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Meta-Analysis of Interleukin Polymorphisms and NSAID Usage Indicates Correlations to the Risk of Developing Cancer

Nagao M, Sato Y* and Yamauchi A

Department of Pharmaceutical Information Science, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan

Abstract

Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) is correlated to reduced risk of developing cancer through reduction of inflammation, which is an important risk factor for cancer. Several studies have investigated the possible association between polymorphisms in the gene encoding inflammatory cytokines and use of NSAIDs with cancer risk; however, these studies have obtained mixed results. Therefore, we performed a meta-analysis to evaluate the association between genetic polymorphisms of *Interleukin* (*IL*) *1B*, *IL6*, *IL8*, and *IL10*, and NSAID usage with respect to cancer risk. We conducted a comprehensive search in PubMed through May 2013. Odds Ratios (ORs) with corresponding 95% Confidence Intervals (CIs) were calculated using the fixed-effect or the random-effect model. Comprehensive search of databases revealed eight studies fulfilling the inclusion criteria. For *IL6* rs1800795, the minor allele carriers demonstrated a significantly decreased cancer risk compared to those homozygous for the major allele (GG) among NSAID users (OR=0.80, 95% CI=0.68-0.95). For *IL8* rs4073, NSAID users had a significantly decreased cancer risk compared to the non-NSAID users (OR=0.71, 95% CI=0.53-0.96) among those homozygous for the major allele (TT). For the *IL1B* rs1143627 and *IL10* rs1800872 SNPs, we did not observe any significant difference. We identified a correlation between the polymorphisms *IL6* rs1800795 and *IL8* rs4073 and NSAID usage in decreased cancer risk.

Keywords: Meta-analysis; Cancer; NSAIDs; Polymorphism; Interleukin

Abbreviations: IL: Interleukin; NF-KB: Nuclear Factor-Kappa-B; INOS: Inducible Nitric Oxide Synthase; COX: Cyclooxygenase; NSAID: Non-Steroidal Anti-Inflammatory Drugs; PG: Prostaglandin; OR: Odds Ratio; CI: Confidence Interval

Introduction

Based on clinical and epidemiological studies, chronic inflammation has been shown to be a predisposing factor to several types of cancers, including colon, prostate, and pancreatic cancers, and promotes the proliferation of malignant cells [1,2]. Cancer is caused by several mechanisms, including genetic and epigenetic alterations of genes encoding pro-inflammatory cytokines [3,4]. Further to this, polymorphisms of the genes encoding the inflammatory cytokine are related to cancer susceptibility [1]. Cytokines are multifaceted, endogenous, inflammatory, and immune regulatory mediators, demonstrating both positive and negative regulatory activities on various target cells [5]. Interleukin (IL) *1B, IL6, IL8,* etc., are chiefly known as pro-inflammatory cytokines [6]. *IL1B* is an important pro-inflammatory cytokine that can regulate the expression of some molecules related to inflammation [7]. The rs1143627 (-31T>C) SNP is located in the promoter region of the *IL1B* gene. The C variant allele of the rs1143627 locus results in a higher transcription of *IL1B* than of the T allele [8]. IL6 is an important multifaceted inflammatory cytokine mediating immune responses, cell survival, proliferation, and apoptosis. The rs1800795 (-174G>C) SNP is located in the promoter region of the *IL6* gene. Therefore, this SNP affects gene transcription, so that the G allele results in a higher transcription level than the C allele [9]. High expression of *IL6* is associated with tumor development during the initiation, promotion, malignant conversion, invasion, and metastasis stages [1]. *IL8* is known for its leukocyte chemotactic properties and its tumorigenic and proangiogenic activities, and is related to neovascularization-dependent tumor growth, tumor invasion and metastasis [10]. Therefore, it is considered that high expression levels of *IL8* constitutes a risk factor to the development and progression of tumors [10,11]. The rs4073 (-251T>A) SNP is located in the promoter region of the *IL8* gene and the A allele of rs4073 is associated with increased *IL8* production *in vitro* [12]. *IL10*, known as the anti-inflammatory cytokine is a multifunctional cytokine participating in the development and progression of various malignant tumors. The rs1800872 (-592C>A) SNP is located in the promoter region of the *IL10* gene [13]. A haplotype with two other SNPs, rs1800896 (-1082G>A) and rs1800871 (-819C>T) is associated with IL10 production. [14]. *IL10* down-regulates the expression of macrophage costimulatory molecules [15,16]. *IL10* has anti-inflammatory and immunosuppressive activities, and aids the tumors escape immune surveillance. Therefore, it has been suggested that *IL10* has a complex influence on tumor development. *IL10* has anti-tumor activity, yet promotes tumor genesis [16]. Therefore, it is suggested that *IL1B, IL6, IL8*, and *IL10* may be associated with the risk of development of cancer.

These inflammatory cytokines are regulated by nuclear factor kappa-B (NF-κB), which is a key molecule of inflammation-mediated carcinogenesis [4]. NF-κB is emerging as one of the targets in the chemoprevention of diseases involving reactive species overload, because many of the genes targeted by NF-κB are related to the inflammatory cascade (inducible nitric oxide synthase [iNOS], cyclooxygenase [COX]-2, cytokines, and matrix metalloproteinase), anti-apoptotic events, and cell cycle events [17].

***Corresponding author:** Sato Y, Department of Pharmaceutical Information Science, Institute of Health Biosciences, The University of Tokushima Graduate School, 1-78-1 Sho-machi, Tokushima City 770-8505, Japan, Tel: +81-88-633-7253; Fax: +81-88-633-7253; E-mail: youichi.sato@tokushima-u.ac.jp

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Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) reduce inflammation through a decrease in the synthesis of Prostaglandin (PG) as well as the inhibition of NF-κB [18]. NSAIDs are one of the most widely used medicines for the prevention and/or treatment of various diseases. Several epidemiological studies have investigated whether NSAID usage is correlated to a reduced risk of cancer; however, this remains controversial. Information regarding whether polymorphisms in inflammatory cytokine genes influence cancer risk is important with respect to using NSAIDs for the prevention and treatment of cancer.

To date, several studies have investigated whether polymorphisms in the genes encoding the inflammatory cytokine are associated with cancer risk in conjunction with NSAID usage; however, they have obtained mixed results. Therefore, we performed a meta-analysis to determine the association between polymorphisms in the gene encoding IL and the risk of developing cancer in conjunction with NSAID usage.

Materials and Methods

Literature search

We searched for publications in MEDLINE, Science Direct, and the Cochrane Library by using the keywords and strategy terms "interleukin" or "IL", "NSAID", "genotype" or "polymorphism", and "cancer" or "carcinoma" (last search was performed in May 2013). Non-controlled trials were excluded. Randomized controlled trials with three or more groups were retained if at least two groups addressed an eligible comparison.

Inclusion criteria

Studies fulfilling the following criteria were chosen: (1) full-text articles written in English; (2) controlled trials comparing IL polymorphisms and risk of cancer, including NSAID usage status; (3) sufficient published data for estimating odds ratio (OR) or relative risk with 95% confidence interval (CI); and (4) the number of cases, controls, NSAID users, and non-NSAID-users correlated to *IL* genotypes was clarified. The following details were not considered for selection: (1) blinded nature of the trial, (2) type of cancer, (3) type of NSAID, and (4) NSAID dosage method.

Data extraction

Data extraction was performed independently by two authors (Nagao and Sato) by using a standard protocol according to the inclusion criteria. The following data were extracted: the name of the first author, year of publication, country of research institution, type of cancer, study design, age, gender, and the number of cases and controls with NSAID users or non-users by genotype.

Statistical analysis

All statistical analyses were performed using the rmeta package for R, version 2.14.2 (The R Foundation for Statistical Computing, Tsukuba, Japan; http://www.R-project.org). Two-sided probability (*P*) values of <0.05 were considered statistically significant. ORs with 95% CIs were calculated to assess the strength of the following associations: (1) between IL genotype with NSAID users and the risk of developing cancer, (2) between NSAID users homozygous for the major allele and the risk of developing cancer, (3) between *IL* genotype with non-NSAID users and the risk of developing cancer, and (4) between NSAID users with the minor allele and the risk of developing cancer. Hardy-Weinberg Equilibrium (HWE) was assessed by using the Pearson's χ^2 test for genotypes in the control group for each study.

All meta-analyses were appraised for inter-study heterogeneity by using χ^2-based Q statistics for statistical significance of heterogeneity. If there was no heterogeneity based on a Q-test P value of >0.05, a fixed-effect model using the Mantel-Haenszel (M-H) method was used. Otherwise, the random-effects model using the DerSimonian and Laird method was employed. Sensitivity analyses and evaluations of possible publication bias were not performed because of the limited distraction sample sizes in the publications included in the meta-analysis.

Results

Characteristics of eligible studies

Figure 1 shows a flow diagram of the selection process of relevant studies. Sixteen relevant reports were initially identified. Eight of these were initially excluded because they did not perform the analysis for recurring SNPs. Two more studies were excluded because they did not provide the number of subjects used for the calculation of OR. Therefore, only six of the 16 studies were included in the meta-analysis. The baseline characteristics and methodological quality of all included studies are summarized in Table 1 and Supplementary Table 1. The reported studies in each article included the following polymorphisms: *IL6* rs1800795 (n=5), *IL8* rs4073 (n=4), *IL1B* rs1143627 (n=4), and *IL10* rs1800872 (n=4) [19-24].

The genotypes of four SNPs were in HWE in control group of each studies, except for one study on *IL6* rs1800795 (Table 1) (P=0.015) [20].

IL6 rs1800795 polymorphism

Five studies reported an association between the *IL6* rs1800795 polymorphism and the risk of developing cancer in conjunction with NSAID usage. In our meta-analysis, there were no significant differences among those homozygous for the major allele (GG) (Figure 2A; OR=0.87, 95% CI=0.73-1.04, $P_{heterogeneity}$=0.73), or the minor allele carriers (GC+CC) (Figure 2B; OR=0.80, 95% CI=0.62-1.05, $P_{heterogeneity}$=0.003). The minor allele carriers demonstrated a significantly decreased cancer risk compared to those homozygous for the major allele among NSAID users (Figure 2C; OR=0.80, 95% CI=0.68-0.95, $P_{heterogeneity}$=0.33); however, we did not note any significant difference among non-NSAID users (Figure 2D; OR=1.04, 95% CI=0.91-1.18, $P_{heterogeneity}$=0.46).

IL8 rs4073 polymorphism

Four studies reported an association between the *IL8* rs4073 polymorphism and the risk of developing cancer in conjunction with NSAID usage. According to our meta-analysis, use of NSAIDs was significantly correlated with decreased cancer risk among subjects homozygous for the major allele (TT) (Figure 3A; OR=0.71, 95% CI=0.53-0.96, $P_{heterogeneity}$=0.75); however, there were no significant differences among the minor allele carriers (TA+AA) (Figure 3B;

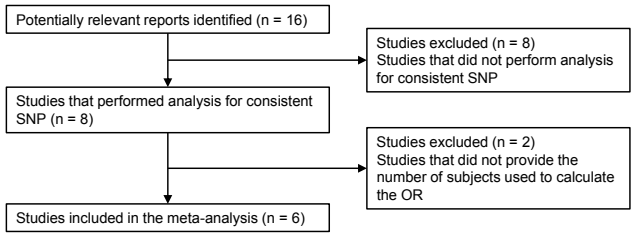

Figure 1: Flow diagram of the literature search and study selection.

Study	Country	Outcome	Study design	Age	Gender	case		control		Genotyping method	Genotype distribution			P value for HWE
					Males/ Females	No	Yes	No	Yes					
IL-6 rs1800795						GC+CC/ GG	GC+CC/ GG	GC+CC/ GG	GC+CC/ GG		GG	CG	CC	
Vogel et al. [19]	Denmark	LC	Nested case-cohort	50-64	631/516	203/73	92/31	368/140	168/61	TaqMan PCR	204	361	179	0.44
Slattery et al. [20]	USA	CC	Case-control	30-79	Without details	664/417	278/214	715/442	529/286	two-step PCR process and mass spectrometry	728	897	347	0.015
Vogel et al. [21]	Denmark	BCC	Nested case-cohort	50-64	293/326	175/48	62/16	153/64	71/24	TaqMan PCR	89	157	69	0.99
Vogel et al. [22]	Denmark	CRC	Nested case-cohort	50-64	618/490	178/62	83/27	383/129	181/53	TaqMan PCR	204	364	185	0.37
Vogel et al. [23]	Denmark	BC	Nested case-cohort	50-64	0/712 (females only)	112/32	147/53	112/34	172/50	TaqMan PCR	98	177	86	0.73
IL-8 rs4073						TA+AA/TT	TA+AA/ TT	TA+AA/TT	TA+AA/ TT		TT	AT	AA	
Vogel et al. [19]	Denmark	LC	Nested case-cohort	50-64	631/516	210/66	100/23	406/102	170/59	TaqMan PCR	161	364	219	0.67
Vogel et al. [21]	Denmark	BCC	Nested case-cohort	50-64	293/326	168/55	63/15	163/54	73/22	TaqMan PCR	76	170	69	0.16
Vogel et al. [22]	Denmark	CRC	Nested case-cohort	50-64	618/490	180/60	87/23	411/101	175/59	TaqMan PCR	160	367	226	0.63
Vogel et al. [23]	Denmark	BC	Nested case-cohort	50-64	0/712 (females only)	114/42	131/69	93/41	148/74	TaqMan PCR	78	167	78	0.54
IL-1B rs1143627						TC+CC/ TT	TC+CC/ TT	TC+CC/ TT	TC+CC/ TT		TT	CT	CC	
Vogel et al. [19]	Denmark	LC	Nested case-cohort	50-64	631/516	172/104	71/52	268/240	125/104	TaqMan PCR	350	310	84	0.22
Vogel et al. [21]	Denmark	BCC	Nested case-cohort	50-64	293/326	121/102	42/36	120/97	59/36	TaqMan PCR	135	142	38	0.94
Vogel et al. [22]	Denmark	CRC	Nested case-cohort	50-64	618/490	131/109	67/43	269/243	130/104	TaqMan PCR	353	312	88	0.14
Macarthur et al. [24]	UK	CRC	Cohort	Without details	360/312	121/71	24/27	188/118	44/41	TaqMan PCR	165	179	59	0.36
IL-10 rs1800872						CA+AA/ CC	CA+AA/ CC	CA+AA/CC	CA+AA/ CC		CC	AC	AA	
Vogel et al. [19]	Denmark	LC	Nested case-cohort	50-64	631/516	117/159	43/80	196/312	94/135	TaqMan PCR	452	250	42	0.34
Vogel et al. [21]	Denmark	BCC	Nested case-cohort	50-64	293/326	88/135	31/47	90/127	30/65	TaqMan PCR	194	106	15	0.92
Vogel et al. [22]	Denmark	CRC	Nested case-cohort	50-64	618/490	85/155	42/68	198/314	98/136	TaqMan PCR	455	256	42	0.45
Macarthur et al. [24]	UK	CRC	Case-control	Without details	360/312	84/108	16/35	114/192	35/50	TaqMan PCR	248	133	22	0.46

Abbreviations: No: non-NSAID users; Yes: NSAID users; LC: Lung Cancer; CC: Colon Cancer; BCC: Basal Cell Carcinoma; CRC: Colorectal Cancer; BC: Breast Cancer; CRA: Colorectal Adenoma

Table 1: Summary of the studies included in the meta-analysis.

OR=0.98, 95% CI=0.82-1.15, $P_{heterogeneity}$=0.16). No significant difference was noted between *IL8* rs4073 polymorphism (TT vs. TA+AA) and the risk of developing cancer, among non-NSAID users (Figure 3C; OR=0.88, 95% CI=0.72-1.07, $P_{heterogeneity}$=0.39) or NSAID users (Figure 3D; OR=1.17, 95% CI=0.91-1.52, $P_{heterogeneity}$=0.57).

IL1B rs1143627 polymorphism

Four studies reported an association between the *IL1B* rs1143627 polymorphism and the risk of developing cancer in conjunction with NSAID usage. No significant differences were noted between NSAID usage and the risk of developing cancer among those homozygous for the major allele (TT) (Figure 4A; OR=1.03, 95% CI=0.81-1.30, $P_{heterogeneity}$=0.87), or the minor allele carriers (TC+CC) (Figure 4B; OR=0.89, 95% CI=0.73-1.09, $P_{heterogeneity}$=0.60), and between the *IL1B* rs1143627 polymorphism (TT vs. TC+CC) and the risk of developing cancer among non-NSAID users (Figure 4C; OR=1.16, 95% CI=0.99-1.37, $P_{heterogeneity}$=0.27) or NSAID users (Figure 4D; OR=1.03, 95% CI=0.79-1.33, $P_{heterogeneity}$=0.45).

IL10 rs1800872 polymorphism

Four studies reported an association between the *IL10* rs1800872 polymorphism and the risk of developing cancer in conjunction with NSAID usage. We found no significant differences between NSAID usage and the risk of developing cancer among those homozygous

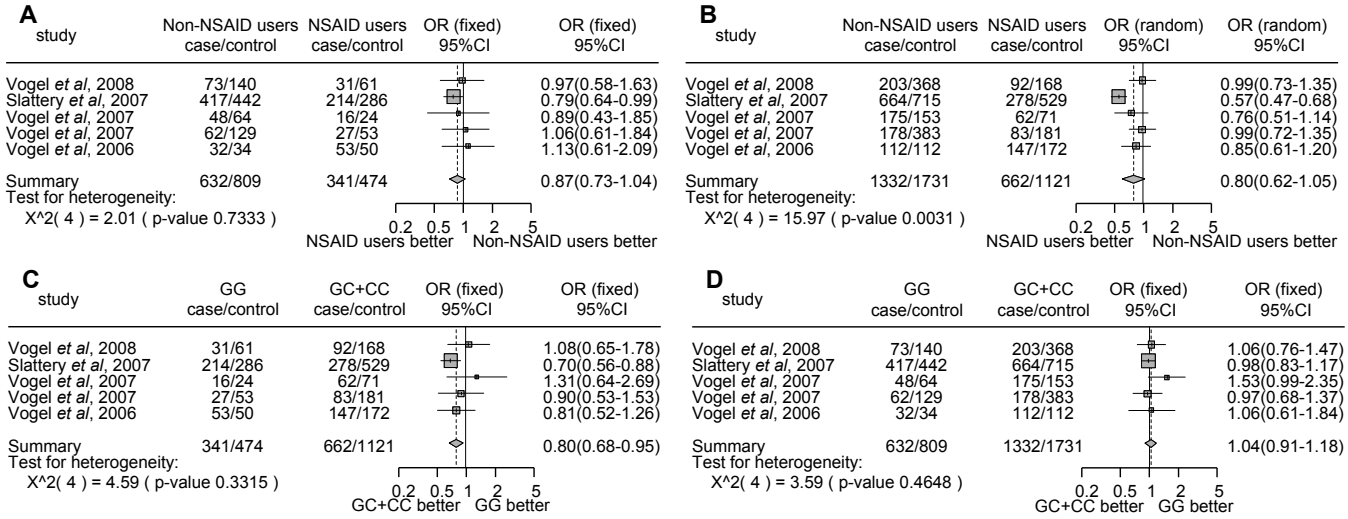

Figure 2: Forest plot of the association between the *IL6* rs1800795 polymorphism and NSAID usage on cancer risk. The difference in the risk of development of cancer between NSAID users and non-NSAID users homozygous for the major allele (A), between NSAID users and non-NSAID users from individuals who are minor allele carriers (B), between non-NSAID users homozygous for the major allele and the minor allele carriers (C), and between NSAID users homozygous for the major allele and the minor allele carriers (D). Squares represent study-specific ORs; horizontal lines represent 95% CIs; the size of the square reflects study-specific statistical weight (inverse of the variance); diamonds represent summary OR and 95% CI.

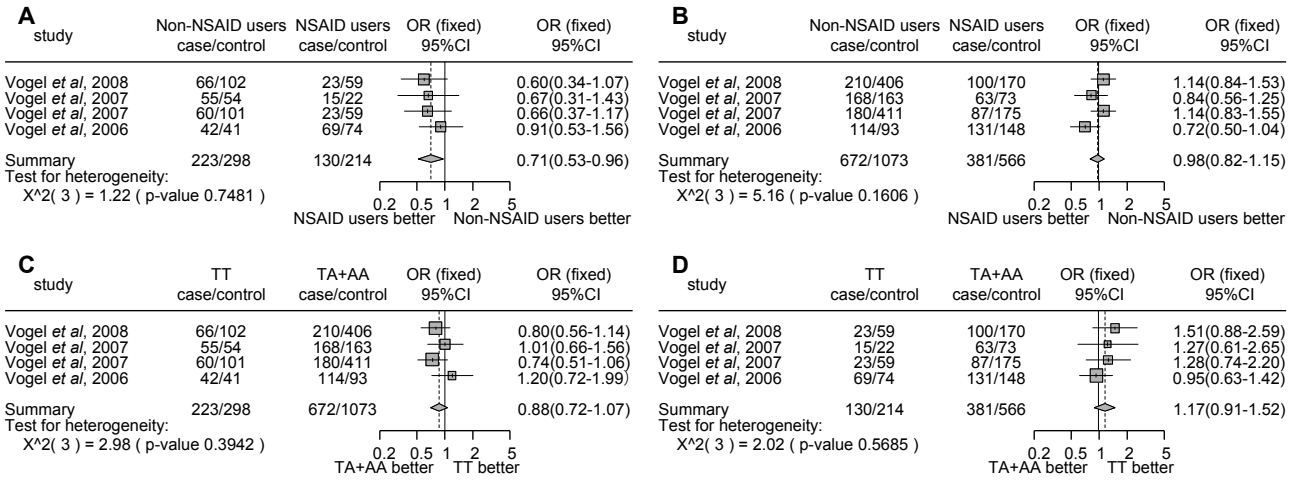

Figure 3: Forest plot of the association between the IL8 rs4073 polymorphism and NSAID usage on cancer risk. The difference in the risk of development of cancer between NSAID users and non-NSAID users homozygous for the major allele (A), between NSAID users and non-NSAID users who are minor allele carriers (B), between non-NSAID users homozygous for the major allele and the minor allele carriers (C), and between NSAID users homozygous for the major allele and the minor allele carriers (D). Squares represent study-specific ORs; horizontal lines represent 95% CIs; the size of the square reflects study-specific statistical weight (inverse of the variance); diamonds represent summary OR and 95% CI.

for the major allele (CC) (Figure 5A; OR=1.01, 95% CI=0.83-1.23, $P_{\text{heterogeneity}}$=0.22), or the minor allele carriers (CA+AA) (Figure 5B; OR=0.86, 95% CI=0.67-1.10, $P_{\text{heterogeneity}}$=0.54), and between the *IL10* rs1800872 polymorphism (CC vs. CA+AA) and the risk of developing cancer among non-NSAID users (Figure 5C; OR=1.05, 95% CI=0.89-1.24, $P_{\text{heterogeneity}}$=0.29) or NSAID users (Figure 5D; OR=0.87, 95% CI=0.67-1.14, $P_{\text{heterogeneity}}$=0.35).

Discussion

One study on IL6 rs1800795 was statistically deviated from HWE. In the study conducted by Slattery et al., n=897 (46%) had the heterozygote genotype *IL6* rs1800795 when we expected n=949 (48%) based on allele frequencies [20]. There was a similar shift of observed and expected genotypes for the homozygote wild-type (37% observed, 36% expected) and the homozygote variant genotype (17% observed, 16% expected). We do not attribute this result to deviation from HWE because the overall concordance rate for blinded quality controls was >92%, although the deviation from HWE could be explained as not only the result of laboratory or genotyping error but from population migration and gene mutations.

In the current study, we searched the literature to determine the association between IL polymorphisms and NSAID usage with respect

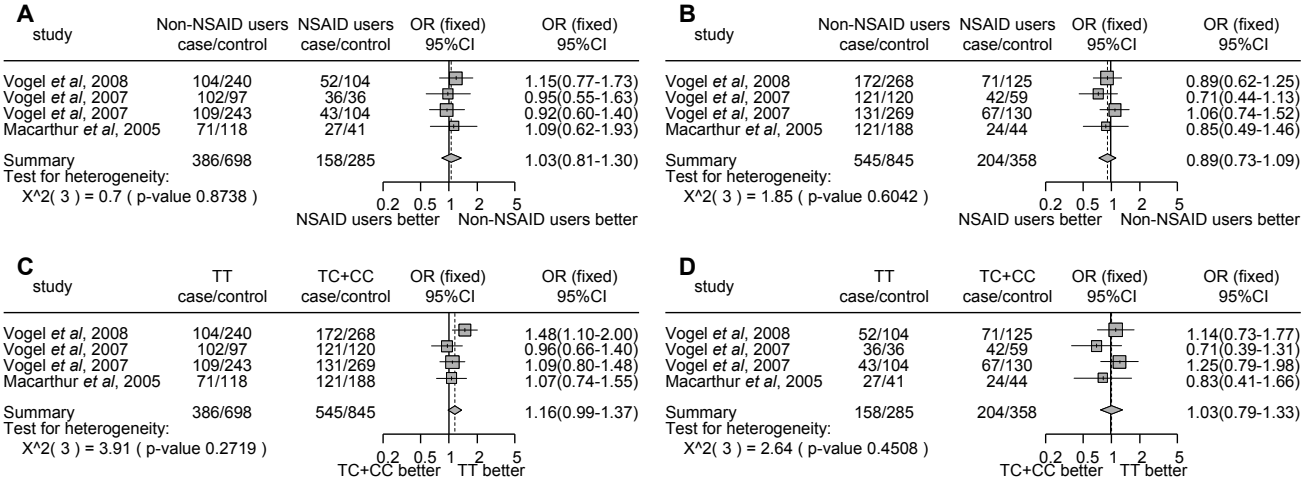

Figure 4: Forest plot of the association between the IL1B rs1143627 polymorphism and NSAID usage on cancer risk. The difference in the risk of development of cancer between NSAID users and non-NSAID users homozygous for the major allele (A), between NSAID users and non-NSAID users who are minor allele carriers (B), between non-NSAID users homozygous for the major allele and the minor allele carriers (C), and between NSAID users homozygous for the major allele and the minor allele carriers (D). Squares represent study-specific ORs; horizontal lines represent 95% CIs; the size of the square reflects study-specific statistical weight (inverse of the variance); diamonds represent summary OR and 95% CI.

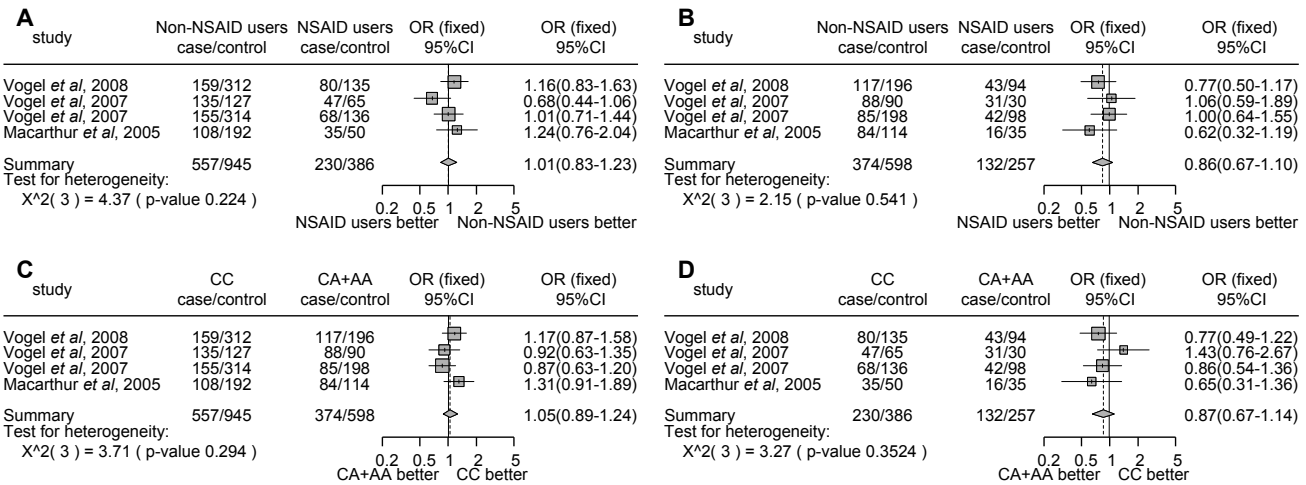

Figure 5: Forest plot of the association between the IL10 rs1800872 polymorphism and NSAID usage on cancer risk. The difference in the risk of development of cancer between NSAID users and non-NSAID users homozygous for the major allele (A), between NSAID users and non-NSAID users who are minor allele carriers (B), between the non-NSAID users homozygous for the major allele and the minor allele carriers (C), and between the NSAID users homozygous for the major allele and the minor allele carriers (D). Squares represent study-specific ORs; horizontal lines represent 95% CIs; the size of the square reflects study-specific statistical weight (inverse of the variance); diamonds represent summary OR and 95% CI.

to the risk of developing cancer. The *IL6* rs1800795 SNP is located in the promoter region of the *IL6* gene. Therefore, this SNP affects gene transcription, where the G allele has a higher transcription level than the C allele [9]. Elevated serum levels of *IL6* have been shown to be associated with an increased incidence of several cancers, including prostate, bladder, colon, and breast cancers [20]. To date, several studies have investigated associations of the *IL6* rs1800795 SNP and risk of cancer; however, these studies have produced mixed results. Slattery et al. reported that the C allele of rs1800795 is associated with lower risk of breast cancer [25]. Theodoropoulos et al. observed that the C allele of the rs1800795 SNP reduced the risk of colorectal cancer, while Landi et al. indicated that individuals with the C allele had an increased risk of colorectal cancer [26,27]. Our meta-analysis showed that the minor allele carriers (GC+CC) were associated with a significantly decreased risk of cancer compared to carriers homozygous for the major allele (GG) among NSAID users. This result shows that the C allele of rs1800795 is associated with lower risk of cancer in conjunction with NSAID usage. It is suggested that because C allele carriers have lower transcription levels of *IL6* than those homozygous for the G allele, NSAID consumption reduces the expression of *IL6*, and decreases the risk of developing cancer.

The *IL8* rs4073 SNP is located in the promoter region of the *IL8* gene and the A allele of rs4073 is associated with increased *IL8* production *in vitro* [12]. There is a significant correlation between *IL8* mRNA expression in bladder cancer and in invasive and high-grade tumors [28]. We found that NSAID users demonstrated a significantly

decreased risk of developing cancer compared with non-NSAID users among those homozygous for the major allele (TT) of the rs4073 SNP, although no significant association was noted between the *IL8* rs4073 polymorphism and the risk of developing cancer among non-NSAID users or NSAID users. This suggests that because homozygosity of the T allele leads to lower production levels of *IL8* than that found in A allele carriers, NSAID usage reduces the expression of *IL8*, and thereby decreases the risk of developing cancer. On the one hand, it is reasonable to assume that the level of *IL8* in minor allele carriers (TA+AA) could also be down regulated through NSAID usage so as to cause a reduced cancer risk as well, but the results did not confirm this hypothesis. Lee et al. reported that variants of the COX-1 gene resulted in significantly lower indomethacin-mediated inhibition of COX-1 activity compared to the wild type [29]. We suggest that the difference in sensitivity to NSAIDs is caused by the variant of the *IL8* gene.

The *IL1B* rs1143627 SNP is also located in the promoter region of the *IL1B* gene. The C variant allele of the rs1143627 SNP has a higher transcription level of *IL1B* than the T allele [8]. *IL1B* is implicated in tumor progression and is up-regulated in many types of tumor. Reducing endogenous *IL1* activity reduces both metastasis and tumor burden [30]. Our meta-analysis did not indicate any significant differences between these two genotypes.

There was no association between the risk of developing cancer, NSAID usage, and the *IL10* rs1800872 polymorphism. The *IL10* rs1800872 SNP is located in the promoter region of the *IL10* gene. Macarthur et al. reported that the A variant allele carriers of rs1800872, who produce less *IL10* had a significantly reduced risk of colorectal cancer when taking aspirin [24]. Therefore, the influence of the *IL10* rs1800872 polymorphism on the risk of developing cancer with NSAID usage may differ by the type of cancer or population investigated. Consequently, in the present study, we have not performed a stratified analysis with respect to the cancer type or population because of the limited number of studies available.

The types of NSAIDs considered (e.g., aspirin, ibuprofen, and other NSAIDs), dose methods (e.g., dosage and duration), study design (e.g., case control study or cohort study), population (e.g., age, gender, type of cancer, and ethnicity), study power, HWE in the controls for each study, and distraction sample size differed among the studies included in this meta-analysis. In addition, there was a lack of specificity for cancer type and topography in our analysis because few studies have investigated the effect of associations between polymorphisms in *IL* genes and NSAID use on cancer risk. Most outcomes show poor correlation between SNPs or NSAID usage and cancer risk, which are mainly due to the dual role that these *ILs* play in the balance between the promotion and inhibition of cancer development. Nonetheless, our results provide limited evidence for these associations. Future emerging studies are expected to resolve the contradictions in the results of the limited evidence available to date.

In conclusion, we found an association between the *IL6* rs1800795 and *IL8* rs4073 polymorphisms and NSAID usage with respect to cancer risk. Thus, the polymorphisms of inflammatory cytokine genes may influence the risk of developing cancer with NSAID usage. Thus, these polymorphisms may be clinically useful for deciding whether NSAIDs should be used for the prevention and treatment of cancer.

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