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Interleukin 10 (IL-10) promoter-1082 A>G polymorphism and risk of cancer: Meta-analysis

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Abstract:

Background: Interleukin-10-1082A>G variant is the most widely investigated polymorphism in the IL-10 gene in cancer susceptibility. A number of case control analysis showed the link between IL-10-1082A >G polymorphism and cancer risk in humans population.

Methods: Twenty three case–control eligible studies, comprising 4753 cases and 6086 controls were selected for the meta-analysis of IL-10-1082 A/G SNP. The statistical analysis was conducted with comprehensive meta-analysis (CMA). We adopted heterozygous (GG vs. AG) model. Odds ratio (OR) with 95% confidence interval (CIs) was calculated to measure the power of the link under heterozygous model (GG vs AG).

Result: Overall result obtained under fixed effect model are [OR: 1.066, 95% CI: 0.989-1.267, P: 0.464].

Conclusion: Our meta-analysis indicates that IL-10 promoter-1082 polymorphism under fixed effect model is not associated with the overall risk of developing cancer, HCV, Bechet's disease and diabetes type-2.

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Keywords:
Meta-analysis, Heterozygous, IL-10 Polymorphism. Cancer

Introduction

The gene programming IL-10 is sited on chromosome 1 (1q31-1q32). Many variants reported in the promoter region of interleukin-10 gene including -1082 A/G (rs 1800896), -819 T/C (rs1800871) and -592 A/C (rs1800872) greatly affect the transcription and translation process of interleukin-10 in vitro [1]. IL-10 possesses immunosuppressive and anti-inflammatory ability which is predominantly governed by T-cells and macrophages. IL-10 also down regulates the expression of macrophages stimulatory molecules and cytokines that are released by T helper 1(Th1) cells. IL-10 may also control the regulation of angiogenesis in different malignancies [2]. Interleukin-10 also plays important role in tumor escape from immune surveillance, increasing tumor progression. Primary central nervous system lymphomas (PCNSLs) and primary vitreoretinal lymphomas (PVRLs) are B-cell lymphomas during which high levels of IL-10are associated with rapid disease development. The IL-10-1082A allele is a potent cause for increased IL-10 levels in PVRLs and PCNSLs. In the near past, many studies reported that single nucleotide polymorphism (SNP) in the promoter region of IL-10(-1082) may be linked with the development of cancers such as gastric, thyroid, prostate, cervicle and lungs cancers [3]. However, the previous data that was applied to find a strong link between the variation in the gene of interleukin-10 and cancer risk is unreliable due to relative small size combined with ethnicity of separate investigations. Therefore, we conducted a meta-analysis with the aim to find a more reliable and concise appraisal link between SNP -1082 in the promoter region of IL-10 and the risk of developing cancers.

Methods

Literature search strategy:

PubMed, Google scholar and library genesis was used for searching the relevant scientific articles. The literature searching strategy for relevant articles (updated on 2014), using the following keywords: genetic variation, gastric, stomach, carcinoma, interleukin-10, IL-10, cancer, tumor, polymorphism and genetic variant. Conferences and abstract were ignored. Only complete text and published papers were selected. References of the included articles were also searched for relevant articles. Furthermore, review articles were also screened for suitable research articles.

Addition and elimination conditions of studies:

Keeping the following points under consideration scientific articles were included in the current meta-analysis: (1) association between IL-10-1082 polymorphism and risk cancer; (2) case–control study; (3) offering satisfactory accessible data to evaluate odds ratio (OR) with 95% confidence interval (CI). The conditions selected for exclusion of articles in the analysis were as follows: (1) the study related to animals; (2) the article that lack control; (3) the study with no data available.

Data extraction:

The following data was cautiously mined from all the case–control studies: the first author's name, publication date, country of origin, ethnicity, total number of cases and controls, genotype frequencies of cases and controls, disagreements about inclusion of studies and interpretation of data were resolved through discussion with our research team.

Statistical analysis:

All the statistical analyses were conducted using comprehensive Meta-Analysis Version 2.2.064 [http://www.meta-analysis.com/pages/demo_download.php].

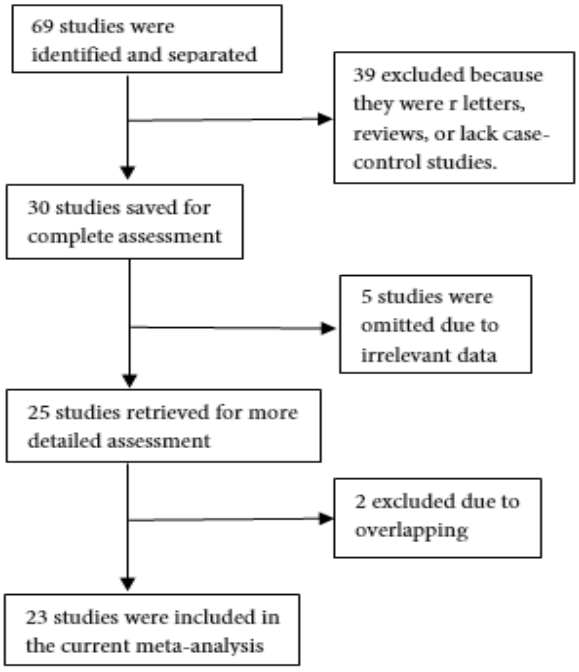

Figure 1: Flow sheet sketch of the studies inclusion

Results

In the present study an attempt was made to find the association between polymorphism -1082 "A/G" (rs 1800896), under the heterozygous model to know whether it is associated with increased risk of cancer or not. Following the inclusion criteria, 23 studies were incorporated and remaining studies were excluded from this meta-analysis (Figure 1). The numbers of cancer cases and healthy controls were 4753 and 6086, respectively for evaluating the association between -1082 A/G (rs 1800896), polymorphism and cancer risk. The publication years of included studies ranged from 2005 to 2014. Overall, nine of these studies were conducted on Chinese populations, three on Korean two on each of USA and Japan and one in each of Africa, Netherlands Turkey, Egypt, Poland, India, and Pakistan. There were eight studies on gastric cancer, four were Hepatocellular Carcinoma (HCC), one on each of type-2 diabetes, PTC, Behcet disease, laryngeal squamous cell carcinoma (LSCC), chronic lymphocytic leukemia (CLL), PVRL, LSV, HCV, prostate, breast and oral cancer. Association between -1082 A/G (rs 1800896) polymorphism and cancer risk summary is given in the Table 1. Genotypic data and frequency of both alleles A and G is given. Heterozygous model with OR, LCI, UCI, P value was determined for each study. Association was determined under GG vs. AG model using fixed effect model [OR: 1.066, 95 %CI: 0.896-1.267, P<0.464].

The overall statistics under heterozygous model (Figure 2) showed that polymorphism, -1082 A/G (rs 1800896) is not associated with cancer risk. Individual statistics of each study included in the current meta-analysis given in the Fig: 1 suggest that GG vs. AG is not associated in the cancer risk, hepatitis C, Bechet,s disease under heterozygous model [OR: 1.066, 95%CI: 0.989-1.267, P:0.464].

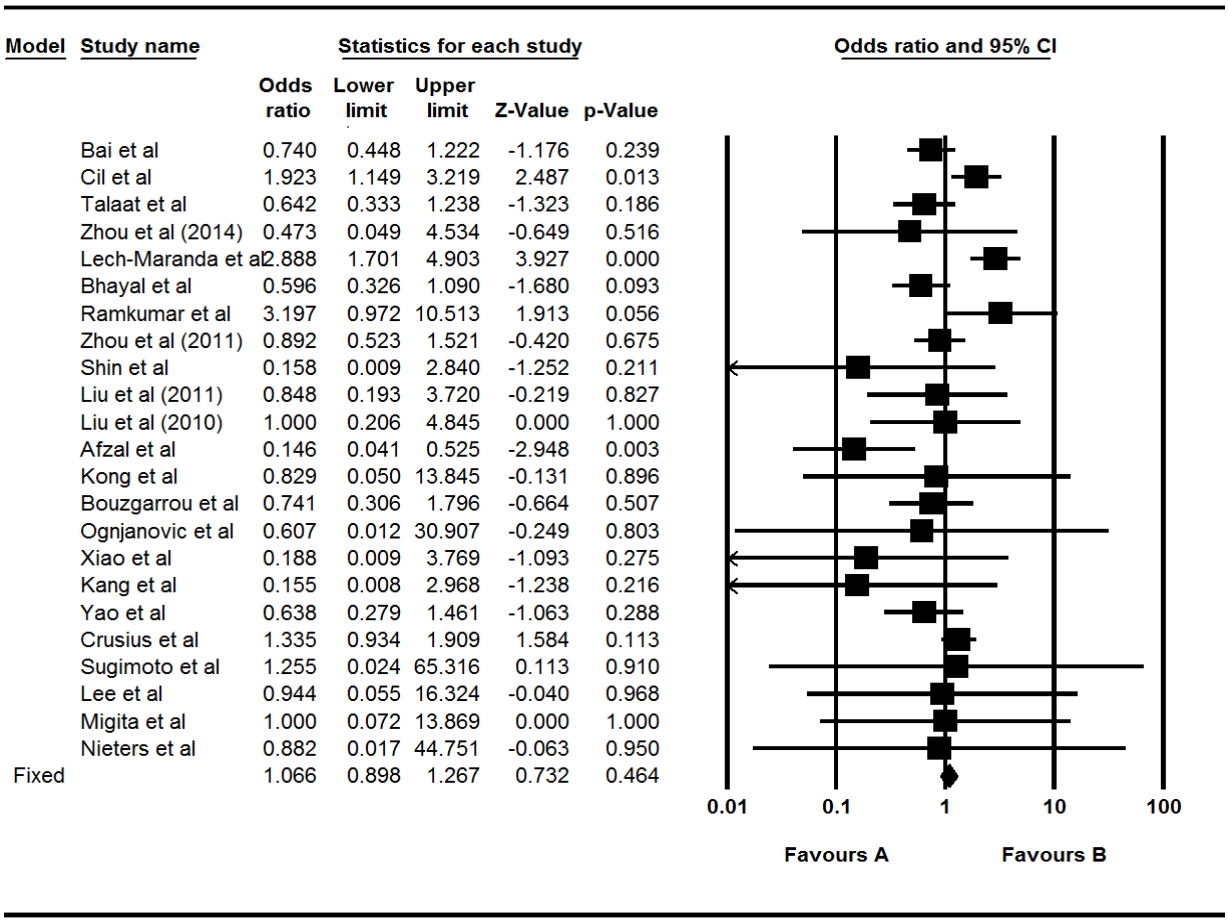

Figure 2: Fixed effect model of IL-10 -1082 under heterozygous model.

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Author	Year	Disorder	Ethnicity	Cases	Control	OR	LCI	UCI	P.Value
Bai *et al* [4]	2014	type-2 diabetes	Chinese	364	677	O.74	0.448	1.221	0.238
Cil *et al* [5]	2014	PTC	Turkish	216	190	1.923	1.149	3.220	0.013
Talaat *et al* [6]	2014	Behcet 's disease	Egyptian	87	97	0.642	0.331	1.232	0.182
Zhou *et al* [7]	2014	LSCC	Chinese	146	119	0.473	0.049	4.530	0.516
Lech-Maranda *et al*[8]	2013	CLL	poland	292	192	2.888	1.701	4.902	0.000
Bhayal *et al*[9]	2012	Gastric cancer	Indian	100	142	0.596	0.326	1.090	0.093
Zhou *et al* [10]	2011	LSC	Chinese	150	150	0.892	0.523	1.522	0.675
Shin *et al*[11]	2011	GC	Korea	632	237	0.158	0.009	2.844	0.221
Liu *et al*[12]	2011	Gastric cancer	Chinese	234	243	0.848	0.193	3.719	0.827
Liu *et al*[13]	2010	prostate cancer	Chinese	270	62	1.000	0.206	4.845	1.000
Afzal *et al*[14]	2010	HCV	Pakistan	89	99	0.146	0.041	0.523	0.003
Kong *et al* [15]	2010	Breast cancer	Chinese	315	321	0.829	0.050	13.834	0.896
Bouzgarrou *et al* [16]	2009	HCC	African	58	145	0.741	0.306	1.796	0.507
Sugimoto *et al* [17]	2007	Gastritis	Japan	168	162	1.255	0.024	65.279	0.910
Xiao *et al* [18]	2009	GC	Chinese	220	624	0.188	0.009	3.777	0.275
Kang *et al* [19]	2009	GC	Korea	334	324	0.155	0.008	2.970	0.216
Yao *et al* [20]	2008	oral cancer	Chinese	280	300	0.638	0.278	1.461	0.288
Crusius *et al* [21]	2008	GC	Netherland	235	1134	1.335	0.934	1.909	0.113
Lee *et al* [22]	2005	Gastric cancer	Korea	122	120	0.944	0.055	16.328	0.969
Nieters *et al* [23]	2005	HCC	Chinese	249	250	0.882	0.017	44.793	0.950

Table 1: Statistics of included studies under heterozygous model [GG vs AG]

				Cases								Control					
Author	Year	Disorder	Ethnicity	Cases	Control	AA	AG	GG	AG+GG	Freq. of A	Freq. of G	AA	AG	GG	AG+GG	Freq. of A	Freq. of G
Bai *et al* [4]	2014	type-2 diabetes	Chinese	364	677	252	72	40	112	0.79	0.21	495	129	53	182	0.83	0.17
Cil *et al* [5]	2014	PTC	Turkish	216	190	80	100	36	136	0.60	0.40	58	78	54	132	0.51	0.49
Talaat *et al* [6]	2014	Behcet 's disease	Egyptian	87	97	21	34	32	66	0.44	0.56	12	53	32	85	0.40	0.60
Zhou *et al* [7]	2014	LSCC	Chinese	146	119	115	26	5	31	0.88	0.12	107	11	1	12	0.95	0.05
Lech-Maranda *et al* [8]	2013	CLL	poland	292	192	82	152	58	210	0.54	0.46	48	94	50	144	0.49	0.51
Bhayal *et al* [9]	2012	Gastric cancer	Indian	100	142	18	35	47	82	0.36	0.65	52	50	40	90	0.54	0.46
Zhou *et al* [10]	2011	LSCC	Chinese	150	150	29	62	59	121	0.40	0.60	52	53	45	98	0.52	0.48
Shin *et al* [11]	2011	Gastric cancer	Korea	632	237	534	91	7	98	0.92	0.08	199	38	0	38	0.92	0.08
Liu *et al* [12]	2011	Gastric cancer	Chinese	234	243	189	39	6	45	0.89	0.11	217	23	3	26	0.94	0.06
Liu *et al* [13]	2010	prostate cancer	Chinese	270	62	240	27	3	30	0.94	0.06	22	36	4	40	0.65	0.35
Afzal *et al* [14]	2010	Hepatitis C	Pakistan	89	99	7	67	15	82	0.46	0.54	4	92	3	95	0.51	0.49
Kong *et al* [15]	2010	Breast cancer	Chinese	315	321	285	29	1	30	0.95	0.05	285	35	1	36	0.94	0.06
Bouzgarrou *et al* [16]	2009	HCC	African	58	145	24	24	10	34	0.62	0.38	56	68	21	89	0.62	0.38
Xiao *et al* [18]	2009	Gastric cancer	Chinese	220	624	176	41	3	44	0.89	0.11	593	31	0	31	0.98	0.02
Kang *et al* [19]	2009	Gastric cancer	Korea	334	324	281	49	4	53	0.91	0.09	289	35	0	35	0.95	0.05
Yao *et al* [20]	2008	oral cancer	Chinese	280	300	184	75	21	96	0.79	0.21	234	56	10	66	0.87	0.13
Crusius *et al* [21]	2008	Gastric cancer	Netherland	235	1134	54	131	50	181	0.51	0.49	340	526	268	794	0.53	0.47
Sugimoto *et al* [17]	2007	Gastritis	Japan	168	162	134	34	0	34	0.90	0.10	135	27	0	27	0.92	0.08
Lee *et al* [22]	2005	Gastric cancer	Korea	122	120	104	17	1	18	0.92	0.08	101	18	1	19	0.92	0.08
Nieters *et al* [23]	2005	HCC	Chinese	249	250	130	119	0	119	0.76	0.24	115	135	0	135	0.73	0.27

Laryngeal squamous cell carcinoma [LSCC], hepatocellular carcinoma [HCC], primary CNS and vitreoretinallymphomas [PVRL], Chronic Lymphocytic Leukemia [CLL]

Table 2: Characteristics of included studies in the meta-analysis of IL-10 -1082 A>G polymorphism

Discussion

Interleukin-10 is a pleiotropic cytokine that regulates B-cell multiplication and diversity hence has a significant role in immunological and inflammatory reactions [24]. IL-10 also performs the function of anti-inflammatory and immunoregulatory agent which suggests that this cytokine can potentially enhances tumor escape [25]. Numerous studies confirmed that IL-10 regulates angiogenesis in many cancers and can play role in tumor progression [2]. It has been recognized that there are three significant polymorphisms in the 5-flanking area of IL-10 at positions -1082, -819, -592, which are associated to extraordinary transcriptional promoter activity. The IL-10-1082 A allele or ATA haplotype (defined by three SNPs at position of -1082, -819 and -592) were found responsible for production of high levels of IL-10, as compared with the IL-10-1082 G allele or non ATA haplotype [17]. Meta-analysis is an effective analytical procedure for making accurate and broad deductions based on statistics from discrete association studies of large samples. In our meta-analysis, no significant finding could be noted with the overall risk of developing cancer and other disorders under the fixed-effect model. In this model we adopt that all studies in the meta-analysis share a shared (true) effect size. Put another way, all factors that could influence the effect size are the same in all the studies, and therefore the true effect size is the same (hence the label fixed) in all the studies. Based on the findings of cumulative meta-analyses, the preferences toward significant relations in cancer and IL-10- 1082 GG/GA polymorphism under fixed effect model was not associated with risk of developing cancer hepatitis C, Bechet disease and diabetes-2 [OR: 1.066, 95 %CI: 0.896-1.267, P<0.464]. The IL-10- 1082 GG-plus-GA genotypes may seem to be more susceptible to gastric cancer in Asians but this hypothesis needs further evaluation in the future [26].

A number of studies have found higher risks in GG or GA carriers compared to AA carriers in intestinal and diffused type gastric cancer [27], whereas analogous link was not established in another study [22]. In the last meta-analysis remains a reflective investigation that is subject to the methodological shortages of the comprised studies. Thus, we try to reduce the likelihood of unfairness by evolving a comprehensive procedure before beginning the study and execution a careful examination for published studies.

In conclusion, IL-10-1082 polymorphism is not associated under heterozygous model (GG vs AG) with the overall risk of developing cancer. Further studies are needed with very large number of cases and control to reach a final conclusion of polymorphism IL-10-1082 and the risk of cancers and other complicated disease.

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