Research Article

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Meta-analysis of the relationship between MnSOD polymorphism and cancer in the Turkish and Cypriot population

MnSOD polimorfizmi ile kanser arasındaki ilişkinin Türk ve Kıbrıs toplumundaki meta analizi

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Abstract

Objectives: The association between manganese superoxide dismutase (MnSOD) p.Val16Ala polymorphism and cancer has been shown in various studies. The aim of this study is to investigate the relationship between MnSOD polymorphism (V/V, V/A, A/A) and cancer in the Turkish and Cypriot population through meta-analysis.

Material and methods: The present study included meta-analysis of 14 publications covering 2413 cancer patients and 2907 healthy control groups from 2005 to 2016. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using the random effect model of DerSimonian and Laird for each study. Publication bias was checked with funnel plot by Begg's and Egger's test statistics.

Results: Meta-analysis of MnSOD polymorphism was performed in the additive model (AV vs. VV; OR = 1.133, 95% CI: 1.002–1.282), allele contrast (A vs. V; OR = 1.016, 95% CI: 0.930–1.278), homozygote model (AA vs. VV; OR = 0.983, 95% CI: 0.839–1.153), dominant model (AA + AV vs. VV; OR = 1.090, 95% CI: 0.971–1.223) and recessive model (AA vs. AV + VV; OR = 0.924, 95% CI: 0.803–1.064). The A/V genotype polymorphism was found be significant for cancer.

Conclusion: The frequency of the A/V heterozygote genotype of the MnSOD polymorphisms is found to be higher in the Cypriot and Turkish populations than any other genotype.

Keywords: MnSOD (p.Val16Ala); Polymorphism; Cancer; Meta-analysis; Cypriot population; Turkish population.

Özet

Amaç: Çalışmalarda mangan süperoksit dismutaz (MnSOD) p.Val16Ala polimorfizmi ile kanser arasındaki ilişki gösterilmiştir. Bu çalışmanın amacı, meta-analizle Türk ve Kıbrıs toplumundaki MnSOD polimorfizmi (V/V, V/A, A/A) ve kanser arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Bu çalışma, 2005-2016 yılları arasındaki 2413 kanser hastasını ve 2907 sağlıklı kontrol grubunu kapsayan 14 araştırmanın meta-analizini içermektedir. Her bir çalışma için odds oranı (OR) ve % 95 güven aralığı (CI) değerleri Dersimonian ve Laird'nin tesadüfi etki modeli kullanılarak belirlendi. Yayın yanlılığı, Begg ve Egger' in test istatistiklerine göre funnel plot ile kontrol edildi.

Bulgular: MnSOD polimorfizminin meta analizi, additif model (AV vs. VV: OR = 1,133, % 95 CI: 1,002–1,282), alel kontrast (A vs. V; OR = 1,016, % 95 CI: 0,930–1,278), homozigot model (AA vs. VV; OR = 0,983, % 95 CI: 0,839–1,153) dominant model (AA + AV vs. VV; OR = 1,090, % 95 CI: 0,971–1,223)ve resesif model (AA vs. AV + VV; OR = 0,924, % 95 CI: 0,803–1,064) olarak yapıldı. A/V genotip polimorfizmi kanser için önemli olduğu bulundu.

Sonuç: MnSOD polimorfizminin A/V heterozigot genotip sıklığı, Kıbrıs ve Türk popülasyonlarında diğer genotiplerden daha yüksek bulunmuştur.

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Anahtar Kelimeler: MnSOD (p.Val16Ala); Polimorfizmi; Kanser; Meta-analiz; Kıbrıs popülasyon; Türk popülasyonu.

Introduction

Manganese superoxide dismutase (MnSOD) is an antioxidant enzyme located in the mitochondrial matrix [1]. MnSOD that has tumor suppressor activity, is encoded by a gene located on chromosome 6q25.3 [2]. MnSOD plays an important role in the protection of cells from oxidative damage induced by reactive oxygen species (ROS) and catalyzes the destruction of superoxide radicals in hydrogen peroxide and oxygen [1]. MnSOD is a nuclear protein transported after translocation through the N-terminal signal sequence in mitochondria [3, 4]. The signal sequence is important for protein transport activity by mitochondria [5]. The polymorphism on the second exon of the MnSOD gene (SOD2), and the change from valine to alanine (Val16Ala) position at the amino acid position 16, results in the signal sequence at position -9 (Ala-9Val) of the enzyme MnSOD (rs4880) [6]. This polymorphism may alter the mitochondrial transport and structural conformation of MnSOD [6, 7]. Consequently, alanine-containing protein exhibitions normally transport 30–40% more active enzyme forms than the valine form of the enzyme [8]. The low expression of MnSOD is suggested to be responsible for different types of cancer. Additionally, this protein overexpression inhibits the proliferation of the cancerous cell, indicating that it is a tumor suppressor gene [9]. MnSOD may act as a tumor suppressor by altering pathways, including cellular apoptosis and proliferation [10].

The association between MnSOD Val16Ala polymorphism and cancer has been shown in various studies. The Val allele and Val/Val genotype are found to be related with an increased risk of bladder and lung cancers [11, 12]. Ala allele is related with the increased risk of prostate, ovarian and breast cancers [13–17]. However, the results of some molecular epidemiological studies have presented

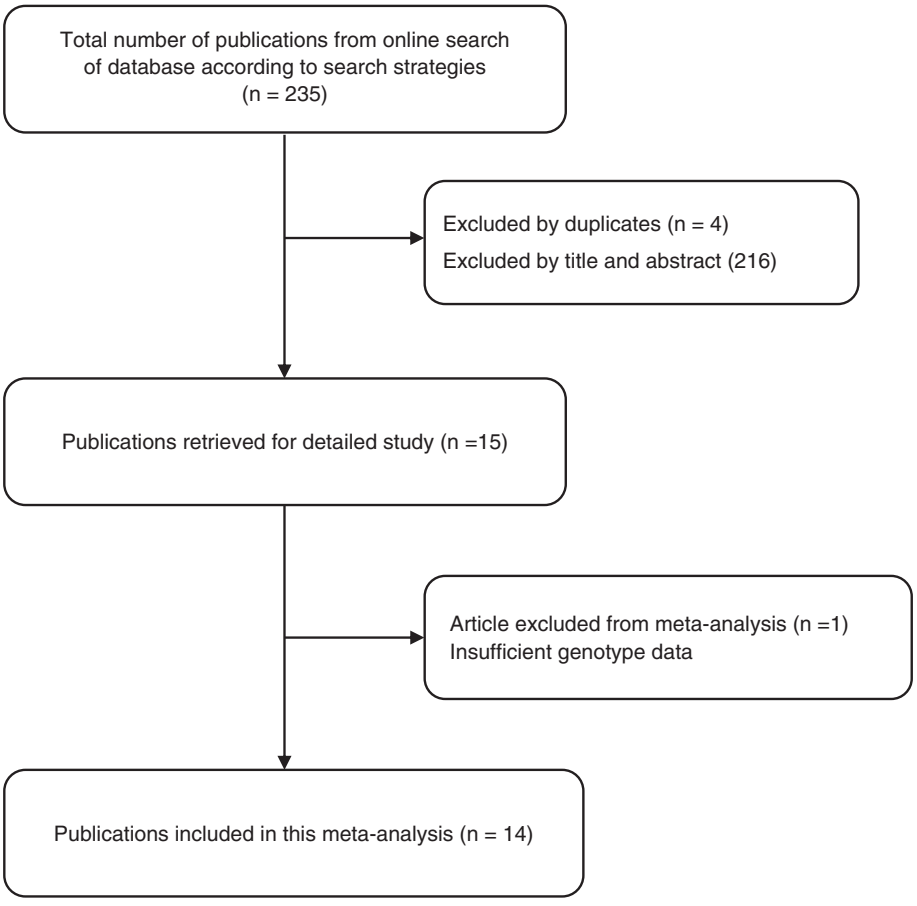

Figure 1: Flowchart of study selection.

Table 1: MnSOD polymorphism and risk of cancers in case-control studies.

Study	Year	Method	Cancer group						Control group						p (HWE)	Cancer type	Population
			Age	F/M	Val/Val	Val/Ala	Ala/Ala	Total	Age	F/M	Val/Val	Val/Ala	Ala/Ala	Total			
Kocabas et al. (2005) [20]	2005	RFLP	NA	84/0	28	38	18	84	NA	103/0	28	40	35	103	0.1488	Breast	Turkey
Eras et al. (2006) [25]	2006	RFLP	49.01±9.26	83/0	50	27	6	83	51.97±11.48	104/0	46	47	11	104	0.0830	Breast	Turkey
Ergen et al. (2007) [14]	2007	RFLP	68.11±9.13	0/50	19	25	6	50	64.36±8.68	0/50	32	18	0	50	0.0088	Prostate	Turkey
Ergul et al. (2007) [26]	2007	RFLP	NA	172/0	46	98	28	172	NA	246/0	74	121	51	246	0.1331	Breast	Turkey
Dalan et al. (2008) [27]	2008	RFLP	45.20±9.79	55/0	30	19	6	55	42.17±5.51	51/0	28	17	6	51	0.5648	Ovarian	Turkey
Eras-Erdogan et al. (2009) [28]	2009	RFLP	51.08±9.34	250/0	107	113	30	250	49.43±8.06	330/0	150	141	39	330	0.8799	Breast	Turkey
Zejnilovic et al. (2009) [29]	2009	RFLP	59.90±10.46	4/96	54	42	4	100	57.68±9.656	11/39	34	3	13	50	0.3526	Lung	Turkey
Kucukgergin et al. (2012) [30]	2012	RFLP	64.10±7.48	0/134	43	65	26	134	62.5±7.53	0/159	66	69	24	159	0.2368	Prostate	Turkey
Kucukgergin et al. (2012) [31]	2012	RFLP	63.20±10.86	22/135	52	68	37	157	61.7±8.39	45/179	89	99	36	224	0.0434	Bladder	Turkey
Kose et al. (2012) [32]	2012	RFLP	59.50±20.15	18/121	34	79	26	139	47.09±13.39	86/179	83	123	59	265	0.2284	Head & neck	Turkey
Eken et al. (2013) [33]	2013	RFLP	64.63±8.94	0/33	7	17	9	33	67.52±9.31	0/81	31	37	13	81	0.1465	Prostate	Turkey
Parlaktas et al. (2013) [34]	2013	RFLP	63.27±8.08	0/49	23	23	3	49	64.81±6.77	0/49	24	20	5	49	0.6564	Prostate	Turkey
Atilgan et al. (2014) [35]	2014	RFLP	NA	12/29	10	17	14	41	NA	13/37	23	19	8	50	0.0154	Renal cell	Turkey
Kakkoura et al. (2016) [36]	2016	SGA	NA	1066/0	342	512	212	1066	NA	1145/0	343	550	252	1145	0.2628	Breast	Greek-Cypriot
Total			59.01±7.39	1766/647	845	1143	425	2413	57.26±8.27	2134/773	1051	1304	552	2907			
Frequency				73.19/26.81	35.02	47.37	17.61			73.41/26.59	36.15	44.86	18.99				

RFLP, Restriction fragment length polymorphism; SGA, SNP genotyping assays; NA, not available.

Table 2: MnSOD Val16Ala polymorphism and risk of cancer.

Study	A vs. V		AA vs. VV		AV vs. VV		AA vs. AV+VV		AA+AV vs. VV	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Kocabas et al. (2005) [20]	0.687	0.456–1.035	0.514	0.237–1.114	0.950	0.478–1.888	0.530	0.273–1.027	0.747	0.399–1.399
Eras et al. (2006) [25]	0.619	0.390–0.980	0.502	0.172–1.466	0.529	0.284–0.982	0.659	0.233–1.863	0.523	0.291–0.940
Ergen et al. (2007) [14]	2.675	1.394–5.135	21.667	1.156–406.06	2.339	1.020–5.366	14.753	0.81–269.34	2.901	1.288–6.534
Ergul et al. (2007) [26]	0.978	0.741–1.290	0.883	0.490–1.593	1.303	0.827–2.052	0.743	0.447–1.237	1.178	0.764–1.819
Dalan et al. (2008) [27]	0.988	0.543–1.796	0.933	0.269–3.236	1.043	0.454–2.399	0.918	0.276–3.054	1.014	0.472–2.181
Eras-Erdogan et al. (2009) [28]	1.065	0.834–1.362	1.078	0.630–1.844	1.123	0.791–1.595	1.017	0.613–1.690	1.114	0.800–1.551
Zejnilovic et al. (2009) [29]	0.816	0.477–1.397	0.194	0.058–0.643	8.815	2.532–30.69	0.119	0.036–0.387	1.810	0.888–3.691
Kucukgergin et al. (2012) [30]	1.331	0.955–1.855	1.663	0.847–3.265	1.446	0.866–2.413	1.354	0.736–2.492	1.502	0.929–2.429
Kucukgergin et al. (2012) [31]	1.337	0.998–1.792	1.759	0.992–3.118	1.176	0.742–1.864	1.610	0.964–2.689	1.331	0.869–2.040
Kose (2012) [32]	1.069	0.799–1.430	1.076	0.585–1.980	1.568	0.962–2.557	0.803	0.480–1.345	1.408	0.884–2.244
Eken et al. (2013) [33]	1.774	0.996–3.161	3.066	0.941–9.989	2.035	0.748–5.538	1.962	0.744–5.169	2.303	0.893–5.938
Parlaktas et al. (2013) [34]	0.953	0.517–1.754	0.626	0.134–2.924	1.200	0.524–2.747	0.574	0.129–2.546	1.085	0.491–2.398
Atilgan et al. (2014) [35]	2.259	1.242–4.109	4.025	1.284–12.619	2.058	0.765–5.536	2.722	1.007–7.357	2.641	1.069–6.522
Kakkoura et al. (2016) [36]	0.918	0.815–1.033	0.844	0.666–1.069	0.934	0.770–1.131	0.880	0.716–1.080	0.905	0.756–1.084
Pooled OR	1.090	0.930–1.278	1.055	0.763–1.459	1.261	1.002–1.282	0.940	0.706–1.253	1.212	0.987–1.487
p (OR)	0.289		0.746		0.041		0.674		0.066	
I^2 (%)	64.5		61.2		55.1		60.4		55.1	
p (I^2)	0.001		0.001		0.007		0.002		0.007	
Publication Bias Egger's test (p)	0.357		0.590		0.883		0.017		0.488	
Begg's test (p)	0.913		0.428		0.743		0.300		0.827	
Power of p (%)	98.19		78.30		90.98		83.63		93.23	

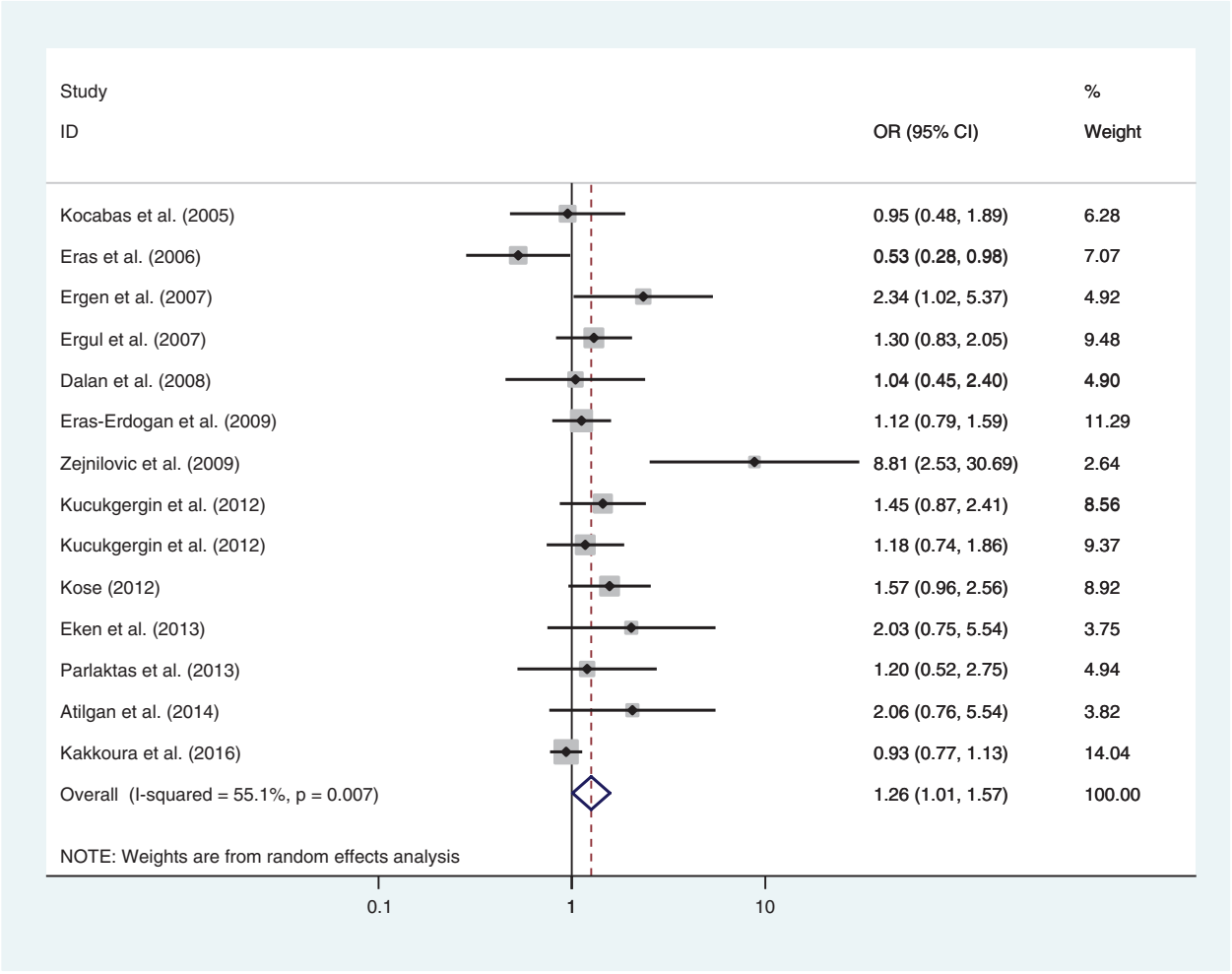

Figure 2: Forest plot of pooled odds ratio AV v.s VV and 95% confidence interval of individual studies and pooled data for the association between polymorphism of MnSOD and cancer risk.

contradictory results regarding the relationship between MnSOD Ala-9Val gene polymorphism and cancer risk [18, 19]. Ala allele was only observed in individuals with breast cancer risk in only three populations, among many others [9, 13, 15, 20]. The Val allele is associated with lung and bladder cancer; while Woodson et al. and Kang et al. showed that the Ala allele was related with prostate cancer [12, 17, 21]. The aim of this study is to investigate the relationship between MnSOD polymorphism and cancer in the Turkish and Cypriot populations through meta-analysis.

Materials and methods

Literature search

For the meta-analysis, PubMed, Web-of-Science, Turkish Medline, Turkish Journal of Medical Science, Journal of Turkish Oncology, the Turkish Council of Higher Education Theses Database and Google scholar were searched and data was obtained from the electronic databases using the keywords "MnSOD polymorphism, cancer, Turkish population and Cypriot population". Moreover, keywords were searched in both Turkish and English languages.

Selection criteria

The case-control groups of the studies on MnSOD polymorphism and cancer related to the Cypriot and Turkish population were included in the meta-analysis. In the investigation of the MnSOD polymorphism (V/V, V/A and A/A genotype) and cancer association, the genotype frequencies were detailed in the control and case groups and constituted the criteria for inclusion in the meta-analysis study. In the present study, publications in the control group that did not match the Hardy-Weinberg equality

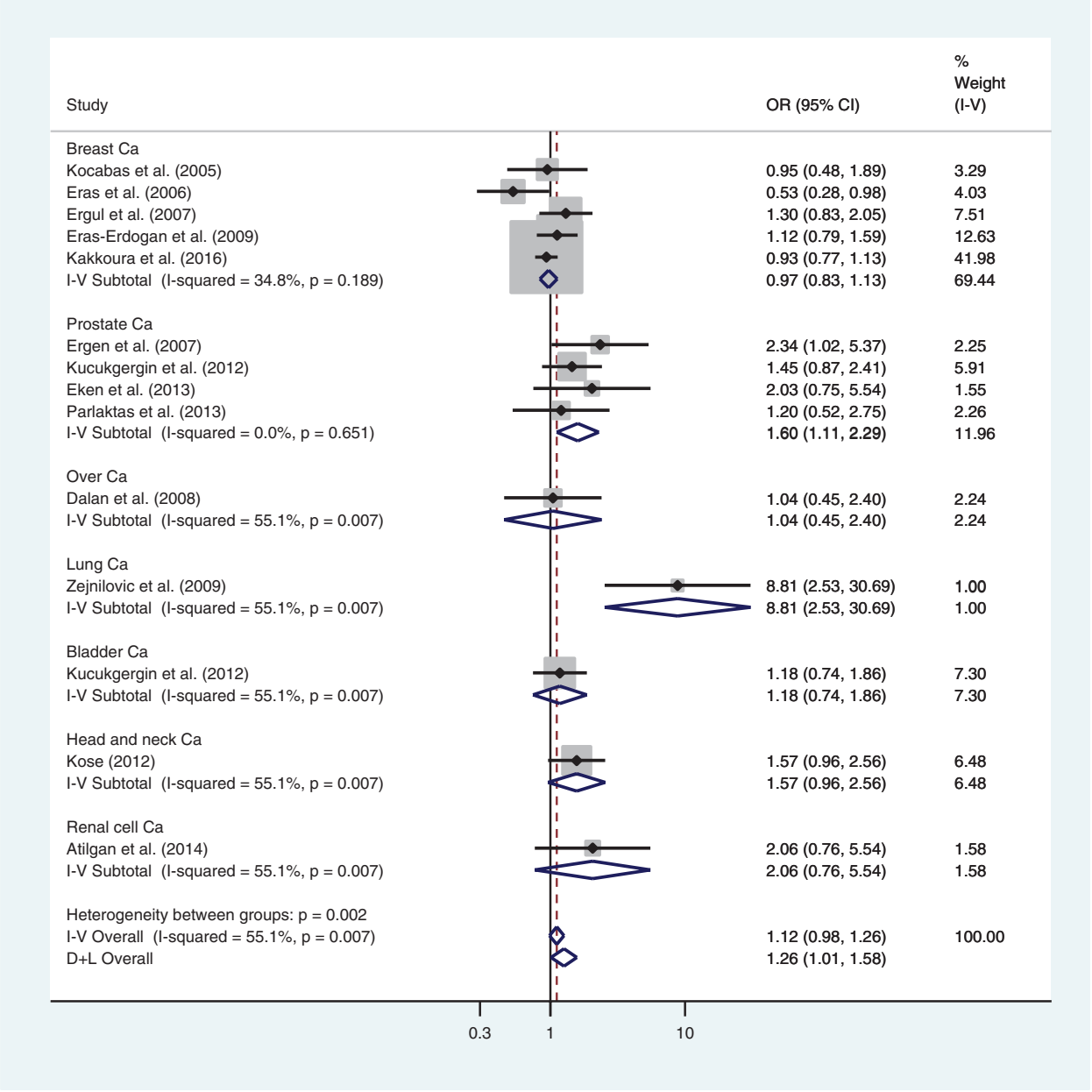

Figure 3: Forest plot of pooled odds ratio AV vs. VV and 95% confidence interval of individual studies and pooled data for the association cancer risk.

were not excluded from the meta-analysis. There is no consensus on the use of control groups that do not comply with the Hardy-Weinberg equation (HWE) in statistical analysis [22]. It has also been observed that this situation was not accepted as the exclusion criteria in similar meta-analyses of different populations [23, 24] (Figure 1).

Exclusion criterion

The control group was not included in the studies that were not composed of healthy individuals, the letter of the editor, meta-analysis publications and the studies without a control group or only healthy individuals were not included in the meta-analysis.

Statistical analysis

Meta-analysis was performed using STATA software version 14.2 (StataCorp, College, TX, USA). The pooled odds ratio (OR) and 95% confidence interval (CI) values for each study were calculated using the random effect model of DerSimonian and Laird and forest plots were

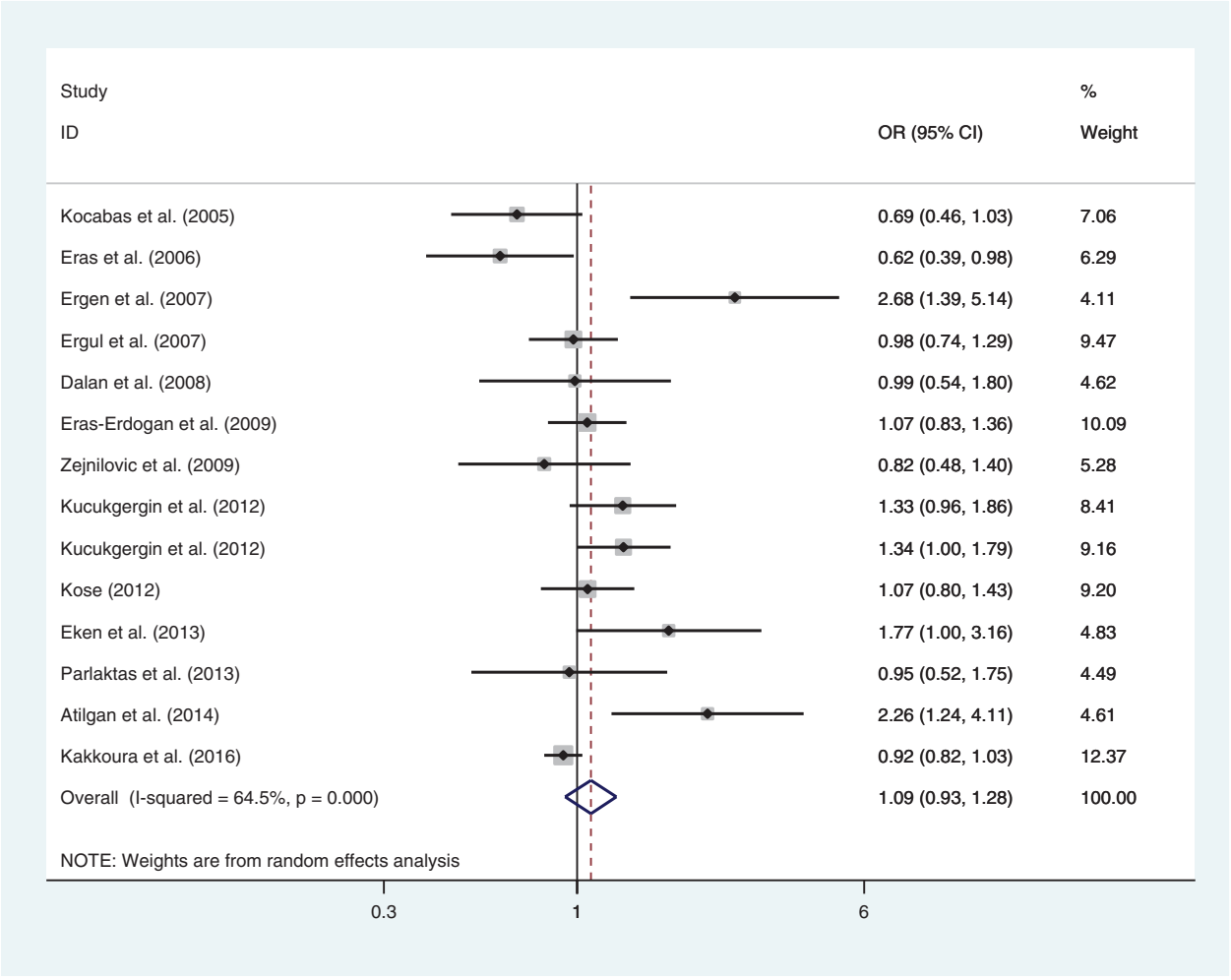

Figure 4: Forest plot of pooled odds ratio Ala vs. Val and 95% confidence interval of individual studies and pooled data for the association between polymorphism of MnSOD and cancer risk.

generated. As the studies were conducted on the Turkish and Cypriot population, a random effect model is used for heterogeneity. Publication bias was checked using the Begg's and Egger's test regression statistics. A funnels-plot graph was used to assess neutrality. Deviations from HWE in the control groups were calculated using the Genhwcci Stata module and power of the Q-test was calculated by using the PowerQ Stata module. A $p < 0.05$ was considered significant.

Results

A total of 12 publications and two unpublished theses covering 2413 cancer patients and 2907 healthy control groups were analyzed. The patients included breast (68.59%), prostate (11.02%), bladder (6.51%), head and neck and laryngeal (5.76%), lung (4.14%), ovarian (2.28%), and renal cell (1.70%) cancers.

In analyses of the MnSOD gene; the frequencies of V/V, V/A and A/A genotypes were found to be 36.15%, 44.86% and 18.99% in the control group and 35.02%, 47.37% and 17.61% in the cancer group, respectively (Table 1). Ala and Val alleles were found as 58.58%, 41.42% in the control group and 58.70% and 41.30% in the cancer group, respectively.

Meta-analysis results, Heterogeneity test, Publication Bias results and Power analysis are given in Table 2. There was a significant correlation between the additive genetic model (AV vs. VV: OR = 1.133, 95% CI: 1.002–1.282), and cancer (Figure 2). The risk of cancer in heterozygous individuals is increased 1.13-fold. The highest risk group in this model is lung cancer. In heterozygous individuals in the Turkish population,

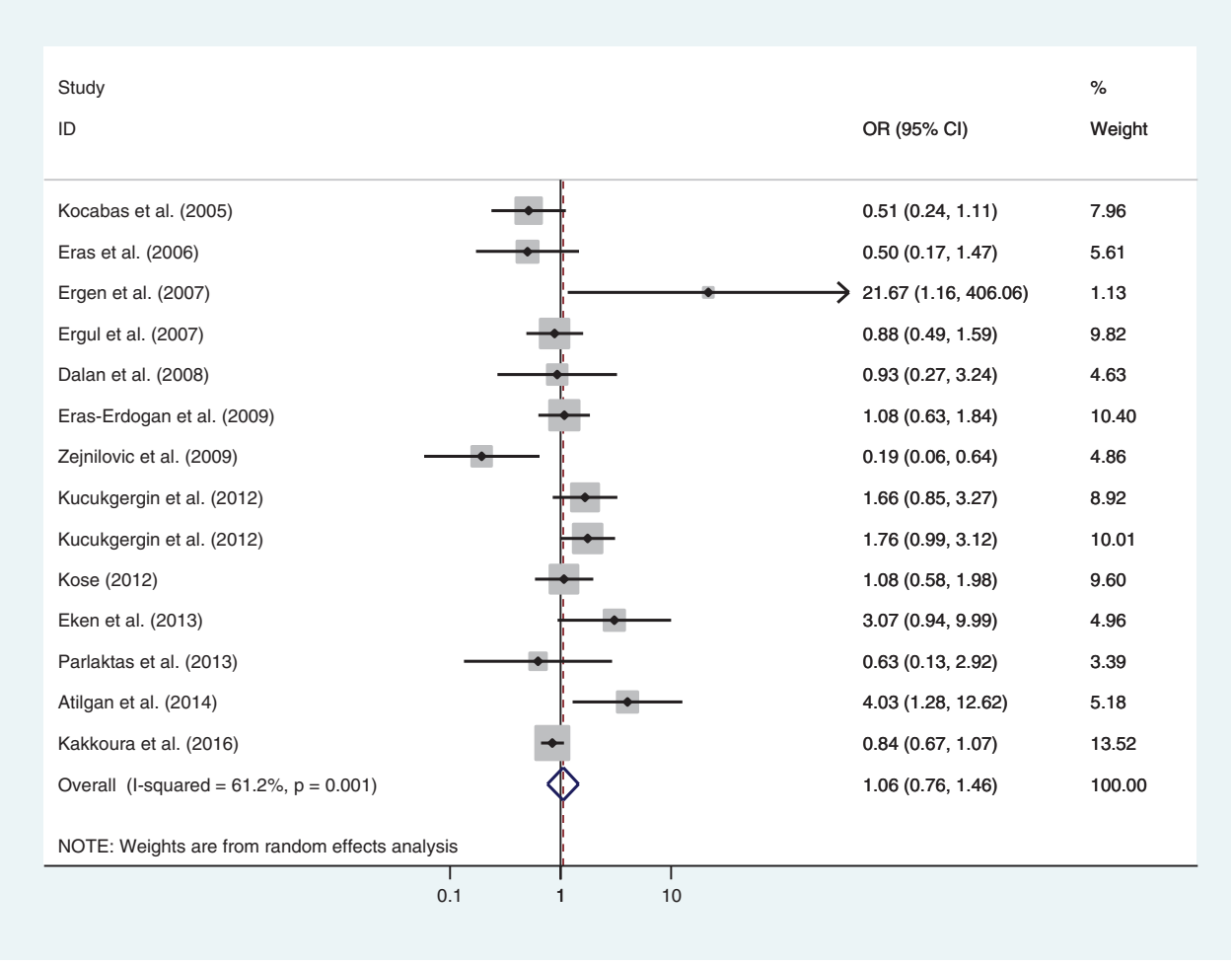

Figure 5: Forest plot of pooled odds ratio AA vs. VV and 95% confidence interval of individual studies and pooled data for the association cancer risk.

the risk of lung cancer is increased 8.81-fold (95% CI: 2.53, 30.69). The lowest risk group among both the Cypriot and the Turkish population was breast cancer (Figure 3). Breast cancer group showed a OR = 0.97 (95% CI: 0.83, 1.13). The OR were calculated in four genetic models as recessive, dominant, homozygous and additive types. No meaningful relationship was found between cancer and allele contrast (A vs. V: OR = 1.0165, 95% CI: 0.930–1.278), homozygote genetic model (AA vs. VV: OR = 0.983, 95% CI: 0.839–1.153), the dominant genetic model (AA + AV vs. VV: OR = 1.090, 95% CI: 0.971–1.223) and the recessive genetic model (AA vs. AV + VV: OR = 0.924, 95% CI: 0.803–1.064) (Figures 4–7). Higher heterogeneity ($I^2 > 50\%$) was determined in all models. In this meta-analysis study, evaluated in terms of Publication Bias, no bias was found (Figure 8) except for the recessive genetic model (p = 0.014).

Discussion

Meta-analysis is conducted to evaluate the results of working with a large number of different studies that belong to a specific domain. The meta-analysis findings are the result of statistical evaluation of large-scale aggregated studies [31, 32]. The aim is to investigate the relationship between MnSOD polymorphism (A/A, A/V, V/V) and cancer by using meta-analysis. For this purpose, 14 publications were examined.

Recently, different polymorphisms of the MnSOD gene have been noted in the etiology of various cancers. The MnSOD Val16Ala polymorphism has been shown to be associated with the development of various types of cancer such as PCA, breast and lung [14, 17, 37–43]. In a meta-analysis study on prostate cancer, it was observed that the MnSOD Val16Ala polymorphism increased the

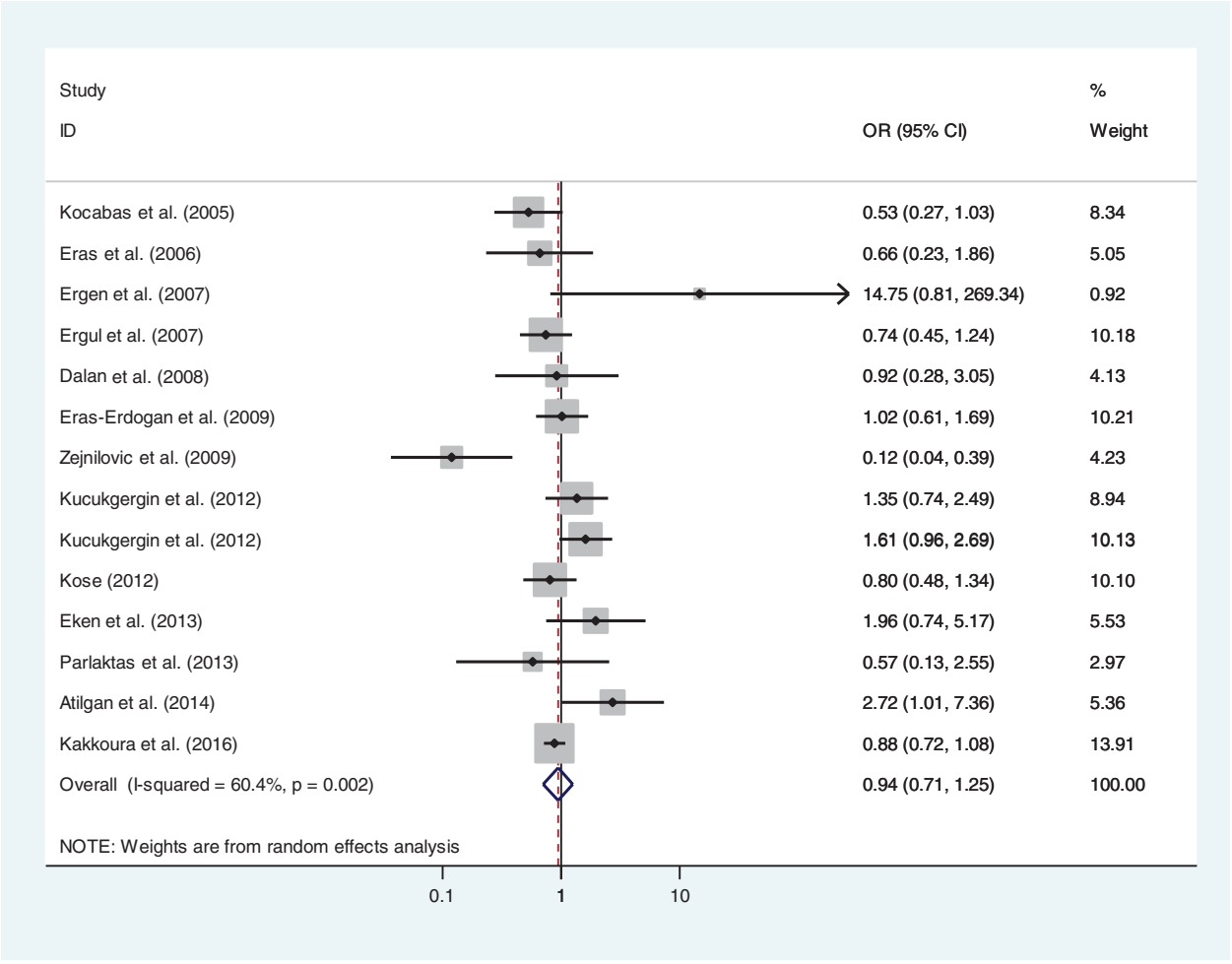

Figure 6: Forest plot of pooled odds ratio AA vs. VA + VV and 95% confidence interval (CI) of individual studies and pooled data for the association cancer risk.

cancer risk in the heterozygous model (OR = 1.14; 95% CI: 1.05–1.24), the homozygote model (OR = 1.18; 95% CI: 1.02–1.36), the dominant model (OR = 1.24; 95% CI: 1.07–1.44) and the recessive model (OR = 1.10; 95% CI: 0.96–1.24) [43]. In the present meta-analysis study, it was determined that prostate cancer risk increased (OR 1.60; 95% CI (1.11, 2.29) in the A/V heterozygote model in the Turkish population.

In the study conducted by Wang et al. [19], the MnSODVal-9Ala polymorphism was associated with prostate cancer. For the heterogeneity tests, both homozygous (Ala/Ala) and heterozygotes (Val/Ala) were detected in prostate cancer when compared with the wild-type Val/Val homozygotes (Val/Ala vs. Val/Val: OR = 1.1, 95% CI: 1.0–1.3, p = 0.72, Ala/Ala vs. Val/Val: OR = 1.3, 95% CI: 1.0–1.6, p = 0.04). MnSOD is known as a tumor suppressor in prostate cancers [10, 44–46]. Prostate cancer cells were increased in hydrogen peroxide levels. H_2O_2 is an intracellular oxidase, which induces DNA degradation in prostate cancer cells [47]. The different ala allele has been associated with an increased risk of breast cancer among premenopausal women with low antioxidant consumption [48].

Val16Ala polymorphism is associated with breast cancer. Bergman et al. [49] found that Val/Val and Val/Ala [OR = 2.7; (95% CI), 2.2–5.5 and OR = 3.0; 95% CI: 1.4–6.5] have increased breast cancer risk in individuals with genotypes. The Ala allele has been found to be associated with prostate cancer risk in the Turkish population [14]. In this meta-analysis study conducted on the Cypriot and Turkish populations, breast cancer risk (OR = 0.97, 95% CI: 0.83, 1.13) was found to increase in the A/V heteozygotic model. In the homozygous, recessive, and dominant models of the MnSOD polymorphisms, it

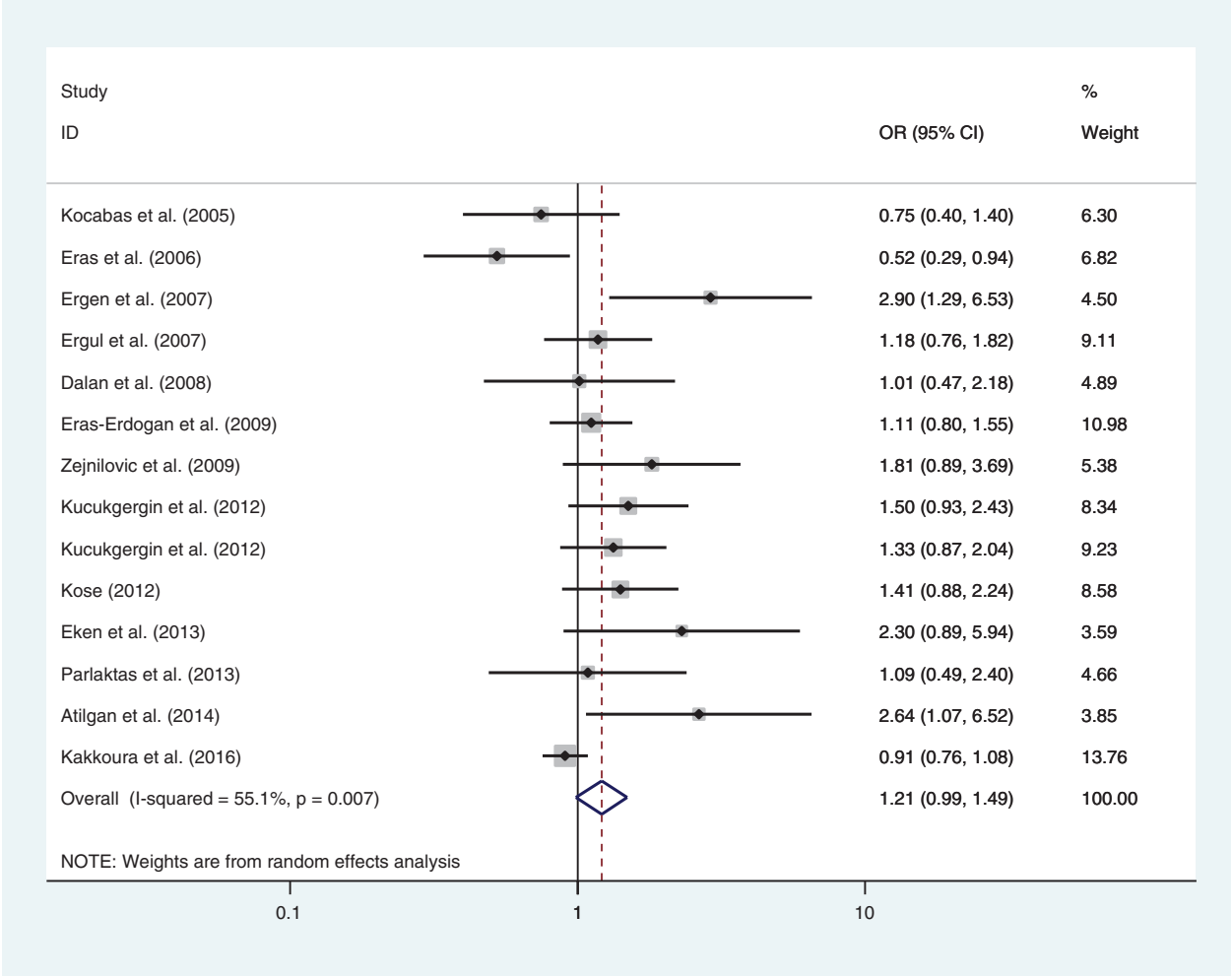

Figure 7: Forest plot of pooled odds ratio AA + AV vs. VV and 95% confidence interval of individual studies and pooled data for the association cancer risk.

is associated with a decreased risk of lung cancer. In the study by Sun et al. [50], the Ala allele has been shown to be associated with prostate and esophageal cancer risk, but not lung cancer. Low MnSOD expressions in the cells lead to increased ROS in the mitochondria. Increased accumulated ROS causes genomic instability, DNA, protein and lipid breakdown [51, 52]. In a study, supporting this finding, MnSOD Ala/Ala genotype was associated with a 1.7-fold increased risk of prostate cancer, a 1.9-fold increase risk of esophageal cancer, and a significant risk of breast cancer [15, 17, 53]. Data (3375 cases and 4050 controls) from six studies on lung cancer, homozygous (Ala/Ala vs. Val/Val, OR = 0.68; 95% CI: 0.59–0.78) and dominant models (Val/Ala + Ala/Ala vs. Val/Val, OR = 0.83, 95% CI: 0.75–0.92) of MnSOD polymorphism were associated with a reduction in lung cancer risk. MnSOD polymorphism has not been associated with the heterozygous model in prostate cancer studies with 4182 cases and 6885 controls [50]. According our results, in heterozygous models A/V (OR = 8.81; 95% CI (2.53–30.69) was associated with a high risk of lung cancer according to only one publication. In our study, complete neutral genotyping methods were used.

In conclusion, our meta-analysis with the Cyprus and Turkish populations showed that the A/V heterozygote genotype of MnSOD polymorphism is significant, and that genetic factors play a role in cancer development. Increase of ROS due to MnSOD polymorphism in the mitochondria may cause mtDNA degradation, which leads to cancer risk. More related studies to extend the effective risk factors in cancer patients from these populations are needed.

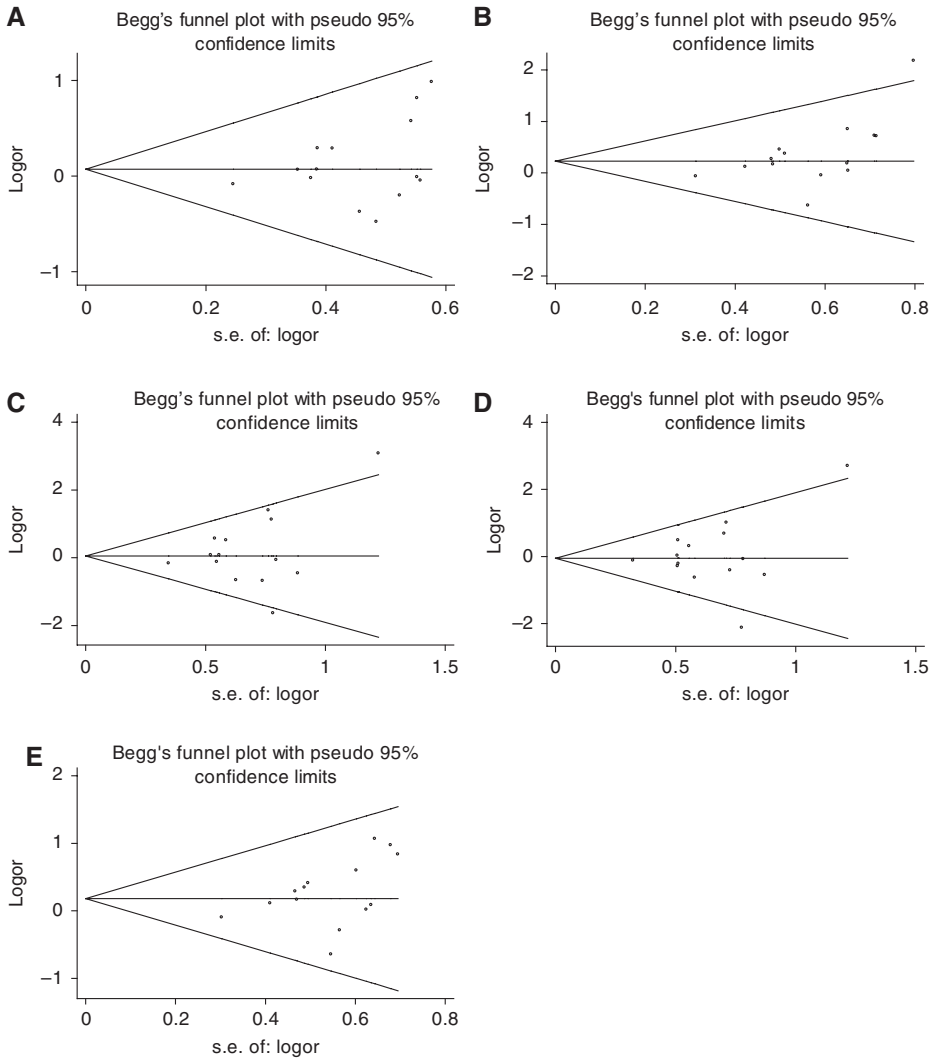

Figure 8: Begg's funnel plots for MnSOD polymorphism and susceptibility of cancer. (A) Ala vs. Val t = 1.25, p = 0.234; (B) AV vs. VV t = – 0.15; p = 0.883; (C) AA vs. VV t = 0.55, p = 0.590; (D) AA vs. VA + VV t = 2.80, p = 0.017; (E) AA + AV vs. VV t = – 0.71, p = 0.488.

Conflict of interests: The authors declare no conflict of interests.

References

1. Barra D, Schinina ME, Simmaco M, Bannister JV, Bannister WH, Rotilio G, et al. The primary structure of human liver manganese superoxide dismutase. J Biol Chem 1984;259:12595–601.
2. Zhong W, Oberley LW, Oberley TD, St Clair DK. Suppression of the malignant phenotype of human glioma cells by overexpression of manganese superoxide dismutase. Oncogene 1997;14:481–90.
3. Church SL. Manganese superoxide dismutase: nucleotide and deduced amino acid sequence of a cDNA encoding a new human transcript. Biochim Biophys Acta 1990;1087:250–2.
4. Church SL, Grant JW, Ridnour LA, Oberley LW, Swanson PE, Meltzer PS, et al. Increased manganese superoxide dismutase expression suppresses the malignant phenotype of human melanoma cells. Proc Natl Acad Sci USA 1993;90:3113–7.
5. Nelson DL, Lehninger AL, Cox MM. Lehninger principles of biochemistry. New York, W.H. Freeman: Macmillan, 2008.
6. Shimoda-Matsubayashi S, Matsumine H, Kobayashi T, Nakagawa-Hattori Y, Shimizu Y, Mizuno Y. Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene. A predictive evidence for conformational change to influence mitochondrial transport and a study of allelic association in Parkinson's disease. Biochem Biophys Res Commun 1996;226:561–5.
7. Rosenblum JS, Gilula NB, Lerner RA. On signal sequence polymorphisms and diseases of distribution. Proc Natl Acad Sci USA 1996;93:4471–3.

8. Sutton A, Khoury H, Prip-Buus C, Cepanec C, Pessayre D, Degoul F. The Ala16Val genetic dimorphism modulates the import of human manganese superoxide dismutase into rat liver mitochondria. Pharmacogenetics 2003;13:145–57.
9. Tamimi RM, Hankinson SE, Spiegelman D, Colditz GA, Hunter DJ. Manganese superoxide dismutase polymorphism, plasma antioxidants, cigarette smoking, and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:989–96.
10. Li N, Oberley TD, Oberley LW, Zhong W. Overexpression of manganese superoxide dismutase in DU145 human prostate carcinoma cells has multiple effects on cell phenotype. Prostate 1998;35:221–33.
11. Hung RJ, Boffetta P, Brennan P, Malaveille C, Gelatti U, Placidi D, et al. Genetic polymorphisms of MPO, COMT, MnSOD, NQO1, interactions with environmental exposures and bladder cancer risk. Carcinogenesis 2004;25:973–8.
12. Wang LI, Miller DP, Sai Y, Liu G, Su L, Wain JC, et al. Manganese superoxide dismutase alanine-to-valine polymorphism at codon 16 and lung cancer risk. J Natl Cancer Inst 2001;93:1818–21.
13. Ambrosone CB, Freudenheim JL, Thompson PA, Bowman E, Vena JE, Marshall JR, et al. Manganese superoxide dismutase (MnSOD) genetic polymorphisms, dietary antioxidants, and risk of breast cancer. Cancer Res 1999;59:602–6.
14. Ergen HA, Narter F, Timirci O, Isbir T. Effects of manganase superoxide dismutase Ala-9Val polymorphism on prostate cancer: a case-control study. Anticancer Res 2007;27:1227–30.
15. Mitrunen K, Sillanpaa P, Kataja V, Eskelinen M, Kosma VM, Benhamou S, et al. Association between manganese superoxide dismutase (MnSOD) gene polymorphism and breast cancer risk. Carcinogenesis 2001;22:827–9.
16. Olson SH, Carlson MD, Ostrer H, Harlap S, Stone A, Winters M, et al. Genetic variants in SOD2, MPO, and NQO1, and risk of ovarian cancer. Gynecol Oncol 2004;93:615–20.
17. Woodson K, Tangrea JA, Lehman TA, Modali R, Taylor KM, Snyder K, et al. Manganese superoxide dismutase (MnSOD) polymorphism, alpha-tocopherol supplementation and prostate cancer risk in the alpha-tocopherol, beta-carotene cancer prevention study (Finland). Cancer Causes Control 2003;14:513–8.
18. Millikan RC, Player J, de Cotret AR, Moorman P, Pittman G, Vannappagari V, et al. Manganese superoxide dismutase Ala-9Val polymorphism and risk of breast cancer in a population-based case-control study of African Americans and whites. Breast Cancer Res 2004;6:R264–74.
19. Wang S, Wang F, Shi X, Dai J, Peng Y, Guo X, et al. Association between manganese superoxide dismutase (MnSOD) Val-9Ala polymorphism and cancer risk – a meta-analysis. Eur J Cancer 2009;45:2874–81.
20. Kocabas NA, Sardas S, Cholerton S, Daly AK, Elhan AH, Karakaya AE. Genetic polymorphism of manganese superoxide dismutase (MnSOD) and breast cancer susceptibility. Cell Biochem Funct 2005;23:73–6.
21. Kang D, Lee KM, Park SK, Berndt SI, Peters U, Reding D, et al. Functional variant of manganese superoxide dismutase (SOD2 V16A) polymorphism is associated with prostate cancer risk in the prostate, lung, colorectal, and ovarian cancer study. Cancer Epidemiol Biomarkers Prev 2007;16:1581–6.
22. Trikalinos TA, Salanti G, Khoury MJ, Ioannidis JP. Impact of violations and deviations in Hardy-Weinberg equilibrium on postulated gene-disease associations. Am J Epidemiol 2006;163:300–9.
23. Pereira TV, Rudnicki M, Pereira AC, Pombo-de-Oliveira MS, Franco RF. 5,10-Methylenetetrahydrofolate reductase polymorphisms and acute lymphoblastic leukemia risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1956–63.
24. Zacho J, Yazdanyar S, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. Hyperhomocysteinemia, methylenetetrahydrofolate reductase c.677C > T polymorphism and risk of cancer: cross-sectional and prospective studies and meta-analyses of 75,000 cases and 93,000 controls. Int J Cancer 2011;128:644–52.
25. Eras N. The Relationship between the Risk of Breast Cancer and the Ala-9Val Polymorphism of Manganese Superoxide Dismutase (MnSOD) Gene. Mersin University, Institute of Health Sciences, Department of Medical Biology and Genetics Master Thesis, 2006.
26. Ergul E, Sazci A, Akpinar G, Utkan NZ, Cantürk NZ, Dulger M. Meme Kanserinde Mangan-Superoksit Dismutaz (Mn-Sod) Gen Polimorfizmi. Eur J Breast Health 2007;3:85.
27. Dalan AB, Ergen A, Yilmaz H, Karateke A, Isbir T. Manganese superoxide dismutase gene polymorphism, MnSOD plasma levels and risk of epithelial ovarian cancer. J Obstet Gynaecol Res 2008;34:878–84.
28. Eras-Erdogan N, Akbas E, Senli H, Kul S, Colak T. Relationship between polymorphism in the manganese superoxide dismutase gene and breast cancer. Mutat Res 2009;680:7–11.
29. Zejnilovic J, Akev N, Yilmaz H, Isbir T. Association between manganese superoxide dismutase polymorphism and risk of lung cancer. Cancer Genet Cytogenet 2009;189:1–4.
30. Kucukgergin C, Sanli O, Tefik T, Aydin M, Ozcan F, Seckin S. Increased risk of advanced prostate cancer associated with MnSOD Ala-9-Val gene polymorphism. Mol Biol Rep 2012;39:193–8.
31. Kucukgergin C, Sanli O, Amasyali AS, Tefik T, Seckin S. Genetic variants of MnSOD and GPX1 and susceptibility to bladder cancer in a Turkish population. Med Oncol 2012;29:1928–34.
32. Kose G. Xeroderma Pigmentosum Group D (XPD), Manganese Superoxide Dismutase (MnSOD, SOD2), Glutathione Peroxidase 1 (GPX1 polymorphisms of genes in head and neck region cancer research. Ankara University, Institute of Health Sciences, Department of Pharmaceutical Toxicology PhD Thesis, 2012.
33. Eken A, Erdem O, Arsova-Sarafinovska Z, Akay C, Sayal A, Matevska N, et al. Association between gene polymorphism of manganese superoxide dismutase and prostate cancer risk. J Biochem Mol Toxicol 2013;27:213–8.
34. Parlaktas BS, Atilgan D, Gencten Y, Benli I, Ozyurt H, Uluocak N, et al. A pilot study of the association of manganese superoxide dismutase and glutathione peroxidase 1 single gene polymorphisms with prostate cancer and serum prostate specific antigen levels. Arch Med Sci 2015;11:994–1000.
35. Atilgan D, Parlaktas BS, Uluocak N, Kolukcu E, Erdemir F, Ozyurt H, et al. The relationship between ALA16VAL single gene polymorphism and renal cell carcinoma. Adv Urol 2014;2014:932481.
36. Kakkoura MG, Demetriou CA, Loizidou MA, Loucaides G, Neophytou I, Malas S, et al. MnSOD and CAT polymorphisms modulate the effect of the Mediterranean diet on breast cancer risk among Greek-Cypriot women. Eur J Nutr 2016;55:1535–44.
37. Arsova-Sarafinovska Z, Matevska N, Petrovski D, Banev S, Dzikova S, Georgiev V, et al. Manganese superoxide dismutase (MnSOD) genetic polymorphism is associated with risk of early-onset prostate cancer. Cell Biochem Funct 2008;26:771–7.

38. Bica CG, de Moura da Silva LL, Toscani NV, da Cruz IB, Sa G, Graudenz MS, et al. MnSOD gene polymorphism association with steroid-dependent cancer. Pathol Oncol Res 2009;15:19–24.
39. Choi JY, Neuhouser ML, Barnett M, Hudson M, Kristal AR, Thornquist M, et al. Polymorphisms in oxidative stress-related genes are not associated with prostate cancer risk in heavy smokers. Cancer Epidemiol Biomarkers Prev 2007;16:1115–20.
40. Choi JY, Neuhouser ML, Barnett MJ, Hong CC, Kristal AR, Thornquist MD, et al. Iron intake, oxidative stress-related genes (MnSOD and MPO) and prostate cancer risk in CARET cohort. Carcinogenesis 2008;29:964–70.
41. Iguchi T, Sugita S, Wang CY, Newman NB, Nakatani T, Haas GP. MnSOD genotype and prostate cancer risk as a function of NAT genotype and smoking status. In Vivo 2009;23:7–12.
42. Mikhak B, Hunter DJ, Spiegelman D, Platz EA, Wu K, Erdman JW, Jr., et al. Manganese superoxide dismutase (MnSOD) gene polymorphism, interactions with carotenoid levels and prostate cancer risk. Carcinogenesis 2008;29:2335–40.
43. Wang LI, Neuberg D, Christiani DC. Asbestos exposure, manganese superoxide dismutase (MnSOD) genotype, and lung cancer risk. J Occup Environ Med 2004;46:556–64.
44. Duan H, Zhang HJ, Yang JQ, Oberley LW, Futscher BW, Domann FE. MnSOD up-regulates maspin tumor suppressor gene expression in human breast and prostate cancer cells. Antioxid Redox Signal 2003;5:677–88.
45. Plymate SR, Haugk KH, Sprenger CC, Nelson PS, Tennant MK, Zhang Y, et al. Increased manganese superoxide dismutase (SOD-2) is part of the mechanism for prostate tumor suppression by Mac25/insulin-like growth factor binding-protein-related protein-1. Oncogene 2003;22:1024–34.
46. Venkataraman S, Jiang X, Weydert C, Zhang Y, Zhang HJ, Goswami PC, et al. Manganese superoxide dismutase overexpression inhibits the growth of androgen-independent prostate cancer cells. Oncogene 2005;24:77–89.
47. Lim SD, Sun C, Lambeth JD, Marshall F, Amin M, Chung L, et al. Increased Nox1 and hydrogen peroxide in prostate cancer. Prostate 2005;62:200–7.
48. Li H, Kantoff PW, Giovannucci E, Leitzmann MF, Gaziano JM, Stampfer MJ, et al. Manganese superoxide dismutase polymorphism, prediagnostic antioxidant status, and risk of clinical significant prostate cancer. Cancer Res 2005;65:2498–504.
49. Bergman M, Ahnstrom M, Palmeback Wegman P, Wingren S. Polymorphism in the manganese superoxide dismutase (MnSOD) gene and risk of breast cancer in young women. J Cancer Res Clin Oncol 2005;131:439–44.
50. Sun GG, Wang YD, Lu YF, Hu WN. Different association of manganese superoxide dismutase gene polymorphisms with risk of prostate, esophageal, and lung cancers: evidence from a meta-analysis of 20,025 subjects. Asian Pac J Cancer Prev 2013;14:1937–43.
51. Orrenius S, Gogvadze V, Zhivotovsky B. Mitochondrial oxidative stress: implications for cell death. Annu Rev Pharmacol Toxicol 2007;47:143–83.
52. Trachootham D, Lu W, Ogasawara MA, Nilsa RD, Huang P. Redox regulation of cell survival. Antioxid Redox Signal 2008;10:1343–74.
53. Murphy SJ, Hughes AE, Patterson CC, Anderson LA, Watson RG, Johnston BT, et al. A population-based association study of SNPs of GSTP1, MnSOD, GPX2 and Barrett's esophagus and esophageal adenocarcinoma. Carcinogenesis 2007;28:1323–8.