RESEARCH ARTICLE

Meta-Analysis of the Association between H63D and C282Y Polymorphisms in HFE and Cancer Risk

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Abstract

Background: Previous studies suggested that the H63D and C282Y polymorphisms in the HFE genes were susceptible to many cancer types, nevertheless, the present results were inconclusive. Thus, the present study was aimed to evaluate the association between the HFE polymorphisms (H63D and C282Y) and cancer risk via meta-analysis. Materials and Methods: We retrieved PubMed, Google Scholar, Embase and Web of Science databases for all eligible studies up to April 1, 2015. All the statistical analysis was conducted by STATA 12.0. Results: Finally, a total of 20 publications including 24 case-control studies, comprising 6,524 cases and 31,080 controls for HFE-C282Y polymorphism and 19 publications including 21 case control studies, comprising 5,648 cases and 14,257 controls for HFE-H63D polymorphism were enrolled in our analysis. An increased risk for overall cancer risk was identified in HFE-H63D polymorphism under allele contrast (D *vs* H: OR=1.153; 95%CI=1.031-1.289, Pheterogeneity=0.002), homozygotes *vs* wide type (DD *vs* HH: OR=1.449; 95%CI=1.182-1.777, Pheterogeneity=0.391), dominant model (DD+HD *vs* HH: OR=1.145; 95%CI=1.007-1.301, Pheterogeneity=0.002) and recessive model (DD *vs* HD+HH: OR=1.416 ; 95%CI=1.156-1.735, Pheterogeneity=0.549), as well as HFE-C282Y under homozygotes *vs* wide type (YY *vs* CC: OR=1.428, 95%CI=1.017-2.006, Pheterogeneity=0.220). In addition, in the stratified analysis by cancer type, an increased risk was identified in hepatocellular carcinoma and breast cancer in C282Y polymorphism, as well as pancreatic cancer in H63D polymorphism, whereas a decreased risk of colorectal cancer was identified in C282Y polymorphism. Conclusions: Present study suggested that H63D and C282Y polymorphisms associated with an increased risk of overall cancer. Nevertheless, well-designed study with large sample size will be continued on this issue of interest.

Keywords: HFE - polymorphism - cancer - meta-analysis

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Introduction

It has been reported that approximately 12.7 million new cancer cases around the world, along with 7.6 million cancer deaths occurred in 2012(Torre et al., 2015). Nevertheless, the underlying mechanisms of the tumorigenesis were still unknown, with a handful of treatment options available. Previous studies suggested that the storing of iron that may increase the cancer risk and mortality (Okada, 1996; Weinberg, 1996). Moreover, the aberration of the iron metabolism that may cause excessive iron deposition, potentially contributed to pathogenesis of autosomal recessive disorder of hereditary hemochromatosis (Adams et al., 2013), which is regarded as the most common genetic disease in Caucasian population.

Hemochromatosis (*HFE*) gene is located on 6p22.2. There are two common missense mutations in *HFE* {His63Asp (H63D) in exon 2 and Cys282Tyr (C282Y) in exon 4} gene in hereditary hemochromatosis (Feder et al., 1996). In addition, studies also identified that these two polymorphisms associated with an increased risk of cancer, such as leukemia (Kennedy et al., 2014), hepatocellular carcinoma (Gharib et al., 2011), breast cancer (Abraham et al., 2005) and etc., by triggering overload of serum iron. The pro-oxidative properties of iron may result in genomic instability, contributing to carcinogenesis process (Dubacq et al., 2006). Nevertheless, the present data reported were conflicting and inconclusive. Thus, we performed meta-analysis to further assess the association between polymorphisms (H63D and C282Y) in *HFE* and cancer risk.

Materials and Methods

Study identification and selection

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Eligible publications were retrieved by searching for the PubMed, Web of Science, Google Scholar and Embase databases before April 1, 2015. The search criteria "hemochromatosis gene OR *HFE*", "polymorphism OR variant OR mutation", AND "cancer OR carcinoma OR tumor OR malignancy". Moreover, we also searched for the additional publications from the reference lists of the retrieved articles or reviews which were missed by the above retrieved.

Inclusion criteria and exclusion criteria

Eligible studies were enrolled in the meta-analysis according to the following criteria: 1) publications that evaluated the association between the polymorphisms in *HFE* and cancer risk; 2) these publications should be designed as case-control studies; 3) we can get the detail genotype frequency from the cases and controls, or we can calculate it from the provided information. Studies were excluded when they were: 1) case-only study, abstract, review or case report; 2) we cannot get efficient genotype frequency data; 3) overlapped data; 4) the publications concerned about Animals.

Data extraction

We will gather the following details from the publications: the first author, the year of publication, the ethnicity of the population, the frequency of the cases and controls, and the *p* value for the Hardy-Weinberg Equilibrium (HWE) in controls. Two authors (Meng Zhang and Hu Xiong) extracted the data, independently, and all disagreements were reached a consensus.

Statistical analysis

We performed the OR and 95% CI to evaluate the strength of the association between polymorphisms (H63D and C282Y) in *HFE* and cancer risk under five genetic models: allele contrast (D *vs* H or Y *vs* C), co-dominant model {homozygotes *vs* wide type (DD *vs* HH or YY *vs* CC) and heterozygotes *vs* wide type (DH *vs* HH or YC *vs* CC)}, dominant model (DD+HD *vs* HH or YY+CY *vs* CC) and recessive model (DD *vs* DH+HH or YY *vs* YC+CC). In addition, we also conducted stratified analysis by ethnicity and the cancer types. Nevertheless, when one cancer type covered less than two case-control studies, we combined it to the group of ''Other Cancers''. Z test and Q test were conducted to determine the statistical significance of the summary OR and heterogeneity separately. The fixed-effects model (the Mantel-Haenszel method) will be selected when the *P* value>0.10 (indicating a lack of heterogeneity) to estimate the pooled OR. Otherwise, the random-effects model (the DerSimonian and Laird method) will be selected (Mantel and Haenszel, 1959; DerSimonian and Laird, 1986). The Hardy-Weinberg equilibrium (HWE) was tested by a professional web-based program (http://ihg2.helmholtz-muenchen.de/cgibin/hw/hwa1.pl) for the control group (Zamora-Ros et al., 2013); HWE balance will be indicated when the *P* value was larger than 0.05 in the control group. Otherwise, we will further conduct sensitivity analysis to assess the stability of the pool OR by excluding a single data from the enrolled reports to reveal the impression of the separate data set on the pooled ORs (Tobias and Campbell, 1999). In the end, we applied Begg's test and Egger's test to investigate the potential publication bias of these publications(Begg and Mazumdar, 1994; Egger et al., 1997), and $P<0.05$ was considered as statistically significant. All statistical tests were conducted by STATA 12.0 (version 12.0; Stata Corporation, College Station, TX).

Results

Eligible studies

Reports were enrolled in our analysis based on the inclusion and exclusion criteria above. Here, we presented a flow chart to describe the publications selecting process (Figure 1). Finally, a total of 20 publications comprised 24 case-control studies including 6,524 cases and 31,080 controls for *HFE*-C282Y polymorphism (7 breast cancer, 6 liver cancer, 4 colorectal cancer, 2 pancreatic cancer and 5 other cancers) (Beckman et al., 1999; Lauret et al., 2002; Boige et al., 2003; Cauza et al., 2003; Shaheen et al., 2003; Abraham et al., 2005; Festa et al., 2005; Kallianpur et al., 2005; Robinson et al., 2005; Kondrashova et al., 2006; Hucl et al., 2007; Ropero et al., 2007; Ezzikouri et al., 2008; Shi et al., 2009; Osborne et al., 2010; Batschauer et al., 2011; Gharib et al., 2011; Rodriguez-Lopez et al., 2013; Graff et al., 2014; Zhao et al., 2014) and 19 publications comprised 21 case-control studies including 5,648 cases and 14,257 controls for *HFE*-H63D polymorphism (7 hepatocellular carcinoma, 5 breast cancer, 3 colorectal cancer, 2 Pancreatic cancer, and 4 other cancers) (Lauret et al., 2002; Boige et al., 2003; Cauza et al., 2003; Shaheen et al., 2003; Abraham et al., 2005; Robinson et al., 2005; Gunel-Ozcan et al., 2006; Kondrashova et al., 2006; Hucl et al., 2007; Ropero et al., 2007; Ezzikouri et al., 2008; Shi et al., 2009; Batschauer et al., 2011; Gharib et al., 2011; Agudo et al., 2013; Motawi et al., 2013; Rodriguez-Lopez et al., 2013; Graff et al., 2014; Zhao et al., 2014) were enrolled in the meta-analysis. Nevertheless, there are 7 reports including 9 case-control studies deviated from the HWE (Table 1 and Table 2) (Beckman et al., 1999; Boige et al., 2003; Cauza et al., 2003; Shaheen et al., 2003; Kallianpur et al., 2005; Ropero et al., 2007; Zhao et al., 2014).

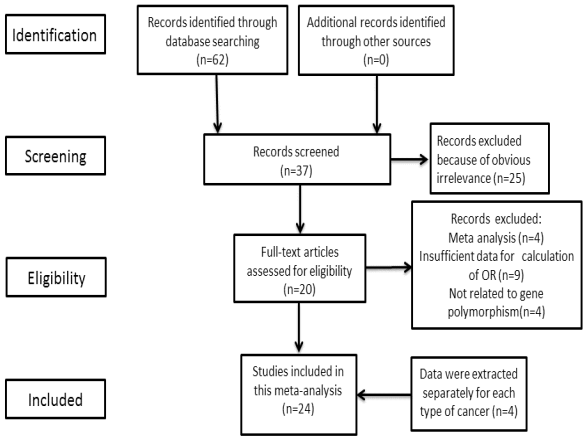

Figure 1. Flow Chart Showing the study Selection Process

Meta-analysis

To sum up, an increased risk for overall cancer risk was uncovered in *HFE*-H63D {allele contrast (D *vs* H: OR=1.153; 95%CI=1.031-1.289, $P_{heterogeneity}$=0.002, Figure 2a), homozygotes *vs* wide type (DD *vs* HH: OR=1.449; 95%CI=1.182-1.777, $P_{heterogeneity}$=0.391), dominant model (DD+HD *vs* HH: OR=1.145; 95%CI=1.007-1.301, $P_{heterogeneity}$=0.002) and recessive model (DD *vs* DH+HH: OR=1.416 ; 95%CI=1.156-1.735, $P_{heterogeneity}$=0.549)} and *HFE*-C282Y polymorphisms {homozygotes *vs* wide type (YY *vs* CC: OR=1.428, 95%CI=1.017-2.006, $P_{heterogeneity}$=0.220)} (Table 3 and Table 4).

In the stratified analysis by cancer type, an increased risk was identified in hepatocellular carcinoma {allele contrast model (Y *vs* C: OR=1.567; 95%CI=1.115-2.201, $P_{heterogeneity}$=0.306, Figure 2b), dominant model (YY+CY *vs* CC: OR=1.499; 95%CI=1.037-2.167, $P_{heterogeneity}$=0.384)} and breast cancer {homozygotes *vs* wide type model (YY *vs* CC: OR=1.756; 95%CI=1.048-2.943, $P_{heterogeneity}$=0.425), and recessive model (YY *vs* YC+CC: OR=1.709; 95%CI=1.020-2.863, $P_{heterogeneity}$=0.472} in C282Y polymorphism, as well as pancreatic cancer in H63D polymorphism {allele contrast model (D *vs* H: OR=1.220; 95%CI=1.073-1.387, $P_{heterogeneity}$=0.724), homozygotes *vs* wide type model (DD *vs* HH: OR=1.564; 95%CI=1.097-2.230, $P_{heterogeneity}$=0.905), dominant model (DD+HD *vs* HH: OR=1.210; 95%CI=1.043-1.403, $P_{heterogeneity}$=0.587) and recessive model (DD *vs* DH+HH: OR=1.511 ; 95%CI=1.063-2.149, $P_{heterogeneity}$=0.951}, whereas a decreased risk of colorectal cancer under homozygotes *vs* wide type model (YY *vs* CC: OR=0.355; 95%CI=0.133-0.949, $P_{heterogeneity}$=0.436) and recessive model (YY *vs* CY+CC: OR=0.350, 95%CI=0.131-0.935, $P_{heterogeneity}$=0.430) was identified in C282Y polymorphism.

We further conducted a stratified analysis for source of control, and an significant increased risk of overall cancer was identified in hospital based group under homozygotes *vs* wide type model (YY *vs* CC: OR=2.094; 95%CI=1.129-3.884, $P_{heterogeneity}$=0.298) and recessive model (YY *vs* YC+CC: OR=2.020; 95%CI=1.092-3.736, $P_{heterogeneity}$=0.330} in C282Y polymorphism, while an significant increased risk in population based group was identified under homozygotes *vs* wide type model (DD *vs* HH: OR=1.521; 95%CI=1.183-1.956, $P_{heterogeneity}$=0.316) and recessive model (DD *vs* DH+HH: OR=1.498; 95%CI=1.166-1.924, $P_{heterogeneity}$=0.384),

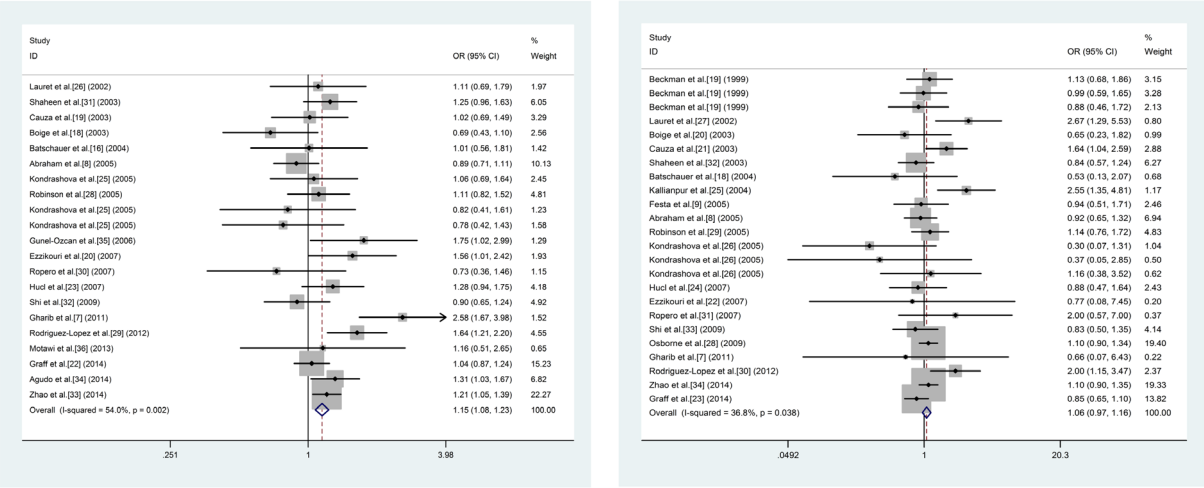

Figure 2. A). Meta-analysis of the Association between HFE-H63D Polymorphism and Overall Cancer Risk (D *vs* H). B). Meta-analysis of the association between HFE-C282Y Polymorphism and Overall Cancer Risk (Y *vs* C)

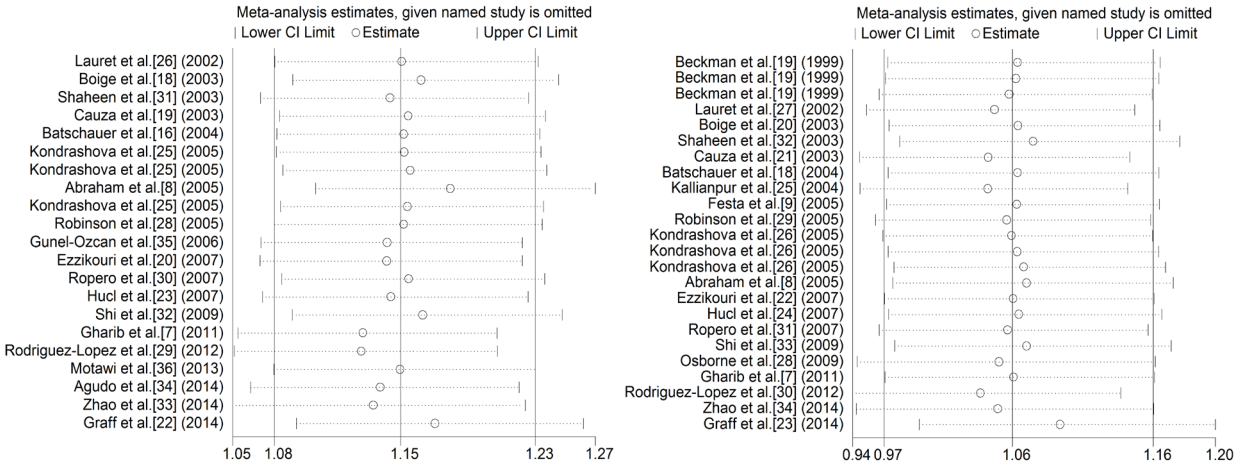

Figure 3. A). Sensitivity analysis for HFE-H63D (D *vs* H) of Overall OR Co-efficients. B). Results were Calculated by Omitting Each Study in Turn, and the two Ends of the Dotted Lines Represent the 95%CI

as well as hospital based group under recessive model (DD *vs* DH+HH: OR=1.261; 95%CI=0.887-1.792, $P_{heterogeneity}$=0.543) in H63D polymorphism (Table 3 and Table 4). When a stratified analysis was conducted for HWE (Y or N), an increased risk was identified in Y group of H63D polymorphism under allele contrast model (D *vs* H: OR=1.182; 95%CI=1.033-1.353, $P_{heterogeneity}$=0.002), homozygotes *vs* wide type model (DD *vs* HH: OR=1.449; 95%CI=1.114-1.885, $P_{heterogeneity}$=0.267), dominant model (DD+HD *vs* HH: OR=1.181; 95%CI=1.012-1.377, $P_{heterogeneity}$=0.002), and recessive model (DD *vs* DH+HH: OR=2.461; 95%CI=1.478-4.100, $P_{heterogeneity}$=0.537), as well as C282Y polymorphism under recessive model (YY *vs* YC+CC: OR=1.771; 95%CI=1.160-2.705, $P_{heterogeneity}$=0.556) (Table 3 and Table 4).

Publication bias and sensitivity analysis

Then, we performed a sensitivity analysis to assess the influence of each case on the integrated data by excluding a single study each time, and no single study influenced

Table 1. Characteristics of Eligible Case-control Studies about HFE-H63D Polymorphism Included in the Meta-analysis

First Author	Year	Etihnicity	Genotypin Method	Source of Control	Cancer Type	Case			Control			PHWE	HWE
						HH	HD	DD	HH	HD	DD		
Gunel-Ozcan et al.	2006	Caucasian	PCR-RFLP	P-B	Breast cancer	49	39	0	73	26	1	0.43	Y
Robinson et al.	2005	Caucasian	PCR-RFLP	P-B	Colorectal cancer	236	83	8	241	73	8	0.39	Y
Abraham et al.	2005	Caucasian	TaqMan	P-B	Breast cancer	404	134	12	450	170	16	0.99	Y
Motawi et al.	2013	Caucasian	PCR-RFLP	H-B	Hepatocellular carcinoma	29	10	0	62	18	0	0.26	Y
Rodriguez et al.	2012	Caucasian	TaqMan	P-B	Acute lymphoblastic leukemia	243	168	46	114	60	5	0.38	Y
Gharib et al.	2011	Caucasian	PCR-RFLP	H-B	Hepatocellular carcinoma	52	43	5	153	45	2	0.51	Y
Kondrashova et al.	2005	Caucasian	PCR-RFLP	H-B	Ovarian cancer	30	9	1	180	75	5	0.38	Y
Kondrashova et al.	2005	Caucasian	PCR-RFLP	H-B	Endometrial cancer	41	10	2	180	75	5	0.38	Y
Kondrashova et al.	2005	Caucasian	PCR-RFLP	H-B	Breast cancer	67	30	2	180	75	5	0.38	Y
Ezzikouri et al.	2007	Caucasian	PCR-RFLP	H-B	Hepatocellular carcinoma	59	34	3	160	60	2	0.16	Y
Cauza et al.	2003	Caucasian	PCR	H-B	Hepatocellular carcinoma	128	31	3	529	133	9	0.85	Y
Lauret et al.	2002	Caucasian	PCR-RFLP	H-B	Hepatocellular carcinoma	52	25	0	234	92	3	0.06	Y
Hucl et al.	2007	Caucasian	PCR	H-B	Pancreatic adenocarcinoma	117	48	3	1181	372	18	0.06	Y
Shi et al.	2009	Caucasian	TaqMan	P-B	Colorectal cancer	110	33	5	2954	1129	103	0.69	Y
Agudo et al.	2014	Caucasian	PCR	H-B	Hastric cancer	230	82	11	885	249	23	0.27	Y
Graff et al.	2014	Caucasian	TaqMan	H-B	Breast cancer	553	196	16	1009	323	36	0.1	Y
Batschauer et al.	2004	Mixed	PCR-RFLP	P-B	Breast cancer	49	13	6	57	25	3	0.9	Y
Shaheen et al.	2003	Mixed	PCR	P-B	Colon cancer	382	83	10	697	124	12	0.02	N
Ropero et al.	2007	Caucasian	PCR	P-B	Hepatocellular carcinoma	81	4	9	41	6	5	0	N
Boige et al.	2003	Caucasian	PCR	H-B	Hepatocellular carcinoma	92	41	0	59	40	1	0.04	N
Zhao et al.	2014	Asian	TaqMan	P-B	Pancreatic cancer	956	356	74	1005	331	50	0.0007	N

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; Y: polymorphisms conformed to HWE in the control group; N: polymorphisms; didn`t conform to HWE in the control group. H-B: hospital based; P-B: population based

Table 2. Characteristics of Eligible Case-control Studies about HFE-C282Y Polymorphism Included in the Meta-analysis

First Author	Year	Etihnicity	Genotypin Method	Source of Control	Cancer Type	Case			Control			P_{HWE}	HWE
						CC	CY	YY	CC	CY	YY		
Festa et al.	2005	Caucasian	PCR-RFLP	P-B	Basal cell carcinoma	222	17	2	236	22	1	0.53	Y
Gharib et al.	2011	Caucasian	PCR-RFLP	H-B	Hepatocellular carcinoma	99	1	0	197	3	0	0.91	Y
Rodriguez et al.	2012	Caucasian	TaqMan	P-B	Acute lymphoblastic leukemia	404	58	13	157	16	0	0.52	Y
Abraham et al.	2005	Caucasian	TaqMan	P-B	Breast cancer	494	55	1	566	69	1	0.46	Y
Robinson et al.	2005	Caucasian	PCR-RFLP	P-B	Colorectal cancer	275	50	2	279	39	4	0.06	Y
Batschauer et al.	2004	Mixed	PCR-RFLP	P-B	Breast cancer	65	3	0	78	7	0	0.69	Y
Zhao et al.	2014	Asian	TaqMan	P-B	Pancreatic cancer	1191	184	11	1207	170	9	0.26	Y
Graff et al.	2014	Caucasian	TaqMan	H-B	Breast cancer	682	78	5	1192	168	8	0.43	Y
Shi et al.	2009	Caucasian	TaqMan	P-B	Colorectal cancer	143	17	0	4104	560	18	0.81	Y
Hucl et al.	2007	Caucasian	PCR	H-B	Pancreatic adenocarcinoma	158	9	1	1457	111	3	0.56	Y
Lauret et al.	2002	Caucasian	PCR-RFLP	H-B	Hepatocellular carcinoma	65	12	0	337	22	0	0.55	Y
Boige et al.	2003	Caucasian	PCR	H-B	Hepatocellular carcinoma	126	7	0	93	6	1	0.03	N
Cauza et al.	2003	Caucasian	PCR	H-B	Hepatocellular carcinoma	139	18	5	603	63	5	0.02	N
Ezzikouri et al.	2007	Caucasian	PCR-RFLP	P-B	Hepatocellular carcinoma	95	1	0	219	3	0	0.92	Y
Ropero et al.	2007	Caucasian	PCR	P-B	Hepatocellular carcinoma	8	4	1	17	6	0	0.47	Y
Shaheen et al.	2003	Mixed	PCR	P-B	Colon cancer	436	39	0	764	57	12	<0.01	N
Beckman et al.	1999	Caucasian	PCR	P-B	Breast cancer	139	25	1	255	35	4	0.04	N
Beckman et al.	1999	Caucasian	PCR	P-B	Colorectal cancer	150	21	2	255	35	4	0.04	N
Beckman et al.	1999	Caucasian	PCR	P-B	Multiple myeloma	81	10	1	255	35	4	0.04	N
Kondrashova et al.	2005	Caucasian	PCR-RFLP	H-B	Breast cancer	98	2	0	243	17	0	0.59	Y
Kondrashova et al.	2005	Caucasian	PCR-RFLP	H-B	Ovarian cancer	39	1	0	243	17	0	0.59	Y
Kondrashova et al.	2005	Caucasian	PCR-RFLP	H-B	Endometrial cancer	50	2	1	243	17	0	0.59	Y
Kallianpur et al.	2004	Mixed	PCR	H-B	Breast cancer	26	10	5	107	15	7	<0.01	N
Osborne et al.	2009	Caucasian	PCR	P-B	Breast cancer	565	90	9	14046	2263	90	0.91	Y

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; Y: polymorphisms conformed to HWE in the control group; N: polymorphisms; didn`t conform to HWE in the control group. H-B: hospital based; P-B: population based

Table 3. Results of Meta-analysis for HFE-H63D Polymorphism and Cancer Risk

Variables	Case/Control	D *vs* H			DD *vs* HH			DH *vs* HH		
		OR (95%CI)	P^a	`	OR (95%CI)	P^a	I^2	OR (95%CI)	P^a	I^2
Total	5648/14257	1.153(1.031-1.289)*	0.002	54	1.449(1.182-1.777)*	0.391	5.3	1.113(0.978-1.267)	0.004	51.4
Pancreatic cancer	1554/2957	1.220(1.073-1.387)*	0.724	0	1.564(1.097-2.230) *	0.905	0	1.162(0.994-1.358)	0.484	0
Breast cancer	1570/2449	1.033(0.877-1.218)	0.248	26	0.911(0.597-1.388)	0.735	0	1.068(0.810-1.408)	0.044	59.2
Hepatocellular carcinoma	701/1654	1.173(0.819-1.680)	0.001	72.1	1.577(0.830-2.995)	0.217	29.1	1.151(0.757-1.752)	0.002	70.4
Colorectal cancer	950/5341	1.096(0.909-1.322)	0.306	15.5	1.288(0.758-2.188)	0.837	0	1.058(0.816-1.373)	0.194	39.1
Other cancers	873/1856	1.212(0.896-1.639)	0.078	56	2.587(1.553-4.309)*	0.453	0	1.068(0.773-1.474)	0.141	45.1
Source of controls										
Population based	3593/7779	1.141(0.979-1.331)	0.024	54.7	1.521(1.183-1.956)*	0.316	14.1	1.069(0.887-1.288)	0.025	54.4
Hospital based	2055/6478	1.160(0.974-1.382)	0.007	57.4	1.311(0.922-1.864)	0.383	6.4	1.152(0.952-1.394)	0.019	51.7
HWE										
Y		1.182(1.033-1.353)*	0.002	56.2	1.449(1.114-1.885)*	0.267	16.30%	1.146(0.983-1.336)	0.006	52.8
N		1.052(0.823-1.345)	0.072	57.2	1.450(1.050-2.002)	0.546	0.00%	0.988(0.730-1.336)	0.07	57.4

	Case/Control	DD+DH *vs* HH			DD *vs* DH+HH		
		OR (95%CI)	P^a	I^2	OR (95%CI)	P^a	I^2
Total	5648/14257	1.145(1.007-1.301)*	0.002	54.2	1.416(1.156-1.735)*	0.549	0
Pancreatic cancer	1554/2957	1.210(1.043-1.403)*	0.587	0	1.511(1.063-2.149)*	0.951	0
Breast cancer	1570/2449	1.064(0.838-1.352)	0.092	49.9	0.914(0.601-1.388)	0.607	0
Hepatocellular carcinoma	701/1654	1.183(0.781-1.794)	0.001	72.7	1.530(0.805-2.909)	0.404	2
Colorectal cancer	950/5341	1.081(0.853-1.369)	0.227	32.7	1.281(0.754-2.177)	0.818	0
Other cancers	873/1856	1.144(0.815-1.607)	0.09	53.7	2.461(1.478-4.100)*	0.537	0
Source of controls							
Population based	3593/7779	1.116(0.936-1.331)	0.025	54.4	1.498(1.166-1.924)*	0.384	6.2
Hospital based	2055/6478	1.168(0.958-1.423)	0.007	57.5	1.261(0.887-1.792)*	0.543	0
HWE							
Y	3650/11866	1.181(1.012-1.377)*	0.002	56.4	1.413(1.087-1.837)*	0.383	6.1
N	2088/2371	1.024(0.775-1.355)	0.074	56.8	1.421(1.032-1.958)*	0.658	0

I^2: 0–25, means no heterogeneity; 25–50, means modest heterogeneity; >50, means high heterogeneity; PCR-RFLP: polymerase chain reaction-restriction fragment; length polymorphism; HWE: Hardy-Weinberg equilibrium; Y: polymorphisms conformed to HWE in the control group; N: polymorphisms didn`t conform; to HWE in the control group; *Pa*: *P* value of Q test for heterogeneity test; * means statistically significant ($P<0.05$)

Table 4. Results of Meta-analysis for HFE-C282Y Polymorphism and Cancer Risk

Variables	Case/Control	D *vs* H			DD *vs* HH			DH *vs* HH		
		OR (95%CI)	P^a	`	OR (95%CI)	P^a	I^2	OR (95%CI)	P^a	I^2
Total	6524/31080	1.059(0.967-1.160)	0.038	36.8	1.428(1.017-2.006)*	0.22	19.6	1.021(0.924-1.129)	0.285	12.7
Pancreatic cancer	1554/2957	1.078(0.888-1.309)	0.492	0	1.352(0.587-3.118)	0.462	0	1.055(0.854-1.303)	0.306	4.7
Breast cancer	2353/19171	1.010(0.882-1.157)	0.024	58.6	1.756(1.048-2.943)*	0.425	0	0.941(0.810-1.092)	0.086	45.9
Colorectal cancer	1135/6131	0.941(0.756-1.171)	0.677	0	0.355(0.133-0.949)*	0.436	0	1.108(0.874-1.406)	0.671	0
Hepatocellular carcinoma	581/1575	1.567(1.115-2.201)*	0.306	16.7	2.671(0.927-7.698)	0.23	31.9	1.397(0.949-2.059)	0.422	0
Other cancers	901/1246	1.219(0.894-1.661)	0.194	34.1	3.585(1.172-10.966)*	0.351	8.4	0.972(0.687-1.375)	0.524	0
Source of controls										
Population based	4885/25902	1.062(0.957-1.179)	0.6	0	1.221(0.811-1.838)	0.258	18.9	1.051(0.938-1.179)	0.937	0
Hospital based	1639/5178	1.050(0.874-1.262)	0.003	64.5	2.094(1.129-3.884)*	0.298	17.9	0.931(0.757-1.145)	0.019	54.5
HWE										
Y	5324/28594	1.044(0.943-1.155)	0.121	29.7	1.779(1.166-2.716)	0.559	0	0.984(0.881-1.100)	0.238	18.5
N	1200/2486	1.122(0.919-1.370)	0.041	54.2	0.958(0.530-1.730)	0.039	54.7	1.200(0.954-1.510)	0.608	0

	Case/Control	YY+CY *vs* CC			YY *vs* CY+CC		
		OR (95%CI)	P^a	I^2	OR (95%CI)	P^a	I^2
Total	6524/31080	1.042(0.946-1.148)	0.156	22.7	1.403(0.999-1.970)	0.24	17.9
Pancreatic cancer	1554/2957	1.069(0.870-1.314)	0.385	0	1.340(0.581-3.088)	0.447	0
Breast cancer	2353/19171	0.974(0.843-1.126)	0.044	53.6	1.709(1.020-2.863)*	0.472	0
Colorectal cancer	1135/6131	1.018(0.808-1.283)	0.744	0	0.350(0.131-0.935)*	0.43	0
Hepatocellular carcinoma	581/1575	1.499(1.037-2.167)*	0.384	5.1	2.622(0.911-7.546)	0.241	29.7
Other cancers	901/1246	1.098(0.788-1.530)	0.348	10.2	3.563(1.161-10.937)*	0.358	7
Source of controls							
Population based	4885/25902	1.058(0.947-1.183)	0.887	0	1.206(0.801-1.816)	0.251	19.6
Hospital based	1639/5178	0.991(0.813-1.208)	0.007	60.1	2.020(1.092-3.736)*	0.33	13.3
HWE							
Y	5324/28594	1.014(0.910-1.130)	0.186	23.1	1.771(1.160-2.705)*	0.556	0
N	1200/2486	1.161(0.934-1.443)	0.254	22.9	0.921(0.510-1.664)	0.052	52

I^2: 0–25, means no heterogeneity; 25–50, means modest heterogeneity; >50, means high heterogeneity; PCR-RFLP: polymerase chain reaction-restriction fragment; length polymorphism; HWE: Hardy-Weinberg equilibrium; Y: polymorphisms conformed to HWE in the control group; N: polymorphisms didn`t conform; to HWE in the control group; *Pa*: *P* value of Q test for heterogeneity test; * means statistically significant ($P<0.05$)

the pooled OR was identified (Figure 3a and Figure 3b). In addition, we conducted Egger's test and Begg's funnel plot to assess the publication bias. Similarly, no apparent publication bias was uncovered by these tests in *HFE* polymorphisms {*HFE*-H63D (D *vs* H: Begg's test: P=0.450; Egger's test: P= 0.836, Figure 4a) and *HFE*-C282Y (Y *vs* C: Begg's test: P=0.747; Egger's test: P= 0.874, Figure 4b)}.

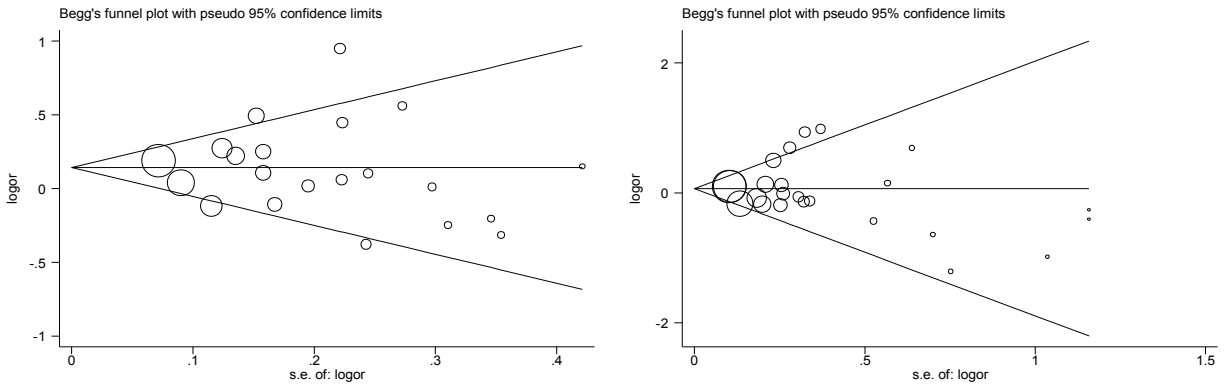

Figure 4. A). Begg's Funnel Plot for Publication Bias Test. (HFE H63D: D *vs* H) Each point represents a separate study for the indicated association, and the circles represent the weight of individual study. **B)**. Begg's Funnel Plot for Publication Bias Test. (HFE C282Y: Y *vs* C) Each point represents a separate study for the indicated association, and the circles represent the weight of individual study

Discussion

HFE encoded a membrane protein may function to the iron absorption process by regulating the interaction of the transferrin receptor with transferrin. Hereditary hemochromatosis is always presented with iron storage disorder that mainly result from the defects of the gene. Previous studies suggested that the mutations or polymorphisms in *HFE* were associated with this disease, particularly for *HFE*-C282Y polymorphism. Approximately 1/200 of people who were Northern European origin have two copies of this variant (C282Y), with a high risk of developing hemochromatosis.[3] In addition, the pro-oxidative properties of iron also can result in genomic instability(Dubacq et al., 2006), may increase the cancer risk, and several studies validated this hypothesis that an increased risk was identified in leukemia(Kennedy et al., 2014), hepatocellular carcinoma(Gharib et al., 2011), breast cancer(Abraham et al., 2005). Two mechanisms have been investigated to explain the potential role of iron as an epidemic factor in the carcinogenesis process: 1) the ability of iron to induce oxidative stress; and 2) during the process of cancer cell growth, iron is an essential cofactor (Agudo et al.).

In our present work, we performed a comprehensive meta-analysis to examine the association between polymorphisms in *HFE* (C282Y and H63D) and cancer risk. The study uncovered that H63D polymorphism and C282 were associated with an increased risk of overall cancer. In the stratified analysis by cancer type, an increased risk was identified in hepatocellular carcinoma and breast cancer in C282Y polymorphism, as well as pancreatic cancer in H63D polymorphism, whereas a decreased risk of colorectal cancer was identified in C282Y polymorphism. In addition, we also conducted a sensitivity analysis to further validate the association between the two polymorphisms and cancer risk and a positive result was uncovered.

To date, plenty of studies have elaborated the association between C282Y and H63D polymorphisms and cancer risk. Nevertheless, the data was conflicting and inconclusive. The first study was conducted by Beckman et al.(Beckman et al., 1999) to investigate the association between the polymorphisms in *HFE* gene and breast cancer risk. Subsequent investigations were focus on hepatocellular carcinoma (Boige et al., 2003), colorectal cancer (Osborne et al., 2010), ovarian cancer (Kondrashova et al., 2006) and etc.

Although we have conducted a comprehensive retrieve for all eligible studies associated with the polymorphisms (C282Y and H63D) in *HFE* and cancer risk, there are still several limitations that should be noted. Firstly, when a stratified analysis was performed for cancer type, control source, ethnicity, the analysis were restricted to the limited number of the reports and the relatively small sample size. Secondly, most of the enrolled reports were Caucasian, and rare studies were concerned in Asian, particularly, no data was available for African. Thirdly, most of the enrolled reports provided no efficient original data such as smoking and drinking frequency, residential environment and etc., so that we cannot perform further assessment for the potential gene-gene coactions or gene-environment coactions.

In conclusion, the present work has successfully illustrated the association between the H63D not C282Y polymorphisms and cancer risk. However, further well designed studies with large sample size will be continued on this issue of interest in order to refine the conclusion.

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