyu Song G.:** Vitamin D receptor FokI, BsmI, TaqI, ApaI, and EcoRV polymorphisms and susceptibility to melanoma: a meta-analysis. J BUON 2015, 20, 235-243.
14. **Zhao X.Z., Yang B.H., Yu G.H., Liu S.Z., Yuan Z.Y.:** Polymorphisms in the vitamin D receptor (VDR) genes and skin cancer risk in European population: a meta-analysis. Arch Dermatol Res 2014, 306, 545-553.
15. **Orlow I., Reiner A.S., Thomas N.E., Roy P., Kanetsky P.A., Luo L., et al.:** Vitamin D receptor polymorphisms and survival in patients with cutaneous melanoma: a population-based study. Carcinogenesis 2016, 37, 30-38.
16. **Zeljic K., Kandolf-Sekulovic L., Supic G., Pejovic J., Novakovic M., Mijuskovic Z., et al.:** Melanoma risk is associated with vitamin D receptor gene polymorphisms. Melanoma Res 2014, 24, 273-279.
17. **Aranow C.:** Vitamin D and the immune system. J Investig Med 2011, 59, 881-886.
18. **Zenata O., Vrzal R.:** Fine tuning of vitamin D receptor (VDR) activity by post-transcriptional and post-translational modifications. Oncotarget 2017, 8, 35390-35402.
19. **Khoram-Abadi K.M., Forat-Yazdi M., Kheirandish S., Saeidi N., Zarezade Z., Mehrabi N., et al.:** DNMT3B -149 CT and -579 GT polymorphisms and risk of gastric and colorectal cancer: a meta-analysis. Asian Pacific J Cancer Prev 2016, 17, 3015-3020.
20. **DerSimonian R., Laird N.:** Meta-analysis in clinical trials. Control Clin Trials 1986, 7, 177-188.
21. **Mantel N., Haenszel W.:** Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959, 22, 719-748.
22. **Begg C.B., Mazumdar M.:** Operating characteristics of a rank correlation test for publication bias. Biometrics 1994, 50, 1088-1101.
23. **Egger M., Davey Smith G., Schneider M., Minder C.:** Bias in meta-analysis detected by a simple, graphical test. BMJ 1997, 315, 629-634.
24. **Hutchinson P.E., Osborne J.E., Lear J.T., Smith A.G., Bowers P.W., Morris P.N., et al.:** Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. Clin Cancer Res 2000, 6, 498-504.
25. **Cauci S., Maione V., Buligan C., Linussio M., Serraino D., Stinco G.:** BsmI (rs1544410) and FokI (rs2228570) vitamin D receptor polymorphisms, smoking, and body mass index as risk factors of cutaneous malignant melanoma in northeast Italy. Cancer Biol Med 2017, 14, 302-318.
26. **Santonocito C., Capizzi R., Concolino P., et al.:** Association between cutaneous melanoma, Breslow thickness and vitamin D receptor BsmI polymorphism. Br J Dermatol 2007, 156, 277-282.

27. **Cai J., Zhang Z.:** An analysis of IL-10/IL-10R genetic factors related to risk of colon cancer and inflammatory bowel disease in a Han Chinese population. Clin Lab 2016, 62, 1147-1154.
28. **Han J., Colditz G.A., Hunter D.J.:** Polymorphisms in the MTHFR and VDR genes and skin cancer risk. Carcinogenesis 2006, 28, 390-397.
29. **Li C., Liu Z., Zhang Z., Strom S.S., Gershenwald J.E., Prieto V.G., et al.:** Genetic variants of the vitamin d receptor gene alter risk of cutaneous melanoma. J Investig Dermatol 2007, 127, 276-280.
30. **Randerson-Moor J.A., Taylor J.C., Elliott F., Chang Y.M., Beswick S., Kukalizch K., et al.:** Vitamin D receptor gene polymorphisms, serum 25-hydroxyvitamin D levels, and melanoma: UK case-control comparisons and a meta-analysis of published VDR data. Eur J Cancer 2009, 45, 3271-3281.
31. **Barroso E., Fernandez L.P., Milne R.L., Pita G., Sendagorta E., Floristan U., et al.:** Genetic analysis of the vitamin D receptor gene in two epithelial cancers: melanoma and breast cancer case-control studies. BMC Cancer 2008, 8, 385.
32. **Gapska P., Scott R.J., Serrano-Fernandez P., Mirecka A., Rassoud I., Górski B., et al.:** Vitamin D receptor variants and the malignant melanoma risk: apopulation-based study. Cancer Epidemiol 2009, 33, 103-107.
33. **Peña-Chilet M., Ibarrola-Villava M., Martin-González M., Feito M., Gomez-Fernandez C., Planelles D., et al.:** rs12512631 on the group specific complement (vitamin D-binding protein GC) implicated in melanoma susceptibility. PLoS One 2013, 8, e59607.
34. **Gunter M.J., Canzian F., Landi S., Chanock S.J., Sinha R., Rothman N.:** Inflammation-related gene polymorphisms and colorectal adenoma. Cancer Epidemiol Biomarkers Prev 2006, 15, 1126-1131.
35. **Halsall J.A., Osborne J.E., Epstein M.P., Pringle J.H., Hutchinson P.E.:** The unfavorable effect of the A allele of the vitamin D receptor promoter polymorphism A-1012G has different mechanisms related to susceptibility and outcome of malignant melanoma. Dermatoendocrinology 2009, 1, 54-57.
36. **Povey J.E., Darakhshan F., Robertson K., Bisset Y., Mekky M., Rees J., et al.:** DNA repair gene polymorphisms and genetic predisposition to cutaneous melanoma. Carcinogenesis 2007, 28, 1087-1093.
37. **Gapska P., Scott R.J., Serrano-Fernandez P., Mirecka A., Rassoud I., Górski B., et al.:** Vitamin D receptor variants and the malignant melanoma risk: a population-based study. Cancer Epidemiol 2009, 33, 103-107.
38. **Iqbal M un N., Khan T.A.:** Association between Vitamin D receptor (Cdx2, Fok1, Bsm1, Apa1, Bgl1, Taq1, and Poly (A)) gene polymorphism and breast cancer: a systematic review and meta-analysis. Tumor Biology 2017, 39, 101042831773128.
39. **Liu S., Cai H., Cheng W., Zhang H., Pan Z., Wang D.:** Association of VDR polymorphisms (Taq I and Bsm I) with prostate cancer: a new meta-analysis. J Int Med Res 2017, 45, 3-10.
40. **Ou C., Zhao H.L., Zhu B., Huang L., Li P., Lao M.:** Association of vitamin D receptor gene polymorphism with the risk of renal cell carcinoma: a meta-analysis. J Recept Signal Transduct 2014, 34, 463-468.
41. **Sheng S., Chen Y., Shen Z.:** Correlation between polymorphism of vitamin D receptor TaqI and susceptibility to colorectal cancer. Medicine 2017, 96, e7242.
42. **Sobhan M.R., Yazdi M.F., Mazaheri M., Shehneh M.Z., Neamatzadeh H.:** Association between the DNA repair gene XRCC3 rs861539 polymorphism and risk of osteosarcoma: a systematic review and meta-analysis. Asian Pac J Cancer Prev 2017, 18, 549-555.
43. **Sobhan M.R., Mehdinejad M., Jamaladini M.H., Mazaheri M., Zare-Shehneh M., Neamatzadeh H.:** Association between aspartic acid repeat polymorphism of the asporin gene and risk of knee osteoarthritis: a systematic review and meta-analysis. Acta Orthop Traumatol Turc 2017, 51, 409-415.
44. **Namazi A., Forat-Yazdi M., Jafari M., Farahnak S., Nasiri R., Foroughi E., et al.:** Association of interleukin-10 -1082 a/G (Rs1800896) polymorphism with susceptibility to gastric cancer: meta-analysis of 6,101 cases and 8,557 controls. Arq Gastroenterol 2018, 55, 33-40.
45. **Sadeghiyeh T., Hosseini Biouki F., Mazaheri M., Zare-Shehneh M., Neamatzadeh H., Poursharif Z.:** Association between catechol-o-methyltransferase Val158Met (158G/A) polymorphism and suicide susceptibility: a meta-analysis. J Res Health Sci 2017, 17, e00383.
46. **Nedooshan J.J., Yazdi M.F., Neamatzadeh H., Shehneh M.Z., Kargar S., Seddighi N.:** Genetic association of XRCC1 gene rs1799782, rs25487 and rs25489 polymorphisms with risk of thyroid cancer: a systematic review and meta-analysis. Asian Pac J Cancer Prev 2017, 18, 263-270.
47. **Kamali M., Hantoushzadeh S., Borna S., Neamatzadeh H., Mazaheri M., Noori-Shadkam M., et al.:** Association between thrombophilic genes polymorphisms and recurrent pregnancy loss susceptibility in the Iranian population: a systematic review and meta-analysis. Iran Biomed J 2018, 22, 78-89.
48. **Nedooshan J.J., Kargar S., Neamatzadeh H., Haghighi F., Abadi R.D.M., Seddighi N.:** Lack of association of the fat mass and obesity associated (FTO) gene rs9939609 polymorphism with breast cancer risk: a systematic review and meta-analysis based on case-control studies. Asian Pac J Cancer Prev 2017, 18, 1031-1037.

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