A Meta-Analysis of Interleukin-10-819 Promoter Polymorphism Associated with Gastric Cancer Risk

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Potential functional allele T/C single nucleotide polymorphism (SNP) of Interleukin 10 (IL-10) promoter -819 has been implicated in gastric cancer risk. We aimed to explore the role of T/C SNP of IL-10 -819 in the susceptibility to gastric cancer through a systematic review and meta-analysis. Each initially included article was scored for quality appraisal. Desirable data were extracted and registered into databases. 10 studies were ultimately eligible for the meta-analysis of IL-10 -819 T/C SNP. We adopted the most probably appropriate genetic model (recessive model). Potential sources of heterogeneity were sought out via subgroup and sensitivity analyses, and publication biases were estimated. IL-10 -819 TT genotype is associated with the overall reduced gastric cancer risk among Asians and even apparently observed among high quality subgroup Asians. IL-10-592 TT genotype is not statistically associated with the overall reduced gastric cancer susceptibility in persons with *H. pylori* infection compared with controls without *H. pylori* infection. IL-10 -819 TT genotype is reversely associated with diffuse-subtype risk but not in intestinal-subtype risk. IL-10 -819 TT genotype is not reversely associated with non-cardia or cardia subtupe gastric cancer susceptibility. IL-10 -819 TT genotype seems to be more protective from gastric cancer in Asians. Whether IL-10 -819 TT genotype may be protective from gastric cancer susceptibility in persons infected with *H. pylori* or in diffuse-subtype cancer needs further explored in the future.
well-designed high quality studies among different ethnicity populations. Genotyping methods like direct sequencing should be highly advocated to be conducted.

**Key words:** Interleukin 10; gene; single nucleotide polymorphism; association; gastric cancer

**Introduction**

Nowadays, worldwide gastric cancer incidence has decreased but its mortality still ranks second [1-3]. In Asia [4], especially China [5], gastric cancer constitutes the top lethal malignancy. As is widely known, infectious, dietary, environmental, and genetic factors are implicated in gastric carcinogenesis, but only a minority of persons exposed to risk factors such as *Helicobacter pylori* (*H. pylori*) infection ultimately develop gastric cancer [6], which implies that host genetic susceptibility plays an important role in developing gastric cancer [7-9]. Such various susceptibilities could be explained, in part, by single nucleotide polymorphisms (SNPs) of susceptible genes [7-9]. During the long pathogenesis from chronic gastritis to gastric cancer spawned by *H. pylori* infection, host-activated neutrophils and mononuclear cells can produce not only proinflammatory cytokines such as interleukin (IL)-1 β, IL-6, IL-8 and tumor necrosis factor (TNF)- α but also anti-inflammatory cytokines like IL-10. Rivetingly, the level of IL-10 besides those of IL-1 and TNF- α could also be elevated in gastric mucosa infected with *H. pylori*.

IL-10, a potent pleiotropic cytokine, has the dual ability to immunosuppress or
immunostimulate anti-cancer properties [10]. Interleukin-10 inhibits the production of pro-inflammatory cytokines by inhibition of T-helper 1 (Th1) lymphocytes and stimulation of B lymphocytes and Th2 lymphocytes and thus downregulates the inflammatory response [10-12]. The human IL-10 gene, located on chromosome 1q31-32, consists of five exons and four introns and one of polymorphisms is reported in its promoter region at position -819 C/T SNP [13].

In 2003, Wu MS et al. [14] first published their study on IL-10-819 C/T SNP. Since then, researchers have consecutively reported associations of IL-10-819 C/T SNP with the susceptibility to gastric cancer, but with mixed or conflicting results [15-23]. Up to now, there has been only one published meta-analysis article focusing on IL-10-819 C/T SNP [24], but that meta-analysis failed to adopt the most likely appropriate genetic model, and thus the authentic values of statistical results could be compromised.

Accordingly, the aim of our meta-analysis was to shed more light, using the most appropriate genetic model, on the role of IL-10-819 C/T SNP in the risk of developing gastric cancer and to identify possible sources of heterogeneity among the eligible studies.

**Materials and Methods**

**Search Strategy**

A systematic literature search was performed for articles regarding IL-10-819 C/T SNP associated with the risk of developing gastric cancer. The MEDLINE, EMBASE databases, Chinese National Knowledge Infrastructure (CNKI), Web of Science, and
BIOSIS databases were used simultaneously with the combination of terms “Interleukin 10”, “IL-10”, “interleukin”, or “cytokine”; “gene”; “polymorphism”, “variant”, or “SNP”; and “gastric cancer”, “gastric carcinoma”, “diffuse gastric cancer” or “stomach cancer” from January 2000 to September 2011. The search was performed without any restriction on language. The scope of computerized literature search was expanded according to the reference lists of retrieved articles. The relevant original articles were also sought manually.

**Study Selection**

Studies concerning the association of IL-10-819 C/T SNP with the risk of developing gastric cancer were included if the following conditions were met: (i) any study described the association of IL-10-819 C/T SNP with gastric cancer; (ii) any study reported the numbers of both controls and gastric cancer cases; (iii) results were expressed as odds ratio (OR) with 95% confidence intervals (CI); and (iv) studies were case-control or nested case-control ones.

**Methodological Quality Appraisal**

To identify high-quality studies, we mainly adopted predefined criteria for Quality Appraisal [25, 26, 7-9]. The criteria cover credibility of controls, representativeness of cases, consolidation of gastric cancer, genotyping examination, and association assessment [7-9]. Methodological quality was independently assessed by two investigators (B. Lin and J. An). Disagreements were resolved through discussion. Scores ranged from the lowest zero to the highest ten. Articles with the
score lower than 6.5 were considered “low or moderate quality” ones, whereas those
no lower than 6.5 were thought of as “high quality” ones.

**Data Extraction**

The following data from each article were extracted: authors, year of publication,
country, ethnicity of participants (categorized as Caucasians, Asians, Latinos, etc.),
study design, source of controls, number of controls and of cases, genotyping method,
distribution of age and gender, Lauren’s classification (intestinal, diffuse, or mixed),
and anatomical classification (cardia or non-cardia cancer).

The data were extracted and registered into two databases independently by two
investigators (B. Lin and J An) who were blind to journal names, institutions or fund
grants. Any discrepancy between these two investigators was resolved by the third
investigator (H. Xue), who participated in the discussion with them and made an
ultimate decision.

**Statistical Analysis**

All statistical analyses were performed using STATA statistical software (Version
10.1, STATA Corp, College Station, TX). Two-sided Ps < 0.05 were considered
statistically significant. HWE in controls was calculated again in our meta-analysis.
The chi-square goodness of fit was used to test deviation from HWE (significant at
the 0.05 level). Odds ratios (OR) and 95% confidence intervals (95% CI) were
employed to assess the strength of associations between IL-10-819 T/C SNP with
gastric cancer risk. OR1, OR2, and OR3 regarding IL-10-819 T/C SNP were calculated
for genotypes TT versus CC, CT versus CC, and TT versus CT, respectively.
The above pairwise differences were used to determine the most appropriate genetic model. If $\text{OR}_1 = \text{OR}_3 \neq 1$ and $\text{OR}_2 = 1$, then a recessive model is suggested. If $\text{OR}_1 = \text{OR}_2 \neq 1$ and $\text{OR}_3 = 1$, then a dominant model is implied. If $\text{OR}_2 = 1/\text{OR}_3 \neq 1$ and $\text{OR}_1 = 1$, then a complete overdominant model is suggested. If $\text{OR}_1 > \text{OR}_2 > 1$ and $\text{OR}_1 > \text{OR}_3 > 1$, or $\text{OR}_1 < \text{OR}_2 < 1$ and $\text{OR}_1 < \text{OR}_3 < 1$, then a codominant model is indicated [27]. If a dominant model was indicated, the original grouping was collapsed and the new group of T carriers (TT+CT) was compared with CC genotype; if a recessive model was suggested, TT was compared to the group of CC plus CT; if a complete overdominant model was implied, the group of TT plus CC was compared with CT; or if a codominant model was insinuated, TT was compared with CT and with CC, respectively.

The Q statistic was used to test for heterogeneity among the studies included in the meta-analysis. A fixed-effects model, using Mantel–Haenszel (M-H) method, was used to calculate the pooled ORs when homogeneity existed on the basis of Q-test p value no less than 0.05. By contrast, a random-effects model, using DerSimonian and Laird method (D+L), was utilized if there was heterogeneity based on Q-test p value less than 0.05. The significance of pooled ORs was tested by Z test ($P<0.05$ was considered significant).

Sensitivity analysis was performed, in which the meta-analysis estimates were computed after every one study being omitted in each turn.

Finally, publication bias was assessed by performing funnel plots qualitatively, and estimated by Begg’s and Egger’s tests quantitatively.
Results

Literature Search and Study Selection

After comprehensive searching, a total of 236 articles in English and 6 in Chinese were retrieved. In our meta-analysis were initially included altogether 10 studies [14-23] which catered to the inclusion criteria. Those 10 studies were preliminarily appropriate to the meta-analysis of the associations with gastric cancer regarding IL-10-819 T/C SNP.

One study [20] was deviated from HWE. Generally speaking, any study that deviated from Hardy-Weinberg equilibrium through our calculation should have been removed; however, considering that the number of participants in that study was large and given that sensitivity analyses would be conducted, we remained that study in our meta-analysis. Thus, 10 studies [14-23] with a total of 3682 controls and 1407 cases were ultimately eligible for the meta-analysis of IL-10-819 T/C SNP. The corresponding characteristics were seen in Table 1. The flow chart of literature search and study selection was omitted due to the length of paper.

Overall Meta-analysis among Different Ethnicity Populations

OR₁ (p value), OR₂ (p value), and OR₃ (p value) of IL-10-819 T/C SNP for overall ethnicities were 0.87 (p=0.253), 0.86 (p=0.084), and 0.88 (p=0.118), respectively, hardly insinuating a probably suitable genetic model effect of putative protective T allele. Meanwhile, after ethnicity subgroup analysis, OR₁ (p value), OR₂
(p value), and OR$_3$ (p value) of IL-10-819 T/C SNP among Asians were 0.82 (p=0.156), 0.96 (p=0.778), and 0.83 (p=0.033), respectively, suggesting a recessive genetic model effect of putative protective T allele (OR$_1$=OR$_3$<1 and OR$_2$ =1).

Thus, the genotype TT was compared with the combined genotype CT-plus-CC. As in figure 1, for overall gastric cancer no statistically significant finding could be observed among Caucasians, whereas a statistically significant finding could be noted among Asians from the facts that the pooled ORs (95% CI, p value) were 1.09 (0.74-1.59, p=0.665) for the former, respectively, but 0.82 (0.69-0.97, p=0.020) for the latter.

**Further Subgroup Analysis**

Specific data for IL-10-819 T/C SNP were classified in accordance with the quality appraisal scores, into high quality (scores no less than 6.5) and median-and-low quality (scores less than 6.5) subgroups among different ethnicities. A statistically significant reverse association was only witnessed in Asians high quality subgroup but not in Asians median-and-low quality subgroup, on the grounds that the pooled ORs (95% CIs, p value) were 0.69 (0.55-0.86, p=0.001) for the former and 1.05 (0.81-1.36, p=0.719) for the latter. Interestingly, completely opposite associations were found between Caucasians high quality subgroup and Caucasians median-and-low quality subgroup, given that the pooled ORs (95% CIs, p value) were 0.71 (0.42-1.23, p=0.225) and 1.87 (1.07-3.26, p=0.028), respectively, though a significant association for the latter. If Asians high quality subgroup and Caucasians
high quality subgroup were combined, and Asians median-and-low quality subgroup
and Caucasians median-and-low quality subgroup were also combined, the pooled
ORs (95% CIs, p value) were 0.69 (0.57-0.85, p=0.000) for the former (the combined
high quality subgroup) and 1.15 (0.91-1.46, p=0.240) for the latter (the combined
median-and-low quality subgroup), further indirectly demonstrating the recessive
genetic model in our initial option among the combined high quality subgroup
populations no matter which ethnicity was considered (Figure 2). To further confirm
the recessive genetic model, the above OR\(_1\) (p value), OR\(_2\) (p value), and OR\(_3\) (p
value) of IL-10-819 T/C SNP in the combined high quality subgroup for overall
ethnicities were 0.62 (p=0.003), 0.81 (p=0.064), and 0.73 (p=0.004), respectively,
again indicating a recessive genetic model effect of putative protective T allele
(OR\(_1\)=OR\(_3\)<1 and OR\(_2\)=1).

When gastric cancer was classified into non-cardia (or distal) and cardia
subtypes, no statistically significant findings were found among non-cardia subtype
or among cardia subtype on the grounds that the pooled ORs (95% CIs, p value)
were 0.82 (0.38-1.76, p=0.603) among non-cardia subtype and 1.02 (0.67-1.56,
\(p=0.913\)) among cardia subtype. In terms of pathology, gastric cancer could be
classified into intestinal, diffuse, or mixed subtypes, and no statistically significant
finding was observed in intestinal-subtype cancer but in diffuse-subtype cancer, for
the pooled ORs (95% CIs, p value) were 0.78 (0.48-1.27, p=0.318) in the former and
0.32 (0.12-0.84, p=0.021) in the latter.
In terms of *H. pylori* infection status, no statistically significant reverse association was noted among either *H. pylori* positive cancer patients compared with *H. pylori* negative controls or among *H. pylori* positive cancer patients compared with *H. pylori* positive controls, for pooled ORs (95% CIs, p value) were 0.64 (0.39-1.04, p=0.072) in the former and 0.90 (0.63-1.29, p=0.575) in the latter, but the p value was approximate to 0.05 in the former.

And when genotyping techniques were considered, a statistically significant finding was noted in direct sequencing subgroup but not in any other genotyping technique subgroup. In the direct sequencing, TaqMan, ABI Genetic Analyzer, Pyrosequencing, RFLP, ASP, and ABI real-time PCR genotyping technique subgroups, pooled ORs (95% CIs, p value) were 0.54 (0.37-0.79, p=0.001), 1.38 (0.56-3.42, p=0.484), 0.98 (0.61-1.58, p=0.939), 1.37 (0.29-6.48, p=0.695), 0.97 (0.77-1.21, p=0.757), 0.64 (0.39-1.04, p=0.072), and 0.70 (0.38-1.31, p=0.265), respectively.

**Sensitivity Analysis**

Meta-analyses were conducted repeatedly when each particular study had been removed. The results indicated that fixed-effects estimates and/or random-effects estimates before and after the deletion of each study were similar at large, suggesting moderate to high stability of the meta-analysis results. The most influencing single study on the overall pooled estimates seemed to be the study conducted by Wu et al.[14], the sensitivity analysis, however, indicated moderate stability of the results.
from the facts that the ORs (95% CI, p value) were 0.86 (0.74-1.00, p=0.05) before the removal of that study and 0.94 (0.80-1.12, p=0.488) after the removal of that study (The illustrating figure was omitted due to the length of paper).

**Cumulative Meta-analysis**

Cumulative meta-analyses of IL-10-819 T/C SNP association were also conducted among Asians (Figure 3A) and among Caucasians (Figure 3B) via the assortment of total number of sample size. As shown in Figure 3A, the inclination toward significant reverse associations with overall gastric cancer, though somewhat undulated, was obviously seen among Asians, whereas in Figure 3B, the opposite tendency was observed among Caucasians with undulation.

**Publication Bias Analysis**

Publication bias was preliminarily examined by funnel plots qualitatively and estimated by Begg’s and Egger’s tests quantitatively. Its funnel plot (Figure 4) showed that dots nearly symmetrically distributed, predominantly within pseudo 95% confidence limits. P values were 0.858 in Begg’s test and 0.898 in Egger’s test, separately, also suggesting no publication bias.

**Discussion**

In our meta-analysis, a statistically significant finding could be noted with the overall reduced risk of gastric cancer among Asians but not among Caucasians (TT vs
CT-plus-CC); the opposite tendency toward the risk of gastric cancer could also be observed between Caucasians and Asians via cumulative meta-analysis sorted by publication time and total sample size. Thus, IL-10-819 TT genotype may seem to be more protective from overall gastric cancer susceptibility among Asians. To be sure, the different or even conflicting risk associations, if so, among different ethnicities should be further meticulously investigated and reconfirmed in the future.

Our further subgroup analyses also indicate that a statistically significant reverse association was witnessed in Asians high quality subgroup but not in Asians median-and-low quality subgroup; the reverse association tendency was also observed in Caucasians high quality subgroup, although the statistical significance could not be reached. The consistent reverse association trend between Asians high quality subgroup and Caucasians high quality subgroup could be apparently seen. The strong statistical significant reverse association could be found among the combined high quality subgroup regardless of ethnicities, indirectly demonstrating the correctness of our initial option of recessive genetic model in our meta-analysis. Furthermore, the recessive genetic model was confirmed through the recalculation of OR$_1$ (p value), OR$_2$ (p value), and OR$_3$ (p value) in the combined high quality subgroup regardless of ethnicities. Therefore, it should be advocated that more rigorous high-quality studies should be designed in the future so as to accurately explore the real associations between IL-10-819 TT genotype and gastric cancer susceptibility among different ethnicities.
Additionally, 4[17-19, 20] out of 15 eligible studies were dealt with noncardia-subtype gastric cancer and 4 [15, 18-20] with cardia-subtype gastric cancer. No statistically significant findings could be noted with either subtype TT vs CT-plus-CC). 2 studies [18, 19] in our meta-analysis were dealt with pathologically intestinal-subtype gastric cancer and only 1 [19] out of 15 studies was dealt with pathologically diffuse-subtype gastric cancer. No statistically significant finding could be noted in intestinal-subtype but in diffuse- subtype cancer (TT vs CT-plus-CC). As is known, cardia-subtype gastric cancer differs from noncardia-subtype gastric cancer in etiology, pathology, carcinogenesis, and/or prognosis [28-30], so is intestinal-subtype cancer versus diffuse-subtype cancer. It could be said that the indiscriminate combination of cardia-subtype and noncardia-subtype cases or intestinal-subtype and diffuse-subtype cases in the majority of eligible studies may mask or at least underestimate the strength of the real associations [7-9].

Furthermore, it was reported that gastric cancer develops in those with H. pylori infection rather than in uninfected ones [31]. In our meta-analysis, no statistically significant reverse association with gastric cancer was found either among H. pylori positive cancer patients compared with H. pylori negative controls or among H. pylori positive cancer patients compared with H. pylori positive controls (TT vs CT-plus-CC), but the p value in the former was approximate to 0.05, insinuating that IL-10-819 TT genotype may seem to be more protective from overall gastric cancer susceptibility in persons infected with H. pylori. Certainly, the real association
between *H pylori* infection and IL-10-819 TT genotype and gastric cancer susceptibility should be further meticulously investigated in the future.

With the advent of new genotyping technologies like seminested polymerase chain reaction, TaqMan allelic discrimination test, direct sequencing, the allele specific primer–polymerase chain reaction, pyrosequencing, or real-time PCR, we may witness an upsurge of genetic association studies in the future. In our meta-analysis, a statistically significant reverse association with gastric cancer susceptibility was only noted in direct sequencing genotyping technique subgroup but not in any other subgroup. Indeed, the sensitivity and specificity of those genotyping techniques need to be further explored so as to seek out the optimal approaches which could minimize the genotyping errors [7-9]. We advocate that direct sequencing should be further conducted in future well-designed high quality studies among different ethnicity populations.

Finally, the strength of our meta-analysis could be summarized as follows. We sought to find as many publications as we could by means of various searching approaches. We laid more emphasis on assessing biases across studies and pinpointing the potential sources of heterogeneity via subgroup analyses, and sensitivity analyses. We comprehensively assessed the publication biases using several means like Begg’s and Egger’s tests as well as funnel plot tests. In view of this, we convince that the results of our meta-analysis, in essence, are sound and reliable.
Certainly, there are some unavoidable limitations in our meta-analysis. Firstly, the offered information from the included studies is inconsistent. Put it another way, the information about overall gastric cancer susceptibility is predominantly provided, while more important information about pathologic subtypes or anatomic subtypes of gastric cancer is less provided. Thus, the specific subtype results should be considered with caution. Secondly, with the merely published studies included in our meta-analysis, publication bias is very likely to occur, though no statistically significant publication bias is found in our meta-analysis. Thirdly, moderate to severe heterogeneity could be witnessed among the included studies. So as to minimize the potential bias, we designed a rigorous protocol before the conduction of meta-analysis, and performed a scrupulous search for published studies using explicit methods for study selection, data extraction, statistical analysis, adoption of the most appropriate genetic model with extreme caution and sensitivity analysis.

In conclusion, IL-10-819 TT genotype may seem to be more protective from overall gastric cancer susceptibility among Asians and even more protective in high quality subgroup Asians. IL-10-819 TT genotype is not statistically associated with gastric cancer susceptibility in persons infected with *H. pylori*. IL-10-819 TT genotype is not associated with pathologic intestinal subtype but in diffuse subtype and not with anatomic subtypes (non-cardia or cardia) of gastric cancer susceptibility in our meta-analysis. Such genotyping methods as direct sequencing should be highly advocated to be conducted in future well-designed high quality studies among different ethnicities or populations.
References


Figure Legends

Figure 1- Odds ratios (ORs) for associations between IL-10-819 T/C SNP and gastric cancer risk (TT vs CT-plus-CC) among different ethnicity populations, in order of increasing publication year, 2003–2011. Studies were entered into the meta-analysis.
sequentially by year of publication. The sizes of the squares indicate the relative weight of each study. Bars, 95% confidence interval (CI).

**Figure 2** - Odds ratios (ORs) for associations between IL-10-819 T/C SNP and gastric cancer risk (TT vs CT-plus-CC) among high quality subgroup participants regardless of ethnicities and among median-and-low quality subgroup participants regardless of ethnicities. The sizes of the squares indicate the relative weight of each study. Bars, 95% confidence interval (CI).

**Figure 3** - Cumulative meta-analysis of associations between the IL-10-819 TT genotype, as compared with the combined CT-plus-CC genotype, and gastric cancer risk among different ethnicity populations sorted by publication year and the total sample size. Horizontal line, the accumulation of estimates as each study was added rather than the estimate of a single study. A) among Asians; B) among Caucasians.

**Figure 4** - Funnel plot of publication bias for IL-10-819 SNP (TT vs CT-plus-CC). Note: Funnel plot with pseudo 95% confidence limits was used.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight %</th>
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<tbody>
<tr>
<td>Asians</td>
<td></td>
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<tr>
<td>Wu MS et al. (2003)</td>
<td>0.54 (0.37, 0.79)</td>
<td>20.98</td>
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<tr>
<td>Savage SA et al. (2004)</td>
<td>0.98 (0.61, 1.58)</td>
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<td>Sugimoto M et al. (2007)</td>
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<td>11.18</td>
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<tr>
<td>Xiao H et al. (2009)</td>
<td>1.08 (0.79, 1.47)</td>
<td>21.78</td>
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<td>Su SP et al. (2010)</td>
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<td>0.90 (0.63, 1.29)</td>
<td>17.37</td>
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<tr>
<td>Subtotal (I-squared = 49.1%, p = 0.081)</td>
<td>0.82 (0.69, 0.97)</td>
<td>85.99</td>
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<td>Caucasians</td>
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Figure 1
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<td>Subtotal (I-squared = 0.0%, p = 0.570)</td>
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Figure 2
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<td>0.54 (0.37, 0.79)</td>
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<tr>
<td>Savage SA et al.</td>
<td>2004</td>
<td>0.68 (0.51, 0.91)</td>
</tr>
<tr>
<td>Sugimoto M et al.</td>
<td>2007</td>
<td>0.67 (0.52, 0.86)</td>
</tr>
<tr>
<td>Xiao H et al.</td>
<td>2009</td>
<td>0.81 (0.67, 0.98)</td>
</tr>
<tr>
<td>Su SP et al.</td>
<td>2010</td>
<td>0.80 (0.66, 0.97)</td>
</tr>
<tr>
<td>Liu J et al.</td>
<td>2011</td>
<td>0.82 (0.69, 0.97)</td>
</tr>
</tbody>
</table>
Figure 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpízar-Alpízar W et al.</td>
<td>2005</td>
<td>1.37 (0.29, 6.48)</td>
</tr>
<tr>
<td>Zambon CF et al.</td>
<td>2005</td>
<td>1.88 (1.08, 3.28)</td>
</tr>
<tr>
<td>Kamangar F et al.</td>
<td>2006</td>
<td>1.57 (0.96, 2.58)</td>
</tr>
<tr>
<td>Crusius JB et al.</td>
<td>2008</td>
<td>1.15 (0.78, 1.70)</td>
</tr>
</tbody>
</table>
Figure 5

Funnel plot with pseudo 95% confidence limits
Additional files provided with this submission:

Additional file 1: Table 1.doc, 71K
http://www.biomedcentral.com/imedia/1780140789623705/supp1.doc