RESEARCH

CYP1A1 rs4646903 T>C and rs1048943 A>G polymorphisms and the risk of colorectal cancer: an updated meta-analysis

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ABSTRACT

Aim: To find an association between the *CYP1A1* rs4646903 T>C and rs1048943 A>G polymorphisms and the risk of colorectal cancer by compiling recent studies.

Methods: We performed a meta-analysis on recently published articles available on PubMed and Google search engines. After extensive search, a total of 33 publications were identified. Out of the 33 publications, a total of 18 recent studies were included in the meta-analysis, which contains 2190 cases and 3977 controls for rs4646903 T>C and 2300 cases and 3789 controls for rs1048943 A>G polymorphisms.

Results: The pooled analysis indicated that *CYP1A1* rs4646903 T>C polymorphism is not a risk factor associated with colorectal cancer. The analysis of pooled data however, indicated a significant association between rs1048943 A>G and the risk of colorectal cancer [Over dominant model: OR=0.97, 95%CI (0.86-1.10); Dominant model: OR=0.97, 95% CI (0.86-1.09); Recessive model: OR=0.98, 95% CI (0.74-1.30); GA vs. AA: OR=0.97, 95% CI (0.86-1.10); GG vs. AA: OR=0.97, 95% CI (0.74-1.27)]. The comparison of the heterozygous genotypes has also shown the association. Further, alcohol and tobacco consumption increased colorectal cancer risk significantly. Our results are in line with the previous studies showing that *CYP1A1* rs1048943 A>G polymorphism increases the risk of colorectal cancer and *CYP1A1* rs4646903 T>C does not have any association with the risk of colorectal cancer.

Conclusion: Our study suggests that *CYP1A1* rs1048943 A>G is a risk factor for the development of colorectal cancer. In addition to that, consumption of tobacco and alcohol also significantly increase the risk ($p = 0.035$). *CYP1A1* rs4646903 T>C showed no significant association with colorectal cancer.

KEYWORDS: CYP1A1; colorectal cancer; rs4646903 T>C; rs1048943 A>G; Cytochrome-P450; xenobiotics; polymorphisms; meta-analysis

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INTRODUCTION

Colorectal cancer is the fourth most predominant reason for malignancy-related deaths globally. This ever-increasing death toll is estimated to rise by 60%, claiming more than 1 million lives and affecting 2 million new patients by the year 2030 (Arnold et al., 2017; Siegel et al., 2020). Malignancies arise from the aberrancy in the delicate and normal genetic makeup of a cell as a consequence of interactions between various factors (Rudolph et al., 2016). These factors can be of various origins, such as environmental or genetic and account for 70% of colorectal cancer incidence in the USA (Jemal et al., 2010). Xenobiotics' exposures are the most often studied environmental factor leading to CRC pathogenesis (Croom et al., 2012) and includes pollutants, polycyclic A hydrocarbons, drugs, synthetic polymers, and food additives. These xenobiotic compounds possess severe threats to the normal functioning of the body if not metabolized properly (Croom et al., 2012; Qadir et al., 2017).

The stability between the riddance and absorption of these xenobiotic compounds plays a crucial role in DNA damage (Hatagima et al., 2002). Enzymes metabolizing these xenobiotics function as a front-line barrier against various mutagenic substances (Laczmanska et al., 2007). Various studies have correlated the polymorphisms in various genes coding for xenobiotic-metabolizing enzymes with cancer occurrence (Indulski and Lutz et al., 2000; Terry et al., 2003; Chang et al., 2003; Jan et al., 2011). These enzymes metabolize the xenobiotics by two-step reactions, viz. phase I and phase II (Bozina et al., 2009). Principle enzyme systems participating in the conversion of the xenobiotics are phase I enzymes; for instance, cytochrome P450s (Raunio et al., 2015). The same classes of enzymes are linked with the pro-carcinogen chemical's activation, while the elimination of the xenobiotic compounds takes place by phase II enzymes (Koutros et al., 2011). Enzyme superfamily cytochrome P450 includes various subfamilies, importantly the CYP1A subfamily that includes *CYP1A1* and *CYP1A2*. Both of these enzymes catalyze the metabolism of xenobiotic compounds. A recent meta-analysis showed no correlation between the *CYP1A2* and colorectal cancer risk (Vukovic et al., 2016). *CYP1A1* has shown to be widely distributed in various body parts including the gastrointestinal tract and is implicated in the polycyclic aromatic hydrocarbons (PAHs) metabolism. The activation of PAHs by *CYP1A1* has been closely linked with tumor pathogenesis (Crewe et al., 2002). Being cytochrome 450's isozyme, *CYP1A1* is found on chromosome 15. To date, two single nucleotide polymorphisms (SNPs) of *CYP1A1* i.e., rs4646903 T>C and rs1048943 A>G and their association with cancer risk have been studied most often. rs4646903 T>C polymorphism (T to C) is present in the exon 3'-flanking region of the gene and three genotypes arise that are TT (wild type), TC (heterozygous), and CC (homozygous). This substitution of T by C creates a restriction site for MSPI. Another SNP i.e., Ile/Val also called exon 7 polymorphism occurs as a consequence of A to G transition and has three genotypes i.e., AA (wild type), AG (heterozygous), and GG (homozygous) (Sivaraman et al., 1994). The substitution of isoleucine to valine occurs from A to G transition in codon 462.

Various dietary habits, such as alcoholism and smoking (Hamachi et al., 2013; Öztaş et al., 2016) have been shown to increase colorectal cancer predisposition in the presence of *CYP1A1* polymorphisms. Various studies have also indicated that the intake of food high in flavonoids (Cho et al., 2017) reduces CRC risk significantly. However, some meta-analyses studies found no association with the development of colorectal cancer. Due to a great deal of ambiguity in the data available supporting or contradicting the role of *CYP1A1* polymorphisms in the development of colorectal cancer, we undertook this meta-analysis to analyze the recent data from the latest studies with an aim to reach at a positive or negative conclusive correlation between the dietary habits of people

from different ethnicities, genetic polymorphisms and the risk of colorectal cancer.

MATERIALS & METHODS

Search strategy and selection criteria

The online search was performed in various databases such as PubMed and GoogleScholar using the search strings "*CYP1A1*", "cytochrome-P450", AND "colorectal cancer" or "colon or rectal cancer". Also, related studies were taken from the citations of the original articles. The studies included were then screened for duplication, and selected according to the following inclusion criteria: a) case-control study, b) cohort study, c) published in English language, d) Last 10-year studies, e) genotype frequency data. Studies were omitted based on the following exclusion criteria: a) only case study, b) uncertain genotype data, c) non-English language, d) Studies preceding 2011, e) not about *CYP1A1* (Figure 1). In this study, only the most recent studies with complete information have been included.

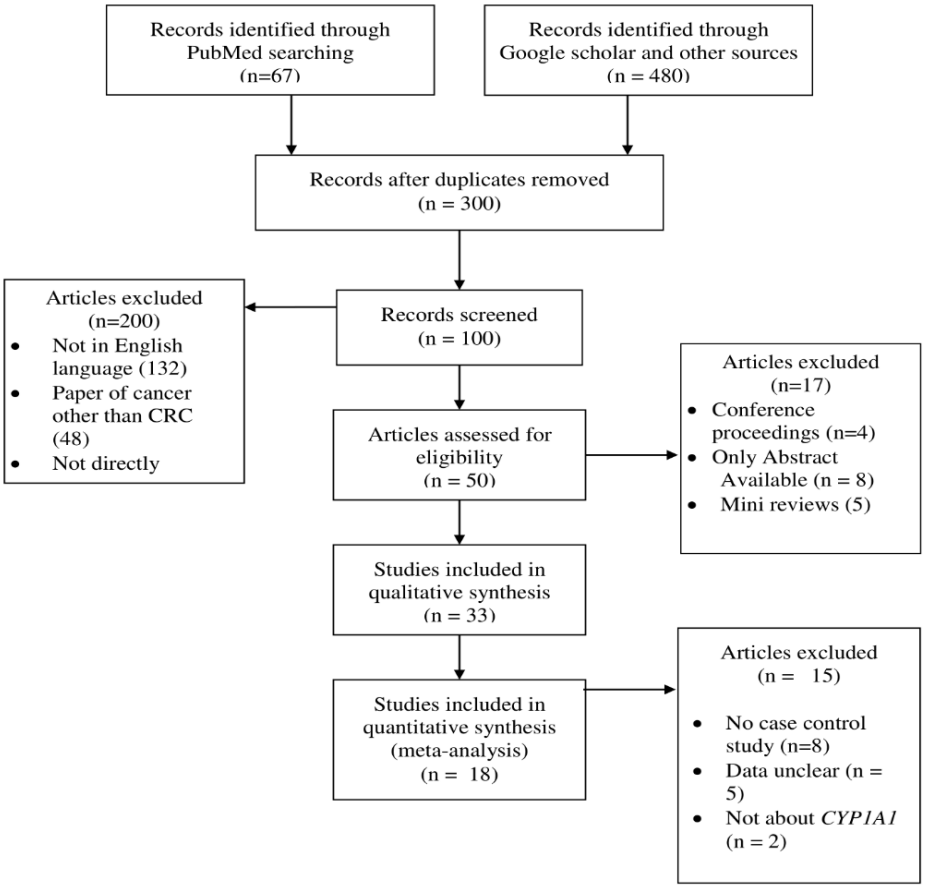

Figure 1: Flow chart of Study search and selection.

Data Extraction and statistical analysis

From all the selected eligible studies, the following data were collected- publication year, the last name of the first author, ethnicity, origin country, factors associated, the total number of patients, and controls. Based on data, the ethnic groups were characterized as Caucasians, Asians, and Mixed Population (having more than one ethnic descent). As per the above-mentioned criteria of inclusion and exclusion, 10 studies on rs4646903 T>C and 8 studies on rs1048943 A>G polymorphisms of the *CYP1A1* gene were taken into account to perform

this meta-analysis. We used the Metagenyo web tool for data analysis (Martorell-Marugan et al., 2017). Through the Metagenyo tool, the HWE of genotypes was determined to calculate the P-value for every study in the control population to signify the quality of studies. The genetic models for allele and genotype contrasts for rs4646903 T>C (CT vs. TT; TT vs. CC) and rs1048943 A>G (GA vs. AA; AA vs. GG) polymorphisms included over-dominant, dominant, and recessive models.

To deduce the intensity of the relationship between the incidence of colorectal cancer and *CYP1A1* polymorphisms, statistical analysis for the computation of 95% confidence intervals (CIs) and odds ratios (ORs) were done. A Forest plot was also drawn. In addition, to determine the heterogeneity among studies Cochran's Q statistics and I^2 tests were also conducted, and according to heterogeneity P-value, two different statistical models were included i.e., fixed effect model (FEM) and random effects model (REM). According to the MetaGenyo tool, the heterogeneity P-value < 0.1 suggested using the REM model, else FEM can be used. Sensitivity analyses was conducted to identify sensitive studies in the pool. To investigate the publication bias in our study, Begg's funnel plot was prepared, the results thus obtained were further confirmed by Egger's test.

RESULTS

Study characteristics

The selection strategy for the is depicted in Figure 1. After a wide search through PubMed and GoogleScholar databases, we identified 33 studies that matched our keywords. After screening and reading full-text versions, their suitability according to the criteria mentioned above, we selected 18 studies for meta-analysis. This meta-analysis evaluated the relationship between rs1048943 A>G and rs4646903 T>C polymorphisms in the *CYP1A1* gene and the risk of colorectal cancer. The genotype frequencies in the study are documented in Table 1. Further, in order to calculate the variations across the studies, heterogeneity test was done, showing values for *CYP1A1* rs4646903 T>C (τ^2=0.095, H=1.40, I^2=49%, Q=15.63, p-value=0.05) (Figure 2a) and for *CYP1A1* rs1048943 A>G polymorphism (τ^2=0.036, H=1.10, I^2=17%, Q=7.26, p-value=0.30) (Fig. 2b).

The methods used for genotyping analysis in most of the studies were PCR-RFLP, allele-specific, and TaqMan PCR assay. Also, for most of the studies, colorectal cancer was confirmed histopathologically and all controls were matched according to their demographical characteristics.

Table 1: Features of articles included in the meta-analysis.

Reference	Ethnicity	Country	Factors Studied	Cases			Control			HWE *p*-value
*CYP1A1 MSP*I Polymorphism				TT	TC	CC	TT	TC	CC	
(Darazy et al., 2011)	Asian	Lebanon		42	2	2	54	1	1	0
(Saeed et al., 2013)	Asian	Saudi		3	21	70	0	6	73	0.726
(Hamachi et al., 2013)	Asian	Japan	Smoking	174	219	62	388	508	156	0.623
(Proença et al., 2015)	Mixed population	Brazil	Smoking and Drinking habits	54	17	3	129	55	16	0.007

(Fernandes et al., 2016)	Mixed population	Brazil	Tobacco consumption and Alcoholism	165	53	9	246	125	29	0.022
(Öztaş et al., 2016)	Caucasian	Europe	smoking	162	28	3	221	27	0	0.365
(Cho et al., 2017)	Asian	Korea	Flavonoids	268	323	106	525	646	229	0.204
(Kamiza et al., 2018)	Asian	Taiwan		52	62	10	92	129	43	0.844
(Ibrahem et al., 2021)	Asian	Iraq		94	60	46	100	66	34	0.0002
(Sindi et al., 2021)	Asian	Saudi Arabia	non-smoking	45	35	0	48	30	0	0.036
CYP1A1 Ile462Val Polymorphism				AA	AG	GG	AA	AG	GG	
(Jan et al., 2011)	Egyptians	Egypt	Smoking and other dietary habits that have pro-carcinogens	35	4	1	19	1	0	0.90
(Hamachi et al., 2013)	Asian	Japan	smoking	281	152	22	611	389	52	0.32
(Gil et al., 2014)	Caucasian	Poland		414	59	3	369	29	2	0.09
(Fernandes et al., 2016)	Mixed population	Brazil	Smoking and Alcoholism	193	30	4	312	75	13	0.002
(Cho et al., 2017)	Asian	Korea	flavonoids	422	237	36	804	483	84	0.31
(Kamiza et al., 2018)	Asian	Taiwan	Meat	98	26	3	188	75	5	0.42
(Sindi et al., 2021)	Asian	South Arabia		65	15	0	69	9	0	0.58
(Ibrahem et al., 2021)	Asian	Iraq		112	66	22	138	50	12	0.01

Quantitative Data Analysis

Total 10 eligible studies were included for *CYP1A1* rs4646903 T>C polymorphism, which included 7 studies on Asians, 1 study on Caucasians and 2 studies on mixed populations. The 10 studies had a total of 2190 cases and 3977 controls. Statistically, no association between rs4646903 T>C polymorphism and the risk of colorectal cancer was observed (Over-dominant model (CT vs. CC+TT): OR=0.99, 95% CI: 0.88-1.10; Dominant model

(CC+CT vs. TT): OR= 0.92, 95% CI: 0.82-1.03; Recessive model (CC vs. CT+TT): OR= 0.87, 95% CI: 0.73-1.03; CT vs.TT OR=0.94, 95% CI (0.83-1.06); TT vs.CC OR=0.88, 95% CI (0.72-1.05)) (Table 2) (Fig. 2a).

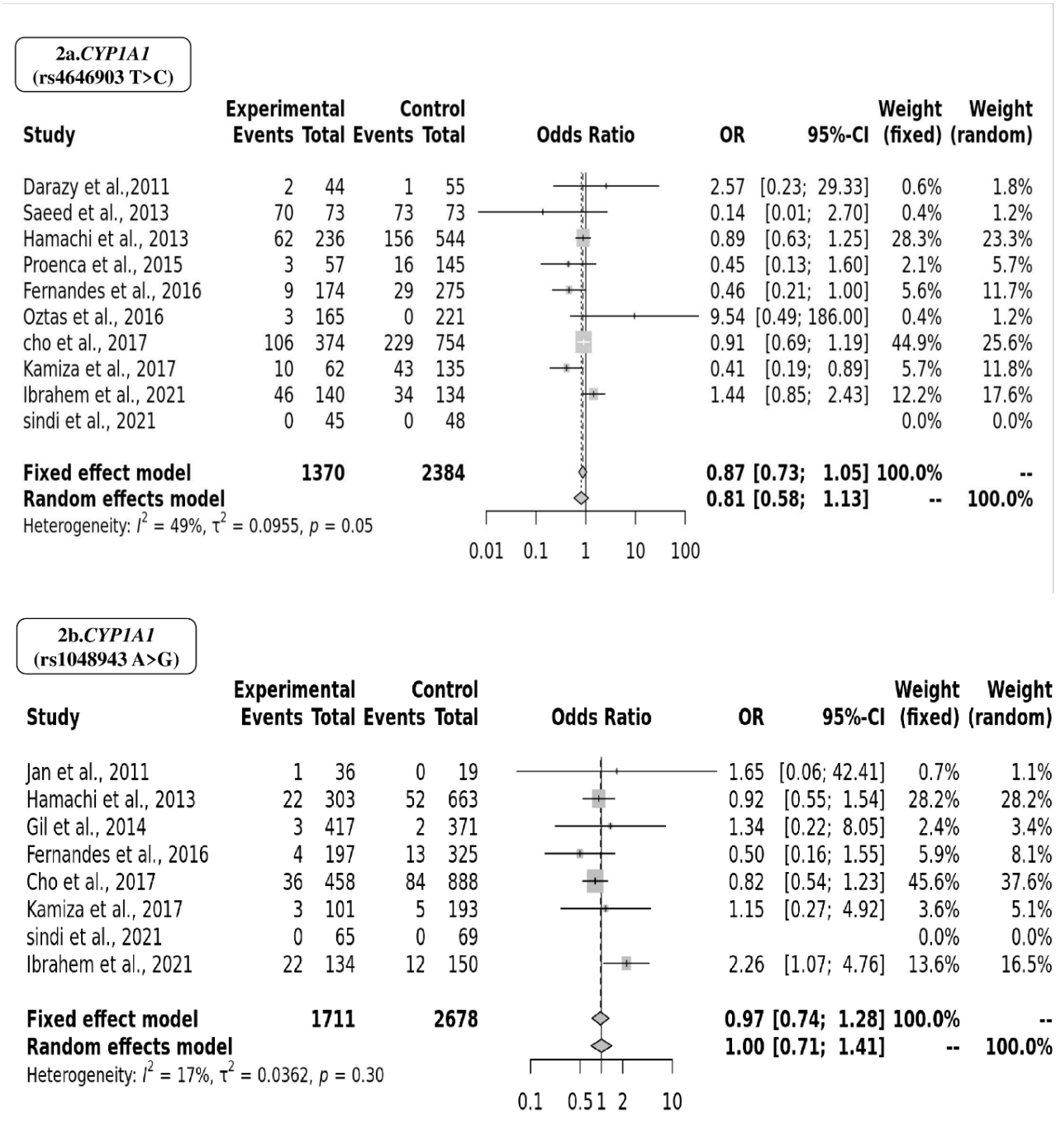

Figure 2- Forest plot for *CYP1A1* polymorphisms and CRC risk. 2a (upper panel): rs4646903 T>C polymorphism (TT vs. CC) showing the moderate risk susceptibility to CRC with fixed effect model (FEM) (OR=0.87 (0.73; 1.05)) with heterogeneity (I^2 =49%, p=0.05) and 2b. rs1048943 A>G polymorphism (AA vs. GG) shows risk factor for CRC with (FEM) (OR=0.97 (0.74; 1.28)) with heterogeneity (I^2= 17%, p=0.30).

Table 2- Results of the meta-analysis on CYP1A1 polymorphisms and CRC risk.

	OR (95% CI)		Heterogeneity (Q test)		Publication bias
		p-value	I^2 %	P-value	Egger's test P-value
MspI polymorphism (Overall)					
Dominant model (CC+CT vs. TT)	0.92 (0.82-1.03)	0.064	0.71	3e-04	0.75
Recessive model (CC vs. CT+TT)	0.87 (0.73-1.03)	0.09	0.60	0.01	0.67
Overdominant model (CT vs. CC+TT)	0.99 (0.88-1.10)	0.16	0.43	0.07	1.00
CT vs. TT	0.94 (0.83-1.06)	0.29	0	0.45	0.88
TT vs. CC	0.87(0.73-1.05)	0.14	0.48	0.05	0.74
Ile462Val Polymorphism					
Dominant model (GG+GA vs. AA)	0.97 (0.86-1.10)	0.60	0.73	4e-04	0.32
Recessive model (GG vs. GA+AA)	0.98 (0.74-1.29)	0.90	0	0.50	0.60
Overdominant model (GA vs. GG+AA)	0.97 (0.85-1.10)	0.56	0.71	9e-04	0.32
GA vs. AA	0.97 (0.85-1.10)	0.57	0.17	0.37	0.60
AA vs. GG	0.96 (0.74-1.27)	0.82	0.66	0.00	0.36

CYP1A1 rs1048943 A>G and susceptibility to CRC

On the other hand, a total of 8 studies were included in *CYP1A1* rs1048943 A>G polymorphism, which consisted of 4 studies on Asians, (1 Egyptian), 1 study on Caucasians, and 1 study on mixed populations. These 8 studies included a total of 2300 cases and 3789 controls. Analysis using various genetic models suggested statistical association between rs1048943 A>G and CRC risk, (Overdominant model: OR=0.96, 95%CI (0.86-1.10); Dominant model: OR=0.97, 95% CI (0.86-1.08); Recessive model: OR=0.98, 95% CI (0.74-1.29); GA vs. AA: OR=0.97, 95%CI (0.85-1.10); AA vs. GG: OR=0.96, 95%CI (0.73-1.27)) (Table 1) (Figure 2b).

Sensitivity analysis and publication bias

One study at a time was excluded to do the sensitivity analysis. The sensitivity analysis did not show a significant change in the pooled ORs for both *CYP1A1* rs4646903 T>C and rs1048943 A>G polymorphisms (Figure 3). For *CYP1A1* rs4646903 T>C polymorphism, the control group of three studies did not follow Hardy-Weinberg equilibrium (HWE) (Darazy et al., 2011; Proença et al., 2015; Ibrahem et al., 2021) and in rs1048943 A>G polymorphism, one study did not follow the HW equillibrium (Fernandes et al., 2016).

To assess the publication bias, Begg's funnel plot was used. Since rs4646903 T>C polymorphism didn't show a significant role in the CRC risk and development, it is not discussed. Whereas, a small standard error in Begg's funnel plot for rs1048943 A>G polymorphism due to small sample size was found (Figure 4), this result was further confirmed by Egger's test that showed a value of rs4646903

T>C p=0.742 and rs1048943 A>G p=0.595, indicating no publication bias in our study.

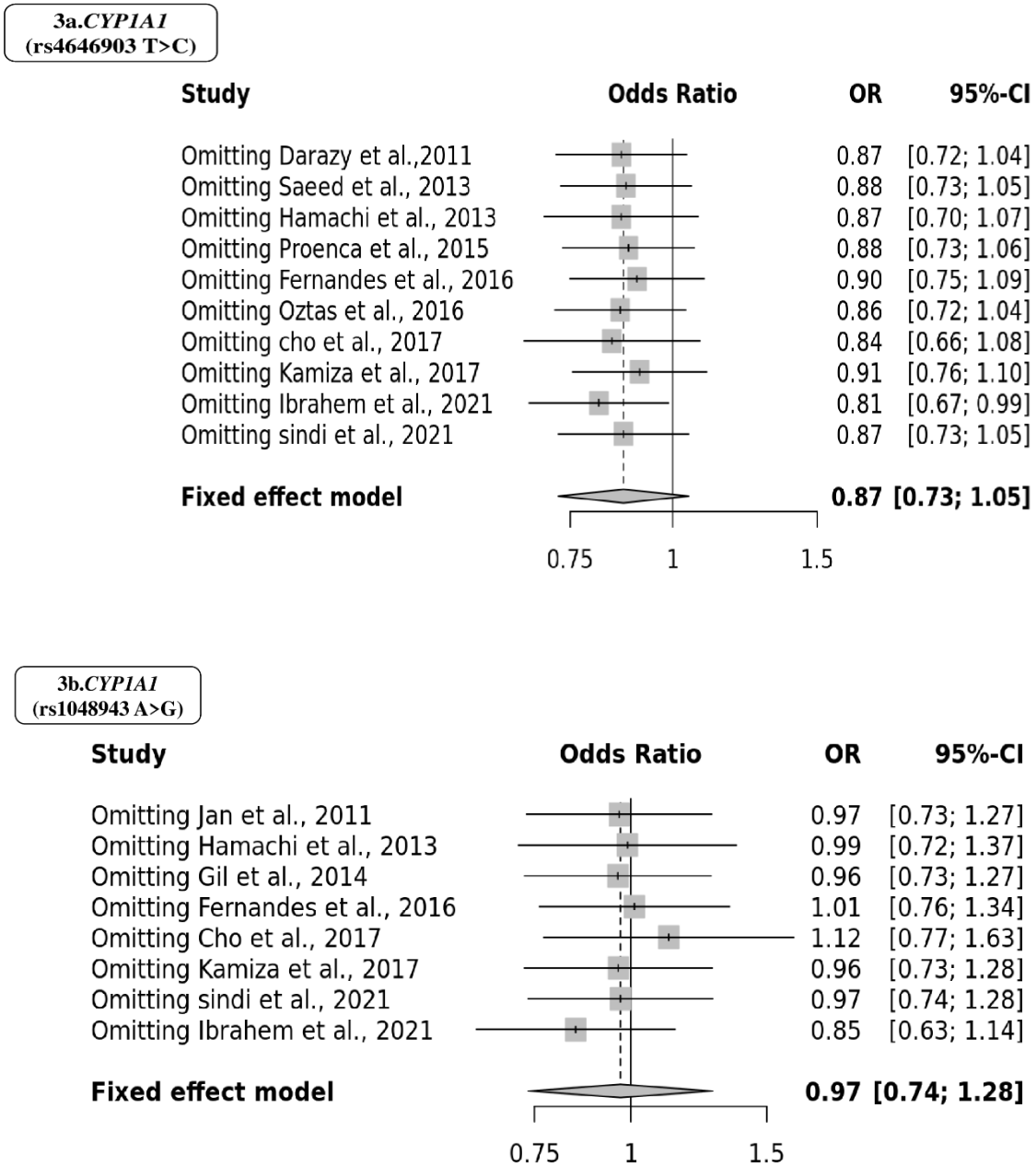

Figure 3. Sensitivity plot of CRC risk incidence and *CYP1A1* fixed effect model (FEM) depicted by excluding one study at a time did not show a significant change in study in 3a. rs4646903 T>C polymorphism (TT vs. CC) (OR (0.87 (0.73; 1.05)) and 3b. rs1048943 A>G polymorphism (AA vs. GG) (OR (0.97 (0.74; 1.28).

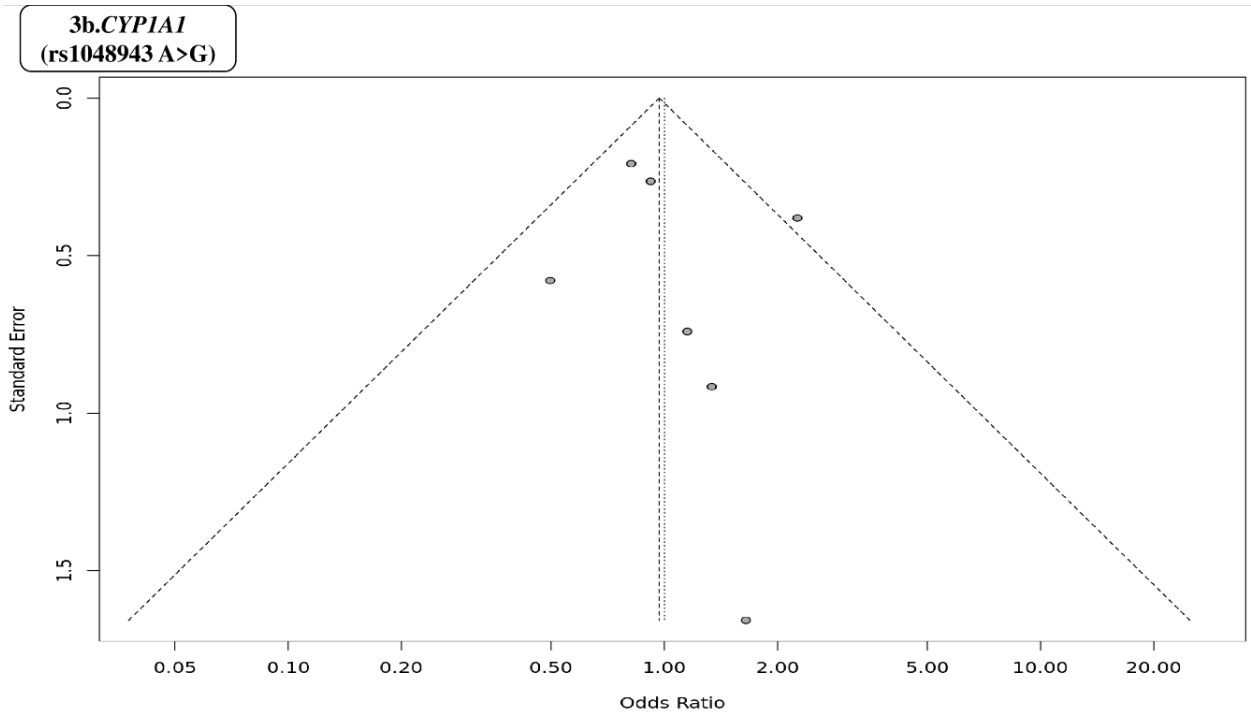

Figure 4: Funnel plot of *CYP1A1* rs1048943 A>G polymorphism in association with the risk of colorectal cancer. Study bias depicts slight standard error mainly due to small sample size.

DISCUSSION

Meta-analysis helps to summarize all the studies to reduce the problem of small size and differences in various genetic studies, ultimately providing better results than individual case-control studies. A detailed in-depth meta-analysis was carried out to check for association between the *CYP1A1* polymorphisms rs4646903 T>C and rs1048943 A>G and cancer risk. Our meta-analysis showed that genotype variants at rs4646903 T>C are not a functional risk factor for colorectal cancer. The findings of our study are in line with the previous studies (Little et al., 2006; Zheng et al., 2012). Our study also complies with the studies done by Zheng et al., (2012), Jin et al., (2011), Zhu et al., (2016), and Xu et al., (2020) which show that the rs1048943 A>G polymorphism in the *CYP1A1* plays a role in the risk of colorectal cancer. The transition change of nucleotide from Adenine (A) to Guanine (G) leads to genetic instability and change from Isoleucine to valine amino acid at codon 462. These changes can increase the activity of the *CYP1A1* enzyme and hence the activation of carcinogens could escalate the risk of colorectal cancer (Akiyama and Gonzalez et al., 2003). The polymorphism of *CYP1A1* has also been found in other diseases including ulcerative colitis, myocardial infarction, colorectal adenoma, and many more.

In this study, we analyzed 18 studies with 2190 cases and 3977 controls for rs4646903 T>C polymorphism and 2300 cases and 3789 control for rs1048943 A>G polymorphism. The *CYP1A1* rs4646903 T>C was not directly associated with CRC, however, the polymorphism *CYP1A1* rs1048943 A>G has shown a statistically significant association with the risk of CRC. Our meta-analysis has compiled studies conducted on *CYP1A1* polymorphism and CRC risk in the last 10 years. The sensitivity analysis that was conducted has not shown the direct influence of any one study on ORs and 95% CIs for the *CYP1A1* rs1048943 A>G. However, the heterogeneity between studies exists which indicates heterogeneities due to control HWE and ethnicity. Similarly, heterogeneity for rs4646903 T>C is due to ethnicity, source of control

samples, and the deviation from the HW equillibrium. In addition, the Odd-ratio for the over-dominant model of rs1048943 A>G (OR=0.96, 95%CI (0.86-1.10)), has shown to be a risk factor for CRC, which is supported by Jin et al., (2011) and Sindi et al., (2021). The analysis of ethnic groups showed a significant risk due to *CYP1A1* polymorphism in Asians and Caucasians, which is also backed by a previous study (Zheng et al., 2012).

Being a phase I xenobiotic-metabolizing enzyme, *CYP1A1* is involved in the activation of procarcinogens mainly present in the PAHs (Koutros et al., 2011; Gil et al., 2014; Kamiza et al., 2018). PAHs are found in the smoke of tobacco, smoked eatables, and are abundantly present in the city environment and function as the risk factor for the development of various malignancies. The procarcinogens present in the PAHs get activated by *CYP1A1*before their binding with the DNA. These carcinogens then bind to DNA and form aromatic adducts and these are often considered the initiators of carcinogenesis (Masson et al., 2005). Considering the vast and crucial roles of *CYP1A1*, it is conceivable that the polymorphisms in the *CYP1A1* gene are capable of colorectal cancer risk modulation.

While interpreting the results, various limitations of present study also need to be taken into consideration. The major limitation is that the literature published in English language only was considered for inclusion in this study. The studies published in languages other than English may have data representing a particular ethnicity and present supportive or contradictory results. Due to the unavailability of sufficient conclusive concrete data for meta-analysis to be performed, the influence of several factors such as vitamins intake, obesity, and inflammation was also not analyzed (Boland et al., 2010; Rheem et al., 2010). The small size of the sample in some studies might also hinder the reliability of their findings and hence studies with larger sample size may provide a clearer picture.

Our study proposes that the rs1048943 A>G polymorphism in the *CYP1A1* gene act as a moderate risk factor for the initiation and development of colorectal cancer. Contrary to that rs4646903 T>C polymorphism showed no ability to modulate the risk factor of colorectal cancer (Saeed et al., 2013). More studies are needed to be done for assessing CRC risk by studying the molecular mechanism of rs1048943 A>G polymorphism in carcinogenesis.

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Author's contribution

SS, VSB performed a literature search; SS, VSB, NKV and DS performed meta-analysis; SS, AKD, VD, AKT wrote the first draft; SKP, SD, NKV and DS critically reviewed the manuscript.

Conflict of interest

There is no conflict of interest

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Declaration of originality

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REFERENCES

Akiyama TE, Gonzalez FJ. Regulation of P450 genes by liver-enriched transcription factors and nuclear receptors. Biochimica et biophysica acta. 2003;1619(3):223-34.

Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91.

Boland CR. Chronic inflammation, colorectal cancer and gene polymorphisms. Dig Dis. 2010;28(4-5):590-95.

Bozina N, Bradamante V, Lovrić M. Genetic polymorphism of metabolic enzymes P450 (CYP) as a susceptibility factor for drug response, toxicity, and cancer risk. Arhiv za higijenu rada i toksikologiju. 2009;60(2):217-42.

Chang BL, Zheng SL, Isaacs SD, Turner A, Hawkins GA, Wiley KE, et al. Polymorphisms in the *CYP1A1* gene are associated with prostate cancer risk. International journal of cancer. 2003;106(3):375-8.

Cho YA, Lee J, Oh JH, Chang HJ, Sohn DK, Shin A, et al. Dietary Flavonoids, *CYP1A1* Genetic Variants, and the Risk of Colorectal Cancer in a Korean population. Scientific reports. 2017;7(1):128.

Crewe HK, Notley LM, Wunsch RM, Lennard MS, Gillam EM. Metabolism of tamoxifen by recombinant human cytochrome P450 enzymes: formation of the 4-hydroxy, 4'-hydroxy and N-desmethyl metabolites and isomerization of trans-4-hydroxytamoxifen. Drug metabolism and disposition: the biological fate of chemicals. 2002;30(8):869-74.

Croom E. Metabolism of xenobiotics of human environments. Progress in molecular biology and translational science. 2012;112:31-88.

Darazy M, Balbaa M, Mugharbil A, Saeed H, Sidani H, Abdel-Razzak Z. *CYP1A1*, CYP2E1, and GSTM1 gene polymorphisms and susceptibility to colorectal and gastric cancer among Lebanese. Genetic testing and molecular biomarkers. 2011;15(6):423-9.

Fernandes GM, Russo A, Proença MA, Gazola NF, Rodrigues GH, Biselli-Chicote PM, et al. *CYP1A1*, CYP2E1 and EPHX1 polymorphisms in sporadic colorectal neoplasms. World J Gastroenterol. 2016;22(45):9974-83.

Gil J, Gaj P, Misiak B, Ostrowski J, Karpinski P, Jarczynska A et al. CYP1A1 Ile462Val polymorphism and colorectal cncer risk in Polish patients. Med Oncol. 2014;31(7):72-72.

Hamachi T, Tajima O, Uezono K, Tabata S, Abe H, Ohnaka K, et al. *CYP1A1*, GSTM1, GSTT1 and NQO1 polymorphisms and colorectal adenomas in Japanese men. World J Gastroenterol. 2013;19(25):4023-30.

Hatagima A. Genetic polymorphisms and metabolism of endocrine disruptors in cancer susceptibility. Cadernos de saude publica. 2002;18(2):357-77.

Ibrahem SQ, Al-Dalawi ZT, Bahaaldin AS. Sequence Polymorphism in Xenobiotic Metabolising Genes in Iraqi Colorectal Cancer Patients. Asian Pacific journal of cancer prevention: APJCP. 2021;22(4):1203-10.

Indulski JA, Lutz W. Metabolic genotype in relation to individual susceptibility to environmental carcinogens. International archives of occupational and environmental health. 2000;73(2):71-85.

Jan R, Yacoub M, Sokkar M. Complex Interplay of CYP1A1 Genetic Polymorphism on Colorectal Cancer Susceptibility. Bulletin of Egyptian Society for Physiological Sciences.2011;31(2):251-61.

Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA: a cancer journal for clinicians. 2010;60(5):277-300.

Jin J-Q, Hu Y-Y, Niu Y-M, Yang G-L, Wu Y-Y, Leng W-D, et al. *CYP1A1* Ile462Val polymorphism contributes to colorectal cancer risk: a meta-analysis. World J Gastroenterol. 2011;17(2):260-66.

Kamiza AB, You JF, Wang WC, Tang R, Chang CY, Chien HT, et al. Polymorphisms of xenobiotic-metabolizing genes and colorectal cancer risk in patients with lynch syndrome: A retrospective cohort study in Taiwan. Environmental and molecular mutagenesis. 2018;59(1):69-78.

Koutros S, Andreotti G, Berndt SI, Hughes Barry K, Lubin JH, Hoppin JA, et al. Xenobiotic-metabolizing gene variants, pesticide use, and the risk of prostate cancer. Pharmacogenet Genomics. 2011;21(10):615-23.

Laczmanska I, Gil J, Karpinski P, Stembalska A, Trusewicz A, Pesz K, et al. Polymorphism in nucleotide excision repair gene XPC correlates with bleomycin-induced chromosomal aberrations. Environmental and molecular mutagenesis. 2007;48(8):666-71.

Little J, Sharp L, Masson LF, Brockton NT, Cotton SC, Haites NE, et al. Colorectal cancer and genetic polymorphisms of *CYP1A1*, GSTM1 and GSTT1: a case-control study in the Grampian region of Scotland. International journal of cancer. 2006;119(9):2155-64.

Martorell-Marugan J, Toro-Dominguez D, Alarcon-Riquelme ME, Carmona-Saez P. MetaGenyo: a web tool for meta-analysis of genetic association studies. BMC bioinformatics. 2017;18(1):563.

Masson LF, Sharp L, Cotton SC, Little J. Cytochrome P-450 1A1 gene polymorphisms and risk of breast cancer: a HuGE review. American journal of epidemiology. 2005;161(10):901-15.

Öztaş E, Ozhan G, Daly AK. The Effect of the CYP1A1*2A Allele on Colorectal Cancer Susceptibility in a British Population. Genetic testing and molecular biomarkers. 2016;20(8):475-7.

Proença MA, Fernandes GM, Russo A, Lelis RB, Netinho JG, Cunrath GS, et al. A case-control study of CYP2E1 (PstI) and *CYP1A1* (MspI) polymorphisms in colorectal cancer. Genetics and molecular research: GMR. 2015;14(4):17856-63.

Qadir A, Hashmi MZ, Mahmood A. Xenobiotics, Types, and Mode of Action. In: Hashmi MZ, Kumar V, Varma A, editors. Xenobiotics in the Soil Environment: Monitoring, Toxicity and Management. Cham: Springer International

Publishing; 2017. p. 1-7.
Raunio H, Kuusisto M, Juvonen RO, Pentikäinen OT. Modeling of interactions between xenobiotics and cytochrome P450 (CYP) enzymes. Front Pharmacol. 2015;6:123-23.
Rheem DS, Baylink DJ, Olafsson S, Jackson CS, Walter MH. Prevention of colorectal cancer with vitamin D. Scand J Gastroenterol. 2010;45(7-8):775-84.
Rudolph A, Chang-Claude J, Schmidt MK. Gene-environment interaction and risk of breast cancer. British journal of cancer. 2016;114(2):125-33.
Saeed HM, Alanazi MS, Nounou HA, Salaby MA, Semlali A, Azzam N, et al. Cytochrome P450 1A1, 2E1 and GSTM1 gene polymorphisms and susceptibility to colorectal cancer in the Saudi population. Asian Pacific journal of cancer prevention : APJCP. 2013;14(6):3761-8.
Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA: a cancer journal for clinicians. 2020;70(3):145-64.
Sindi IA, Babalghith AO, Tayeb MT, Mufti AH, Naffadi H, Ekram SN, et al. Risk of Colorectal Carcinoma May Predispose to the Genetic Variants of the GST, CYP450, and TP53 Genes Among Nonsmokers in the Saudi Community. Int J Gen Med. 2021;14:1311-23.
Sivaraman L, Leatham MP, Yee J, Wilkens LR, Lau AF, Le Marchand L. *CYP1A1* genetic polymorphisms and in situ colorectal cancer. Cancer Res. 1994;54(14):3692-5.
Terry KL, Titus-Ernstoff L, Garner EO, Vitonis AF, Cramer DW. Interaction between *CYP1A1* polymorphic variants and dietary exposures influencing ovarian cancer risk. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2003;12(3):187-90.
Vukovic V, Ianuale C, Leoncini E, Pastorino R, Gualano MR, Amore R, et al. Lack of association between polymorphisms in the CYP1A2 gene and risk of cancer: evidence from meta-analyses. BMC Cancer. 2016;16:83-83.
Xu L, He X, Wang X. Evaluation of association studies, a systematic review and meta-analysis of *CYP1A1* polymorphisms, and colorectal cancer risk. Authorea Preprints. 2020.
Zheng Y, Wang JJ, Sun L, Li HL. Association between *CYP1A1* polymorphism and colorectal cancer risk: a meta-analysis. Molecular biology reports. 2012;39(4):3533-40.
Zhu X, Wang Z, He J, Wang W, Xue W, Wang Y, et al. Associations between *CYP1A1* rs1048943 A > G and rs4646903 T > C genetic variations and colorectal cancer risk: Proof from 26 case-control studies. Oncotarget. 2016;7(32):51365-74.