RESEARCH ARTICLE

Statistical meta-analysis to investigate the association between the Interleukin-6 (IL-6) gene polymorphisms and cancer risk

Md. Harun-Or-Roshid[1], Md. Borqat Ali[1], Jesmin[2]*, Md. Nurul Haque Mollah[1]*

1 Bioinformatics Laboratory, Department of Statistics, University of Rajshahi, Rajshahi, Bangladesh,
2 Department of Genetic Engineering and Biotechnology, University of Dhaka, Dhaka, Bangladesh

* mollah.stat.bio@ru.ac.bd (MNHM); jesmin@univdhaka.edu (J)

Abstract

A good number of genome-wide association studies (GWAS), including meta-analyses, reported that single nucleotide polymorphisms (SNPs) of the IL-6 gene are significantly associated with various types of cancer risks, though some other studies reported insignificant association with cancers, in the literature. These contradictory results may be due to variations in sample sizes and/or deficiency of statistical modeling. Therefore, an attempt is made to provide a more comprehensive understanding of the association between the IL-6 gene SNPs (rs1800795, rs1800796, rs1800797) and different cancer risks, giving the weight on a large sample size, including different cancer types and appropriate statistical modeling with the meta-dataset. In order to attain a more reliable consensus decision about the association between the IL-6 gene polymorphisms and different cancer risks, in this study, we performed a multi-case statistical meta-analysis based on the collected information of 118 GWAS studies comprising of 50053 cases and 65204 control samples. Results from this Meta-analysis indicated a significant association (p-value < 0.05) of the IL-6 gene rs1800796 polymorphism with an overall increased cancer risk. The subgroup analysis data based on cancer types exhibited significant association (p-value < 0.05) of the rs1800795 polymorphism with an overall increased risk of cervical, liver and prostate cancers; the rs1800796 polymorphism with lung, prostate and stomach cancers; and the rs1800797 polymorphism with cervical cancer. The subgroup analysis of ethnicity data showed a significant association (p-value < 0.05) of an overall cancer risk with the rs1800795 polymorphism for the African and Asian populations, the rs1800796 polymorphism for the Asian only and the rs1800797 polymorphism in the African population. Comparative discussion showed that our multi-case meta-analyses received more support than any previously reported individual meta-analysis about the association between the IL-6 gene polymorphisms and cancer risks. Results from this study, more confidently showed that the IL-6 gene SNPs (rs1800795, rs1800796 and rs1800797) in humans are associated with increased cancer risks. Therefore, these three polymorphisms of the IL-6 gene have the potential to be evaluated as a population based rapid, low-cost PCR prognostic biomarkers for different types of cancers diagnosis and research.

Introduction

Cancer is a leading cause of death worldwide. According to the World Health Organization (WHO), 9.6 million deaths occurred in 2018 from 18.1 million cancer patients all over the globe. It has been estimated that the incidence of cancer occurrences might be increased by 50% to 15 million new cases by the year 2020 [1]. The GLOBOCAN database published the extent of mortality and outbreak in 2018 from 36 types of cancer in 185 countries [2]. According to the recent literature reviews, it is very much evident now that cancer is a multi-factorial progressive disorder that developed under the influence of genes and their interactions [2–4].

Interleukin-6 (IL-6) gene encodes a cytokine that functions in inflammation and has been reported in association with cancers in the literature for many years [3, 4]. Growing evidence suggests an important role for pro-inflammatory cytokines like the IL-6 gene in the microenvironment of tumor development and regarded as an important tumor promoting factor in various types of human cancers including breast, oral, gastrointestinal, prostate, and, colorectal cancer [5–12]. The IL-6 rs1800795 (-174G/C) polymorphism is a significant predictor for susceptibility of prostate cancer and bone metastasis in northwest Iranian population [11]. A number of meta-analysis of the IL-6 gene polymorphisms with cancer risk were conducted based on small sample sizes [123–130]. Some GWA studies have also reported that some polymorphisms of the IL-6 gene are insignificantly associated with blood cancer [13–25] and significantly associated with breast cancer [26–36] whereas some other studies [37–40] reported no association with breast cancer. Similarly, for cervical and colon cancer development, some studies reported a significant association [41–46 and 49–56 respectively] whereas other studies reported no significant association [44, 47, 48, 57–61 respectively]. The same scenario persists for liver cancer: associated [62–68] and not "associated [69–71]; lung cancer: associated [72–77] and not associated [78–83]; prostate cancer: associated [11, 84–91] and not associated [92–98]; stomach cancer: claimed a significant association [106–112] and some other studies claimed insignificant association [111, 113–115]. Also, some GWA studies investigated the association of the IL-6 gene polymorphisms with thyroid cancer [116, 117], ovarian cancer [118], pancreatic cancer [119], neuroblastoma [120, 121] and renal cell carcinoma [122]. Thus we observed from the above discussion that different types of cancers were influenced by the three SNPs (rs1800795, rs1800796 and rs1800797) of the IL-6 gene. We also observed that the reported results varied across studies and therefore, remain inconclusive, which may be occurred due to the smaller sample size and different ethnic populations.

To overcome the ambiguity of GWAS findings, some Author's performed meta-analysis based on only one of three important SNPs (rs1800795, rs1800796 and rs1800797) of the IL-6 gene or only one type of cancer to take more reliable and valid conclusion [123–129]. It should be mentioned here that a meta-analysis is conducted by the complete coverage of all relevant studies, solving the heterogeneity problem, and exploring the robustness of main findings using sensitivity analysis. Those meta-analysis reported that (i) the rs1800795 polymorphism of the IL-6 gene shows significant association with cervical [123] and colorectal [124] cancers, but insignificant association with stomach cancer [128, 129], (ii) thers1800796 polymorphism shows contradictory association with stomach cancer [111] and insignificant association with lung cancer [126, 127] and (iii) thers1800797 polymorphism shows insignificant association with colorectal cancer [124], stomach cancer [129] and all type of risks [128]. Thus those meta-analysis reports on the IL-6 gene were not consistent in their common issues. Zhou et al. [131] performed multi-case meta-analysis considering all of three important SNPs of the IL-6 gene as mentioned previously, three different ethnicities (Asian, African, Caucasian), nine types of cancers based on 49,408 cancers and 61,790 control cases. They reported that the IL-6 gene is significantly associated with the overall cancer risk. Particularly, they reported

significant association of IL-6 gene with 2 types of cancer risks (liver and prostate) and insignificant association with 7 types of cancer risks (breast, cervical, colorectal, gastric, lung, lymphoma and myeloma) by the sub-group analysis of cancer types. Obviously, their specific report [130] contradicts with the results of other single-case meta-analyses [123–129] in the cases of their common interest, which may be happened due to smaller sample sizes, ethnicity and the deficiency of statistical modeling with the meta-dataset. For example, none of those meta-analyses [123–130] checked the model adequacy by the goodness of fit test. To estimate the combined effects, all of them used fixed effect (FE) or random effect (RE) models corresponding to the homogeneity or heterogeneity of effects which cannot give the guarantee of model adequacy [133].Therefore, in this paper, an attempt was made to provide a more comprehensive understanding about the association between the IL-6 gene SNPs (rs1800795, rs1800796, rs1800797) and different types of cancer risks, giving the weight on large sample size, more cancer types and appropriate statistical modeling based on the goodness of fit test [133] with the multi-case meta-dataset.

Materials and methods

Search strategy

Text mined data of the competent articles retrieved from PubMed, PubMed Central, Google Scholar, Web of Science and other online literature databases, published up to February 2019 in the English language were only considered for this meta-analysis. The following keywords were used for searching: (i) IL-6, (ii) IL-6, Cancer, (iii) IL-6, rs1800795, (iv) IL-6, rs1800796, (v) IL-6, rs1800797, (vi) IL-6 -174G/C or -572G/C or -597G/A, (vii) polymorphisms, (viii) GWAS, (ix) case-control study.

Eligibility criteria

Two authors independently investigated the title and abstract for all papers and primarily removed the irrelevant and incomplete studies. For the final review the following inclusion-exclusion criteria were used: if the study was (i) designed to measures the association between the IL-6 gene polymorphisms (rs1800795, rs1800796, rs1800797) and cancer risk, (ii) case-control design and (iii) sufficient to provide necessary information of genotypic frequency, it selected for this meta-analysis.

Data extraction

From the eligible studies several information was compiled for each selected study such as first author, year of the study, country of origin, ethnicity of the study subject, number of case-control, types of cancer, allelic and genotypic distribution and so on. To test the validity of any selected studies for this meta-analysis, Hardy-Weinberg equilibrium (HWE) test was performed using the Chi-square statistic. A selected study was considered as a good study for meta-analysis if $Pr\{\chi2_{obs} \leq \chi2\} \geq .05$ (Table 1).

Statistical modeling for meta-analysis

Meta-analysis is a collection of statistical methods to compile the results of similar independent studies. It is used to take the overall decision across a number of similar studies. Let us now introduce the statistical methods that are used in this paper for taking the overall decision about the relationship between the IL-6 gene polymorphisms and cancer risk. At first we have checked the quality of existing studies by testing the Hardy-Weinberg equilibrium (HWE). The HWE test is performed using the Chi-square statistic with the null hypothesis that the

Table 1. Characteristic of eligible studies included in meta-analysis of the IL-6 gene (rs1800795, rs1800796, rs1800797) polymorphisms.

Study	Year	Country	Ethnicity	Cancer	Case/Control	HWE
rs1800795						
Zheng et al. [105]	2000	Sweden	Caucasian	Skin Cancer	73/128	0.357(Y)
El-Omar et al. [113]	2003	USA	Mixed	Stomach Cancer	213/209	0.913(Y)
Hwang (b) et al. [114]	2003	USA	Caucasian	Stomach Cancer	30/30	0.399(Y)
Hwang (a) et al. [114]	2003	USA	Asian	Stomach Cancer	30/30	1.000(Y)
Howell et al. [104]	2003	UK	Caucasian	Skin Cancer	161/224	0.258(Y)
Landi et al. [55]	2003	France	Caucasian	Colon Cancer	361/311	0.761(Y)
Sun et al. [98]	2004	USA	Caucasian	Prostate Cancer	1337/753	0.492(Y)
Bushley et al. [118]	2004	USA	Mixed	Ovarian Cancer	182/218	0.020(N)
Campa et al. [81]	2004	France	Caucasian	Lung Cancer	243/207	0.818(Y)
Smith et al. [34]	2004	UK	Caucasian	Breast Cancer	144/224	0.258(Y)
Zhang et al. [105]	2004	China	Caucasian	Skin Cancer	241/260	0.993(Y)
Campa et al. [79]	2005	France	Caucasian	Lung Cancer	1995/1982	0.448(Y)
Seifart et al. [80]	2005	Germany	Caucasian	Lung Cancer	182/243	0.163(Y)
Migita et al. [71]	2005	Japan	Asian	Liver Cancer	48/188	1.000(Y)
Hefler et al. [36]	2005	Austria	Caucasian	Breast Cancer	269/227	0.935(Y)
Snoussi et al. [33]	2005	Tunisia	African	Breast Cancer	305/200	0.829(Y)
Leibovici et al. [88]	2005	USA	Caucasian	Prostate Cancer	444/443	0.000(N)
Festa et al. [103]	2005	Sweden	Caucasian	Skin Cancer	241/260	0.993(Y)
Cordano et al. [23]	2005	UK	Caucasian	Blood Cancer	408/349	0.167(Y)
Basturk et al. [123]	2005	Turkey	Caucasian	Renal cell	25/49	0.007(N)
Mazur et al. [25]	2005	Poland	Caucasian	Blood Cancer	54/50	0.239(Y)
Kamangar et al. [115]	2006	Finland	Caucasian	Stomach Cancer	102/152	0.004(N)
Xing et al. [111]	2006	China	Asian	Stomach Cancer	65/71	0.141(Y)
Michaud et al. [97]	2006	USA	Caucasian	Prostate Cancer	484/613	0.832(Y)
Vairaktaris et al. [101]	2006	Greece	Caucasian	Oral Cancer	162/156	0.298(Y)
Cozen et al. [21]	2006	USA	Caucasian	Blood Cancer	146/125	0.333(Y)
Gunter et al. [61]	2006	USA	Caucasian	Colon Cancer	204/190	0.385(Y)
Theodoropoulos et al. [54]	2006	Greece	Caucasian	Colon Cancer	222/200	0.055(Y)
Noguetra et al. [45]	2006	Brazil	Mixed	Cervical Cancer	56/253	0.001(N)
Balasubramanian et al. [39]	2006	UK	Caucasian	Breast Cancer	497/490	0.759(Y)
Gonzalez-Zuloeta et al. [40]	2006	Netherland	Caucasian	Breast Cancer	171/3651	0.290(Y)
Lan et al. [22]	2006	USA	Caucasian	Blood Cancer	510/590	0.358(Y)
Rothman et al. [24]	2006	USA	Caucasian	Blood Cancer	3066/3499	0.506(Y)
Slattery et al. [62]	2007	USA	Caucasian	Colon Cancer	1579/1977	0.015(N)
Slattery et al. [27]	2007	USA	Caucasian	Breast Cancer	650/678	0.122(Y)
Deans et al. [107]	2007	UK	Caucasian	Stomach Cancer	197/224	0.258(Y)
Gatti et al. [108]	2007	Brazil	Mixed	Stomach Cancer	56/112	0.509(Y)
Duch et al. [19]	2007	Brazil	Mixed	Blood Cancer	52/60	0.442(Y)
Vishnoi et al. [70]	2007	India	Asian	Liver Cancer	124/200	0.936(Y)
Gonullu et al. [32]	2007	Turkey	Caucasian	Breast Cancer	38/24	0.000(N)
Vogel et al. [38]	2007	Denmark	Caucasian	Breast Cancer	361/361	0.728(Y)
Nearman et al. [20]	2007	USA	Caucasian	Blood Cancer	28/362	0.120(Y)
Crusius et al. [111]	2008	France	Caucasian	Stomach Cancer	243/1138	0.044(N)
Kesarwani et al. [96]	2008	India	Asian	Prostate Cancer	200/200	0.100(Y)
Vairaktaris et al. [100]	2008	Greece	Caucasian	Oral Cancer	162/156	0.000(N)
Colakogullari et al. [78]	2008	Turkey	Caucasian	Lung Cancer	44/58	0.221(Y)

(Continued)

Table 1. (Continued)

Study	Year	Country	Ethnicity	Cancer	Case/Control	HWE
rs1800795						
Upadhyay et al. [67]	2008	India	Asian	Liver Cancer	168/201	0.586(Y)
Kury et al. [60]	2008	France	Caucasian	Colon Cancer	1023/1121	0.079(Y)
Wilkening et al. [53]	2008	Germany	Caucasian	Colon Cancer	303/580	0.481(Y)
Ennas et al. [18]	2008	Italy	Caucasian	Blood Cancer	39/112	0.506(Y)
Slattery et al. [51]	2009	USA	Caucasian	Colon Cancer	750/1250	0.016(N)
Slattery et al. [52]	2009	USA	Caucasian	Colon Cancer	1839/2014	0.015(N)
Gangwar et al. [41]	2009	India	Asian	Cervical Cancer	160/200	0.371(Y)
Ozgen et al. [117]	2009	Turkey	Caucasian	Thyroid Cancer	42/340	0.009(N)
Moore et al. [93]	2009	USA	Caucasian	Prostate Cancer	957/847	0.152(Y)
Pierce et al. [94]	2009	USA	Caucasian	Prostate Cancer	175/1934	0.132(Y)
Wang et al. [95]	2009	USA	Caucasian	Prostate Cancer	253/280	0.448(Y)
Zabaleta et al. [96]	2009	USA	Caucasian	Prostate Cancer	74/401	0.000(N)
Talar-Wojnarowska et al. [119]	2009	Poland	Caucasian	Pancreatic Cancer	97/50	0.191(Y)
Aladzsity et al. [16]	2009	Hungary	Caucasian	Blood Cancer	97/99	0.101(Y)
Falleti et al. [66]	2009	Italy	Caucasian	Liver Cancer	219/236	0.536(Y)
Ognjanovic et al. [69]	2009	USA	Mixed	Liver Cancer	117/221	0.000(N)
Tsilidis et al. [58]	2009	USA	Caucasian	Colon Cancer	203/367	0.537(Y)
Vasku et al. [59]	2009	Czech Republic	Caucasian	Colon Cancer	100/100	0.601(Y)
Cherel et al. [30]	2009	France	Caucasian	Breast Cancer	293/82	0.695(Y)
DeMichele et al. [31]	2009	USA	Caucasian	Breast Cancer	339/100	0.569(Y)
Andrie et al. [17]	2009	Greece	Caucasian	Blood Cancer	81/81	0.777(Y)
Ognjanovic et al. [50]	2010	USA	Mixed	Colon Cancer	271/539	0.000(N)
Zhao et al. [112]	2010	China	Asian	Stomach Cancer	142/200	0.943(Y)
Dossus et al. [87]	2010	Germany	Mixed	Prostate Cancer	7937/8508	0.035(N)
Cacev et al. [56]	2010	Croatia	Caucasian	Colon Cancer	160/160	0.582(Y)
Hawken et al. [63]	2010	Canada	Caucasian	Colon Cancer	1133/1125	0.461(Y)
Abuli et al. [49]	2011	Spain	Caucasian	Colon Cancer	1416/1424	0.672(Y)
Grimm et al. [46]	2011	Austria	Caucasian	Cervical Cancer	131/208	0.990(Y)
Gaur et al. [99]	2011	India	Caucasian	Oral Cancer	140/200	0.069(Y)
Giannitrapani et al. [65]	2011	Italy	Caucasian	Liver Cancer	105/95	0.402(Y)
Lima junior et al. [48]	2012	Brazil	Mixed	Cervical Cancer	345/345	0.093(Y)
Pooja et al. [28]	2012	India	Asian	Breast Cancer	200/200	0.000(N)
Totaro et al. [120]	2013	Italy	Caucasian	Neuroblastoma	326/511	0.646(Y)
Pohjnen et al. [109]	2013	Finland	Caucasian	Stomach Cancer	56/179	0.706(Y)
Chen et al. [72]	2013	China	Asian	Lung Cancer	1237/1252	0.903(Y)
Bai et al. [73]	2013	China	Asian	Lung Cancer	193/210	0.145(Y)
Oduor et al. [13]	2014	Kenya	African	Blood Cancer	117/88	1.000(Y)
Mandal et al. [85]	2014	USA	Caucasian	Prostate Cancer	164/140	0.001(N)
Gu et al. [14]	2014	China	Asian	Blood Cancer	157/435	0.159(Y)
Cao et al. [111]	2014	China	Asian	Stomach Cancer	162/162	0.210(Y)
Shi et al. [43]	2014	China	Asian	Cervical Cancer	518/518	0.349(Y)
Cil et al. [116]	2014	Turkey	Caucasian	Thyroid Cancer	190/216	0.722(Y)
Slattery et al. [29]	2014	USA	Mixed	Breast Cancer	3567/4157	0.000(N)
Chen et al. [89]	2015	China	Asian	Prostate Cancer	212/236	0.267(Y)
Talaat et al. [15]	2015	Egypt	Mixed	Blood Cancer	100/119	0.568(Y)
Sampaio et al. [110]	2015	Portugal	Caucasian	Stomach Cancer	50/50	0.608(Y)

(Continued)

Table 1. (Continued)

Study	Year	Country	Ethnicity	Cancer	Case/Control	HWE
rs1800795						
Sa-Nguanraksa et al. [37]	2016	Thailand	Asian	Breast Cancer	391/79	0.000(N)
Pu et al. [42]	2016	China	Asian	Cervical Cancer	360/728	0.310(Y)
Abana et al. [26]	2017	USA	Caucasian	Breast Cancer	277/711	0.490(Y)
Winchester et al. [84]	2017	USA	Caucasian	Prostate Cancer	625/532	0.169(Y)
Attar et al. [106]	2017	Iran	Mixed	Stomach Cancer	100/361	0.000(N)
Sabrina et al. [44]	2017	Tunisia	African	Cervical Cancer	112/164	0.002(N)
DargahiAbbasabad et al. [86]	2018	Iran	Mixed	Prostate Cancer	112/250	0.000(N)
Zhao et al. [121]	2018	China	Asian	Neuroblastoma	130/50	0.585(Y)
Dos Santos et al. [112]	2018	Brazil	Mixed	Stomach Cancer	52/87	0.517(Y)
Taheri et al. [86]	2018	Iran	Mixed	Prostate Cancer	130/200	0.194(Y)
Shuwei Wang et al. [64]	2018	China	Asian	Colon Cancer	186/200	0.160(Y)
rs1800796						
Hwang (a) et al. [114]	2003	USA	Caucasian	Stomach Cancer	30/30	0.020(N)
Hwang (b) et al. [114]	2003	USA	Asian	Stomach Cancer	30/30	0.394(Y)
Sun et al. [98]	2004	USA	Caucasian	Prostate Cancer	1337/753	0.211(Y)
Xing et al. [111]	2006	China	Asian	Stomach Cancer	65/71	0.141(Y)
Seow et al. [75]	2006	Singapore	Asian	Lung Cancer	124/162	0.560(Y)
Kamanger et al. [116]	2006	USA	Caucasian	Stomach Cancer	102/152	0.004(N)
Slattery et al. [62]	2007	USA	Caucasian	Colon Cancer	1573/1972	0.015(N)
Bao et al. [91]	2008	China	Asian	Prostate Cancer	136/120	0.000(N)
Slattery et al. [51]	2009	USA	Caucasian	Colon Cancer	750/1205	0.000(N)
Kang et al. [111]	2009	Korea	Asian	Stomach Cancer	332/326	0.078(Y)
Pierce et al. [93]	2009	USA	Caucasian	Prostate Cancer	175/1934	0.161(Y)
Wang et al. [94]	2009	USA	Caucasian	Prostate Cancer	253/280	0.405(Y)
Tsilidis et al. [58]	2009	USA	Caucasian	Colon Cancer	203/367	0.019(N)
Su et al. [82]	2010	China	Asian	Lung Cancer	363/370	0.298(Y)
Lim et al. [83]	2011	Singapore	Asian	Lung Cancer	298/718	0.250(Y)
Bai et al. [73]	2013	China	Asian	Lung Cancer	193/210	0.145(Y)
Chen et al. [72]	2013	China	Asian	Lung Cancer	615/638	0.990(Y)
Liang et al. [74]	2013	China	Asian	Lung Cancer	138/138	0.625(Y)
Kiyohara et al. [77]	2014	Japan	Asian	Lung Cancer	462/379	0.919(Y)
Cao et al. [111]	2014	China	Asian	Stomach Cancer	162/162	0.210(Y)
Tang et al. [68]	2014	China	Asian	Liver Cancer	505/395	0.474(Y)
Chen et al. [89]	2015	China	Asian	Prostate Cancer	212/236	0.851(Y)
Haung et al. [90]	2016	China	Asian	Prostate Cancer	236/256	0.094(Y)
Zhang et al. [111]	2017	China	Asian	Stomach Cancer	473/474	0.750(Y)
Xie et al. [111]	2017	China	Asian	Stomach Cancer	400/400	0.859(Y)
Zhu et al. [35]	2017	China	Asian	Breast Cancer	1514/1540	0.204(Y)
Dos Santos et al. [112]	2018	Brazil	Mixed	Stomach Cancer	52/87	0.555(Y)
rs1800797						
Hwang et al. [114]	2003	USA	Caucasian	Stomach Cancer	30/30	0.399(Y)
Snoussi et al. [33]	2005	Tunisia	African	Breast Cancer	305/200	0.830(Y)
Festa et al. [102]	2005	Sweden	Caucasian	Skin Cancer	241/260	0.385(Y)
Rothman et al. [24]	2006	USA	Caucasian	Blood Cancer	2658/3068	0.124(Y)
Castro et al. [46]	2009	Sweden	Caucasian	Cervical Cancer	973/1763	0.584(Y)
Pierce et al. [93]	2009	USA	Caucasian	Prostate Cancer	175/1934	0.437(Y)

(Continued)

Table 1. (Continued)

Study	Year	Country	Ethnicity	Cancer	Case/Control	HWE
rs1800795						
Tsilidis et al. [58]	2009	USA	Caucasian	Colon Cancer	203/362	0.931(Y)
Vasku et al. [89]	2009	Czech Republic	Caucasian	Colon Cancer	100/100	0.661(Y)
DeMichele et al. [31]	2009	USA	Caucasian	Breast Cancer	339/100	0.316(Y)
Gu et al. [14]	2014	China	Asian	Blood Cancer	93/204	0.831(Y)
Sa-Nguanraksa et al. [37]	2016	Thailand	Asian	Breast Cancer	391/79	0.863(Y)
Leng et al. [76]	2016	USA	Caucasian	Lung Cancer	242/336	0.346(Y)
Sabrina et al. [44]	2017	Tunisia	African	Cervical Cancer	112/164	0.000(N)
Winchester et al. [84]	2017	USA	Caucasian	Prostate Cancer	625/532	0.075(Y)
Huang et al. [57]	2018	USA	Caucasian	Colon Cancer	135/269	0.745(Y)
Dos Santos et al. [112]	2018	Brazil	Mixed	Stomach Cancer	52/87	0.446(Y)

HWE: Hardy-Weinberg equilibrium; Y: Yes; N: No; All the included studies are ordered by the year of publication.

https://doi.org/10.1371/journal.pone.0247055.t001

genotypic ratio is consistent for the control population of all studies. The chi-square statistic for this test is given by:

$$\chi^2 = \sum\nolimits_{i=1}^{3} \frac{(O_i - E_i)^2}{E_i} \qquad (1)$$

which follows chi-square distribution with 1 degree freedom. Here O_i and E_i represents observe and expected frequency of the genotype, respectively. If p and q are the probabilities of C and G allele, respectively and $O_i = obs(i)$ is observe frequency of ith genotype among the 3 genotypes CC, CG and GG. Then p is calculated as:

$$p = \frac{2 \times obs(CC) + obs(CG)}{2 \times (obs(CC) + (obs(CG) + obs(GC))}; \quad \text{and } q = 1 - p \qquad (2)$$

The expected frequency of ith genotype is denoted by $E_i = E(i)$ defined as $E(CC) = p^2 n$, $E(CG) = 2pqn$, $E(GG) = q^2 n$, where n is the total number of observation.

The heterogeneity of different studies has been examined by using Cochran's Q statistic and its extended Higgin's & Thompson I^2 statistic [131, 132]. The Cochran's Q statistic is defined as:

$$Q = \sum\nolimits_{k=1}^{K} w_k \left(\hat{\theta}_k - \frac{\sum_{k=1}^{K} w_k \hat{\theta}_k}{\sum_{k=1}^{K} w_k} \right)^2, \qquad (3)$$

which follows the chi-square distribution with K-1 degrees of freedom. Here $\hat{\theta}_k = \ln(\mathrm{OR}_k)$ for the kth study, and $w_k = \frac{1}{\hat{\sigma}_k^2}$ is the weight of kth study. The variance of the kth study can be calculated as:

$$\hat{\sigma}_k^2 = var\left(\ln \left(OR_k \right) \right) = \frac{1}{m_{1k}} + \frac{1}{m_{2k}} + \frac{1}{m_{3k}} + \frac{1}{m_{4k}} \qquad (4)$$

where m_{1k} and m_{2k} indicates the number of exposures and m_{3k} and m_{4k} indicates non-exposures, in the case-control groups of kth study, respectively (that is, for the genetic model C vs. G, the allele C is exposer and G is non-exposer). The Higgin's& Thompson I^2 statistic is

defined as:

$$I^2 = \max\left\{0, \frac{Q - (K - 1)}{Q} \times 100\%\right\} \qquad (5)$$

The values of I^2 greater than 25%, 50% and 75% indicates the low, moderate, and high heterogeneity among the individual studies, respectively.

The pooled odds ratio (OR) has been applied for checking the significant association between the IL-6 gene polymorphisms and cancer risk under different genetic models like as dominant models [CC + CG vs. GG or AA + AG vs. GG], homozygote models [CC vs. GG or AA vs. GG], over-dominant models [CG vs. CC + GG or AG vs. AA + GG], recessive models [CC vs. CG + GG or AA vs. AG + GG], and allelic contrast models [C vs. G or A vs. G]. To calculate pooled OR for each genetic combination, we have used the random effect model if the Q-test suggests the highly significant heterogeneity (p-value < 0.10) among different studies; otherwise, fixed effect model are used. We have also estimated 95% confidence interval (CI) of OR based on Z-statistic [131, 132]. The OR for the kth study is calculated as:

$$OR_k = \frac{\frac{m_{1k}}{m_{2k}}}{\frac{m_{3k}}{m_{4k}}} = \frac{m_{1k} m_{4k}}{m_{2k} m_{3k}}, \qquad (6)$$

For the fixed effect model, overall OR is calculated by using the Mentel—Haenszel (M-H) method as follows:

$$\hat{\theta}_k = \theta_F + \epsilon_k; \quad \text{where } \epsilon_k \sim N(0, \hat{\sigma}_k^2) \qquad (7)$$

where $\hat{\theta}_F = \widehat{OR}_{MH} = \dfrac{\sum_{k=1}^{K}\left(\frac{m_{1k} m_{4k}}{N_k}\right)}{\sum_{k=1}^{K}\left(\frac{m_{2k} m_{3k}}{N_k}\right)}$

$$= \sum_{k=1}^{K}\left(\frac{\frac{m_{2k} m_{3k}}{N_k}}{\sum_{i=1}^{K}\left(\frac{m_{2k} m_{3k}}{N_k}\right)}\right) \times OR_k, \qquad (8)$$

and $N_k = m_{1k} + m_{2k} + m_{3k} + m_{4k}$, and the variance and 95% C.I. of overall effect can be defined as:

$$Var\left(\hat{\theta}_F\right) \frac{1}{\sum_{k=1}^{K}\left(\frac{m_{2k} m_{3k}}{N_k}\right)}; \hat{\theta}_F \pm 1.96\sqrt{Var\left(\hat{\theta}_F\right)}, \qquad (9)$$

For the random effect model, overall OR is calculated by using the inverse variance method as follows:

$$\hat{\theta}_k = \theta_R + v_k + \epsilon_k; \quad \text{where, } v_k \sim N(0, \tau^2) \qquad (10)$$

The random parameter θ_R is calculated as,

$$\hat{\theta}_R = \frac{\sum_{k=1}^{K} w_{kR} \hat{\theta}_k}{\sum_{k=1}^{K} w_{kR}}, \qquad (11)$$

Where

$$se(\hat{\theta}_R) = \sqrt{var(\hat{\theta}_R)} = \sqrt{\frac{1}{\sum_{k=1}^{K} w_{kR}}};$$

$$w_{kR} = \frac{1}{\sigma_k^2 + \tau^2}, \quad \text{and} \quad \tau^2 = \frac{Q - (K-1)}{\sum w_k - \left(\frac{\sum w_k^2}{\sum w_k}\right)} \tag{12}$$

However, *Q*-test cannot give the assurance of model adequacy. Therefore we also considered the goodness of fit test to check the model adequacy. To check the model adequacy, we performed three distinct goodness of fit (GoF) tests proposed by Chen et al. [133]. These three GoF tests known as Anderson-Darling (AD) test [134, 135], Cramer-von Mises (CvM) test [135–137] and Shapiro-Wilk (SW) test [138] for testing the null hypothesis that the individual effects follow the normal distribution. If individual effects are significantly normal, then random effect model is used for estimating the combined effect else fixed effect model is used. The test statistic of each normality test is defined as:

$$AD = -K - \sum_{k=1}^{K} \left(\frac{2k-1}{k}\right)\left[\ln F(\hat{\theta}_k) + \ln\left(1 - F(\hat{\theta}_{K+1-k})\right)\right], \tag{13}$$

$$CvM = \frac{1}{12K} + \sum_{k=1}^{K} \left[\frac{2k-1}{2K} - F(\hat{\theta}_k)\right]^2, \tag{14}$$

$$SW = \frac{\left(\sum_{k=1}^{K} a_k \hat{\theta}_k\right)^2}{\sum_{k=1}^{K} (\hat{\theta}_k - \bar{\theta})^2}, \tag{15}$$

where, $\hat{\theta}_k$ is the ordered data, $\bar{\theta}$ is sample mean of $\hat{\theta}_k$, *K* is sample size means number of individual study, $F(\hat{\theta}_k)$ is cumulative distribution function of normal distribution with *k*th order statistic, a_k is constants generated from means, variances, and covariances of the order statistics. To perform these three tests, Chen et al. [133] proposed the following steps:

Step 1. Compute ad_0, cvm_0, and sw_0 from AD, CvM, and SW statistics, respectively, for given $\hat{\theta}_k = \ln(OR_k)$, *k* = 1, 2, . . ., *K*;

Step 2. Resample B = 10^5 sub-samples from $MVN(0, \hat{\Sigma})$, where,

$$\hat{\Sigma} = \begin{bmatrix} \hat{\sigma}_1^2 + \hat{\tau}^2 & 0 & \cdots & 0 \\ 0 & \hat{\sigma}_2^2 + \hat{\tau}^2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \hat{\sigma}_K^2 + \hat{\tau}^2 \end{bmatrix}$$

Then, compute ad_j, cvm_j, and sw_j by using AD, CvM, and SW statistics, respectively, for each sample *j* (*j* = 1, 2, . . .,*B)*.

Step 3. Compute *p*-values by using $\sum_{j=1}^{B} I_{[ad_j > ad_0]}/B$, $\sum_{j=1}^{B} I_{[cvm_j > cvm_0]}/B$ and

$\sum_{j=1}^{B} I_{[sw_j < sw_0]}/B$ for the above three tests, respectively, where $I_{[s > s_0]} = \begin{cases} 1 \; for \; s > s_0; \\ 0, \; otherewise. \end{cases}$

Then the respective *z*-score is calculated as follows:

$$
Z = \begin{cases}
\dfrac{\sum_k w_k \hat{\theta}_k}{\sqrt{\sum_k w_k}}, & \text{for fixed effect model} \\[4ex]
\dfrac{\sum_k w_{kR} \hat{\theta}_k}{\sqrt{\sum_k w_{kR}}}, & \text{for random effect model}
\end{cases}
\tag{16}
$$

Subgroup analyses are also executed based on ethnicity and type of cancer by using the techniques mentioned above.

We have performed the sensitivity analysis using the full data and the reduced data that are obtained by removing the studies those are failed to pass the HWE validation and publication bias test. The publication bias is examined for each study visually by funnel plot and significantly by Egger regression test [139] and Begg's test [140]. The Egger regression test statistic is defined as:

$$
T = \frac{\hat{a}}{se(\hat{a})}
\tag{17}
$$

which follows the *t*-distribution with (*K*-2) degrees of freedom under the null hypothesis H$_0$: α = 0 (no publication bias), $\hat{\alpha}$ is obtained by the least square estimation using one of the following models:

$$
\hat{\theta}_k \sqrt{w_k} = \alpha + \mu \sqrt{w_k} + \varepsilon_k, \quad \text{for fixed effect model, and}
\tag{18}
$$

$$
\hat{\theta}_k \sqrt{w_{kR}} = \alpha + \mu \sqrt{w_{kR}} + \varepsilon_k, \quad \text{for random effect model,}
\tag{19}
$$

where $\varepsilon_k \sim iid\ N(0, \sigma^2)$. The Begg's test statistic is defined as:

$$
Z = \frac{C - D}{\sqrt{K(K-1)(2K+5)/18}},
\tag{20}
$$

which follows asymptotically *N*(0,1) under the null hypothesis H$_0$: α = 0 (no publication bias). Here *C* and *D* are the number of concordant and discordant, respectively, those are obtained by using the Kendall's ranking of t_k^* and $\hat{\sigma}_k^2$ or $\hat{\sigma}_{kR}^2$. Here:

$$
t_k^* = \frac{t_k - \bar{t}}{\sqrt{\vartheta_k^*}}
\tag{21}
$$

where, $t_k = \text{OR}_k$ is the OR of kth study, and:

$$\bar{t} = \begin{cases} \dfrac{\sum_k w_k t_k}{\sqrt{\sum_k w_k}}, & \text{for fixed effect model} \\[4mm] \dfrac{\sum_k w_{kR} t_k}{\sqrt{\sum_k w_{kR}}}, & \text{for random effect model} \end{cases} \tag{22}$$

$$\vartheta_k^* = \begin{cases} \hat{\sigma}_k^2 - \dfrac{1}{\sum w_k}, & \text{for fixed effect model} \\[4mm] \hat{\sigma}_{kR}^2 - \dfrac{1}{\sum w_{kR}}, & \text{for random effect model} \end{cases} \tag{23}$$

We have used the 'meta' R-package (http://meta-analysis-with-r.org/) for implementing the above statistical methods for the meta-analysis.

Results

Study characteristics

In this meta-analysis, first we reviewed 580 articles which mentioned the IL-6 gene in their titles and abstracts. Then 477 articles were selected after removing the duplication. Again we removed 337 articles due to the absence of full text, case-control and cancer related studies. Finally 118 articles were selected for final review by removing some studies having incomplete information. The flow chart of the studies selection process was shown in Fig 1. The finally selected articles included 103 studies for the rs1800795 SNP with 45238 cases and 57255 controls (Table 2), 27 studies for the rs1800796 SNP with 10733 cases and 13405 controls (Table 3), 16 studies for the rs1800797 SNP with 6674 cases and 9493 controls (Table 4). These articles were classified to different types of cancer such as blood cancer, breast cancer, cervical cancer, colon cancer, liver cancer, lung cancer, neuroblastoma, oral cancer, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer and thyroid cancer. For being the single study, ovarian cancer, renal cell carcinoma (RCC) and pancreatic cancer for the rs1800795
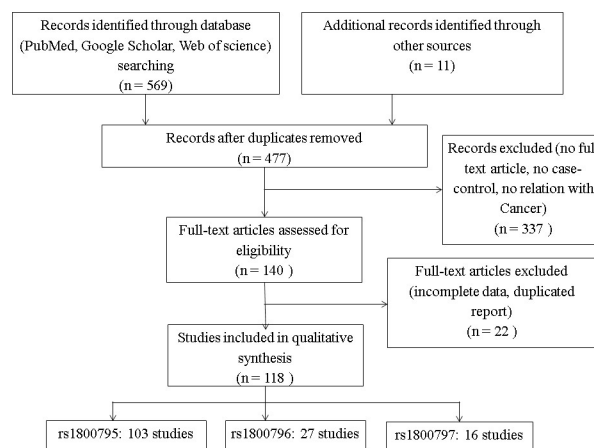

Fig 1. Flow diagram of study selection for the IL-6 gene polymorphisms; where 'n' is the number of studies.

SNP, breast cancer and liver cancer for rs1800796 SNP and, lung cancer and skin cancer for the rs1800797 SNP were organized in a subgroup entitled as other cancer (Tables 2–4).

Quantitative synthesis

IL-6 rs1800795 SNP.   In the overall analysis, we found that the rs1800795 SNP was not associated with overall risk of cancer under five genetic models [C vs. G: OR = 1.02, 95% CI = 0.97–1.06, p-value = 0.445; CC vs. GG: OR = 1.06, 95% CI = 0.98–1.16, p-value = 0.1429; CC vs. CG + GG: OR = 1.05, 95% CI = 0.98–1.12, p-value = 0.2054; CC + CG vs. GG: OR = 1.02, 95% CI = 0.99–1.05, p-value = 0.0615; CG vs. CC + GG: OR = 0.99, 95% CI = 0.96–1.01, p-value = 0.2689] (Table 2 and S1A–S1E Fig in S1 File).

The subgroup analysis through the types of cancer showed the significant association that the IL-6 -174G/C polymorphism performed a protective role in liver cancer for four genetic models [C vs. G: OR = 0.73, 95% CI = 0.62–0.86, p-value = 0.0002; CC vs. GG: OR = 0.61, 95% CI = 0.42–0.88, p-value = 0.0082; CC vs. CG + GG: OR = 0.68, 95% CI = 0.48–0.97, p-value = 0.0321; CC + CG vs. GG: OR = 0.69, 95% CI = 0.56–0.85, p-value = 0.0004]; increased the risk for cervical cancer under four genetic models [C vs. G: OR = 1.29, 95% CI = 1.07–1.56, p-value = 0.0075; CC vs. GG: OR = 1.63, 95% CI = 1.06–2.52, p-value = 0.0266; CC vs. CG + GG: OR = 1.57, 95% CI = 1.25–1.97, p-value = 0.0001; CC + CG vs. GG: OR = 1.31, 95% CI = 1.05–1.64, p-value = 0.0178]; as well as increasing

Table 2. Meta-analysis of the IL-6 -174G/C polymorphism association with cancer risk.

	Study Number	Sample Size	CC vs. GG		CC vs. CG + GG		CC + CG vs. GG		CG vs. CC + GG		C vs. G	
			OR[a] (95% CI[b])	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Overall	103	102493	1.06 [0.98; 1.16]	0.1429	1.05 [0.98; 1.12]	0.2054	1.02 [0.99; 1.05]	0.0615	0.99 [0.96; 1.01]	0.2681	1.02 [0.97; 1.06]	0.4459
Blood Cancer	13	10824	1.04 [0.86; 1.26]	0.6246	1.06 [0.86; 1.29]	0.6289	0.98 [0.87; 1.10]	0.7399	0.99 [0.90; 1.08]	0.7508	1.01 [0.96; 1.07]	0.8411
Breast Cancer	14	18686	0.93 [0.84; 1.02]	0.1329	0.96 [0.88; 1.05]	0.4042	0.95 [0.82; 1.11]	0.5291	0.98 [0.91; 1.04]	0.4804	1.00 [0.90; 1.11]	0.9619
Cervical Cancer	7	4098	**1.63 [1.06; 2.52]**	**0.0266**	**1.57 [1.25; 1.97]**	**0.0001**	**1.31 [1.05; 1.64]**	**0.0178**	1.14 [0.89; 1.47]	0.2927	**1.29 [1.07; 1.56]**	**0.0075**
Colon Cancer	15	21263	0.98 [0.85; 1.13]	0.8097	0.98 [0.87; 1.08]	0.4136	1.02 [0.92; 1.14]	0.6893	1.02 [0.97; 1.08]	0.4196	1.01 [0.93; 1.09]	0.7632
Liver Cancer	6	1922	**0.61 [0.42; 0.88]**	**0.0082**	**0.68 [0.48; 0.97]**	**0.0321**	**0.69 [0.56; 0.85]**	**0.0004**	0.75 [0.54; 1.05]	0.0908	**0.73 [0.62; 0.86]**	**0.0002**
Lung Cancer	6	7846	1.08 [0.85; 1.36]	0.5296	0.97 [0.76; 1.23]	0.7981	1.08 [0.86; 1.84]	0.5137	1.07 [0.86; 1.34]	0.5334	1.01 [0.87; 1.18]	0.9102
Neuroblastoma	2	1017	1.18 [0.71; 1.95]	0.5244	1.15 [0.71; 1.88]	0.5731	1.06 [0.84; 1.81]	0.6865	1.05 [0.80; 1.37]	0.7259	1.08 [0.88; 1.33]	0.4570
Oral Cancer	3	896	0.69 [0.08; 6.27]	0.7430	0.74 [0.18; 3.04]	0.6714	0.80 [0.16; 4.09]	0.7864	0.86 [0.25; 2.95]	0.8160	0.81 [0.25; 2.58]	0.7197
Prostate Cancer	14	28441	**1.24 [1.05; 1.46]**	**0.0096**	**1.19 [1.03; 1.39]**	**0.0202**	1.09 [0.98; 1.22]	0.1142	0.97 [0.91; 1.05]	0.4773	**1.09 [1.00; 1.19]**	**0.0441**
Skin Cancer	4	1588	0.99 [0.75; 1.32]	0.968	0.96 [0.76; 1.20]	0.6564	1.05 [0.84; 1.31]	0.6808	1.08 [0.88; 1.31]	0.4597	1.00 [0.87; 1.16]	0.9912
Stomach Cancer	14	4503	1.12 [0.85; 1.50]	0.4087	1.07 [0.81; 1.40]	0.6405	1.08 [0.92; 1.22]	0.4317	1.04 [0.90; 1.19]	0.6024	1.04 [0.94; 1.16]	0.4517
Thyroid Cancer	2	788	1.20 [0.67; 2.13]	0.5364	1.30 [0.75; 2.27]	0.3477	0.87 [0.63; 1.21]	0.4149	0.79 [0.57; 1.10]	0.1680	0.97 [0.76; 1.25]	0.8399
Other Cancers	3	621	1.10 [0.58; 2.10]	0.7683	1.09 [0.73; 1.61]	0.6802	1.29 [0.80; 2.13]	0.3236	1.07 [0.74; 1.56]	0.7148	1.14 [0.85; 1.54]	0.3711
Ethnicity[C]												
African	3	986	1.58 [0.68; 3.66]	0.2895	1.40 [0.61; 3.25]	0.4248	**1.66 [1.20; 2.3]**	**0.0027**	**1.64 [1.17; 2.30]**	**0.0037**	**1.54 [1.16; 2.04]**	**0.0030**
Asian	19	10043	**1.56 [1.19; 2.03]**	**0.0011**	**1.37 [1.22; 1.53]**	**0.0001**	**1.17 [1.08; 1.29]**	**0.0024**	0.93 [0.85; 1.02]	0.1151	**1.20 [1.12; 1.29]**	**0.00001**
Caucasian	66	62535	1.01[0.92; 1.11]	0.8193	1.00 [0.94; 1.07]	0.9469	1.00 [0.97; 1.04]	0.8788	1.00 [0.97; 1.04]	0.9164	1.00 [0.95; 1.05]	0.9291
Mixed	15	28929	0.97 [0.74; 1.27]	0.8224	1.02 [0.80; 1.31]	0.8629	0.89 [0.77; 1.04]	0.1493	0.89 [0.78; 1.03]	0.1134	0.93 [0.82; 1.06]	0.2676

Statistical significance presented in Bold.

[a]Odds Ratio;

[b]Confidence Interval ORs for the ethnicity subgroups are for overall cancer risk.

https://doi.org/10.1371/journal.pone.0247055.t002

Table 3. Meta-analysis of the IL-6 -572G/C polymorphism association with cancer risk.

	Study Number	Sample size	CC vs. GG		CC vs. CG + GG		CC + CG vs. GG		CG vs. CC + GG		C vs. G	
			OR[a] (95% CI[b])	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Overall	27	24138	1.03 [0.85; 1.25]	0.7635	0.99 [0.86; 1.14]	0.8582	1.07 [0.94; 1.22]	0.2931	**1.12 [1.01; 1.23]**	**0.0288**	1.04 [0.95; 1.15]	0.3839
Colon Cancer	3	6070	1.04 [0.67; 1.64]	0.8507	1.05 [0.73; 1.50]	0.8000	1.04 [0.67; 1.63]	0.8507	1.07 [0.85; 1.36]	0.5552	1.10 [0.79; 1.53]	0.5613
Lung Cancer	7	4808	1.13 [0.75; 1.69]	0.5575	0.93 [0.74; 1.17]	0.5400	**1.31 [1.04; 1.65]**	**0.0228**	**1.31 [1.08; 1.59]**	**0.0072**	1.19 [0.98; 1.43]	0.0734
Prostate Cancer	6	5928	**0.52 [0.37; 0.72]**	**0.0001**	**0.67 [0.53; 0.84]**	**0.0005**	**0.74 [0.61; 0.90]**	**0.0025**	1.00 [0.84; 1.18]	0.9811	**0.74 [0.64; 0.85]**	**0.0000**
Stomach Cancer	9	3378	**1.41 [1.10; 1.81]**	**0.0076**	**1.29 [1.07; 1.55]**	**0.0080**	**1.41 [1.09; 1.81]**	**0.0088**	1.02 [0.79; 1.31]	0.8940	**1.16 [1.03; 1.30]**	**0.0069**
Other Cancer	2	3954	1.13 [0.47; 2.68]	0.7852	0.90 [0.78; 1.04]	0.1400	1.03 [0.64; 1.67]	0.8922	1.12 [0.99; 1.28]	0.0841	1.05 [0.72; 1.53]	0.7878
Ethnicity[C]												
Asian	18	12883	1.02 [0.79; 1.31]	0.8812	1.00 [0.83; 1.20]	0.9636	1.06 [0.91; 1.25]	0.4557	**1.13 [1.01; 1.27]**	**0.0293**	1.04 [0.92; 1.19]	0.4974
Caucasian	8	11116	1.07 [0.76; 1.49]	0.7105	0.97 [0.78; 1.21]	0.7964	1.10 [0.87; 1.39]	0.4398	1.12 [0.89; 1.40]	0.3391	1.04 [0.87; 1.26]	0.6445
Mixed	1	139	3.20 [.28; 36.45]	0.3487	3.44 [.30; 38.90]	0.3181	0.83 [0.37; 1.86]	0.6590	0.70 [0.30; 1.63]	0.4130	0.97 [0.48; 1.98]	0.9379

Statistical significance presented in Bold.

[a]Odds Ratio;

[b]Confidence Interval;

[C] ORs for the ethnicity subgroups are for overall cancer risk.

https://doi.org/10.1371/journal.pone.0247055.t003

the risk for prostate cancer [C vs. G: OR = 1.09, 95% CI = 1.00–1.19, p-value = 0.0441; CC vs. GG: OR = 1.24, 95% CI = 1.05–1.46, p-value = 0.0096; CC vs. CG + GG: OR = 1.19, 95%

Table 4. Meta-analysis of the IL-6 -597G/A polymorphism association with cancer risk.

	Study Number	Sample size	AA vs. GG		AA vs. AG + GG		AA + AG vs. GG		AG vs. AA + GG		A vs. G	
			OR[a] (95% CI[b])	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Overall	16	16167	0.96 [0.85; 1.08]	0.5152	0.97 [0.87; 1.07]	0.5064	1.00 [0.93; 1.08]	0.9289	0.98 [0.91; 1.05]	0.5025	0.99 [0.94; 1.04]	0.7169
Blood Cancer	2	6023	0.97 [0.83; 1.13]	0.7353	0.90 [0.84; 1.12]	0.6699	1.01 [0.47; 6.86]	0.8045	0.97 [0.88; 1.07]	0.5815	1.75 [0.48; 6.46]	0.3981
Breast Cancer	3	1414	1.11 [0.63; 1.92]	0.7097	1.07 [0.64; 1.79]	0.7980	1.24 [0.82; 1.88]	0.0800	0.79 [0.59; 1.06]	0.1176	1.20 [0.95; 1.52]	0.1221
Cervical Cancer	2	3012	**0.79 [0.63; 0.98]**	**0.0390**	**0.82 [0.68; 1.00]**	**0.0474**	0.93 [0.75; 1.23]	0.3969	0.94 [0.80; 1.09]	0.4312	0.91 [0.82; 1.02]	0.0667
Colon Cancer	3	1174	0.84 [0.60; 1.20]	0.3674	0.86 [0.64; 1.18]	0.3700	0.93 [0.72; 1.20]	0.5885	0.97 [0.77; 1.24]	0.8488	0.93 [0.78; 1.10]	0.3887
Prostate Cancer	2	3266	0.97 [0.71; 1.31]	0.8243	1.07 [0.81; 1.42]	0.6183	0.87 [0.72; 1.05]	0.1708	1.17 [0.97; 1.41]	0.0944	0.95 [0.83; 1.09]	0.4591
Stomach Cancer	2	199	1.71 [0.54; 5.34]	0.3551	1.83 [0.60; 5.57]	0.2846	0.98 [0.54; 1.76]	0.9657	1.21 [0.67; 2.20]	0.5301	1.10 [0.69; 1.76]	0.6853
Other Cancers	2	1079	1.36 [0.96; 1.92]	0.0744	1.20 [0.90; 1.60]	0.2122	1.29 [0.96; 1.73]	0.0524	0.91 [0.71; 1.16]	0.4556	**1.19 [1.00; 1.41]**	**0.0450**
Ethnicity[C]												
African	2	781	0.80 [0.37; 1.70]	0.5600	0.69 [0.32; 1.46]	0.3323	**1.48 [1.08; 2.03]**	**0.0135**	**0.61 [0.44; 0.84]**	**0.001**	**1.28 [0.98; 1.67]**	**0.0191**
Asian	2	767	0.61 [.02; 15.10]	0.7600	0.62 [0.02; 15.24]	0.7669	2.11 [0.91; 4.85]	0.0602	0.56 [0.11; 2.89]	0.0800	2.11 [0.93; 4.81]	0.0753
Caucasian	11	14480	0.97 [0.85; 1.10]	0.5965	0.97 [0.87; 1.08]	0.5689	0.98 [0.91; 1.05]	0.5254	1.00 [0.93; 1.07]	0.9640	0.97 [.87; 1.08]	0.5689
Mixed	1	139	1.29 [0.36; 4.67]	0.6900	1.44 [0.42; 4.96]	0.5672	0.86 [0.43; 1.72]	0.6774	1.30 [0.65; 2.62]	0.4600	0.98 [0.57; 1.04]	0.9343

Statistical significance presented in Bold.

[a]Odds Ratio;

[b]Confidence Interval;

[C] ORs for the ethnicity subgroups are for overall cancer risk.

https://doi.org/10.1371/journal.pone.0247055.t004

CI = 1.03–1.39, p-value = 0.0202]. The blood cancer, breast cancer, colon cancer, lung cancer, neuroblastoma, oral cancer, skin cancer, stomach cancer, thyroid cancer, ovarian cancer and pancreatic cancer showed insignificant associations with the IL-6 -174G/C polymorphism (Table 2).

The subgroup analysis according to ethnicity showed that the IL-6 -174G/C polymorphism was not significantly associated with the cancer risk of Caucasian and mixed populations (Table 2). The subgroup analysis showed the significant association with the increasing overall cancer risk of Asian population under four genetic models [C vs. G: OR = 1.20, 95% CI = 1.12–1.29, p-value = 0.0000; CC vs. GG: OR = 1.56, 95% CI = 1.08–2.03, p-value = 0.0011; CC vs. CG + GG: OR = 1.37, 95% CI = 1.22–1.53, p-value = 0.0001; CC + CG vs. GG: OR = 1.17, 95% CI = 1.08–1.29, p-value = 0.0024] and African population [C vs. G: OR = 1.54, 95% CI = 1.16–2.04, p-value = 0.0030; CC + CG vs. GG: OR = 1.66, 95% CI = 1.20–2.30, p-value = 0.0027; CG vs. CC + GG: OR = 1.64, 95% CI = 1.17–2.30, p-value = 0.0037] (Table 2).

Source of heterogeneity. We observed significant heterogeneity in the analysis of the IL-6 rs1800795 (-174G /C) polymorphism for overall cancer [CC vs.GG: Q = 258.44, df = 97, p-value = 0.0001,τ^2 = 0.0747, I^2 = 62.47%; CC vs. CG + GG: Q = 228.48, df = 97, p-value = 97, τ^2 = .0478, I^2 = 57.53%; CC + CG vs. GG: Q = 333.19, df = 100, p-value = 0.0001, τ^2 = .0485, I^2 = 69.98%; CG vs. CC + GG: Q = 297.07, df = 100, p-value = 0.0001, τ^2 = .0385, I^2 = 66.34%; C vs. G: Q = 378.15, df = 100, p-value = 0.0001, τ^2 = .0290, I^2 = 73.56%]. The subgroup analysis corresponding to cancer type and ethnicity were performed to observe the sources of heterogeneity. The results of our analysis suggested that the studies in breast cancer, cervical cancer, colon cancer, lung cancer, oral cancer, prostate cancer, stomach cancer, and the ethnicity of Asian, Caucasian and Mixed population were the main sources of heterogeneity (S1 Table).

IL-6 rs1800796 SNP. The results generated through this meta-analysis showed that the IL-6 -572G/C polymorphism was significantly associated with the overall cancer risk in the case of over-dominant model [CG vs. CC + GG: OR = 1.12, 95% CI = 1.01–1.23, p-value = 0.0288] (Table 3 and S1F–S1J Fig in S1 File). Though, it was not significantly associated with the overall cancer risk under the other four genetic models (Allelic, dominant, recessive and homozygote).

The subgroup analysis through the types of cancer showed the significant association that the IL-6 rs1800796 (-572G/C) performed a protective role in prostate cancer for four genetic models [C vs. G: OR = 0.74, 95% CI = 0.64–0.85, p-value = 0.0000; CC vs. GG: OR = 0.52, 95% CI = 0.37–0.72, p-value = 0.0001; CC vs. CG + GG: OR = 0.67, 95% CI = 0.53–0.84, p-value = 0.0005; CC + CG vs. GG: OR = 0.74, 95% CI = 0.61–0.90, p-value = 0.0025]. The IL-6 -572G/C polymorphism was also exhibited significant association with the increasing risk of stomach cancer under four genetic models [C vs. G: OR = 1.16, 95% CI = 1.03–1.30, p-value = 0.0069; CC vs. GG: OR = 1.41, 95% CI = 1.10–1.81, p-value = 0.0076; CC vs. CG + GG: OR = 1.29, 95% CI = 1.07–1.55, p-value = 0.0080; CC + CG vs. GG: OR = 1.41, 95% CI = 1.09–0.81, p-value = 0.0088] and lung cancer for genetic models [CC + CG vs. GG: OR = 1.31, 95% CI = 1.04–1.65, p-value = 0.0228; CG vs. CC + GG: OR = 1.31, 95% CI = 1.08–1.59, p-value = 0.0072]. The colon, breast and liver cancers showed insignificant association with this polymorphism (Table 3).

The subgroup analysis based on ethnicity, the Asian population suggested that the IL-6 -572G/C polymorphism was significantly associated with increasing overall cancer risk for the over-dominant model [CG vs. CC + GG: OR = 1.13, 95% CI = 1.01–1.27, p-value = 0.0293]. The Caucasian and mixed ethnic group showed insignificant association of the IL-6 -572G/C polymorphism with the overall cancer risk (Table 3).

Source of heterogeneity. We found the significant heterogeneity of different studies in the analysis of IL-6 -572G/C polymorphism for overall cancer risk under the all genetic models

[C vs. G: Q = 89.96, df = 26, p-value = 0.0001, τ^2 = .0391, I^2 = 71.04; CC vs. GG: Q = 55.82, df = 26, p-value = 0.0006, τ^2 = .1033, I^2 = 53.41%; CC vs. CG + GG: Q = 49.23, df = 26, p-value = .0039, τ^2 = .0459, I^2 = 47.18%; CC + CG vs. GG: Q = 76.19, df = 26, p-value = .0001, τ^2 = .0618, I^2 = 65.88%; CG vs. CC + GG: Q = 54.40, df = 26, p-value = .0009, τ^2 = .0293, I^2 = 52.21%]. We also explored the sources of heterogeneity by the subgroup analysis based on cancer type and ethnic group. The results of our analysis suggested that the colon, lung, breast and liver cancers with the ethnic group of Asian and Caucasian were the main sources of heterogeneity of different studies (S1 Table).

IL-6 rs1800797 SNP. The finding of our analysis suggested that the IL-6 rs1800797 (-597G/A) polymorphism were not significantly associated with overall cancer risk under genetic models [A vs. G: OR = 0.99, 95% CI = 0.94–1.04, p-value = 0.7169; AA vs.GG: OR = 0.96, 95% CI = 0.85–1.08, p-value = 0.5152; AA + AG vs. GG: OR = 1.00, 95% CI = 0.93–1.08, p-value = 0.9289; AA vs. AG + GG: OR = 0.97, 95% CI = 0.87–1.07, p-value = 0.5064; AG vs. AA + GG: OR = 0.98, 95% CI = 0.91–1.05, p-value = 0.5025] (Table 4 and S1K–S1O Fig in S1 File).

The subgroup analysis based on cancer type showed that the blood, breast, colon, prostate and stomach cancers were not significantly associated with the IL-6 -597G/A polymorphism (Table 4). It also showed the significant role of IL-6 -597G/A polymorphism with the decreasing of cervical cancer risk under some genetic models [AA vs. GG: OR = 0.79, 95% CI = 0.63–0.98, p-value = 0.0390; AA vs. AG + GG: OR = 0.82, 95% CI = 0.68–1.00, p-value = 0.0474] and increasing of lung and skin cancer risks under the allelic model [A vs. G: OR = 1.19, 95% CI = 1.00–1.41, p-value = 0.0450] (Table 4).

The subgroup analysis based on ethnicity, the Asian, Caucasian and mixed population suggested that the IL-6 rs1800797 (-597G/A) polymorphism was not significantly associated with the overall cancer risk. Only for African population showed the significant association between this polymorphism and overall cancer risk by three genetic models [A vs. G: OR = 1.28, 95% CI = 0.98–1.67, p-value = 0.0191; AA + AG vs. GG: OR = 1.48, 95% CI = 1.08–2.03, p-value = 0.0135; AG vs. AA + GG: OR = 0.61, 95% CI = 0.44–0.84, p-value = 0.0010] (Table 4).

Source of heterogeneity. We found the insignificant heterogeneity of different studies in the analysis of IL-6 -597G/A polymorphism for overall cancer risk under the all genetic models. The subgroup analysis corresponding to cancer type and ethnic group were performed to observe the sources of heterogeneity. We found that only blood cancer was the main source of heterogeneity [A vs. G: Q = 6.56, df = 1, p-value = 0.0104, τ^2 = 0.7679, I^2 = 84.80%; AA + AG vs. GG: Q = 6.66, df = 1, p-value = 0.0099, τ^2 = 0.8110, I^2 = 85.00%] (S1 Table).

Publication bias

In this study the funnel plot was used to check the publication bias of IL-6 -174G/C and IL-6 -572G/C polymorphisms with the allelic model C versus G and IL-6 -597G/A polymorphism with the allelic model A versus G. According to the funnel plot, the distribution of ORs in terms of standard errors (SEs) was symmetric for each of three polymorphisms (-174G/C, -572G/C, -597G/A) and no publication bias was observed among the selected studies for this meta-analysis (Fig 2). Also, publication bias was checked through performing Begg's test and Egger's linear regression test. Results generated through both the Egger's and Begg's tests also suggested that there is no significant publication bias for the polymorphisms with the genetic models [C vs. G: p-value = 0.4778 (0.8030), and CC vs. GG: p-value = 0.5667 (0.7403) for the rs1800795 SNP; C vs. G: p-value = 0.3267 (0.6022) and CC vs. GG: p-value = 0.1664 (0.2347) for the rs1800796 SNP; A vs. G: p-value = 0.1175 (0.1768) and AA vs. GG: p-value = 0.6016
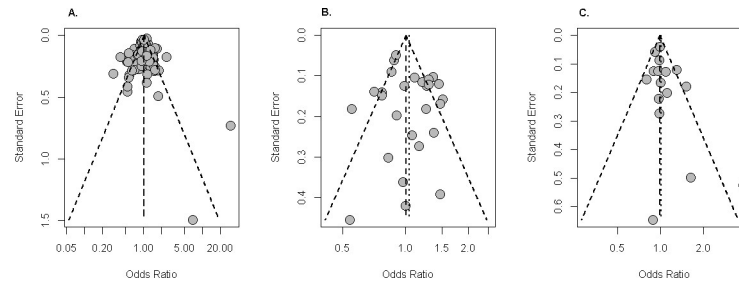
Fig 2. Funnel plot of the IL-6 polymorphisms to showing visual evidence of no publication bias. (A) -174G/C for C vs. G, (B) -572G/C for C vs. G and (C) -597G/A for A vs. G.

(0.7290) for the rs1800797 SNP] (see also S2A and S2B Table in S2 File). The p-value inside the first parenthesis was obtained by the Begg's test.

Sensitivity analysis

The sensitivity analysis was conducted to increase the reliability of this meta-analysis. First, the meta-analysis was conducted considering all studies. Then, the studies that did not pass the HWE test were removed and the meta-analysis was performed again using the reduced dataset of the respective genetic models. The analyzed results showed an insignificant change of association which suggested that the meta-analysis analysis data generated through this study is both stable and robust (see S2C–S2E Table in S2 File).

Discussion and conclusion

In this paper we discussed the way of statistical modeling for meta-data analyses in details incorporating the goodness of fit test for checking the model adequacy. Then multi-case meta-analysis was conducted to find out the association of cancer risk with each of three SNPs (rs1800795, rs1800796, rs1800797) of the IL-6 gene. A total of 118 individual studies which included 50053 case and 65204 control samples, based on different cancers and ethnic groups were included in this extensive meta- analysis. The results computed through this study suggested that the IL-6 rs1800795 polymorphism is insignificantly associated with the overall cancer risk, but significantly reduced the risk of liver cancer under four genetic models (CC vs. GG; CC vs. CG + GG; CC + CG vs. GG; CG vs. CC + GG; C vs. G), which is in line with the previously reported multi-case meta-analysis in [130]. Also, this SNP showed significant association with the increasing risk of cervical and prostate cancers, where the results of cervical cancer are supported by the previous single-case meta-analysis in [123], but not with the multi-case meta-analysis in [130]. The results calculated for IL-6 rs1800796 polymorphism also showed significant association with overall cancer risk for one genetic model. This polymorphism showed significant association with the prostate and stomach cancers under four genetic models (CC vs. GG; CC vs. CG + GG; CC + CG vs. GG; C vs. G), where these results are supported by the previous multi-case meta-analysis in [130] and single-case meta-analysis in [111], respectively. Moreover, the results generated through this meta-analysis indicated that the rs1800796 polymorphism is significantly associated with the increasing risk of lung cancer. The IL-6 rs1800797 polymorphism analyzed data showed insignificant association with cancer risk, which is supported by previous single-case meta-analysis in [125]. Also, the results of this study showed the significant association of IL-6 rs1800797 polymorphism with increasing risk of cervical cancer, which showed insignificant association in [130].

The ethnicity based subgroup analysis data showed significant association between the rs1800795 polymorphism and the overall cancer risk of both African under three genetic models and Asian populations under four genetic models(CC vs. GG; CC vs. CG + GG; CC + CG vs. GG; C vs. G). For rs1800796 polymorphisms results suggested the significant association with the cancer risk of Asian populations. Also, the rs1800797 polymorphism was significantly associated with African ethnic groups for the cancer risk. All the results of subgroup analysis by ethnicity were supported by the previous multi-case meta-analysis in [130]. Thus, we observed that our multi-case meta-analysis results received more support than the previous multi-case meta-analysis results in [130] from the other single-case meta-analysis results in [123–129].

It should be mentioned here again that all of the previous meta-analyses [123–130] did not check the model adequacy through the goodness of fit test. To estimate the combined effects, all of them used fixed effect (FE) or random effect (RE) models based on Cochran's homogeneity test though the sample sizes were small for some individual studies. For being small sample sizes, the individual effects may not be followed the normal distribution and the Cochran's test may be produced misleading results about the homogeneity of individual effects. However, in our case, we used the GoF test suggested by Chen et al. [133] to fix the lack of model fitting. We observed that some of our fitted models contradict with the fitted models based on Cochran's homogeneity test and significant changes in association between gene polymorphisms and cancer risks. In particularly, we observed the changes with some overall and subgroup cases of all polymorphisms (rs1800795, rs1800796, rs1800797). Due to the contradictory model selections, contradictory associations were also observed for three cases of rs1800795 polymorphism (liver cancer: CG vs. CC + GG; Asian ethnicity: CC + CG vs.GG and C vs. G) and single case of the rs1800796 polymorphism (stomach cancer: CC + CG vs. GG). However, there were some limitations on conducting this meta-analysis like for heterogeneity factors such as age, sex, family history, levels of IL-6 expression were not considered and that might affect the association. The literature reviewed and selected for this study was in English language only; therefore, the publication bias could not be completely avoided or some selection bias might occur. Also, the small sample size may affect the results for some types of cancer.

In conclusion, the results of this study indicated that the IL-6 gene is significantly associated with the overall cancer risk. Particularly, this gene showed significant association with 5 types of cancer risks (liver, prostate, cervical, stomach and lung) and insignificant association with 11 types of cancer risks (blood, breast, colon, neuroblastoma, oral, skin, thyroid, ovarian, pancreatic and renal cell carcinoma) by the sub-group analysis of cancer types. Comparative discussion showed that our current multi-case meta-analysis results received more support than any other individual previous meta-analysis results about the association between the IL-6 gene SNPs (rs1800795, rs1800796 and rs1800797) and different types of cancer risks. Therefore, the results generated through this detailed systematic meta-analysis based on larger sample size of the IL-6 gene polymorphisms provides more evidence for further exploring the IL-6 gene as a very potent prognostic biomarker for early detection of various types of cancers.

Supporting information

S1 Table. Heterogeneity analysis of IL-6 gene polymorphisms.
(DOCX)

S1 File. Forest plot of IL-6 gene polymorphisms (rs1800795, rs1800796, rs1800797) for five genetic models.
(DOCX)

S2 File. Egger's linear regression and Begg's test of IL-6 gene polymorphisms for checking the publication bias.
(DOCX)

S3 File. PRISMA checklist.
(DOC)

S1 Data. Full dataset of IL-6 gene rs1800795 polymorphism.
(XLSX)

S2 Data. Full dataset of IL-6 gene rs1800796 polymorphism.
(XLSX)

S3 Data. Full dataset of IL-6 gene rs1800797 polymorphism.
(XLSX)

Acknowledgments

Author Contributions

Conceptualization: Jesmin, Md. Nurul Haque Mollah.

Data curation: Md. Harun-Or-Roshid, Md. Borqat Ali, Jesmin.

Formal analysis: Md. Harun-Or-Roshid, Md. Borqat Ali, Jesmin, Md. Nurul Haque Mollah.

Funding acquisition: Md. Harun-Or-Roshid, Md. Nurul Haque Mollah.

Investigation: Md. Harun-Or-Roshid.

Methodology: Md. Harun-Or-Roshid, Md. Nurul Haque Mollah.

Project administration: Md. Nurul Haque Mollah.

Resources: Md. Harun-Or-Roshid, Jesmin.

Software: Md. Harun-Or-Roshid.

Supervision: Md. Nurul Haque Mollah.

Writing – original draft: Md. Harun-Or-Roshid.

Writing – review & editing: Jesmin, Md. Nurul Haque Mollah.

References

1. Cancer statistics 2018, WHO (https://www.who.int/news-room/fact-sheets/detail/cancer).

2. International Association of cancer Research (IACR) (http://gco.iarc.fr/).

3. Brocker C, Thompson D, Matsumoto A, Nebert DW, Vasiliou V (Oct 2010). "Evolutionary divergence and functions of the human interleukin (IL) gene family". Human Genomics. 5 (1): 30–55. https://doi.org/10.1186/1479-7364-5-1-30 PMC 3390169. PMID: 21106488.

4. Li J, Mo HY, Xiong G, Zhang L, He J, Huang ZF, et al. (October 2012). "Tumor microenvironment macrophage inhibitory factor directs the accumulation of interleukin-17-producing tumor-infiltrating lymphocytes and predicts favorable survival in nasopharyngeal carcinoma patients". The Journal of Biological Chemistry. 287 (42): 35484–95. https://doi.org/10.1074/jbc.M112.367532 PMID: 22893706

5. Xie G, Yao Q, Liu Y, Du S, Liu A, Guo Z, et al. (April 2012). "IL-6-induced epithelial-mesenchymal transition promotes the generation of breast cancer stem-like cells analogous to mammosphere cultures".

International Journal of Oncology. 40 (4): 1171–9. https://doi.org/10.3892/ijo.2011.1275 PMC 3584811. PMID: 22134360.

6. Miao JW, Liu LJ, Huang J (July 2014). "Interleukin-6-induced epithelial-mesenchymal transition through signal transducer and activator of transcription 3 in human cervical carcinoma". International Journal of Oncology. 45 (1): 165–76. https://doi.org/10.3892/ijo.2014.2422 PMID: 24806843.

7. Gasche JA, Hoffmann J, Boland CR, Goel A (September 2011). "Interleukin-6 promotes tumorigenesis by altering DNA methylation in oral cancer cells". International Journal of Cancer. 129 (5): 1053–63. https://doi.org/10.1002/ijc.25764 PMC 3110561. PMID: 21710491.

8. "Cancer Patients Typically Have Increased Interleukin-6 Levels". American Society of Clinical Oncology 2006 Annual Meeting, Abstracts 8632 and 8633. Medscape.com. 2006-06-26.

9. Vainer N, Dehlendorff C, Johansen JS. Systematic literature review of IL-6 as a biomarker or treatment target in patients with gastric, bile duct, pancreatic and colorectal cancer. Oncotarget. 2018 Jul 3; 9 (51):29820–29841. https://doi.org/10.18632/oncotarget.25661 eCollection 2018 Jul 3. Review. PMID: 30038723;PubMed Central PMCID: PMC6049875.

10. Kumari N, Dwarakanath BS, Das A, Bhatt AN. Role of interleukin-6 in cancer progression and therapeutic resistance. Tumour Biol. 2016 Sep; 37(9):11553–11572. Epub 2016 Jun 3. Review. https://doi.org/10.1007/s13277-016-5098-7 PMID: 27260630.

11. DargahiAbbasabad G, BananKhojasteh SM, EskandariNaji H, Zamani MR, Hajipour H, Serati-Nouri H. An Interleukin-6 Single Nucleotide Polymorphism and Susceptibility to Prostate Adenocarcinoma and Bone Metastasis in an Iranian Population. Asian Pac J Cancer Prev. 2018 Jun 25; 19(6):1717–1720. https://doi.org/10.22034/APJCP.2018.19.6.1717 PMID: 29938471; PubMed Central PMCID: PMC6103583.

12. Anam MT, Ishika A, Hossain MB, Jesmin; 2015. A meta-analysis of hypoxia inducible factor 1-alpha (HIF1A) gene polymorphisms: association with cancers. Biomark Res. 2015 Dec 29; 3:29. https://doi.org/10.1186/s40364-015-0054-z eCollection 2015. PMID: 26715988; PubMed Central PMCID: PMC4693423.

13. Oduor CI, Chelimo K, Ouma C, Mulama DH, Foley J, Vulule J, et al. Interleukin-6 and interleukin-10 gene promoter polymorphisms and risk of endemic Burkitt lymphoma. Am J Trop Med Hyg. 2014 Sep; 91(3):649–54. https://doi.org/10.4269/ajtmh.13-0616 PMID: 25071000

14. Gu X, Shen Y, Fu L, Zuo HY, Yasen H, He P, et al. Polymorphic variation of inflammation-related genes and risk of non-Hodgkin lymphoma for Uygur and Han Chinese in Xinjiang. Asian Pac J Cancer Prev. 2014; 15(21):9177–83. https://doi.org/10.7314/apjcp.2014.15.21.9177 PMID: 25422198

15. Talaat RM, Abdel-Aziz AM, El-Maadawy EA, Abdel-Bary N. CD38 and interleukin 6 gene polymorphism in egyptians with diffuse large B-cell lymphoma (DLBCL). Immunol Invest. 2015; 44(3):265–78. https://doi.org/10.3109/08820139.2014.989328 Epub 2015 Jan 7. PMID: 25564959.

16. Aladzsity I, Kovács M, Semsei A, Falus A, Szilágyi A, Karádi I, et al. Comparative analysis of IL6 promoter and receptor polymorphisms in myelodysplasia and multiple myeloma. Leuk Res. 2009 Nov; 33 (11):1570–3. https://doi.org/10.1016/j.leukres.2009.03.009 Epub 2009 Apr 29. PMID: 19406470.

17. Andrie E, Michos A, Kalampoki V, Pourtsidis A, Moschovi M, Polychronopoulou S, et al. Genetic variants in immunoregulatory genes and risk for childhood lymphomas. Eur J Haematol. 2009 Oct; 83 (4):334–42. https://doi.org/10.1111/j.1600-0609.2009.01288.x Epub 2009 Jun 5. PMID: 19508433.

18. Ennas MG, Moore PS, Zucca M, Angelucci E, Cabras MG, Melis M, et al. Interleukin-1B (IL1B) and interleukin-6 (IL6) gene polymorphisms are associated with risk of chronic lymphocytic leukaemia. HematolOncol. 2008 Jun; 26(2):98–103. https://doi.org/10.1002/hon.843 PMID: 18271063.

19. Duch CR, Figueiredo MS, Ribas C, Almeida MS, Colleoni GW, Bordin JO. Analysis of polymorphism at site -174 G/C of interleukin-6 promoter region in multiple myeloma. Braz J Med Biol Res. 2007 Feb; 40 (2):265–7. https://doi.org/10.1590/s0100-879x2007000200014 PMID: 17273664.

20. Nearman ZP, Wlodarski M, Jankowska AM, Howe E, Narvaez Y, Ball E, et al. Immunogenetic factors determining the evolution of T-cell large granular lymphocyte leukaemia and associated cytopenias. Br J Haematol. 2007 Jan; 136(2):237–48. Epub 2006 Nov 30. https://doi.org/10.1111/j.1365-2141.2006.06429.x PMID: 17156396.

21. Cozen W, Gebregziabher M, Conti DV, Van Den Berg DJ, Coetzee GA, Wang SS, et al. Interleukin-6-related genotypes, body mass index, and risk of multiple myeloma and plasmacytoma. Cancer Epidemiol Biomarkers Prev. 2006 Nov; 15(11):2285–91. https://doi.org/10.1158/1055-9965.EPI-06-0446 PMID: 17119059.

22. Lan Q, Zheng T, Rothman N, Zhang Y, Wang SS, Shen M, et al. Cytokine polymorphisms in the Th1/Th2 pathway and susceptibility to non-Hodgkin lymphoma. Blood. 2006 May 15; 107(10):4101–8. Epub 2006 Jan 31. https://doi.org/10.1182/blood-2005-10-4160 PMID: 16449530; PubMed Central PMCID: PMC1895277.

23. Cordano P, Lake A, Shield L, Taylor GM, Alexander FE, Taylor PR, et al. Effect of IL-6 promoter polymorphism on incidence and outcome in Hodgkin's lymphoma. Br J Haematol. 2005 Feb; 128(4):493–5. https://doi.org/10.1111/j.1365-2141.2004.05353.x PMID: 15686457.

24.   Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006 Jan; 7(1):27–38. https://doi.org/10.1016/S1470-2045(05)70434-4 PMID: 16389181.

25.   Mazur G, Bogunia-Kubik K, Wróbel T, Karabon L, Polak M, Kuliczkowski K, et al. IL-6 and IL-10 promoter gene polymorphisms do not associate with the susceptibility for multiple myeloma. ImmunolLett. 2005 Jan 31; 96(2):241–6. https://doi.org/10.1016/j.imlet.2004.08.015 PMID: 15585329.

26.   Abana CO, Bingham BS, Cho JH, Graves AJ, Koyama T, Pilarski RT, et al. IL-6 variant is associated with metastasis in breast cancer patients. PLoS One. 2017 Jul 21; 12(7):e0181725. https://doi.org/10.1371/journal.pone.0181725 PMID: 28732081.

27.   Slattery ML, Curtin K, Baumgartner R, Sweeney C, Byers T, Giuliano AR, et al. IL6, aspirin, nonsteroidal anti-inflammatory drugs, and breast cancer risk in women living in the southwestern United States. Cancer Epidemiol Biomarkers Prev. 2007 Apr; 16(4):747–55. https://doi.org/10.1158/1055-9965.EPI-06-0667 PMID: 17416766.

28.   Pooja S, Chaudhary P, Nayak LV, Rajender S, Saini KS, Deol D, et al. Polymorphic variations in IL-1β, IL-6 and IL-10 genes, their circulating serum levels and breast cancer risk in Indian women. Cytokine. 2012 Oct; 60(1):122–8. https://doi.org/10.1016/j.cyto.2012.06.241 Epub 2012 Jul 18. PMID: 22818022.

29.   Slattery ML, Herrick JS, Torres-Mejia G, John EM, Giuliano AR, Hines LM, et al. Genetic variants in interleukin genes are associated with breast cancer risk and survival in a genetically admixed population: the Breast Cancer Health Disparities Study. Carcinogenesis. 2014 Aug; 35(8):1750–9. https://doi.org/10.1093/carcin/bgu078 Epub 2014 Mar 26. PMID: 24670917; PubMed Central PMCID: PMC4123645.

30.   Chérel M, Campion L, Bézieau S, Campone M, Charrier J, Gaschet J, et al. Molecular screening of interleukin-6 gene promoter and influence of -174G/C polymorphism on breast cancer. Cytokine. 2009 Sep; 47(3):214–23. https://doi.org/10.1016/j.cyto.2009.06.011 Epub 2009 Jul 28. PMID: 19640729.

31.   DeMichele A, Gray R, Horn M, Chen J, Aplenc R, Vaughan WP, et al. Host genetic variants in the interleukin-6 promoter predict poor outcome in patients with estrogen receptor-positive, node-positive breast cancer. Cancer Res. 2009 May 15; 69(10):4184–91. https://doi.org/10.1158/0008-5472.CAN-08-2989 Epub 2009 May 12. PMID: 19435922; PubMed Central PMCID: PMC4304767.

32.   Gonullu G, Basturk B, Evrensel T, Oral B, Gozkaman A, Manavoglu O. Association of breast cancer and cytokine gene polymorphism in Turkish women. Saudi Med J. 2007 Nov; 28(11):1728–33. PMID: 17965799.

33.   Snoussi K, Strosberg AD, Bouaouina N, Ben Ahmed S, Chouchane L. Genetic variation in pro-inflammatory cytokines (interleukin-1beta, interleukin-1alpha and interleukin-6) associated with the aggressive forms, survival, and relapse prediction of breast carcinoma. Eur Cytokine Netw. 2005 Dec; 16 (4):253–60. PMID: 16464738.

34.   Smith KC, Bateman AC, Fussell HM, Howell WM. Cytokine gene polymorphisms and breast cancer susceptibility and prognosis. Eur J Immunogenet. 2004 Aug; 31(4):167–73. https://doi.org/10.1111/j.1365-2370.2004.00462.x PMID: 15265021.

35.   Zhu R.M., Lin W., Zhang W., Ren J.T., Su Y., He J.R., et al., 2017. Modification effects of genetic polymorphisms in FTO, IL-6, and HSPD1 on the associations of diabetes with breast cancer risk and survival. PLoS One 12, e0178850. https://doi.org/10.1371/journal.pone.0178850 PMID: 28591216

36.   Hefler LA, Grimm C, Lantzsch T, Lampe D, Leodolter S, Koelbl H, et al. Interleukin-1 and interleukin-6 gene polymorphisms and the risk of breast cancer in Caucasian women. Clin Cancer Res. 2005 Aug 15; 11(16):5718–21. https://doi.org/10.1158/1078-0432.CCR-05-0001 PMID: 16115908

37.   Sa-Nguanraksa D, Suntiparpluacha M, Kulprom A, Kummalue T, Chuangsuwanich T, Avirutnan P, et al. Association of Estrogen Receptor Alpha and Interleukin 6 Polymorphisms with Lymphovascular Invasion, Extranodal Extension, and Lower Disease-Free Survival in Thai Breast Cancer Patients. Asian Pac J Cancer Prev. 2016; 17(6):2935–40. PMID: 27356714

38.   Vogel U, Christensen J, Nexø BA, Wallin H, Friis S, Tjønneland A. Peroxisome proliferator-activated [corrected] receptor-gamma2 [corrected] Pro12Ala, interaction with alcohol intake and NSAID use, in relation to risk of breast cancer in a prospective study of Danes. Carcinogenesis. 2007 Feb; 28 (2):427–34. Epub 2006 Sep 6. Erratum in: Carcinogenesis. 2007 Sep;28(9):2062. https://doi.org/10.1093/carcin/bgl170 PMID: 16959787

39.   Balasubramanian SP, Azmy IA, Higham SE, Wilson AG, Cross SS, Cox A, et al. Interleukin gene polymorphisms and breast cancer: a case control study and systematic literature review. BMC Cancer. 2006 Jul 14; 6:188. https://doi.org/10.1186/1471-2407-6-188 PMID: 16842617; PubMed Central PMCID: PMC1553474.

40.   González-Zuloeta Ladd AM, Arias Vásquez A, Witteman J, Uitterlinden AG, Coebergh JW, Hofman A, et al. Interleukin 6 G-174 C polymorphism and breast cancer risk. Eur J Epidemiol. 2006; 21(5):373–6. Epub 2006 May 23. https://doi.org/10.1007/s10654-006-9005-1 PMID: 16721634.

41. Gangwar R, Mittal B, Mittal RD. Association of interleukin-6 -174G>C promoter polymorphism with risk of cervical cancer. Int J Biol Markers. 2009 Jan-Mar; 24(1):11–6. https://doi.org/10.5301/jbm.2009. 5370 PMID: 19404917.

42. Pu X, Gu Z, Wang X. Polymorphisms of the interleukin 6 gene and additional gene-gene interaction contribute to cervical cancer susceptibility in Eastern Chinese women. Arch Gynecol Obstet. 2016 Nov; 294(6):1305–1310. Epub 2016 Aug 18. https://doi.org/10.1007/s00404-016-4175-x PMID: 27535759.

43. Shi WJ, Liu H, Wu D, Tang ZH, Shen YC, Guo L. Stratification analysis and case-control study of relationships between interleukin-6 gene polymorphisms and cervical cancer risk in a Chinese population. Asian Pac J Cancer Prev. 2014; 15(17):7357–62. https://doi.org/10.7314/apjcp.2014.15.17.7357 PMID: 25227842.

44. Sabrina Z, Stayoussef M, Alsaleh BL, Gazouani E, Mezlini A, Ebrahim BH, et al. Relationships between Common and Novel Interleukin-6 Gene Polymorphisms and Risk of Cervical Cancer: a Case-Control Study. PatholOncol Res. 2017 Apr; 23(2):385–392. https://doi.org/10.1007/s12253-016-0127-9 Epub 2016 Oct 8. PMID: 27722983.

45. Nogueira de Souza NC, Brenna SM, Campos F, Syrjänen KJ, Baracat EC, Silva ID. Interleukin-6 polymorphisms and the risk of cervical cancer. Int J Gynecol Cancer. 2006 May-Jun; 16(3):1278–82. https://doi.org/10.1111/j.1525-1438.2006.00521.x PMID: 16803517.

46. Castro FA, Haimila K, Sareneva I, Schmitt M, Lorenzo J, Kunkel N, et al. Association of HLA-DRB1, interleukin-6 and cyclin D1 polymorphisms with cervical cancer in the Swedish population—a candidate gene approach. Int J Cancer. 2009 Oct 15; 125(8):1851–8. https://doi.org/10.1002/ijc.24529 PMID: 19585495.

47. Grimm C, Watrowski R, Baumühlner K, Natter C, Tong D, Wolf A, et al. Genetic variations of interleukin-1 and -6 genes and risk of cervical intraepithelial neoplasia. GynecolOncol. 2011 Jun 1; 121 (3):537–41. https://doi.org/10.1016/j.ygyno.2011.02.019 Epub 2011 Mar 3. PMID: 21376376.

48. Lima Junior SFd, Crovella SO. Avaliac ao dos polimorfismosnosgenes das citocinas IL 6 (RS 1800795) e TGF-b(RS 1982073) e RS1800471) e suasrelac o es com o grau de lesa o cervical empacientesinfectadospeloPapillomavĺrushumano. Recife: UniversidadeFaderal de Pernambuco, Dissertac a o De Mestrado; 2012.

49. Abulí A, Fernández-Rozadilla C, Alonso-Espinaco V, Muñoz J, Gonzalo V, Bessa X, et al. Gastrointestinal Oncology Group of the Spanish Gastroenterological Association. Case-control study for colorectal cancer genetic susceptibility in EPICOLON: previously identified variants and mucins. BMC Cancer. 2011 Aug 5; 11:339. https://doi.org/10.1186/1471-2407-11-339 PMID: 21819567.

50. Ognjanovic S, Yamamoto J, Saltzman B, Franke A, Ognjanovic M, Yokochi L, et al. Serum CRP and IL-6, genetic variants and risk of colorectal adenoma in a multiethnic population. Cancer Causes Control. 2010 Jul; 21(7):1131–8. https://doi.org/10.1007/s10552-010-9540-7 Epub 2010 Mar 24. PMID: 20333461.

51. Slattery ML, Wolff RK, Herrick J, Caan BJ, Samowitz W. Tumor markers and rectal cancer: support for an inflammation-related pathway. Int J Cancer. 2009 Oct 1; 125(7):1698–704. https://doi.org/10.1002/ijc.24467 PMID: 19452524; PubMed Central PMCID: PMC2768342.

52. Slattery ML, Wolff RK, Curtin K, Fitzpatrick F, Herrick J, Potter JD, et al. Colon tumor mutations and epigenetic changes associated with genetic polymorphism: insight into disease pathways. Mutat Res. 2009 Jan 15; 660(1–2):12–21. https://doi.org/10.1016/j.mrfmmm.2008.10.001 Epub 2008 Oct 15. PMID: 18992263; PubMed Central PMCID: PMC2907671.

53. Wilkening S, Tavelin B, Canzian F, Enquist K, Palmqvist R, Altieri A, et al. Interleukin promoter polymorphisms and prognosis in colorectal cancer. Carcinogenesis. 2008 Jun; 29(6):1202–6. https://doi.org/10.1093/carcin/bgn101 Epub 2008 Apr 30. PMID: 18448485.

54. Theodoropoulos G, Papaconstantinou I, Felekouras E, Nikiteas N, Karakitsos P, Panoussopoulos D, et al. Relation between common polymorphisms in genes related to inflammatory response and colorectal cancer. World J Gastroenterol. 2006 Aug 21; 12(31):5037–43. https://doi.org/10.3748/wjg.v12.i31.5037 PMID: 16937502; PubMed Central PMCID: PMC4087409.

55. Landi S, Moreno V, Gioia-Patricola L, Guino E, Navarro M, de Oca J, et al. Bellvitge Colorectal Cancer Study Group. Association of common polymorphisms in inflammatory genes interleukin (IL)6, IL8, tumor necrosis factor alpha, NFKB1, and peroxisome proliferator-activated receptor gamma with colorectal cancer. Cancer Res. 2003 Jul 1; 63(13):3560–6. PMID: 12839942.

56. Huang BZ, Tsilidis KK, Smith MW, Hoffman-Bolton J, Visvanathan K, Platz EA, et al. Polymorphisms in genes related to inflammation and obesity and colorectal adenoma risk. MolCarcinog. 2018 Oct; 57 (10):1278–1288. https://doi.org/10.1002/mc.22842 PMID: 29802748.

57. Cacev T, Jokić M, Loncar B, Krizanac S, Kapitanović S. Interleukin-6-174 G/C polymorphism is not associated with IL-6 expression and susceptibility to sporadic colon cancer. DNA Cell Biol. 2010 Apr; 29(4):177–82. https://doi.org/10.1089/dna.2009.0950 PMID: 20132036.

58. Tsilidis KK, Helzlsouer KJ, Smith MW, Grinberg V, Hoffman-Bolton J, Clipp SL, et al. Association of common polymorphisms in IL10, and in other genes related to inflammatory response and obesity with colorectal cancer. Cancer Causes Control. 2009 Nov; 20(9):1739–51. https://doi.org/10.1007/s10552-009-9427-7 PMID: 19760027; PubMed Central PMCID: PMC4119174.

59. Vasků A, Vokurka J, Bienertová-Vaškú J. Obesity-related genes variability in Czech patients with sporadic colorectal cancer: preliminary results. Int J Colorectal Dis. 2009 Mar; 24(3):289–94. https://doi.org/10.1007/s00384-008-0553-6 Epub 2008 Aug 15. PMID: 18704460.

60. Küry S, Buecher B, Robiou-du-Pont S, Scoul C, Colman H, Le Neel T, et al. Low-penetrance alleles predisposing to sporadic colorectal cancers: a French case-controlled genetic association study. BMC Cancer. 2008 Nov 7; 8:326. https://doi.org/10.1186/1471-2407-8-326 PMID: 18992148; PubMed Central PMCID: PMC2585099.

61. Gunter MJ, Canzian F, Landi S, Chanock SJ, Sinha R, Rothman N. Inflammation-related gene polymorphisms and colorectal adenoma. Cancer Epidemiol Biomarkers Prev. 2006 Jun; 15(6):1126–31. https://doi.org/10.1158/1055-9965.EPI-06-0042 PMID: 16775170.

62. Slattery ML, Wolff RK, Herrick JS, Caan BJ, Potter JD. IL6 genotypes and colon and rectal cancer. Cancer Causes Control. 2007 Dec; 18(10):1095–105. Epub 2007 Aug 13. https://doi.org/10.1007/s10552-007-9049-x PMID: 17694420; PubMed Central PMCID: PMC2442470.

63. Hawken SJ, Greenwood CM, Hudson TJ, Kustra R, McLaughlin J, Yang Q, et al. The utility and predictive value of combinations of low penetrance genes for screening and risk prediction of colorectal cancer. Hum Genet. 2010 Jul; 128(1):89–101. https://doi.org/10.1007/s00439-010-0828-1 Epub 2010 May 1. PMID: 20437058; PubMed Central PMCID: PMC2885303.

64. Wang Shuwei, Ding Zhongyang, Tang Jiandong, Li Gan. The association of interleukin-6 gene polymorphism and risk of colorectal cancer in Chinese patients. Transational Cancer research. Vol 7, No 2 (April 2018). https://doi.org/10.21037/tcr.2018.03.37 (10000.)

65. Giannitrapani L, Soresi M, Giacalone A, Campagna ME, Marasà M, Cervello M, et al. IL-6 -174G/C polymorphism and IL-6 serum levels in patients with liver cirrhosis and hepatocellular carcinoma. OMICS. 2011 Mar; 15(3):183–6. https://doi.org/10.1089/omi.2010.0093 Epub 2011 Feb 17. PMID: 21329460.

66. Falleti E, Fabris C, Toniutto P, Fontanini E, Cussigh A, Bitetto D, et al. Interleukin-6 polymorphisms and gender: relationship with the occurrence of hepatocellular carcinoma in patients with end-stage liver disease. Oncology. 2009; 77(5):304–13. https://doi.org/10.1159/000260057 Epub 2009 Nov 20. PMID: 19940521.

67. Upadhyay R, Jain M, Kumar S, Ghoshal UC, Mittal B. Association of interleukin-6 (-174G>C) promoter polymorphism with risk of squamous cell esophageal cancer and tumor location: an exploratory study. ClinImmunol. 2008 Aug; 128(2):199–204. https://doi.org/10.1016/j.clim.2008.03.519 Epub 2008 May 27. PMID: 18502691.

68. Tang S, Yuan Y, He Y, Pan D, Zhang Y, Liu Y, et al. Genetic polymorphism of interleukin-6 influences susceptibility to HBV-related hepatocellular carcinoma in a male Chinese Han population. Hum Immunol. 2014 Apr; 75(4):297–301. https://doi.org/10.1016/j.humimm.2014.02.006 PMID: 24530755.

69. Ognjanovic S, Yuan JM, Chaptman AK, Fan Y, Yu MC. Genetic polymorphisms in the cytokine genes and risk of hepatocellular carcinoma in low-risk non-Asians of USA. Carcinogenesis. 2009 May; 30 (5):758–62. https://doi.org/10.1093/carcin/bgn286 Epub 2009 Jan 6. PMID: 19126646; PubMed Central PMCID: PMC2675648.

70. Vishnoi M, Pandey SN, Choudhury G, Kumar A, Modi DR, Mittal B. Do TNFA -308 G/A and IL6–174 G/C gene polymorphisms modulate risk of gallbladder cancer in the north Indian population? Asian Pac J Cancer Prev. 2007 Oct-Dec; 8(4):567–72. PMID: 18260730.

71. Migita K, Miyazoe S, Maeda Y, Daikoku M, Abiru S, Ueki T, et al. Cytokine gene polymorphisms in Japanese patients with hepatitis B virus infection—association between TGF-beta1 polymorphisms and hepatocellular carcinoma. J Hepatol. 2005 Apr; 42(4):505–10. Epub 2004 Dec 10. https://doi.org/10.1016/j.jhep.2004.11.026 PMID: 15763337.

72. Chen J, Liu RY, Yang L, Zhao J, Zhao X, Lu D, et al. A two-SNP IL-6 promoter haplotype is associated with increased lung cancer risk. J Cancer Res ClinOncol. 2013 Feb; 139(2):231–42. https://doi.org/10.1007/s00432-012-1314-z Epub 2012 Oct 2. PMID: 23052692; PubMed Central PMCID: PMC4535449.

73. Bai L, Yu H, Wang H, Su H, Zhao J, Zhao Y. Genetic single-nucleotide polymorphisms of inflammation-related factors associated with risk of lung cancer. Med Oncol. 2013 Mar; 30(1):414. https://doi.org/10.1007/s12032-012-0414-6 Epub 2013 Jan 6. PMID: 23292870.

74. Liang J, Liu X, Bi Z, Yin B, Xiao J, Liu H, et al. Relationship between gene polymorphisms of two cytokine genes (TNF-α and IL-6) and occurring of lung cancers in the ethnic group Han of China. MolBiol Rep. 2013 Feb; 40(2):1541–6. https://doi.org/10.1007/s11033-012-2199-2 PMID: 23100065.

75. Seow A., Ng D.P., Choo S., Eng P., Poh W.T., Ming T., et al. 2006. Joint effect of asthma/atopy and an IL-6 gene polymorphism on lung cancer risk among lifetime non-smoking Chinese women. Carcinogenesis 27, 1240–1244. https://doi.org/10.1093/carcin/bgi309 PMID: 16344268.

76. Leng S, Thomas CL, Snider AM, Picchi MA, Chen W, Willis DG, et al. Radon Exposure, IL-6 Promoter Variants, and Lung Squamous Cell Carcinoma in Former Uranium Miners. Environ Health Perspect. 2016 Apr; 124(4):445–51. https://doi.org/10.1289/ehp.1409437 PMID: 26372664.

77. Kiyohara C, Horiuchi T, Takayama K, Nakanishi Y. Genetic polymorphisms involved in the inflammatory response and lung cancer risk: a case-control study in Japan. Cytokine. 2014 Jan; 65(1):88–94. https://doi.org/10.1016/j.cyto.2013.09.015 PMID: 24139238.

78. Colakogullari M, Ulukaya E, Yilmaztepe Oral A, Aymak F, Basturk B, Ursavas A, et al. The involvement of IL-10, IL-6, IFN-gamma, TNF-alpha and TGF-beta gene polymorphisms among Turkish lung cancer patients. Cell BiochemFunct. 2008 Apr; 26(3):283–90. https://doi.org/10.1002/cbf.1419 PMID: 17654453.

79. Campa D, Hung RJ, Mates D, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, et al. Lack of association between polymorphisms in inflammatory genes and lung cancer risk. Cancer Epidemiol Biomarkers Prev. 2005 Feb; 14(2):538–9. https://doi.org/10.1158/1055-9965.EPI-04-0513 PMID: 15734985.

80. Seifart C, Plagens A, Dempfle A, Clostermann U, Vogelmeier C, von Wichert P, et al. TNF-alpha, TNF-beta, IL-6, and IL-10 polymorphisms in patients with lung cancer. Dis Markers. 2005; 21(3):157–65. https://doi.org/10.1155/2005/707131 PMID: 16276011; PubMed Central PMCID: PMC3851050.

81. Campa D, Zienolddiny S, Maggini V, Skaug V, Haugen A, Canzian F. Association of a common polymorphism in the cyclooxygenase 2 gene with risk of non-small cell lung cancer. Carcinogenesis. 2004 Feb; 25(2):229–35. Epub 2003 Nov 6. Erratum in: Carcinogenesis. 2005 Jun;26(6):1157. https://doi.org/10.1093/carcin/bgh008 PMID: 14604894

82. Su M, Zhou B. Association of genetic polymorphisms in IL-6 and IL-1β gene with risk of lung cancer in female non-smokers. ZhongguoFei Ai ZaZhi. 2014 Aug 20; 17(8):612–7. https://doi.org/10.3779/j.issn.1009-3419.2014.08.06 PMID: 25130968.

83. Lim WY, Chen Y, Ali SM, Chuah KL, Eng P, Leong SS, et al. Polymorphisms in inflammatory pathway genes, host factors and lung cancer risk in Chinese female never-smokers. Carcinogenesis. 2011 Apr; 32(4):522–9. https://doi.org/10.1093/carcin/bgr006 PMID: 21252117.

84. Winchester DA, Till C, Goodman PJ, Tangen CM, Santella RM, Johnson-Pais TL, et al. Association between variants in genes involved in the immune response and prostate cancer risk in men randomized to the finasteride arm in the Prostate Cancer Prevention Trial. Prostate. 2017 Jun; 77(8):908–919. https://doi.org/10.1002/pros.23346 PMID: 28317149.

85. Mandal S, Abebe F, Chaudhary J. -174G/C polymorphism in the interleukin-6 promoter is differently associated with prostate cancer incidence depending on race. Genet Mol Res. 2014 Jan 10; 13 (1):139–51. https://doi.org/10.4238/2014.January.10.5 PMID: 24446297.

86. Taheri M, Noroozi R, Rakhshan A, Ghanbari M, Omrani MD, Ghafouri-Fard S. IL-6 Genomic Variants and Risk of Prostate Cancer. Urol J. 2018 Oct 21. https://doi.org/10.22037/uj.v0i0.4543 [Epub ahead of print] PMID: 30345492

87. Dossus L, Kaaks R, Canzian F, Albanes D, Berndt SI, Boeing H, et al. PTGS2 and IL6 genetic variation and risk of breast and prostate cancer: results from the Breast and Prostate Cancer Cohort Consortium (BPC3). Carcinogenesis. 2010 Mar; 31(3):455–61. https://doi.org/10.1093/carcin/bgp307 Epub 2009 Dec 4. PMID: 19965896; PubMed Central PMCID: PMC2832545.

88. Leibovici D, Grossman HB, Dinney CP, Millikan RE, Lerner S, Wang Y, et al. Polymorphisms in inflammation genes and bladder cancer: from initiation to recurrence, progression, and survival. J ClinOncol. 2005 Aug 20; 23(24):5746–56. https://doi.org/10.1200/JCO.2005.01.598 PMID: 16110031.

89. Chen CH, Gong M, Yi QT, Guo JH. Role of interleukin-6 gene polymorphisms in the development of prostate cancer. Genet Mol Res. 2015 Oct 27; 14(4):13370–4. https://doi.org/10.4238/2015.October.26.34 PMID: 26535651.

90. Huang WJ, Wu LJ, Min ZC, Xu LT, Guo CM, Chen ZP, et al. Interleukin-6 -572G/C polymorphism and prostate cancer susceptibility. Genet Mol Res. 2016 Sep 16; 15(3). https://doi.org/10.4238/gmr.15037563 PMID: 27706719.

91. Bao S., Yang W., Zhou S., Ye Z., 2008. Relationship between single nucleotide polymorphisms in -174G/C and -634C/G promoter region of interleukin-6 and prostate cancer. J. Huazhong Univ. Sci. Technolog. Med. Sci. 28, 693–696. https://doi.org/10.1007/s11596-008-0618-3 PMID: 19107369.

92. Moore SC, Leitzmann MF, Albanes D, Weinstein SJ, Snyder K, Virtamo J, et al. Adipokine genes and prostate cancer risk. Int J Cancer. 2009 Feb 15; 124(4):869–76. https://doi.org/10.1002/ijc.24043 PMID: 19035456; PubMed Central PMCID: PMC2879625.

93. Pierce BL, Biggs ML, DeCambre M, Reiner AP, Li C, Fitzpatrick A, et al. C-reactive protein, interleukin-6, and prostate cancer risk in men aged 65 years and older. Cancer Causes Control. 2009 Sep; 20

(7):1193–203. https://doi.org/10.1007/s10552-009-9320-4 Epub 2009 Mar 8. PMID: 19267250; PubMed Central PMCID: PMC2846958.

94. Wang MH, Helzlsouer KJ, Smith MW, Hoffman-Bolton JA, Clipp SL, Grinberg V, et al. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. Prostate. 2009 Jun 1; 69(8):874–85. https://doi.org/10.1002/pros.20933 PMID: 19267370; PubMed Central PMCID: PMC3016874.

95. Zabaleta J, Su LJ, Lin HY, Sierra RA, Hall MC, Sartor AO, et al. Cytokine genetic polymorphisms and prostate cancer aggressiveness. Carcinogenesis. 2009 Aug; 30(8):1358–62. https://doi.org/10.1093/carcin/bgp124 Epub 2009 May 27. PMID: 19474090; PubMed Central PMCID: PMC2718072.

96. Kesarwani P, Ahirwar DK, Mandhani A, Mittal RD. Association between -174 G/C promoter polymorphism of the interleukin-6 gene and progression of prostate cancer in North Indian population. DNA Cell Biol. 2008 Sep; 27(9):505–10. https://doi.org/10.1089/dna.2008.0742 PMID: 18694328.

97. Michaud DS, Daugherty SE, Berndt SI, Platz EA, Yeager M, Crawford ED, et al. Genetic polymorphisms of interleukin-1B (IL-1B), IL-6, IL-8, and IL-10 and risk of prostate cancer. Cancer Res. 2006 Apr 15; 66(8):4525–30. https://doi.org/10.1158/0008-5472.CAN-05-3987 PMID: 16618781.

98. Sun J, Hedelin M, Zheng SL, Adami HO, Bensen J, Augustsson-Bälter K, et al. Interleukin-6 sequence variants are not associated with prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2004 Oct; 13(10):1677–9. PMID: 15466986.

99. Gaur P, Mittal M, Mohanti B, Das S. Functional variants of IL4 and IL6 genes and risk of tobacco-related oral carcinoma in high-risk Asian Indians. Oral Dis. 2011 Oct; 17(7):720–6. https://doi.org/10.1111/j.1601-0825.2011.01831.x Epub 2011 Jul 20. PMID: 21771210.

100. Vairaktaris E., Yapijakis C., Serefoglou Z., Avgoustidis D., Critselis E., Spyridonidou S., et al. 2008. Gene expression polymorphisms of interleukins-1 beta, -4, -6, -8, -10, and tumor necrosis factors-alpha, -beta: regression analysis of their effect upon oral squamous cell carcinoma. J. Cancer Res. Clin. Oncol. 134, 821–832. https://doi.org/10.1007/s00432-008-0360-z PMID: 18273643

101. Vairaktaris E, Yiannopoulos A, Vylliotis A, Yapijakis C, Derka S, Vassiliou S, et al. Strong association of interleukin-6–174 G>C promoter polymorphism with increased risk of oral cancer. Int J Biol Markers. 2006 Oct-Dec; 21(4):246–50. https://doi.org/10.5301/jbm.2008.2814 PMID: 17177164.

102. Festa F, Kumar R, Sanyal S, Undén B, Nordfors L, Lindholm B, et al. Basal cell carcinoma and variants in genes coding for immune response, DNA repair, folate and iron metabolism. Mutat Res. 2005 Jul 1; 574(1–2):105–11. Epub 2005 Mar 26. https://doi.org/10.1016/j.mrfmmm.2005.01.026 PMID: 15914210.

103. Zhang Z, Liu W, Jia X, Gao Y, Hemminki K, Lindholm B. Use of pyrosequencing to detect clinically relevant polymorphisms of genes in basal cell carcinoma. ClinChimActa. 2004 Apr; 342(1–2):137–43. https://doi.org/10.1016/j.cccn.2003.12.010 PMID: 15026274.

104. Howell WM, Turner SJ, Theaker JM, Bateman AC. Cytokine gene single nucleotide polymorphisms and susceptibility to and prognosis in cutaneous malignant melanoma. Eur J Immunogenet. 2003 Dec; 30(6):409–14. https://doi.org/10.1111/j.1365-2370.2003.00425.x PMID: 14675394.

105. Zheng C, Huang DR, Bergenbrant S, Sundblad A, Osterborg A, Björkholm M, et al. Interleukin 6, tumour necrosis factor alpha, interleukin 1beta and interleukin 1 receptor antagonist promoter or coding gene polymorphisms in multiple myeloma. Br J Haematol. 2000 Apr; 109(1):39–45. https://doi.org/10.1046/j.1365-2141.2000.01963.x PMID: 10848780.

106. Attar M, Mansoori M, Shahbazi M. Interleukin-6 Genetic Variation and Susceptibility to Gastric Cancer in an Iranian Population. Asian Pac J Cancer Prev. 2017 Nov 26; 18(11):3025–3029. https://doi.org/10.22034/APJCP.2017.18.11.3025 PMID: 29172275; PubMed Central PMCID: PMC5773787.

107. Deans C, Rose-Zerilli M, Wigmore S, Ross J, Howell M, Jackson A, et al. Host cytokine genotype is related to adverse prognosis and systemic inflammation in gastro-oesophageal cancer. Ann SurgOncol. 2007 Feb; 14(2):329–39. Epub 2006 Nov 11. https://doi.org/10.1245/s10434-006-9122-9 PMID: 17103073.

108. Gatti LL, Burbano RR, Zambaldi-Tunes M, de-Lábio RW, de Assumpção PP, de Arruda Cardoso-Smith M, et al. Interleukin-6 polymorphisms, Helicobacter pylori infection in adult Brazilian patients with chronic gastritis and gastric adenocarcinoma. Arch Med Res. 2007 Jul; 38(5):551–5. https://doi.org/10.1016/j.arcmed.2006.12.011 PMID: 17560462.

109. Pohjanen VM, Koivurova OP, Mäkinen JM, Karhukorpi JM, Joensuu T, Koistinen PO, et al. Interleukin 6 gene polymorphism -174 is associated with the diffuse type gastric carcinoma. Genes Chromosomes Cancer. 2013 Oct; 52(10):976–82. https://doi.org/10.1002/gcc.22093 Epub 2013 Jul 26. PMID: 23893709.

110. Sampaio AM, Balseiro SC, Silva MR, Alarcão A, d'Aguiar MJ, Ferreira T, et al. Association Between IL-4 and IL-6 Expression Variants and Gastric Cancer Among Portuguese Population. GE Port J

Gastroenterol. 2015 Jul 4; 22(4):143–152. https://doi.org/10.1016/j.jpge.2015.04.001 eCollection 2015 Jul-Aug. PMID: 28868397; PubMed Central PMCID: PMC5580160.

111. Wang X, Yang F, Xu G, Zhong S. The roles of IL-6, IL-8 and IL-10 gene polymorphisms in gastric cancer: A meta-analysis. Cytokine. 2018 Nov; 111:230–236. https://doi.org/10.1016/j.cyto.2018.08.024 Epub 2018 Sep 6. PMID: 30195978.

112. Dos Santos MP, Sallas ML, Zapparoli D, Orcini WA, Chen E, Smith MAC, et al. Lack of Association between IL-6 Polymorphisms and Haplotypes with Gastric Cancer. J Cell Biochem. 2018 Dec 7. https://doi.org/10.1002/jcb.28220 [Epub ahead of print] PMID: 30525242.

113. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology. 2003 May; 124(5):1193–201. https://doi.org/10.1016/s0016-5085(03)00157-4 PMID: 12730860.

114. Hwang IR, Hsu PI, Peterson LE, Gutierrez O, Kim JG, Graham DY, et al. Interleukin-6 genetic polymorphisms are not related to Helicobacter pylori-associated gastroduodenal diseases. Helicobacter. 2003 Apr; 8(2):142–8. https://doi.org/10.1046/j.1523-5378.2003.00135.x PMID: 12662382.

115. Kamangar F, Abnet CC, Hutchinson AA, Newschaffer CJ, Helzlsouer K, Shugart YY, et al. Polymorphisms in inflammation-related genes and risk of gastric cancer (Finland). Cancer Causes Control. 2006 Feb; 17(1):117–25. https://doi.org/10.1007/s10552-005-0439-7 PMID: 16411061.

116. Çil E, Kumral A, Kanmaz-Özer M, Vural P, Doğru-Abbasoğlu S, Altuntaş Y, et al. Interleukin-10-1082 gene polymorphism is associated with papillary thyroid cancer. MolBiol Rep. 2014 May; 41(5):3091–7. https://doi.org/10.1007/s11033-014-3169-7 Epub 2014 Jan 28. PMID: 24464184.

117. Ozgen AG, Karadeniz M, Erdogan M, Berdeli A, Saygili F, Yilmaz C. The (-174) G/C polymorphism in the interleukin-6 gene is associated with risk of papillary thyroid carcinoma in Turkish patients. J Endocrinol Invest. 2009 Jun; 32(6):491–4. https://doi.org/10.1007/BF03346494 Epub 2009 Apr 15. PMID: 19494710.

118. Bushley AW, Ferrell R, McDuffie K, Terada KY, Carney ME, Thompson PJ, et al. Polymorphisms of interleukin (IL)-1alpha, IL-1beta, IL-6, IL-10, and IL-18 and the risk of ovarian cancer. GynecolOncol. 2004 Dec; 95(3):672–9. https://doi.org/10.1016/j.ygyno.2004.08.024 PMID: 15581980.

119. Talar-Wojnarowska R, Gasiorowska A, Smolarz B, Romanowicz-Makowska H, Kulig A, Malecka-Panas E. Clinical significance of interleukin-6 (IL-6) gene polymorphism and IL-6 serum level in pancreatic adenocarcinoma and chronic pancreatitis. Dig Dis Sci. 2009 Mar; 54(3):683–9. https://doi.org/10.1007/s10620-008-0390-z Epub 2008 Jul 26. PMID: 18661238.

120. Totaro F, Cimmino F, Pignataro P, Acierno G, De Mariano M, Longo L, et al. Impact of interleukin-6–174 G>C gene promoter polymorphism on neuroblastoma. PLoS One. 2013 Oct 21; 8(10):e76810. https://doi.org/10.1371/journal.pone.0076810 eCollection 2013. PMID: 24204677; PubMed Central PMCID: PMC3804531.

121. Zhao Q, Jin M, Zhang DW, Zhao W, Wang XS, Yue ZX, et al. Serum Interleukin-6 Level and the rs1800795 Polymorphism in its Gene Associated with Neuroblastoma Risk in Chinese Children. Chin Med J (Engl). 2018 May 5; 131(9):1075–1078. https://doi.org/10.4103/0366-6999.230719 PMID: 29692379; PubMed Central PMCID: PMC5937316.

122. Baştürk B, Yavaşçaoğlu I, Vuruşkan H, Göral G, Oktay B, Oral HB. Cytokine gene polymorphisms as potential risk and protective factors in renal cell carcinoma. Cytokine. 2005 Apr 7; 30(1):41–5. https://doi.org/10.1016/j.cyto.2004.10.016 PMID: 15784411.

123. Liu H., Lyu D., Zhang Y., Sheng L., Tang N., 2017. Association between the IL-6 rs1800795 polymorphism and the risk of cervical cancer: a meta-analysis of 1210 cases and 1525 controls. Technol. Cancer Res. Treat. 16, 662–667. https://doi.org/10.1177/1533034616672806 PMID: 27777338

124. Yu Y, Wang W, Zhai S, Dang S, Sun M. IL6 gene polymorphisms and susceptibility to colorectal cancer: a meta-analysis and review. MolBiol Rep. 2012 Aug; 39(8):8457–63. https://doi.org/10.1007/s11033-012-1699-4 Epub 2012 Jun 20. Review. PMID: 22714907.

125. Qian D., Yan S., Pan X., 2017. Association of IL-6–597 G/A polymorphism with cancer risk: evidence from a meta-analysis. Crit. Rev. Eukaryot. Gene Expr. 27, 211–217. https://doi.org/10.1615/CritRevEukaryotGeneExpr.2017019372 PMID: 29199606

126. Wang W, Chen J, Zhao F, Zhang B, Yu H. Lack of association between a functional polymorphism (rs1800796) in the interleukin-6 gene promoter and lung cancer. DiagnPathol. 2014 Jul 1; 9:134. https://doi.org/10.1186/1746-1596-9-134 PMID: 24984610; PubMed Central PMCID: PMC4100037.

127. Zhou W, Zhang S, Hu Y, Na J, Wang N, Ma X, et al. Meta-analysis of the associations between TNF-α or IL-6 gene polymorphisms and susceptibility to lung cancer. Eur J Med Res. 2015 Mar 21; 20:28. https://doi.org/10.1186/s40001-015-0113-9 Retraction in: Zhou W, Zhang S, Hu Y, Na J, Wang N, Ma X, Yuan L, Meng F. Eur J Med Res. 2016;21(1):31. PubMed Central PMCID: PMC4438440. PMID: 25889486

128. Yin YW, Sun QQ, Hu AM, Wang Q, Liu HL, Hou ZZ, et al. Associations between interleukin-6 gene -174G/C and -572G/C polymorphisms and the risk of gastric cancer: a meta-analysis. J SurgOncol. 2012 Dec; 106(8):987–93. https://doi.org/10.1002/jso.23199 Epub 2012 Jun 18. PMID: 22711691.

129. Wang J, He W, Liu J, Nong L, Wei Y, Yang F. Association of IL-6 polymorphisms with gastric cancer risk: evidences from a meta-analysis. Cytokine. 2012 Jul; 59(1):176–83. https://doi.org/10.1016/j.cyto.2012.03.032 Epub 2012 May 1. PMID: 22554382.

130. Zhou L, Zheng Y, Tian T, Liu K, Wang M, Lin S, et al. Associations of interleukin-6 gene polymorphisms with cancer risk: Evidence based on 49,408 cancer cases and 61,790 controls. Gene. 2018 Sep 5; 670:136–147. https://doi.org/10.1016/j.gene.2018.05.104 Epub 2018 May 26. PMID: 29842912.

131. Shein-Chung Chow (book). Applied Meta-Analysis with R. International Standard Book Number-13: 978-1-4665-0600-8 (eBook—PDF).

132. Mathias Harrer, PimCuijpers, Toshi A. Furukawa, David D. Ebert. (ebook). Doing Meta-Analysis in R. https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/

133. Chen Z, Zhang G, Li J. Goodness-of-fit test for meta-analysis. Sci Rep. 2015 Nov 23; 5:16983. https://doi.org/10.1038/srep16983 PMID: 26592212; PMCID: PMC4655309.

134. Anderson T. W. & Darling D. A. A test of goodness of fit. J. Amer. Statist. Assoc. 49, 765–769 (1954).

135. D'Agostino, R. B. Goodness-of-fit-techniques. (CRC press, 1986).

136. Cramér H. On the composition of elementary errors: First paper: Mathematical deductions. ScandActuar J 1928, 13–74 (1928).

137. Von Mises, R. Wahrscheinlichkeit, statistik und wahrheit. (Berlin, 1928).

138. Shapiro S. S. &Wilk M. B. An analysis of variance test for normality (complete samples). Biometrika 52, 591–611 (1965).

139. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–634. [PubMed: 9310563] https://doi.org/10.1136/bmj.315.7109.629 PMID: 9310563

140. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994 Dec; 50(4):1088–101. PMID: 7786990.