RESEARCH ARTICLE

Association between the Interleukin-17A -197G>A (rs2275913) Polymorphism and Risk of Digestive Cancer

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Abstract

Interleukin-17A (IL-17A) is a multifunctional cytokine which plays a crucial role in the initiation and progression of cancer. To date, several studies have investigated associations between IL-17A -197G>A (rs2275913) polymorphism and digestive cancer risk, but the results remain conflicting. We here aimed to confirm the role of this single nucleotide polymorphism (SNP) in susceptibility to digestive cancer through a systemic review and meta-analysis. Ten eligible case-control studies were identified by searching electronic databases, involving 3,087 cases and 3,815 controls. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to estimate the strength of the association. The results of overall analyses indicated that the variant A allele was associated with an increased risk of digestive cancer (AA *vs* GG: OR=1.51, 95%CI=1.18-1.93; AA *vs* GG+GA: OR=1.45, 95%CI=1.12-1.87; A *vs* G: OR=1.21, 95%CI=1.05-1.39). In subgroup analysis stratified by specific cancer type, elevated risk among studies of gastric cancer was found (AA *vs* GG: OR=1.68, 95%CI=1.24-2.28; AA *vs* GG+GA: OR=1.62, 95%CI=1.16-2.26; A *vs* G: OR=1.23, 95%CI=1.04-1.46). According to ethnicity, there was evidence in the Asian populations for an association between this polymorphism and cancer risk (GA *vs* GG: OR=1.19, 95%CI=1.05-1.36; AA *vs* GG: OR=1.56, 95%CI=1.15-2.12; AA+GA *vs* GG: OR=1.28, 95%CI=1.13-1.44; AA *vs* GG+GA: OR=1.42, 95%CI=1.01-2.00; A *vs* G: OR=1.24, 95%CI=1.08-1.44), while in the Caucasian populations an association was found in the recessive model (AA *vs* GG+GA: OR=1.62, 95%CI=1.17-2.24). In conclusion, the results of this meta-analysis suggest that the IL-17A -197G>A polymorphism contributes to an increased risk of human digestive cancer, both in the Asian and Caucasian populations and especially for gastric cancer.

Keywords: Digestive cancer - interleukin-17A - polymorphism - meta-analysis

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Introduction

Cancer is currently a major public health burden worldwide, which results from complicated interactions between genetic and environmental factors (Hoeijmakers, 2001; Bredberg, 2011). Epidemiological studies have revealed that chronic inflammation predisposes individuals to several cancers (Wang et al., 2009). Moreover, inflammation has been linked to the pathogenesis of tumors in up to 15% of human cancers (Kuper et al., 2000). Cytokines are important inflammatory mediators, which act as part of the regulatory network to directly or indirectly activate downstream signaling pathways in the development of malignancies (Karin, 2006; Lin and Karin, 2007). There has been evidence that human predisposition to cancer could be influenced by single nucleotide polymorphisms (SNPs) located in genes encoding cytokines and their receptors, mostly in promoter regions (Bidwell et al., 1999).

Interleukin-17 (IL-17) is a relatively newly described family of pro-inflammatory cytokines that consists of six members, designated IL-17A-F (Kawaguchi et al., 2004). IL-17A is produced by a novel lineage of CD4+CD8+ T helper cells, namely TH17 cells (Moseley et al., 2003; Harrington et al., 2005; Bettelli et al., 2006), participating in both innate and adaptive immune responses. Several researches have found that high expression of IL-17A was associated with various tumor tissues, including gastric cancer, breast cancer, ovarian cancer, multiple myeloma, colorectal cancer and glioma (Kato et al., 2001; Alexandrakis et al., 2006; Zhang et al., 2008; Zhu et al., 2008; Doroudchi et al., 2013; Straus, 2013). IL-17A plays a pro-inflammatory role by recruiting neutrophils and inducing other inflammatory molecules, such as interleukin-1 (IL-1) or tumor necrosis factor-α (TNF-α) (Moseley et al., 2003; Kolls and Linden, 2004). It has been reported that IL-17A promoted angiogenesis via stimulating vascular endothelial growth factor (VEGF) production of cancer cells in colorectal carcinoma and was associated with poor prognosis (Liu et al., 2011). In addition, IL-17A has been proved to be associated with the prognosis of operable non-small cell lung cancer (NSCLC)

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(Zhang et al., 2012). The gene encoding IL-17A is located on chromosome 6p12.1 and contains several important polymorphisms, including rs2275913, rs3819024, rs17880588 (Bazzi et al., 2011; Wang et al., 2012b). The IL-17A -197G>A (rs2275913) polymorphism, which has been linked to several human cancers, leads to a guanine to adenine substitution in the promoter region and this location has been proved to be required for IL-17A expression (Liu et al., 2004). It is believed that cells with this mutation produce elevated level of IL-17A (Moseley et al., 2003), which in turn promotes tumorigenesis.

To date, several case-control studies have been carried out to investigate the role of IL-17A -197G>A polymorphism in predisposition to various cancers, including gastric, bladder, lung, colorectal, breast, cervical, ovarian, esophageal and hepatocellular cancer (Wu et al., 2010; Arisawa et al., 2012; Quan et al., 2012; Wang et al., 2012a; Rafiei et al., 2013; Zhou et al., 2013; Kaabachi et al., 2014; Kutikhin et al., 2014; Li et al., 2014; Qinghai et al., 2014; Yin et al., 2014). Several meta-analyses have been conducted to evaluate the association between IL-17A polymorphisms and cancer risk (Dai et al., 2014; Zhao et al., 2014); nevertheless, the association between IL-17A polymorphism and digestive cancer risk has not been assessed. To clarify the association between IL-17A -197G>A polymorphism and risk of digestive cancer, this meta-analysis was performed by integrating eligible published case-control studies.

Materials and Methods

Search strategy

Relevant reports were retrieved from searching the electronic databases PubMed and Cochrane Library (from inception to August 26, 2014), using the following key words: ("interleukin-17A" or "interleukin17A" or "IL-17A" or "IL17A") and ("tumor" or "cancer" or "carcinoma" or "neoplasm") and ("polymorphism" or "polymorphisms" or "SNP" or "variant" or "variation"). The search was filtered to English-language journals. Besides, we also performed a manual search among the references of the relevant publications and related articles in PubMed.

Study identification

Two authors reviewed the title, abstract and full-text (if necessary) of each retrieved study to select eligible articles for inclusion. The studies with overlapping data by the same investigators or based on the same population were checked prudently, and the most complete or recent articles with the largest numbers of cases and controls were included. The eligible studies in this meta-analysis were required to follow the predetermined criteria: 1) use a case-control study design, 2) evaluate the association between IL-17A -197G>A polymorphism and risk of digestive cancer, 3) report an estimation of odds ratio (OR) and 95% confidence interval (CI), or sufficient data to allow calculation of these two statistics. The main exclusive criteria were: 1) studies did not use a case-control design (eg, case reports, letters, animal studies, reviews, and editorials), 2) duplicate of previous publication, 3) studies involve inherited cancers.

Data extraction

All the eligible studies were independently reviewed by two authors to extract useful data. The following information were collected: the family name of the first author, the year of publication, the ethnicity of study population, the country of origin, sample size of cases and controls, source of controls (hospital-based or population-based), genotype distributions of cases and controls. The disagreements in this process were resolved by discussing and rechecking the data to reach a consensus. For studies with inadequate data, we contacted the corresponding author for further support by e-mail.

Statistical analysis

Meta-analysis was conducted to estimate the strength of the association between IL-17A -197G>A polymorphism and cancer risk, using an odds ratio (OR) with a corresponding 95% confidence interval (CI). The pooled ORs were calculated by comparisons with a codominant model (AA *vs* GG, GA *vs* GG), a dominant model (AA+GA *vs* GG), a recessive model (AA *vs* GG+GA) and an allelic model (A *vs* G). The values of the pooled ORs were tested by Z-test (Breslow and Day, 1987). Stratified analyses were further performed based on ethnicity (Asian or Caucasian) and specific cancer type (gastric or colorectal cancer). Hardy-Weinberg equilibrium (HWE) was estimated by goodness-of-fit test based on chi-square test in the control group of each study (Haber, 1981). Heterogeneity among the included studies was evaluated by chi-square based Q-test and I^2 statistic (Higgins et al., 2003). Pooled ORs were calculated using a fixed (Mantel-Haenszel method (Mantel and Haenszel, 1959) or random (DerSimonian-Laird method (DerSimonian and Laird, 1986)) effective model according to the absence ($p>0.10$ and $I^2<50\%$) or presence ($p<0.10$ or $I^2>50\%$) of heterogeneity. Sensitivity analyses were performed by omitting one study each time to evaluate the stability of the results. The potential publication bias of the included studies was assessed by Begg's funnel plots graphically and Egger's test quantitatively (Sterne et al., 2000).

All the statistical analyses were carried out with Stata/SE software version 12.0 (StataCorp LP, College Station, TX, USA), using two-sides *P*-values and $p<0.05$ was considered to be significant.

Results

Characteristics of eligible studies

A total of 72 records in English were retrieved after searching in the electronic databases. According to the inclusion and exclusion criteria, nine articles were finally included in this meta-analysis (Wu et al., 2010; Arisawa et al., 2012; Rafiei et al., 2013; Gonzalez-Hormazabal et al., 2014; Kutikhin et al., 2014; Omrane et al., 2014; Qinghai et al., 2014; Wang et al., 2014; Yin et al., 2014). The flow process of literature search and study identification was shown in Figure 1.

Among these 9 included articles, one article by Kutikhin et al. investigated the role of IL-17A -197G>A polymorphism in predisposition to colorectal and gastric cancer, respectively (Kutikhin et al., 2014). Finally, a

total of 10 studies from 9 eligible articles were identified, involving 3087 cases and 3815 controls. Five of them were conducted on Asian subjects, four were on Caucasians and the last one was on a mixed population. Seven studies were involved in gastric cancer, two were in colorectal cancer and the last one was involved in esophageal cancer. The control groups of 10 studies were in agreement with HWE, except for 2 studies by Kutikhin et al. The characteristics of each eligible study, including distributions of variant genotype frequency, were summarized in Table 1.

Quantitative synthesis

The main results of the present meta-analysis indicated that the variant genotypes in several genetic models were associated with increased digestive cancer risk in the overall analyses. As shown in Table 2 and Figure 2, significantly increased digestive cancer risk was observed in the codominant model (AA *vs* GG: OR=1.51, 95%CI=1.18-1.93), recessive model (AA *vs* GG+GA: OR=1.45, 95%CI=1.12-1.87) and allelic model (A *vs* G: OR=1.21, 95%CI=1.05-1.39). In subgroup analysis stratified by specific cancer type, elevated risk among studies of gastric cancer was found (AA *vs* GG: OR=1.68, 95%CI=1.24-2.28; AA *vs* GG+GA: OR=1.62, 95%CI=1.16-2.26; A *vs* G: OR=1.23, 95%CI=1.04-1.46). According to ethnicity, there was evidence in the Asian population for an association between IL-17A -197G>A polymorphism and cancer risk (GA *vs* GG: OR=1.19, 95%CI=1.05-1.36; AA *vs* GG: OR=1.56, 95%CI=1.15-2.12; AA+GA *vs* GG: OR=1.28, 95%CI=1.13-1.44; AA *vs* GG+GA: OR=1.42, 95%CI=1.01-2.00; A *vs* G: OR=1.24, 95%CI=1.08-1.44), while in the Caucasian population an association was found in the recessive model (AA *vs* GG+GA: OR=1.62, 95%CI=1.17-2.24).

In addition, we removed 2 studies in which control groups were not in agreement with HWE and the result was consist with overall analysis (GA *vs* GG: OR=1.19, 95%CI=0.97-1.47; AA *vs* GG: OR=1.60, 95%CI=1.21-2.12; AA+GA *vs* GG: OR=1.29, 95%CI=1.07-1.56; AA *vs* GG+GA: OR=1.47, 95%CI=1.08-2.00; A *vs* G: OR=1.27, 95%CI=1.09-1.48).

Test for heterogeneity and Sensitivity analysis

There was extensive heterogeneity observed among the included studies (Table 2). In the overall analysis for the comparison of variant genotypes AA and GG, the P-value for heterogeneity was 0.014 and I^2=56.4%. According to the stratified analyses, we assessed the source of heterogeneity from subgroup analyses of Asian group (p=0.009 and I^2=70.2% for heterogeneity), Caucasian group (p=0.082 and I^2=53.3% for heterogeneity) and gastric cancer group (p=0.011 and I^2=63.6% for heterogeneity).

The results of sensitivity analyses suggested that pooled ORs were not influenced qualitatively by single study, which indicated that the results of the present meta-analysis were relatively stable (Figure 3).

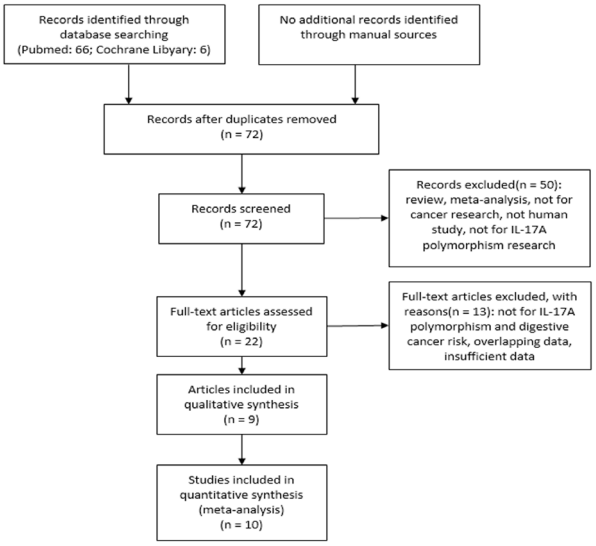

Figure 1. Flow Diagram of the Study Identification Process

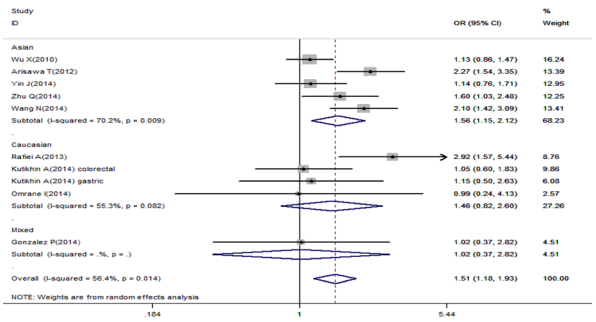

Figure 2. Forest Plot of the Association between IL-17A -197G>A Polymorphism and Digestive Cancer Risk in the Overall Analysis(AA *vs* GG) and between Different Ethnicities

Table 1. Characteristics of Eligible Studies in the Meta-analysis

ID	Study	Sample size (case/control)	Country	Ethnicity	Cancer type	Source of controls	HWE
1	Wu X(2010)	945/768	China	Asian	Gastric	PB	0.351
2	Arisawa T(2012)	333/583	Japan	Asian	Gastric	HB	0.080
3	Rafiei A(2013)	161/171	Iran	Caucasian	Gastric	PB	0.491
4	Yin J(2014)	364/370	China	Asian	Esophageal	HB	0.342
5	Zhu Q(2014)	293/550	China	Asian	Gastric	HB	0.069
6	Kutikhin A(2014) colorectal	220/300	Russia	Caucasian	Colorectal	PB	0.009
7	Kutikhin A(2014) gastric	60/300	Russia	Caucasian	Gastric	PB	0.009
8	Omrane I(2014)	102/139	Tunis	Caucasian	Colorectal	PB	0.387
9	Gonzalez P(2014)	147/172	Chile	Mixed	Gastric	HB	0.937
10	Wang N(2014)	462/462	China	Asian	Gastric	HB	0.124

*PB population-based controls; HB hospital-based controls;HWE Hardy-Weinberg equilibrium

Table 2. Pooled Analysis of Association between IL-17A-197G>A and Digestive Cancer Risk

Varibles	Study	Test of association		Test of heterogeneity		Model	Egger's test
		OR(95%CI)	P-value	Ph	I2(%)		P-value
GA versus GG	Overall	1.09(0.89-1.35)	0.400	0.001	68.9	R	0.542
Ethnicity	Asian	1.19(1.05-1.36)	0.007	0.251	25.5	F	0.707
	Caucasian	1.10(0.61-1.99)	0.742	0.001	82.3	R	0.630
Cancer type	Gastric	1.06(0.86-1.30)	0.607	0.022	59.4	R	0.102
	Colorectal	1.38(0.40-4.82)	0.611	0.000	92.9	R	-
AA versus GG	Overall	1.51(1.18-1.93)	0.001	0.014	56.4	R	0.949
Ethnicity	Asian	1.56(1.15-2.12)	0.004	0.009	70.2	R	0.307
	Caucasian	1.46(0.82-2.60)	0.204	0.082	53.3	R	0.789
Cancer type	Gastric	1.68(1.24-2.28)	0.001	0.011	63.6	R	0.638
	Colorectal	1.04(0.62-1.75)	0.883	0.942	0.0	F	-
AA+GA versus GG	Overall	1.19(0.98-1.44)	0.074	0.001	67.2	R	0.622
Ethnicity	Asian	1.28(1.13-1.44)	0.000	0.344	10.9	F	0.976
	Caucasian	1.22(0.71-2.08)	0.471	0.001	81.1	R	0.614
Cancer type	Gastric	1.19(0.97-1.45)	0.097	0.017	61.3	R	0.248
	Colorectal	1.37(0.46-4.07)	0.573	0.001	91.4	R	-
AA versus GG+GA	Overall	1.45(1.12-1.87)	0.005	0.001	68.6	R	0.491
Ethnicity	Asian	1.42(1.01-2.00)	0.043	0.000	81.6	R	0.239
	Caucasian	1.62(1.17-2.24)	0.004	0.136	45.9	F	0.556
Cancer type	Gastric	1.62(1.16-2.26)	0.005	0.000	76.0	R	0.277
	Colorectal	1.16(0.72-1.87)	0.552	0.418	0.0	F	-
A versus G	Overall	1.21(1.05-1.39)	0.008	0.000	70.3	R	0.843
Ethnicity	Asian	1.24(1.08-1.44)	0.003	0.014	68.0	R	0.300
	Caucasian	1.27(0.90-1.81)	0.179	0.005	76.6	R	0.558
Cancer type	Gastric	1.23(1.04-1.46)	0.015	0.001	73.1	R	0.965
	Colorectal	1.26(0.68-2.32)	0.458	0.014	83.3	R	-

*Ph P-value of Q-test for heterogeneity, R random effects model, F fixed effects model

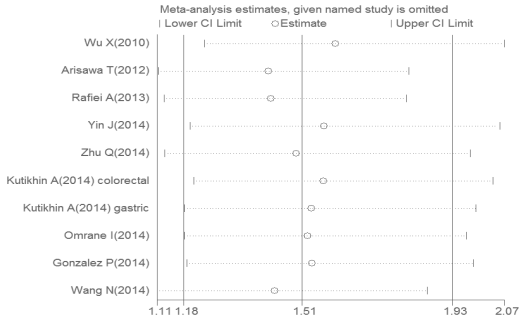

Figure 3. Sensitivity Analysis of the Association between IL-17A -197G>A Polymorphism and Digestive Cancer Risk in the Overall Analysis(AA *vs* GG)

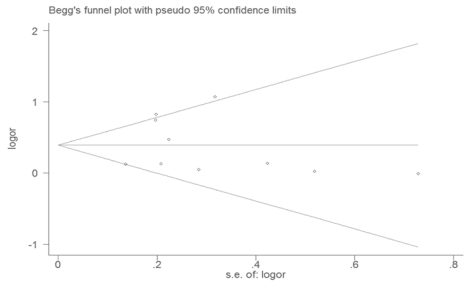

Figure 4. Begg's Funnel Plot of Publication Bias Test in the Overall Analysis (AA *vs* GG). Each point represents a single study for the indicated association. logor: natural logarithm of the OR, s.e. of logor: standard error of the logor

Publication bias

The potential publication bias of eligible literatures was assessed by Begg's funnel plots and Egger's test. The shapes of funnel plots in all genetic models did not show any evidence of obvious asymmetry (Figure 4). Meanwhile, statistical estimates of funnel plots symmetry by Egger's test also indicated no publication bias (GA *vs* GG: p=0.542; AA *vs* GG: p=0.949; AA+GA *vs* GG: p=0.622; AA *vs* GG+GA: p=0.491; A *vs* G: p=0.843).

Discussion

Chronic inflammation has been associated with variant malignancies. Elevated levels of pro-inflammatory cytokines, such as interleukins, have been linked to inflammatory disease exacerbation. A number of functional SNPs in several interleukin genes, such as IL-6, IL-8, IL-10 and IL-16, have been found associated with the risk of digestive cancer (Mustapha et al., 2012; Pan et al., 2013; Yang et al., 2013; Zhang and Wang, 2013). As a relatively newly described interleukin, IL-17A has attracted widespread attention and its effects on digestive tumors has been revealed. Wu X et al. reported that human IL-17A protein promoted cell proliferation and inhibited H_2O_2-induced cell apoptosis in gastric cancer (Wu et al., 2014). In addition, Numasaki and his colleagues transfected murine colon adenocarcinoma (MC 38) and fibrosarcoma (MCA205) with murine IL-17, the results showed that IL-17 promoted angiogenesis by up-regulating elaboration of a variety of pro-angiogenic factors and stimulating vascular endothelial migration (Numasaki et al., 2003). The influence of IL-17A -197G>A polymorphism on IL-17A production has been revealed by two studies (Chen et al., 2010; Espinoza et al., 2011). Espinoza et al. reported that peripheral blood mononuclear cells (PBMCs) from 54 health subjects were isolated and stimulated in vitro with phytohemagglutinin (PHA) and

the results showed that PBMCs with AA/AG genotypes secreted significantly higher levels of IL-17A than the cells with GG genotype (Espinoza et al., 2011). However, in an earlier study, PBMCs from 27 healthy individuals were cultured in the presence of PHA and there was no significant difference in IL-17A levels among cells with different genotypes (Chen et al., 2010). Recently, several studies have been conducted to explore the association between IL-17A -197G>A polymorphism and risk of digestive cancer; however, the results were conflicting.

The present meta-analysis, including 3087 cases and 3815 controls from 10 case-control studies, is first to investigate the association between IL-17A -197G>A polymorphism and risk of digestive cancer. Our results suggested that the A allele might be a risk factor for digestive cancer. By pooling all the eligible studies, the IL-17A -197G>A polymorphism was confirmed to be associated with risk of digestive cancer in several genetic models. In the stratified analyses by ethnicity, this association was found both in the Asian and Caucasian populations. According to specific cancer type, there was an association between this polymorphism and risk of gastric cancer, but not colorectal cancer. Moreover, since there was two studies in which the control group was not in agreement with HWE, we omitted these two studies and repeated the overall analysis. The result was consist with the outcome pooling all the eligible studies.

Some limitations of our meta-analysis should be noted. First, the pooled outcomes were calculated based on unadjusted estimates, which limited a more precise analysis on adjusted estimates by some important factors like sex, age, diet status and etc. Thus, lacking of these original data limited further assessment of the potential interactions because gene-environment, gene-gene interactions might influence cancer susceptibility. Second, most of the literatures included in our present meta-analysis focused on the relationship between IL-17A -197G>A polymorphism and digestive cancer susceptibility, which made it hard to assess the effects of IL-17A haplotypes composed of different IL-17A SNPs on carcinogenesis. There was evidence that IL-17A rs4711998 polymorphism was associated with a decreased risk of esophageal cancer in a Chinese population (Yin et al., 2014). Thus, the status of other IL-17A SNPs might cover up the effect of -197G>A polymorphism on carcinogenesis. Third, limited study number restricted us to perform meta-regression analyses to explore the origin of heterogeneity statistically.

Despite these limitations, advantages in our present meta-analysis should be also acknowledged. First, since we pooled a substantial number of the cases and controls, the statistical power of this meta-analysis was definitely increased. Second, the quality of eligible studies strictly met the selection criteria. Third, no publication bias was observed through Begg's funnel plots and Egger's test, indicating that the pooled outcomes should be unbiased.

With these limitations and advantages in mind, the results of this meta-analysis are statistically credible. The relationship between IL-17A -197G>A polymorphism and digestive cancer risk is assessed and this polymorphism is associated with elevated digestive cancer susceptibility, both in Asians and Caucasians and especially for gastric cancer. To draw a more comprehensive conclusion, further studies should be performed with larger sample size and more detailed individual and environmental information, concerning the effects of haplotypes and other SNPs, enrolling precisely identified cases and well-matched controls, to better evaluate the role of IL-17A polymorphism in carcinogenesis of digestive system.

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