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Flap endonuclease 1 polymorphisms (rs174538 and rs4246215) contribute to an increased cancer risk: Evidence from a meta-analysis

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Abstract. Flap endonuclease-1 (FEN1) is a key factor during the maintenance of genomic stability and protection against tumorigenesis. Since the identification of functional polymorphisms of *FEN1* (rs174538 and rs4246215), numerous studies have evaluated the association between the two single-nucleotide polymorphisms and cancer risk. To derive a more precise estimation, a meta-analysis was performed on the association between the *FEN1* polymorphisms (rs174538 and rs4246215) and cancer risk. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of the associations. Thirteen case-control studies, including 5,108 cases and 6,382 case-free controls, were identified. For rs174538, individuals with the GG or GA genotype had an increased risk of cancer when compared to the -69AA genotype (AA vs. GG: OR, 1.85; 95% CI, 1.65-2.08; P<0.00001; AA vs. GA: OR, 1.43; 95% CI, 1.27-1.60; P<0.00001; AA vs. GG+GA: OR, 1.28; 95% CI, 1.16-1.42; P<0.00001). For rs4246215, similar results were identified, as the GG or GT genotype was significantly associated with the increased cancer risk when compared to TT (TT vs. GG: OR, 1.71; 95% CI, 1.52-1.92; P<0.00001; TT vs. GT: OR, 1.34; 95% CI, 1.20-1.50; P<0.00001; TT vs. GG+GT: OR, 1.50; 95% CI, 1.35-1.67; P<0.00001). The present meta-analysis indicated that *FEN1* rs174538 and rs4246215 polymorphisms may contribute to an increased risk of cancer.

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Introduction

Flap endonuclease 1 (FEN1) is a versatile, structure specific and multifunctional nuclease involved in DNA replication and repair (1,2). Human FEN1, which is the archetypal member of the Rad2 nuclease family (3,4), is located on chromosome 11q12 and consists of two exons and one intron. FEN1 efficiently removed the 5'-flaps generated by Polδ/ε during repair synthesis of long-patch base-excision repair (LP-BER) and removed primers during lagging-strand DNA synthesis and Okazaki fragment processing (3,5,6). Furthermore, FEN1 can be stimulated to promote apoptotic DNA fragmentation following apoptotic stimuli, acting as a 5' exonuclease (1) and a gap-dependent endonuclease (7,8), as reported via its ability to participate in multiple protein-protein interactions. Thus far, >30 FEN1-interacting proteins have been identified (2). Of these FEN1 interaction partners, proliferating cell nuclear antigen (PCNA), which was initially identified as a replication accessory protein, accompanies FEN1 in all FEN1-involved DNA metabolic pathways except for the apoptotic DNA fragmentation pathway, suggesting a critical role of the FEN1/PCNA interaction in regulating LP-BER (9). A tumor suppressor function for FEN1 has been shown in preclinical models (10-14). Therefore, FEN1 has been considered as a key factor during maintenance of genomic stability and protecting against carcinogenesis.

However, being a multifunctional factor, mutation of *FEN1* has been suggested to cause genomic instability and predisposition to cancer. The functional impairment of yeast RAD27 (the homolog of mammalian *FEN1*) leads to a marked increase in the rate of spontaneous mutations (8,15,16). A recent study showed that groups of *FEN1* mutations in cancer specimens that abrogated two of the three nuclease activities lead to cancer initiation and progression (17). Yang *et al* (18) identified two single-nucleotide polymorphisms (SNP), -69G>A (rs174538, in the gene promoter region) and 4150G>T (rs4246215, in gene 3'-untranslated region), following thorough re-sequencing of the *FEN1* locus in 30 Chinese Han healthy volunteers. The study identified that the -69G>A change leads to elevated promoter activity, which is most likely due to a higher binding affinity of the G allele with certain unknown transcriptional inhibitors.

The -69G>A and 4150G>T SNPs influenced gene expression *in vivo* subsequent to examining *FEN1* mRNA in 38 lung normal tissues, 15 esophagus normal tissues, 12 stomach normal tissues and 13 normal tissues through quantitative analyses (18). Abnormal expression and/or function of *FEN1* resulting from SNPs may possibly contribute to different cancer susceptibility. On the basis of the previous findings mentioned, we hypothesized that the functional genetic variants in the *FEN1* gene may affect cancer risk. Meta-analysis is a statistical technique for combining results from different studies to produce a single estimate of the major effect with enhanced precision (19). Therefore, a meta-analysis of the published studies was conducted to derive a more precise estimation of the association between *FEN1* polymorphisms and cancer risk.

Materials and methods

Identification and eligibility of relevant studies. Computer searches were carried out by two investigators independently in Embase, Pubmed, ISI Web of Knowledge and Chinese National Knowledge Infrastructure databases (until March 31, 2014) to collect case-control studies of the *FEN1* SNPs (rs174538 and rs4246215) association with cancer risk. The keywords were as follows: Cancer/carcinoma, Flap endonuclease-1/*FEN1*, -69G>A/rs174538 and 4150G>T/rs4246215 and polymorphism/genotype/SNP. In addition, reference lists of the main studies and reviews were also assessed by a manual search to identify additional relevant publications. The following criteria were used to select studies for further meta-analysis: i) Case-control studies; ii) studies that evaluated the association of *FEN1* SNPs (rs174538 and rs4246215) on cancer risk; iii) studies that contained at least two comparison groups (cancer vs. control group); and iv) studies that included detailed genotyping data.

The following exclusion criteria were used accordingly: i) The design of the experiments were not case-control studies; ii) the source of cases and controls, and other essential information were not provided; iii) the genotype distribution of the control population was departure from Hardy-Weinberg Equilibrium; and iv) reviews and duplicated publications.

Data extraction. Evaluations of studies were performed independently by two investigators and data with discrepancies in identification were discussed by all investigators. For each included study, the following information was collected: First author, year of publication, country of origin, ethnicity, source of control, number of cases and controls, genotyping methods for rs174538 and rs4246215, total number of cases and controls, as well as number of cases and controls with A/A, A/G, G/G and T/T, T/G, G/G genotypes. All the case and control groups were well-controlled.

Statistical analysis. For the control group of each study, the allelic frequency was calculated. The strength of associations between *FEN1* SNPs (rs174538 and rs4246215) and cancer risk were measured by odds ratio (OR) with 95% confidence interval (CI). For rs174538, the AA genotype was used as the reference genotype in all analyses. The risks of the GG and GA genotypes for cancers were estimated, compared to the AA homozygote, and subsequently the risks of GA+GG for cancer were evaluated, respectively. Accordingly, for rs4246215, the TT genotype was used as the reference genotype in all the analyses. The risks of the GT and GG genotypes for cancer were estimated, compared to the TT homozygote, and subsequently the risks of GT+GG for cancers were evaluated. The significance of the pooled OR was determined by the Z test. Statistical heterogeneity among studies was assessed with the Q and I^2 statistics. The Q test and I^2 were claimed to test the variation, which was due to heterogeneity or by random error. When the P-value of heterogeneity tests was $P \leq 0.1$, the random effects model was used. When the P-value of heterogeneity test was $P \geq 0.1$, the fixed effects model was used. Sensitivity analysis was also tested by removing one study at a time to calculate the overall homogeneity and effect size. Publication bias was evaluated by the funnel plot and further assessed by the method of Egger's linear regression test. All the statistical analyses were carried out with the Review Manager version 5.1 software (Revman; The Cochrane Collaboration, Oxford, United Kingdom). All P-values in the meta-analysis were two-sided, and $P<0.05$ were considered to indicate a statistically significant difference.

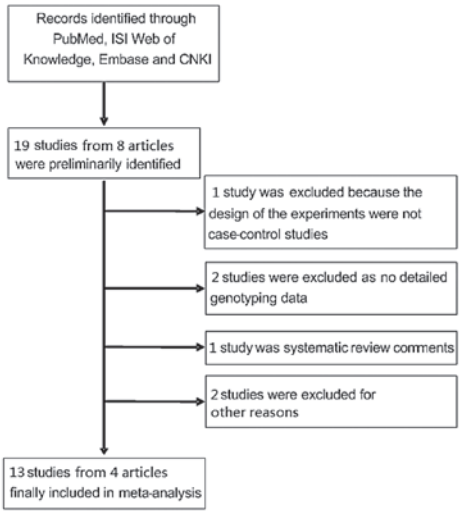

Figure 1. Flow chart of study selection.

Results

Characteristics of studies. A total of 19 sub-studies from 8 studies that fulfilled our search criteria were preliminarily identified for further detailed evaluation (Fig. 1). One study was excluded as the designs of the experiments were not case-control studies. Two studies did not focused on *FEN1* SNPs (rs174538 and rs4246215) and cancer risk. Two studies were excluded as there was no detailed genotyping data. Four studies were review comments. Finally, 13 sub-studies from 4 studies on rs174538 and rs4246215 genotypes and cancer risk were identified (18,20-22), including a total of 5,108 cancer cases and 6,382 case-free controls. The characteristics of the included studies are listed in Table I. The included studies were all based on Chinese populations. All were case-control studies, including lung cancer, breast cancer, glioma, hepatocellular carcinoma, esophageal cancer, gastric cancer and colorectal cancer. All the types of cancer were confirmed by histology or pathology. Additionally, the controls were mainly matched on age, of which all the studies were hospital-based.

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

First author, year (Ref.)	Country	Ethnicity	Cancer type	Genotyping method	Source of control	Total sample size (case/control)
Lv, 2014 (20)						
1	China	Asian	Breast cancer	PCR-RFLP	Hospital	800/800
2	China	Asian	Breast cancer	PCR-RFLP	Hospital	300/600
Chen, 2013 (21)	China	Asian	Glioma	PCR-RFLP	Hospital	317/802
Liu, 2012 (22)						
1	China	Asian	Hepatocellular carcinoma	PCR-RFLP	Hospital	411/423
2	China	Asian	Esophageal cancer	PCR-RFLP	Hospital	266/386
3	China	Asian	Gastric cancer	PCR-RFLP	Hospital	220/250
4	China	Asian	Colorectal cancer	PCR-RFLP	Hospital	126/162
5	China	Asian	Hepatocellular carcinoma	PCR-RFLP	Hospital	237/315
6	China	Asian	Esophageal cancer	PCR-RFLP	Hospital	289/337
7	China	Asian	Gastric cancer	PCR-RFLP	Hospital	192/204
8	China	Asian	Colorectal cancer	PCR-RFLP	Hospital	110/145
Yang, 2009 (18)						
1	China	Asian	Lung cancer	PCR-RFLP	Hospital	1,013/1,131
2	China	Asian	Lung cancer	PCR-RFLP	Hospital	827/827

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Table II. rs174538 polymorphism genotype distribution and allele frequency in cases and controls.

First author, year (Ref.)	Genotype, n								Allele frequency, n (%)			
	Case				Control				Case		Control	
	Total	GG	GA	AA	Total	GG	GA	AA	G	A	G	A
Chen, 2013 (21)	317	160	122	35	802	316	356	130	437 (69)	197 (31)	988 (62)	616 (38)
Liu, 2012 (22)												
1	410	203	173	34	423	174	185	64	579 (71)	241 (29)	533 (63)	313 (37)
2	266	137	105	24	386	163	168	55	379 (71)	153 (29)	494 (64)	278 (36)
3	220	118	86	16	250	108	108	34	322 (73)	118 (27)	324 (65)	176 (35)
4	126	64	51	11	162	65	73	24	178 (71)	73 (29)	203 (63)	121 (37)
5	238	87	117	34	315	96	149	70	281 (59)	195 (41)	341 (54)	289 (46)
6	289	107	144	38	336	100	163	73	358 (62)	220 (38)	393 (54)	309 (46)
7	192	71	96	25	204	61	101	42	138 (49)	146 (51)	223 (55)	185 (45)
8	110	40	53	17	145	44	71	30	133 (60)	87 (40)	159 (55)	131 (45)
Lv, 2014 (20)												
1	800	401	317	82	800	315	355	130	1,119 (70)	481 (30)	985 (62)	615 (38)
2	300	146	120	34	600	200	284	116	412 (69)	188 (31)	784 (65)	416 (35)
Yang, 2009 (18)												
1	1,013	505	402	106	1,131	467	496	168	1,402 (70)	614 (30)	1,430 (63)	832 (37)
2	827	286	394	147	827	257	384	186	966 (58)	688 (42)	898 (54)	756 (46)

Quantitative synthesis. The frequency of the A allele varied widely across the 13 studies, ranging from 23 to 46% in rs174538 among 6,381 healthy controls (Table II). The frequency of the T allele ranged from 35 to 46% in rs4246215 among 6,381 healthy controls (Table III). The average frequencies of the A and T allele in the two polymorphisms (rs174538 and rs4246215) were 39 and 41%, respectively.

The main results of the meta-analysis are listed in Tables IV and V. Overall, there was evidence of an association between the variant genotypes and cancer risk in different genetic

Table III. rs4246215 polymorphism genotype distribution and allele frequency in cases and controls.

First author, year (Ref.)	Genotype, n								Allele frequency, n (%)			
	Case				Control				Case		Control	
	Total	GG	GT	TT	Total	GG	GT	TT	G	T	G	T
Chen 2013 (21)	314	160	120	34	802	309	363	130	440 (70)	188 (30)	981 (61)	623 (39)
Liu, 2012 (22)												
1	411	195	177	39	423	176	187	60	567 (69)	255 (31)	539 (64)	307 (36)
2	249	115	114	20	386	161	172	53	344 (69)	154 (31)	494 (64)	278 (36)
3	210	111	82	17	250	107	110	33	304 (72)	116 (28)	324 (65)	176 (35)
4	119	61	47	11	161	65	74	22	169 (71)	69 (29)	204 (63)	118 (37)
5	237	85	118	34	315	98	148	69	288 (61)	186 (39)	344 (55)	286 (45)
6	289	110	141	38	337	101	164	72	361 (62)	217 (38)	366 (54)	308 (46)
7	192	72	95	25	204	59	102	43	239 (62)	145 (38)	220 (54)	188 (46)
8	110	39	55	16	145	44	71	30	133 (60)	87 (40)	159 (55)	131 (45)
Lv, 2014 (20)												
1	800	365	335	100	800	308	362	130	1,065 (67)	535 (33)	978 (61)	622 (39)
2	300	152	114	34	600	195	289	116	418 (70)	182 (30)	679 (57)	521 (43)
Yang, 2009 (18)												
1	1,013	468	421	124	1,131	460	500	171	1,357 (67)	669 (33)	1,420 (63)	842 (37)
2	827	286	394	147	827	257	383	187	966 (58)	688 (42)	897 (54)	757 (46)

Table IV. Risk of cancer associated with the genotypes of *FEN1* -69G>A (rs174538).

Genotype	OR	95% CI	P-value	Heterogeneity		Effects model
				I^2, %	P-value	
AA	1 (Reference)					
GA	1.43	1.27-1.60	<0.00001	0	0.99	F
GG	1.85	1.65-2.08	<0.00001	0	0.05	R
GA+GG	1.28	1.16-1.42	<0.00001	91	<0.00001	R

AA genotype was the reference genotype in all analyses. OR, odds ratio; CI, confidence interval; F, fixed effects model; R, random effects model.

Table V. Risk of cancer associated with the genotypes of *FEN1* 4150G>T (rs4246215).

Genotype	OR	95% CI	P-value	Heterogeneity		Effects model
				I^2, %	P-value	
TT	1 (Reference)					
GT	1.34	1.20-1.50	<0.00001	0	0.97	F
GG	1.71	1.52-1.92	<0.00001	0	0.56	F
GT+GG	1.50	1.35-1.67	<0.00001	91	0.91	F

TT genotype was the reference genotype in all analyses. OR, odds ratio; CI, confidence interval; F, fixed effects model; R, random effects model.

models when all the studies were pooled into the meta-analysis. As shown in Table IV, carriers of the *FEN1* -69GG genotype showed a significantly elevated risk of cancer compared to -69AA carriers (OR, 1.85; 95% CI, 1.65-2.08; P<0.00001). Logistic regression analyses also revealed that individuals with *FEN1* -69GA genotypes were significantly associated with

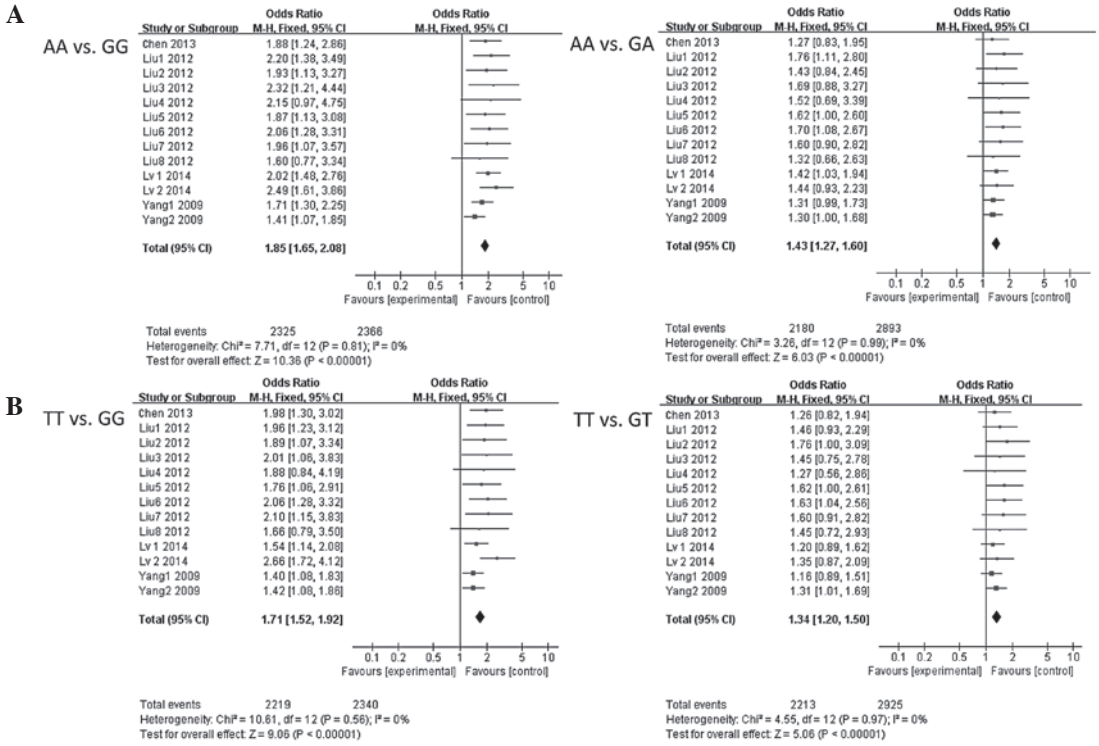

Figure 2. Combined meta-analyses of the associations between the *FEN1* polymorphisms and risk of cancer. (A) -69G>A. (B) 4150G>T. The squares and horizontal lines correspond to the study specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; CI, confidence interval.

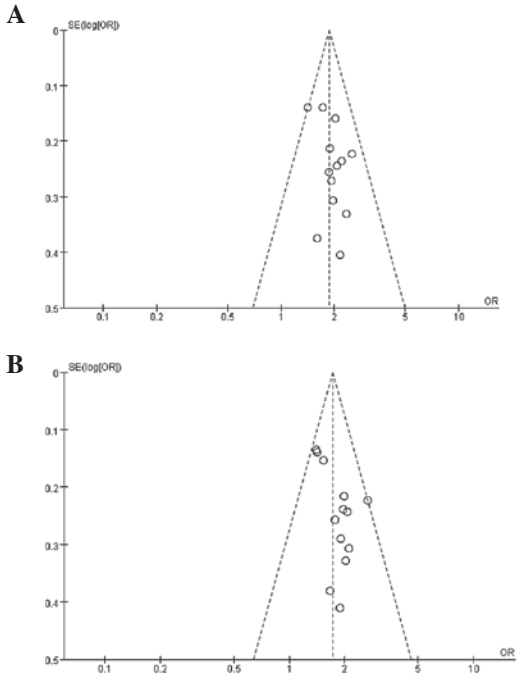

Figure 3. Funnel plot assessing evidence of publication bias from the 13 studies. (A) -69G>A: AA vs. GG. (B) 4150G>T: TT vs. GG. SE, standard error; OR, odds ratio.

increased cancer risk compared to -69AA genotypes (OR, 1.43; 95% CI, 1.27-1.60; P<0.00001). In addition, the variant GG+GA genotypes were associated with an increased cancer risk when compared to the -69AA genotypes (OR, 1.28; 95% CI, 1.16-1.42; P<0.00001). Similar results were observed for the 4150G>T polymorphism. As shown in Table V, the *FEN1* 4150GG genotype showed a significantly elevated risk of cancer compared to 4150TT carriers (OR, 1.71; 95% CI, 1.52-1.92; P<0.00001). Logistic regression analyses also revealed that individuals with the *FEN1* 4150GT genotypes were significantly associated with an increased cancer risk compared to the 4150TT genotypes (OR, 1.34; 95% CI, 1.20-1.50; P<0.00001). The variant GG+GT genotypes were associated with an increased cancer risk when compared to the 4150TT genotypes (OR, 1.50; 95% CI, 1.35-1.67; P<0.00001).

Tests of heterogeneity. Statistically significant heterogeneity was observed between trials of the following analyses using the Q statistic. As shown in Fig. 2, for AA vs. GG: $P_{heterogeneity}$=0.05, I^2=0, and therefore, a random effect model was performed; for AA vs. GA: $P_{heterogeneity}$=0.99, I^2=0, a fixed-effect model was performed; for TT vs. GG: $P_{heterogeneity}$=0.56, I^2=0, a fixed-effect model was performed; and for TT vs. GT: $P_{heterogeneity}$=0.91, I^2=0, a fixed-effect model was performed.

Publication bias. Begg's funnel plot and Egger's test were performed to assess the publication bias. The funnel plots did not reveal any clear asymmetry in all the genotypes (Fig. 3), and the results of Egger's test revealed no publication bias (P>0.05).

Discussion

FEN1 exhibits a prominent role in maintaining genomic stability and protecting against malignant transformation through its involvement in DNA repair and other multiple DNA metabolic pathways (8). Therefore, the structure or

functional deficiency of FEN1 may destroy the genomic stability to increase the risk of cancer. As previously mentioned, *FEN1* mutations reduced nuclease activity to lead to cancer initiation and development (15). *FEN1* -69 G and 4150 G alleles, which were correlated to significantly decreased *FEN1* mRNA expression in normal gastrointestinal tissues, were associated with increased gastrointestinal cancer risks compared to -69A and 4150T alleles in two independent case-control cohorts (21). The *FEN1* polymorphisms, rs174538 and rs4246215, may be common cancer risk factors.

In the present meta-analysis, all 13 case-control studies were pooled in a Chinese population to estimate the overall cancer risk of the SNPs. In the present study, the AA and TT genotypes were used as a reference genotype in all the analyses. For rs174538, it was found that individuals exhibiting the GG and GG/GA genotypes were significantly associated with an increased risk of cancer compared to the -69AA genotype. In the combined meta-analyses, the -69GG genotype had a 1.85-fold increased risk for cancer. Similar results were identified for rs4246215, all the genotypes were significantly associated with an increased cancer risk compared to the TT genotype ($P<0.01$). The present study indicated that functional rs174538 and rs4246215 were significantly associated with an increased risk of cancer. These results are consistent to the findings in breast cancer, lung cancer, hepatocellular carcinoma, esophageal cancer, gastric cancer, colorectal cancer and glioma from different medical centers of China (18,20-22), which confirmed our speculation that the functional genetic variants in the *FEN1* gene may affect cancer risk as common factors.

When interpreting the results of the present study, certain limitations of the meta-analysis must be considered. Firstly, all the cancer cases and controls were hospital-based, and inherent selection bias may exist. Thus, it is important to validate these findings in a population-based prospective study. Secondly, the meta-analysis was based on pooled data and no individual data was available; thus, the risk of cancer could not be assessed according to stratification of gene-environment and other risk factors of cancer. Thirdly, all the subjects were Chinese, and all the genotyping methods in the included studies were polymerase chain reaction-restriction fragment length polymorphism. Further large-scale multicenter studies with more detailed individual data, with different environmental backgrounds are warranted to further validate the gene-gene and gene-environment interactions on SNPs and cancer risk.

In conclusion, the present meta-analysis provides evidence of the effects of *FEN1* SNPs (rs174538 and rs4246215) on the cancer risk. The study indicated that functional rs174538 and rs4246215 were significantly associated with an increased risk of cancer in the Chinese population. Further studies based on different ethnicity are warranted to verify these findings.

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