Chapter 9
Meta-Analysis Reveals no Significant Association of EPHX1 Tyr113His and His139Arg Polymorphisms with the Colorectal Cancer Risk

L.V.K.S. Bhaskar, Akriti Gupta, and Smaranika Pattnaik

Abstract The Tyr113His and His139Arg polymorphisms in microsomal epoxide gene (EPHX1) have been reported to be associated with colorectal cancer (CRC) risk, but the results are inconclusive. Considering the functional importance of these polymorphisms and heterogeneity in genetic association studies, we performed a meta-analysis to investigate the association between the EPHX1 Tyr113His and His139Arg polymorphisms and CRC susceptibility. A comprehensive literature search of PubMed, Embase, and Google Scholar databases were conducted before May 10, 2019. Twenty eligible studies were finally included in this meta-analysis. The pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated. In the overall analysis, both Tyr113His and His139Arg polymorphisms were not associated with CRC in allelic and dominant genetic models. On subgroup analysis, no significant associations were observed in Asians and Caucasians in any of the genetic models for these polymorphisms. Our results were confirmed by sensitivity analysis and no publication bias was found. Taken together, our data indicate that EPHX1 Tyr113His and His139Arg polymorphisms are not associated with the susceptibility to colorectal cancer. Further well-designed studies with large sample size are warranted to establish the role of EPHX1 polymorphisms in CRC, especially for Tyr113His and His139Arg.

Keywords Colorectal cancer · Meta-analysis · Microsomal epoxide hydrolase · EPHX1 · Polymorphism · Susceptibility

L.V.K.S. Bhaskar
Guru Ghasidas University, Bilaspur, Chhattisgarh, India

A. Gupta
Sickle Cell Institute Chhattisgarh, Raipur, India

S. Pattnaik (✉)
Department of Biotechnology and Bioinformatics, Sambalpur University, Sambalpur, Odisha, India

G. S. R. Raju, L.V.K.S. Bhaskar (eds.), *Theranostics Approaches to Gastric and Colon Cancer*, Diagnostics and Therapeutic Advances in GI Malignancies,
https://doi.org/10.1007/978-981-15-2017-4_9

Abbreviations

Arg	Arginine
CI	Confidence intervals
CRC	Colorectal cancer
FEM	Fixed effects model
HCAs	heterocyclic amines
His	Histidin
HPFS	Health Professionals Follow-up Study
HWE	Hardy-Weinberg equilibrium
mEH	microsomal epoxide gene
NHS	Nurses' Health Study
OR	Odds ratio
PAHs	polycyclic aromatic hydrocarbons
PC	Pancreatic cancer
PLCO trial	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
REM	Random effects model
SNPs	Single nucleotide polymorphisms
Tyr	Tyrosine

9.1 Introduction

Colorectal cancer (CRC) is most common malignancy worldwide. The incidence of CRS varies over tenfold in different geographical regions. Developed countries such as Australia, Europe, and North America have higher incidence rates compared to the developing countries like Africa and South-Central Asia (Fitzmaurice et al. 2017). Further, due to early detection of CRC, polypectomy and introduction of effective primary and adjuvant treatments, the death rates from CRC was declined in western countries (Siegel et al. 2019). However in countries lacks strong healthcare infrastructure and limited resources a continuous increment in mortality rates was documented (Center et al. 2009). Although majority of CRCs are sporadic, a considerable inherited susceptibility has been observed in the CRC patients. Hence the likelihood of CRC development is the net results of environmental and genetic factors (Chan and Giovannucci 2010). Modern western lifestyles and clinical environmental factors are often associated with the increased risk of CRC. Several lines of evidences have demonstrated the long-term consumption of processed foods and foods cooked at high temperatures are implicated in CRC risk (Joshi et al. 2015). Cooking meats at high temperatures produce some compound such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) which has carcinogenic and mutagenic properties (Adeyeye 2018).

Microsomal epoxide hydrolase (mEH) (EPHX1; EC 3.3.2.3) is a phase II biotransformation enzyme that detoxifies epoxides, including PAHs and carcinogens

(Okat 2018). The mEH provide protection against the toxicities of reactive epoxide intermediates by converting them as less reactive and less toxic intermediates (Oesch et al. 2004). The EPHX1 gene encoding mEH is positioned at chromosome 1q42.1 and possesses two functional polymorphisms (Hartsfield et al. 1998). The coding region of the EPHX1 gene has two genetic variants (Tyr113His and His139Arg) that alter enzyme activity. In vitro expression studies revealed that the Tyr113His polymorphism decreased mEH enzymatic activity by 40%, while His139Arg polymorphism increased mEH activity by 25% (Hassett et al. 1994). Both polymorphisms exhibit differences in alleles and genotypes among different ethnic populations (Bhaskar et al. 2013; Lakkakula et al. 2013). As mEH involved in detoxification of epoxides together with carcinogens such as PAHs and HCAs present in cigarette smoke also in cooked meats, the functional polymorphisms of EPHX modulate the rate of PAHs metabolism and subsequently modulate CRC risk. A number of studies have analysed the association between EPHX1 gene polymorphisms and the risk of various cancers, but the results are inconclusive. As the results from the previous studies investigating the correlation between colorectal cancer and EPHX1 polymorphism were not similarly conclusive (Harrison et al. 1999; Ikeda et al. 2008; Kiss et al. 2007; Mitrou et al. 2007), we performed a meta-analysis of all available data to investigate the role of *EPHX1* Tyr113His and His139Arg polymorphisms with respect to the colorectal cancer risk.

9.2 Materials and Methods

9.2.1 Data Extraction

Studies related to association between EPHX1 polymorphisms and colorectal cancer risk were collected by searching PubMed, Embase, and Google Scholar. To harvest more comprehensive information published till May 2019, search terms such as "EPHX1 or mEH", "polymorphism or mutation" and "colorectal cancer or carcinoma," were used without any language restrictions. To facilitate the proper elucidation of results, potentially relevant studies were selected based the following criteria: (i) evaluation of the *EPHX1* Tyr113His or His139Arg and risk of CRC, (ii) case-control study, and (iv) availability of genotypes. The studies matching with the above mentioned basic criteria were included in this meta-analysis. After assessing the methodological quality of individual papers, first author's name, publication year, country of origin, and genotype frequencies were collected independently by two authors.

9.2.2 Statistical Analysis

To find the departure of Hardy–Weinberg equilibrium (HWE) in the control groups of EPHX polymorphisms, Chi-Square goodness of fit test was performed. To measure the strength of the association between the EPHX1 polymorphisms and CRC risk of cancer, odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated for each study. The pooled OR with 95% CI was calculated in allelic and dominant genetic models. Between study heterogeneity in these genetic models were calculated using Chi-square test and I2 test. Random effects model (REM) or Fixed effects model (FEM) was selected respectively in the presence or absence of the heterogeneity. Subgroup analysis was also conducted according to ethnicity. To assess the influence of the individual studies to the pooled results, sensitivity analysis was conducted by omitting one study at a time. To test the publication bias, Begg's and Egger's tests were used. MetaGenyo, a web tool was used to calculate results of the meta-analysis in this study (Martorell-Marugan et al. 2017).

9.3 Results

9.3.1 Characteristics of Studies

A total 20 publications dealing with EPHX1 polymorphisms and CRC risk were included in the meta-analysis. The workflow of study identification is illustrated in Fig. 9.1. The characteristics of each study were summarized in Table 9.1. For Tyr113His, 20 publications and for His139Arg, 14 publications from several countries involving Caucasian and Asian subjects were investigated. All genotype distribution in controls was in accordance with HWE with the exception of 4 studies for Tyr113His (Kiss et al. 2007; Sachse et al. 2002; Sahin et al. 2012; Tranah et al. 2005).

9.3.2 Meta-Analysis of EPHX1 Tyr113His Polymorphism with CRC Risk

In this meta-analysis, a total of 20 studies (Cleary et al. 2010; Cotterchio et al. 2008; Fernandes et al. 2016; Harrison et al. 1999; Hlavata et al. 2010; Huang et al. 2005; Ikeda et al. 2008; Kiss et al. 2007; Kury et al. 2008; Landi et al. 2005; Mitrou et al. 2007; Nisa et al. 2013; Northwood et al. 2010; Pande et al. 2008; Sachse et al. 2002; Sahin et al. 2012; Skjelbred et al. 2007; Tranah et al. 2005; van der Logt et al. 2006; Wang et al. 2012) involving 9770 CRC patients and 11,634 controls were included to investigate the associations between EPHX1 Tyr113His and the risk of CRC

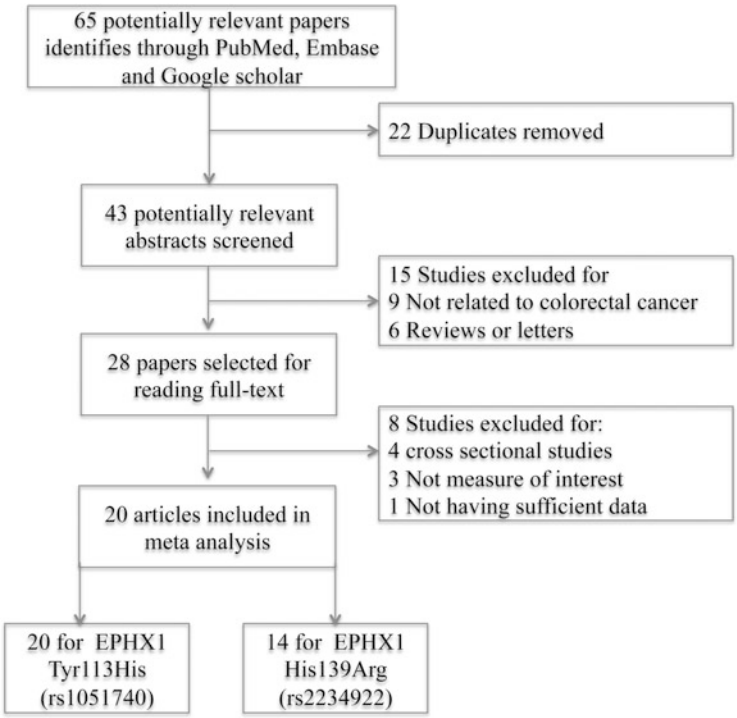

Fig. 9.1 Flow chart of the study selection process identifying studies comparing EPHX1 Tyr113His and His139Arg polymorphisms with the colorectal cancer

(Table 9.1). Pooled data showed that EPHX1 Tyr113His polymorphism was not significantly associated with an increased risk of CRC in both allelic and dominant genetic models (allelic C versus T: OR = 0.95, 95% CI: 0.89–1.02 and dominant **CC + CT** versus TT: OR = 0.94, 95% CI: 0.85–1.03) (Table 9.2; Fig. 9.2). In addition, a further subgroup analysis by ethnicity in Caucasians, Asians and mixed populations indicated that no association between EPHX1 Tyr113His polymorphism and CRC was observed for both allelic and dominant genetic models.

9.3.3 Meta-Analysis Between EPHX1 His139Arg Polymorphism and CRC Risk

A meta-analysis of the association between EPHX1 His139Arg polymorphism and CRC risk included 14 independent studies (Fernandes et al. 2016; Harrison et al. 1999; Hlavata et al. 2010; Huang et al. 2005; Kiss et al. 2007; Landi et al. 2005; Nisa et al. 2013; Northwood et al. 2010; Pande et al. 2008; Sachse et al. 2002; Sahin et al. 2012; Skjelbred et al. 2007; Tranah et al. 2005; van der Logt et al. 2006) with a total

Table 9.1 Characteristics of the studies included in the meta-analysis and their genotype distributions of the EPHX1 Tyr113His and His139Arg gene polymorphisms

S. No.	Author's Name	Country	Ethnicity	Method	Case			Control			HWE p-value	References
Tyr113His (rs1051740)					CC	CT	TT	CC	CT	TT		
1	Fernandes et al. 2016	Brazil	Caucasian	PCR-RFLP	13	88	126	28	158	214	0.874	(Fernandes et al. 2016)
2	Nisa et al. 2013	Japan	Asian	TaqMan	115	342	228	143	396	239	0.347	(Nisa et al. 2013)
3	Wang et al. 2012	USA	Mixed	TaqMan	28	108	167	29	141	188	0.723	(Wang et al. 2012)
4	Sahin et al. 2012	Turkey	Caucasian	PCR-RFLP	12	29	27	8	64	44	0.017	(Sahin et al. 2012)
5	Cleary et al. 2010	Canada	Caucasian	TaqMan	561	502	100	625	549	118	0.871	(Cleary et al. 2010)
6	Hlavata et al. 2010	Czech Republic	European	TaqMan	50	224	221	52	212	231	0.746	(Hlavata et al. 2010)
7	Northwood et al. 2010	Scotland	Caucasian	TaqMan	24	118	166	26	112	158	0.341	(Northwood et al. 2010)
8	Kury et al. 2008	France	Caucasian	TaqMan	89	409	525	88	469	564	0.486	(Kury et al. 2008)
9	Ikeda et al. 2008	Japan	Asian	TaqMan	22	80	120	24	56	26	0.557	(Ikeda et al. 2008)
10	Cotterchio et al. 2008	Ontario	Caucasian	TaqMan	74	354	404	113	526	610	0.980	(Cotterchio et al. 2008)
11	Pande et al. 2008	Texas	Mixed	Pyrosequencing	8	46	66	19	108	130	0.595	(Pande et al. 2008)
12	Skjelbred et al. 2007	Norway	Caucasian	PCR-RFLP	9	41	52	33	134	132	0.908	(Skjelbred et al. 2007)
13	Mitrou et al. 2007	UK	Caucasian	PCR-RFLP	40	295	509	31	285	555	0.450	(Mitrou et al. 2007)
14	Kiss et al. 2007	Hungary	Caucasian	PCR-RFLP	53	227	220	31	221	248	0.046	(Kiss et al. 2007)
15	van der Logt et al. 2006	Netherlands	Caucasian	PCR-RFLP	39	141	185	32	165	194	0.709	(van der Logt et al. 2006)
16	Huang et al. 2005	USA	Caucasian	TaqMan	56	299	357	80	291	358	0.076	(Huang et al. 2005)
17	Landi et al. 2005	Spain	Caucasian	APEX	29	129	168	33	153	177	0.994	(Landi et al. 2005)
18	Tranah et al. 2005	USA	Mixed	TaqMan	160	303	422	208	425	585	<0.001	(Tranah et al. 2005)
19	Sachse et al. 2002	UK	Caucasian	PCR-RFLP	74	187	228	129	193	270	<0.001	(Sachse et al. 2002)

20	Harrison et al. 1999	UK	Caucasian	PCR-RFLP	42	38	21	91	99	13	0.040	(Harrison et al. 1999)
His139Arg (rs2234922)												
					AA	AG	GG	AA	AG	GG		
1	Fernandes et al. 2016	Brazil	Caucasian	PCR-RFLP	153	67	7	235	145	20	0.696	(Fernandes et al. 2016)
2	Nisa et al. 2013	Japan	Asian	TaqMan	485	182	18	525	224	29	0.405	(Nisa et al. 2013)
3	Sahin et al. 2012	Turkey	Caucasian	PCR-RFLP	52	15	1	72	44	0	0.012	(Sahin et al. 2012)
4	Hlavata et al. 2010	Czech	European	TaqMan	297	173	25	290	183	22	0.306	(Hlavata et al. 2010)
5	Northwood et al. 2010	Scotland	Caucasian	TaqMan	185	109	14	173	106	17	0.886	(Northwood et al. 2010)
6	Pande et al. 2008	Texas	Mixed	Pyrosequencing	77	37	6	155	92	10	0.420	(Pande et al. 2008)
7	Skjelbred et al. 2007	Norway	Caucasian	PCR-RFLP	56	27	18	190	90	19	0.068	(Skjelbred et al. 2007)
8	Kiss et al. 2007	Hungary	Caucasian	PCR-RFLP	337	157	6	329	161	10	0.054	(Kiss et al. 2007)
9	van der Logt et al. 2006	Netherland	Caucasian	PCR-RFLP	241	106	24	269	128	17	0.719	(van der Logt et al. 2006)
10	Huang et al. 2005	USA	Caucasian	TaqMan	31	228	443	24	221	479	0.809	(Huang et al. 2005)
11	Landi et al. 2005	Spain	Caucasian	APEX	250	98	13	225	85	11	0.403	(Landi et al. 2005)
12	Tranah et al. 2005	USA	Mixed	TaqMan	584	275	42	789	406	40	0.160	(Tranah et al. 2005)
13	Sachse et al. 2002	UK	Caucasian	PCR-RFLP	329	142	19	378	200	15	0.055	(Sachse et al. 2002)
14	Harrison et al. 1999	UK	Caucasian	PCR-RFLP	147	53	3	76	21	4	0.121	(Harrison et al. 1999)

Table 9.2 Meta-analysis of the relationships of the EPHX1 Tyr113His and His139Arg polymorphisms with the colorectal cancer

EPHX1 Tyr113His	Overall (REM)	Asian	Caucasian	Mixed
Number of studies	20	2	15	3
Allele model (C vs. T)				
I2	0.62	0.95	0.34	<0.001
PHeterogeneity	<0.001	<0.001	0.093	0.659
OR (95% CI)	0.95 (0.89–1.02)	0.62(0.28–1.38)	0.99 (0.93–1.05)	1.00 (0.90–1.12)
Association p value	0.192	0.242	0.755	0.984
Egger's p value	0.078	NA	0.390	0.076
Dominant model (CC + CT vs. TT)				
I2	0.59	0.94	0.35	0.00
PHeterogeneity	<0.001	<0.001	0.091	0.633
OR (95% CI)	0.94 (0.85–1.03)	0.51 (0.16–1.59	0.99 (0.91–1.08)	0.97 (0.84–1.12)
Association p value	0.169	0.245	0.821	0.658
Egger's p value	0.003	NA	0.024	0.070
EPHX1 His139Arg	Overall (FEM)	Asian	Caucasian	Mixed
Number of studies	14	1	11	2
Allele contrast (G vs. A)				
I2	0.32	NA	0.42	0.00
PHeterogeneity	0.115	NA	0.067	0.637
OR (95% CI)	0.95 (0.89–1.01)	0.85 (0.70–1.04)	0.96 (0.86–1.07)	1.00 (0.87–1.15)
Association p value	0.127	0.113	0.440	0.980
Egger's p value	0.998	NA	0.832	NA
Dominant model (GG + GA vs. AA)				
I2	0.00	NA	0.13	0.00
PHeterogeneity	0.505	NA	0.317	0.616
OR (95% CI)	0.92 (0.85–0.99)	0.86 (0.69–1.07)	0.92 (0.83–1.02)	0.94 (0.80–1.12)
Association p value	0.035	0.170	0.106	0.498
Egger's p value	0.617	NA	0.703	NA

of 5532 CRC cases and 6529 controls (Table 9.1). Pooled data revealed that EPHX1 His139Arg polymorphism was correlated with the risk of CRC in the both allelic and dominant model (allelic G versus A: OR = 0.95, 95% CI: 0.89–1.01; dominant GG + GA versus AA: OR = 0.92, 95% CI: 0.85–0.99). In addition, a further subgroup analysis by ethnicity in Caucasians, Asians and mixed populations indicated that no association between EPHX1 His139Arg polymorphism and CRC was observed for both allelic and dominant genetic models.

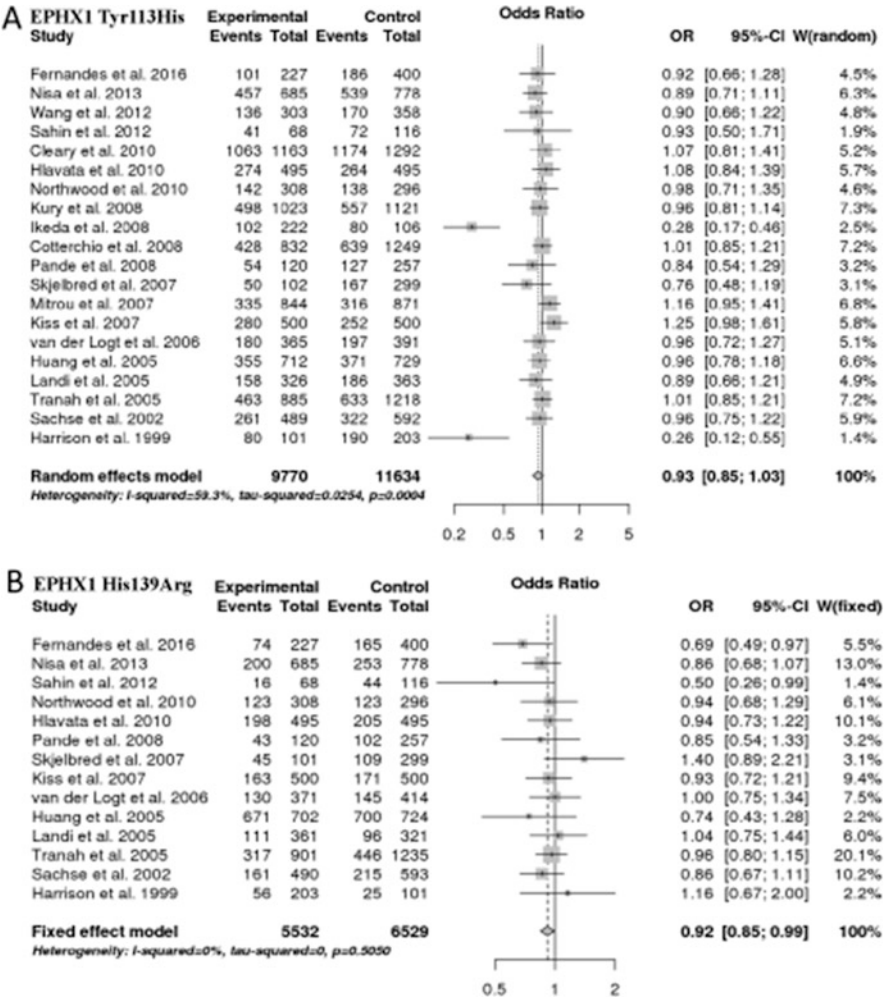

Fig. 9.2 Forest plot of the studies assessing the association between colorectal cancer and EPHX1 gene polymorphisms. (**a**) EPHX1 Tyr113His and colorectal cancer; (**b**) His139Arg and colorectal cancer

9.3.4 Heterogeneity and Sensitivity Analysis

The heterogeneities that observed within the *EPHX1* Tyr113His or His139Arg studies and within each subgroup of studies are shown in Table 9.2. The heterogeneity test showed a moderate heterogeneity between *EPHX1* Tyr113His studies (Dominant model $P_{heterogeneity} = 0.003$, I-squared = 59%). However, no heterogeneity was detected in *EPHX1* His139Arg studies (Dominant model $P_{heterogeneity} = 0.505$, I-squared = 0%). Hence in our meta-analysis, to calculate

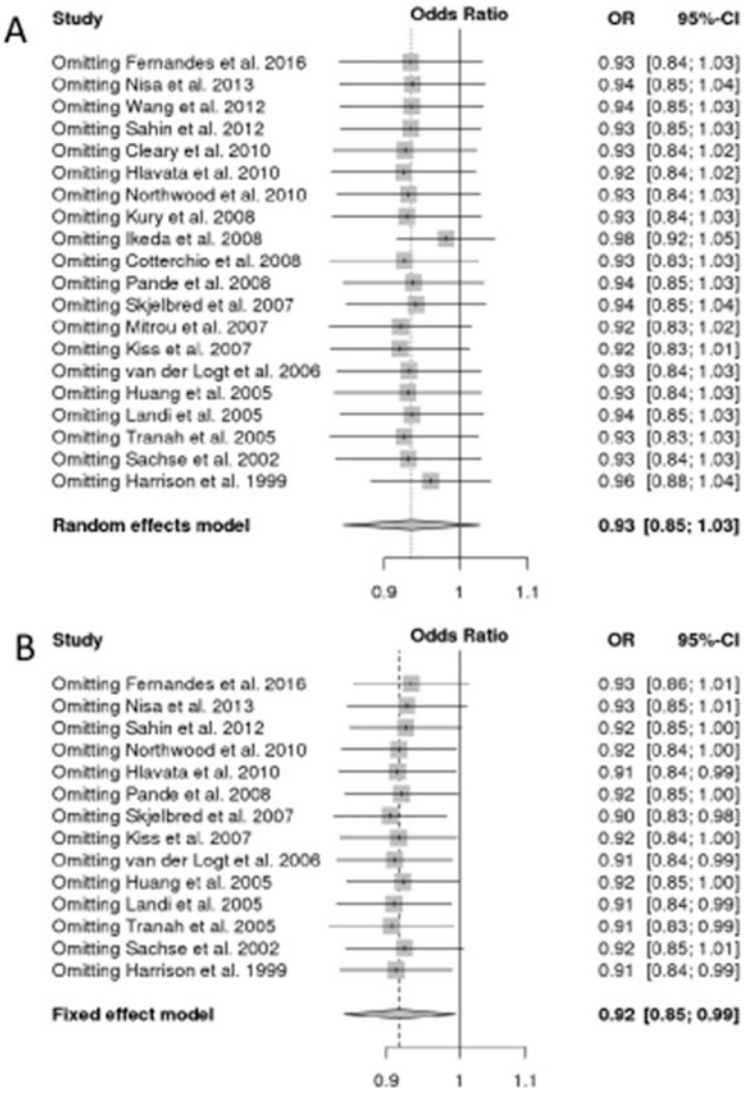

Fig. 9.3 Sensitivity analysis diagram by omitting a single study. (**a**) Sensitivity analysis of the OR coefficients for the association between EPHX1 Tyr113His and colorectal cancer; (**b**) Sensitivity analysis of the OR coefficients for the association between His139Arg and colorectal cancer

the summary ORs we applied REM and FEM respectively for Tyr113His and His139Arg polymorphisms. Further, to evaluate the sensitivity of this meta-analysis, we conducted pooled analyses by omitting one study each time (leave-one-out method). The results of the leave-one-out method for Tyr113His and His139Arg polymorphisms was shown in Fig. 9.3a and b. For both polymorphisms, there is no

change in statistical significance of the results when any single study was omitted indicating the stability and reliability of the results.

9.3.5 *Publication Bias*

The results of publication bias for *EPHX1* Tyr113His and His139Arg studies were shown in Table 9.2 and Fig. 9.4a and b. The shape of Begg's funnel plot did not reveal any obvious asymmetry for both *EPHX1* Tyr113His and His139Arg studies (Fig. 9.4a and b). Further, Egger's linear regression tests did not reveal publication bias for both *EPHX1* Tyr113His and His139Arg studies in all genetic models tested (Table 9.2).

9.4 Discussion

Indeed cancer initiation and progression has been linked to activation of the immune system and oxidative stress. Throughout the life, the colon is exposed to microbiota and free radicals that respectively cause immune responses and oxidative damage. Although the etiology of CRC is not fully known, several lines of evidences indicated that the red meat intake of one of the major risk factors for the CRC (Bernstein et al. 2015; Demeyer et al. 2016; Domingo and Nadal 2017; Zhao et al. 2017a). In contrast to this some studies showed an inverse association of fiber intake with risk of CRC (Lee et al. 2017; Song et al. 2015). The meat cooking processes produce several carcinogens such as PAHs, HCAs and dioxin-like compounds. Dietary consumption is one of the highest sources of these environmental carcinogens (Zhang et al. 2013). To become carcinogenic, these PAHs and aromatic amines have to undergo phase I and phase II biotransformation reactions (Turesky 2004).

Microsomal epoxide hydrolase is one of the biotransformation enzymes that involved either detoxification or bio-activation of a wide range of substrates. Hence it is hypothesized that the polymorphisms of EPHX1 are crucial for the susceptibility of colon cancer. The Tyr113His variation is linked with low enzyme activity and His139Arg variation increases enzyme activity. Two nested case-control studies from the cohorts Nurses' Health Study and Health Professionals' Follow-up Study, did not reveal significant association EPHX1 gene polymorphisms and CRC risk (Tranah et al. 2004). However, individuals with $\geq$25 *pack-year smoking* history showed increased CRC risk (Tranah et al. 2004). The *Prostate*, *Lung*, *Colorectal and* Ovarian (PLCO) Cancer Screening Trial demonstrated that the EPHX1 polymorphisms increased risk of CRC in non-Hispanic current and recent smokers (Huang et al. 2005). Subsequent studies showed that the EPHX1 polymorphisms are not associated with CRC risk (Landi et al. 2005; Mitrou et al. 2007; van der Logt et al. 2006). Meta analysis of interaction of smoking with the EPHX1 Tyr113His polymorphisms showed that the carriers of low metabolizer allele had slightly lower risk

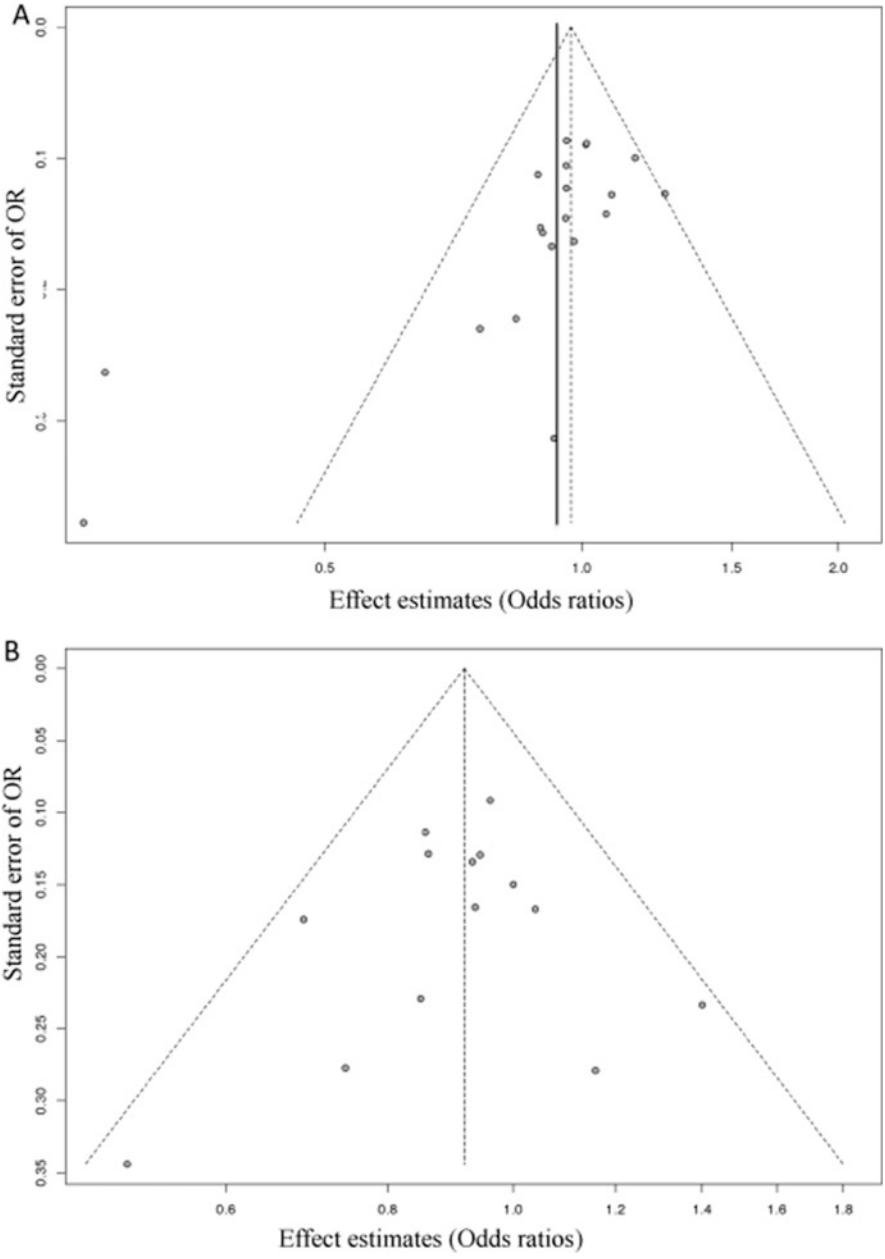

Fig. 9.4 Funnel plots analyses to assess the publication bias between colorectal cancer and EPHX1 gene polymorphisms. (**a**) Funnel plot based on EPHX1 Tyr113His and colorectal cancer; (**b**) Funnel plot based on His139Arg and colorectal cancer. The dotted vertical line indicates the triangular region within which 95% of studies are expected to lie in the absence of bias and heterogeneity. The solid vertical line corresponds to no intervention effect

of CRC compared to its high metabolizer (Raimondi et al. 2009). Analysis of interactions among the charred meat consumption, smoking, EPHX1 polymorphisms and CRC, did not reveal significant association between EPHX1 genotype and colorectal polyps (Burnett-Hartman et al. 2011). However, meta-analysis of observational studies demonstrated that the increased intake of red and processed meat is associated with significantly increased risk of CRC (Xu et al. 2013). Further, meta-analysis also indicated that the red and processed meat intake was associated with an increased CRC incidence but not for CRC recurrence (Zhao et al. 2017b).

This meta-analysis included 20 independent case-control studies of CRC to investigate its correlation with EPHX1 variants. The results of our meta-analysis showed that EPHX1 gene Tyr113His and His139Arg polymorphisms were not associated with the risk of CRC in allelic and dominant genetic comparison models. Further in subgroup analysis by ethnicity, these polymorphisms were not associated with the risk of CRC in both Asian and Caucasians. There was no evidence of publication bias.

9.5 Conclusion

In summary, the results of this meta-analysis demonstrated that no evidence supporting the relationship between EPHX1 polymorphism and CRC risk was detected. As the pathogenesis of CRC is complex and involving interactions of gene with gene and gene with dietary factors some limitations should be taken into consideration when interpreting results. A major limitation of current meta-analysis is non-availability of the data on meat consumption, alcohol intake and smoking, which limited the evaluation of the potential interactions between these risk factors and EPHX1 polymorphisms. Well-designed studies with large sample size are warranted to establish the role of EPHX1 polymorphisms in CRC, especially for Tyr113His and His139Arg.

Conflict of Interest There are no conflicts of interests.

References

Adeyeye SAO (2018) Heterocyclic amines and polycyclic aromatic hydrocarbons in cooked meat products: a review. Polycycl Aromat Compd:1–11

Bernstein AM, Song M, Zhang X, Pan A, Wang M, Fuchs CS, Le N, Chan AT, Willett WC, Ogino S, Giovannucci EL, Wu K (2015) Processed and unprocessed red meat and risk of colorectal Cancer: analysis by tumor location and modification by time. PLoS One 10:e0135959

Bhaskar LV, Thangaraj K, Patel M, Shah AM, Gopal K, Saikrishna L, Tamang R, Singh L, Rao VR (2013) EPHX1 gene polymorphisms in alcohol dependence and their distribution among the Indian populations. Am J Drug Alcohol Abuse 39:16–22

Burnett-Hartman AN, Newcomb PA, Mandelson MT, Adams SV, Wernli KJ, Shadman M, Wurscher MA, Makar KW (2011) Colorectal polyp type and the association with charred meat consumption, smoking, and microsomal epoxide hydrolase polymorphisms. Nutr Cancer 63:583–592

Center MM, Jemal A, Smith RA, Ward E (2009) Worldwide variations in colorectal cancer. CA Cancer J Clin 59:366–378

Chan AT, Giovannucci EL (2010) Primary prevention of colorectal cancer. Gastroenterology 138:2029–2043. e2010

Cleary SP, Cotterchio M, Shi E, Gallinger S, Harper P (2010) Cigarette smoking, genetic variants in carcinogen-metabolizing enzymes, and colorectal cancer risk. Am J Epidemiol 172:1000–1014

Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA (2008) Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive. Oncology 17:3098–3107

Demeyer D, Mertens B, De Smet S, Ulens M (2016) Mechanisms linking colorectal Cancer to the consumption of (processed) red meat: a review. Crit Rev Food Sci Nutr 56:2747–2766

Domingo JL, Nadal M (2017) Carcinogenicity of consumption of red meat and processed meat: a review of scientific news since the IARC decision. Food Chem Toxicol 105:256–261

Fernandes GM, Russo A, Proenca MA, Gazola NF, Rodrigues GH, Biselli-Chicote PM, Silva AE, Netinho JG, Pavarino EC, Goloni-Bertollo EM (2016) CYP1A1, CYP2E1 and EPHX1 polymorphisms in sporadic colorectal neoplasms. World J Gastroenterol 22:9974–9983

Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L, Fleming T, Forouzanfar MH, Hancock J, Hay RJ, Hunter-Merrill R, Huynh C, Hosgood HD, Johnson CO, Jonas JB, Khubchandani J, Kumar GA, Kutz M, Lan Q, Larson HJ, Liang X, Lim SS, Lopez AD, MacIntyre MF, Marczak L, Marquez N, Mokdad AH, Pinho C, Pourmalek F, Salomon JA, Sanabria JR, Sandar L, Sartorius B, Schwartz SM, Shackelford KA, Shibuya K, Stanaway J, Steiner C, Sun J, Takahashi K, Vollset SE, Vos T, Wagner JA, Wang H, Westerman R, Zeeb H, Zoeckler L, Abd-Allah F, Ahmed MB, Alabed S, Alam NK, Aldhahri SF, Alem G, Alemayohu MA, Ali R, Al-Raddadi R, Amare A, Amoako Y, Artaman A, Asayesh H, Atnafu N, Awasthi A, Saleem HB, Barac A, Bedi N, Bensenor I, Berhane A, Bernabe E, Betsu B, Binagwaho A, Boneya D, Campos-Nonato I, Castaneda-Orjuela C, Catala-Lopez F, Chiang P, Chibueze C, Chitheer A, Choi JY, Cowie B, Damtew S, das Neves J, Dey S, Dharmaratne S, Dhillon P, Ding E, Driscoll T, Ekwueme D, Endries AY, Farvid M, Farzadfar F, Fernandes J, Fischer F, TT GH, Gebru A, Gopalani S, Hailu A, Horino M, Horita N, Husseini A, Huybrechts I, Inoue M, Islami F, Jakovljevic M, James S, Javanbakht M, Jee SH, Kasaeian A, Kedir MS, Khader YS, Khang YH, Kim D, Leigh J, Linn S, Lunevicius R, El Razek HMA, Malekzadeh R, Malta DC, Marcenes W, Markos D, Melaku YA, Meles KG, Mendoza W, Mengiste DT, Meretoja TJ, Miller TR, Mohammad KA, Mohammadi A, Mohammed S, Moradi-Lakeh M, Nagel G, Nand D, Le Nguyen Q, Nolte S, Ogbo FA, Oladimeji KE, Oren E, Pa M, Park EK, Pereira DM, Plass D, Qorbani M, Radfar A, Rafay A, Rahman M, Rana SM, Soreide K, Satpathy M, Sawhney M, Sepanlou SG, Shaikh MA, She J, Shiue I, Shore HR, Shrime MG, So S, Soneji S, Stathopoulou V, Stroumpoulis K, Sufiyan MB, Sykes BL, Tabares-Seisdedos R, Tadese F, Tedla BA, Tessema GA, Thakur JS, Tran BX, Ukwaja KN, Uzochukwu BSC, Vlassov VV, Weiderpass E, Wubshet Terefe M, Yebyo HG, Yimam HH, Yonemoto N, Younis MZ, Yu C, Zaidi Z, Zaki MES, Zenebe ZM, Murray CJL, Naghavi M (2017) Global, regional, and National Cancer Incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 Cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 3:524–548

Harrison DJ, Hubbard AL, MacMillan J, Wyllie AH, Smith CA (1999) Microsomal epoxide hydrolase gene polymorphism and susceptibility to colon cancer. Br J Cancer 79:168–171

Hartsfield JK Jr, Sutcliffe MJ, Everett ET, Hassett C, Omiecinski CJ, Saari JA (1998) Assignment1 of microsomal epoxide hydrolase (EPHX1) to human chromosome 1q42.1 by in situ hybridization. Cytogenet Cell Genet 83:44–45

Hassett C, Aicher L, Sidhu JS, Omiecinski CJ (1994) Human microsomal epoxide hydrolase: genetic polymorphism and functional expression in vitro of amino acid variants. Hum Mol Genet 3:421–428

Hlavata I, Vrana D, Smerhovsky Z, Pardini B, Naccarati A, Vodicka P, Novotny J, Mohelnikova-Duchonova B, Soucek P (2010) Association between exposure-relevant polymorphisms in CYP1B1, EPHX1, NQO1, GSTM1, GSTP1 and GSTT1 and risk of colorectal cancer in a Czech population. Oncol Rep 24:1347–1353

Huang WY, Chatterjee N, Chanock S, Dean M, Yeager M, Schoen RE, Hou LF, Berndt SI, Yadavalli S, Johnson CC, Hayes RB (2005) Microsomal epoxide hydrolase polymorphisms and risk for advanced colorectal adenoma. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive. Oncology 14:152–157

Ikeda S, Sasazuki S, Natsukawa S, Shaura K, Koizumi Y, Kasuga Y, Ohnami S, Sakamoto H, Yoshida T, Iwasaki M, Tsugane S (2008) Screening of 214 single nucleotide polymorphisms in 44 candidate cancer susceptibility genes: a case-control study on gastric and colorectal cancers in the Japanese population. Am J Gastroenterol 103:1476–1487

Joshi AD, Kim A, Lewinger JP, Ulrich CM, Potter JD, Cotterchio M, Le Marchand L, Stern MC (2015) Meat intake, cooking methods, dietary carcinogens, and colorectal cancer risk: findings from the colorectal Cancer family registry. Cancer Med 4:936–952

Kiss I, Orsos Z, Gombos K, Bogner B, Csejtei A, Tibold A, Varga Z, Pazsit E, Magda I, Zolyomi A, Ember I (2007) Association between allelic polymorphisms of metabolizing enzymes (CYP 1A1, CYP 1A2, CYP 2E1, mEH) and occurrence of colorectal cancer in Hungary. Anticancer Res 27:2931–2937

Kury S, Buecher B, Robiou-du-Pont S, Scoul C, Colman H, Le Neel T, Le Houerou C, Faroux R, Ollivry J, Lafraise B, Chupin LD, Sebille V, Bezieau S (2008) Low-penetrance alleles predisposing to sporadic colorectal cancers: a French case-controlled genetic association study. BMC Cancer 8:326

Lakkakula S, Maram R, Munirajan AK, Pathapati RM, Visweswara SB, Lakkakula BVKS (2013) EPHX1 gene polymorphisms among south Indian populations. Mol Cell Toxicol 9:219–225

Landi S, Gemignani F, Moreno V, Gioia-Patricola L, Chabrier A, Guino E, Navarro M, de Oca J, Capella G, Canzian F (2005) A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of colorectal cancer. Pharmacogenet Genomics 15:535–546

Lee J, Shin A, Oh JH, Kim J (2017) Colors of vegetables and fruits and the risks of colorectal cancer. World J Gastroenterol 23:2527–2538

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

Mitrou PN, Watson MA, Loktionov AS, Cardwell C, Gunter MJ, Atkin WS, Macklin CP, Cecil T, Bishop DT, Primrose J, Bingham SA (2007) Role of NQO1C609T and EPHX1 gene polymorphisms in the association of smoking and alcohol with sporadic distal colorectal adenomas: results from the UKFSS study. Carcinogenesis 28:875–882

Nisa H, Budhathoki S, Morita M, Toyomura K, Nagano J, Ohnaka K, Kono S, Ueki T, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Maekawa T, Yasunami Y, Takenaka K, Ichimiya H, Terasaka R (2013) Microsomal epoxide hydrolase polymorphisms, cigarette smoking, and risk of colorectal cancer: the Fukuoka colorectal cancer study. Mol Carcinog 52:619–626

Northwood EL, Elliott F, Forman D, Barrett JH, Wilkie MJ, Carey FA, Steele RJ, Wolf R, Bishop T, Smith G (2010) Polymorphisms in xenobiotic metabolizing enzymes and diet influence colorectal adenoma risk. Pharmacogenet Genomics 20:315–326

Oesch F, Hengstler JG, Arand M (2004) Detoxication strategy of epoxide hydrolase-the basis for a novel threshold for definable genotoxic carcinogens. Nonlinearity Biol Toxicol Med 2:21–26

Okat Z (2018) The connection between microsomal epoxide hydrolase enzyme and cancer risk. Int Phys Med Rehab J 3:402–404

Pande M, Amos CI, Osterwisch DR, Chen J, Lynch PM, Broaddus R, Frazier ML (2008) Genetic variation in genes for the xenobiotic-metabolizing enzymes CYP1A1, EPHX1, GSTM1, GSTT1, and GSTP1 and susceptibility to colorectal cancer in Lynch syndrome. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive. Oncology 17:2393–2401

Raimondi S, Botteri E, Iodice S, Lowenfels AB, Maisonneuve P (2009) Gene-smoking interaction on colorectal adenoma and cancer risk: review and meta-analysis. Mutat Res 670:6–14

Sachse C, Smith G, Wilkie MJ, Barrett JH, Waxman R, Sullivan F, Forman D, Bishop DT, Wolf CR (2002) A pharmacogenetic study to investigate the role of dietary carcinogens in the etiology of colorectal cancer. Carcinogenesis 23:1839–1849

Sahin O, Arikan S, Oltulu YM, Coskunpinar E, Eren A, Cacina C, Guler E, Yaylim I (2012) Investigation of a possible relationship between EPHX1 gene polymorphisms and colorectal cancer in Turkish society. Genet Test Mol Biomarkers 16:423–428

Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA Cancer J Clin 69:7–34

Skjelbred CF, Saebo M, Hjartaker A, Grotmol T, Hansteen IL, Tveit KM, Hoff G, Kure EH (2007) Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. BMC Cancer 7:228

Song Y, Liu M, Yang FG, Cui LH, Lu XY, Chen C (2015) Dietary fibre and the risk of colorectal cancer: a case- control study. Asian Pac J Cancer Prev: APJCP 16:3747–3752

Tranah GJ, Giovannucci E, Ma J, Fuchs C, Hankinson SE, Hunter DJ (2004) Epoxide hydrolase polymorphisms, cigarette smoking and risk of colorectal adenoma in the Nurses' health study and the health professionals follow-up study. Carcinogenesis 25:1211–1218

Tranah GJ, Chan AT, Giovannucci E, Ma J, Fuchs C, Hunter DJ (2005) Epoxide hydrolase and CYP2C9 polymorphisms, cigarette smoking, and risk of colorectal carcinoma in the Nurses' health study and the Physicians' health study. Mol Carcinog 44:21–30

Turesky RJ (2004) The role of genetic polymorphisms in metabolism of carcinogenic heterocyclic aromatic amines. Curr Drug Metab 5:169–180

van der Logt EM, Bergevoet SM, Roelofs HM, Te Morsche RH, Dijk Y, Wobbes T, Nagengast FM, Peters WH (2006) Role of epoxide hydrolase, NAD(P)H:quinone oxidoreductase, cytochrome P450 2E1 or alcohol dehydrogenase genotypes in susceptibility to colorectal cancer. Mutat Res 593:39–49

Wang J, Joshi AD, Corral R, Siegmund KD, Marchand LL, Martinez ME, Haile RW, Ahnen DJ, Sandler RS, Lance P, Stern MC (2012) Carcinogen metabolism genes, red meat and poultry intake, and colorectal cancer risk. Int J Cancer 130:1898–1907

Xu X, Yu E, Gao X, Song N, Liu L, Wei X, Zhang W, Fu C (2013) Red and processed meat intake and risk of colorectal adenomas: a meta-analysis of observational studies. Int J Cancer 132:437–448

Zhang X, Lin S, Funk WE, Hou L (2013) Environmental and occupational exposure to chemicals and telomere length in human studies. Occup Environ Med 70:743–749

Zhao Z, Feng Q, Yin Z, Shuang J, Bai B, Yu P, Guo M, Zhao Q (2017a) Red and processed meat consumption and colorectal cancer risk: a systematic review and meta-analysis. Oncotarget 8:83306–83314

Zhao Z, Yin Z, Hang Z, Zhang C, Zhao Q (2017b) Association between red and processed meat intake and colorectal adenoma incidence and recurrence: a systematic review and meta-analysis. Oncotarget 9:32373–32382