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Full Length Research Paper

Association of Tumor Necrosis Factor-alpha-308G/A Polymorphism and Pancreatic Cancer Susceptibility: Evidence from a Meta-analysis

Xing-Dong Xu¹, Ji-Hua Cao¹, Ting Ge², Tao Wang¹ and Sheng-Hua Cao^{1*}

¹Department of General Surgery, The People's Hospital of China Three Gorges University, The First People's Hospital of Yichang, Yichang443000, China.

²Department of Operating Room, The People's Hospital of China Three Gorges University, The First People's Hospital of Yichang, Yichang443000, China.

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Epidemiologic studies have explored the association between tumor necrosis factor-alpha (TNF- α) -308G/A polymorphism and pancreatic cancer susceptibility. However, those studies have yielded contradictory findings on the association. We performed a comprehensive search in the PubMed, Web of Science, Chinese Biological Medicine Database and the Chinese National Knowledge Infrastructure databases to identify relevant studies. A meta-analysis was performed to examine the association between TNF- α -308G/A polymorphism and risk to pancreatic cancer by calculating the pooled odds ratios (ORs) and corresponding 95 % confidence intervals (95 % CIs). Publication bias was analyzed by Begg's funnel plots. Five studies involving a total of 689 cases and 1331 controls were included. Overall, no significant association was found between TNF- α -308G/A polymorphism and risk to pancreatic cancer when all studies were pooled into the meta-analysis using five genetic models (for G vs A: OR=0.993, 95% CI=0.820-1.202, $P=0.940$; for GG vs AA: OR=1.011, 95% CI=0.535-1.912, $P=0.973$; for GA vs AA: OR=1.055, 95% CI=0.546-2.038, $P=0.873$; for GG + GA vs AA: OR=1.018, 95% CI=0.538-1.924, $P=0.957$; for GG vs GA + AA: OR=0.988, 95% CI=0.795-1.227, $P=0.911$). Besides, publication bias analysis showed that there was no publication bias in these five studies. In summary, our meta-analysis suggested that TNF- α -308G/A polymorphism was not associated with pancreatic cancer susceptibility in Caucasian population.

Keywords: TNF- α ; Susceptibility; Pancreatic cancer; Meta-analysis

INTRODUCTION

Pancreatic cancer is a lethal malignancy with very high

mortality rates and less than 5% of patients are still alive five years after diagnosis. It is predicted that a total of 43,920 patients will be diagnosed with pancreatic cancer in the United States, and 37,390 will die of this disease (Capurso et al., 2012; Feig et al., 2012). Both genetic susceptibility factors and environmental factors play a

*Corresponding Author E-Mail: 247553780@qq.com;
Tel: +86-717- 6287681; Fax: +86-717-6221636

great role in the diseases development and prognosis. Many established risk factors include cigarette smoking, which explains about 20–25% of pancreatic cancer cases, family history of pancreatic cancer, chronic pancreatitis, obesity, long-standing diabetes, heavy alcohol consumption and body fatness (Capurso et al., 2012; Melton et al., 2010). Meanwhile, the genetic susceptibility factors for sporadic pancreatic cancer have been investigated in a few case-control studies, most of which have examined common gene polymorphisms such as epidermal growth factor (EGF), transforming growth factor beta (TGF- β) and tumor necrosis factor-alpha (TNF- α) and so on (Mazaki et al., 2011).

TNF- α is an important member of the TNF super-family located on chromo-some 6q21 within the class III region of the major histocompatibility complex, which has been reported to play an important role in the pathogenesis of cancer (Yin et al., 2012). To our knowledge, several polymorphisms have been identified, such as -308G/A (rs1800629), -857C/T (rs179972) and -1031T/C (rs1799964) and so on. Among them, TNF- α 308G/A polymorphism has been most widely studied. It has been reported that TNF- α 308G/A polymorphisms has been confirmed as a risk for a range of cancers such as breast cancer (Wang et al, 2011), squamous cell carcinoma (Wang et al., 2013), cervical cancer (Zhang and Zhang, 2013) and gastric cancer (Lu et al., 2010). However, it is unclear that whether TNF- α -308G/A polymorphism have an association with pancreatic cancer susceptibility. Therefore, we performed a meta-analysis to investigate whether or not TNF- α 308G/A polymorphism contribute to the pancreatic cancer susceptibility. To our knowledge, this is the first meta-analysis examining associations between TNF- α 308G/A polymorphism and pancreatic cancer susceptibility.

METHODS

Literature search strategy

We performed a comprehensive literature search in the PubMed, web of science, Chinese Biological Medicine Database (CBM) and the Chinese National Knowledge Infrastructure (CNKI) databases to identify relevant studies before January 24, 2013. There was no language restriction in the literature search. Search term combinations were as follows: (TNF or tumor necrosis factor) and (polymorphism or genotype or allele) and (pancreatic cancer or pancreatic carcinoma or pancreatic adenocarcinoma or pancreatic neoplasm). All reference lists from relevant studies and reviews were hand searched for additional eligible studies.

Eligible studies

Eligible studies had to meet all of the following criteria: (1) TNF- α -308G/A polymorphism in pancreatic cancer; (2) case-control studies; (3) sufficient data for assessing an odds ratio (OR) with 95% confidence interval (CI); (4) not republished data.

Data extraction

The following data were extracted independently by two reviewers: the name of first author, year of publication, area, ethnicity, sample size (case/control), source of controls, samples, genotyping methods, *P* values for Hardy-Weinberg equilibrium (HWE) evaluation and frequency of TNF- α -308G/A polymorphism in cases and controls.

Statistical methods

The pooled odds ratio (OR) with its corresponding 95 % confidence interval (95 % CI) was calculated to assess the strength of association between TNF- α -308G/A polymorphism and pancreatic cancer risk, and the *Z* test was used to determine the significance of the pooled OR. Cochran's χ^2 -based *Q* statistic test was performed to assess possible heterogeneity between the individual studies (Wang et al., 2011; Yin et al., 2012). The fixed-effects model was used to calculate the pooled OR with its 95% CI when there was no obvious between-study heterogeneity (Wang et al., 2011; Yin et al., 2012). Otherwise, the random-effects model (DerSimonian and Laird's method) was applied to calculate the pooled OR with its 95% CI (Wang et al., 2011; Yin et al., 2012). Publication bias was assessed using the funnel plot and Egger's test (Wang et al., 2011; Yin et al., 2012). All *P* values are two-sided, and *P* < 0.05 were considered statistically significant. Statistical analyses were done with Stata (version 12.0, StataCorp LP, College Station, Texas).

RESULTS

Characteristics of studies

The databases search and studies selection process was shown in Figure 1. We firstly identified 65 eligible studies, of which 54 irrelevant studies excluded based on screening of titles and abstracts. The further review from 11 potentially full-length studies identified 5 studies according to the above four selection criteria (Figure 1). Finally, five studies involving a total of 689 cases and 1331 controls were included into this meta-analysis

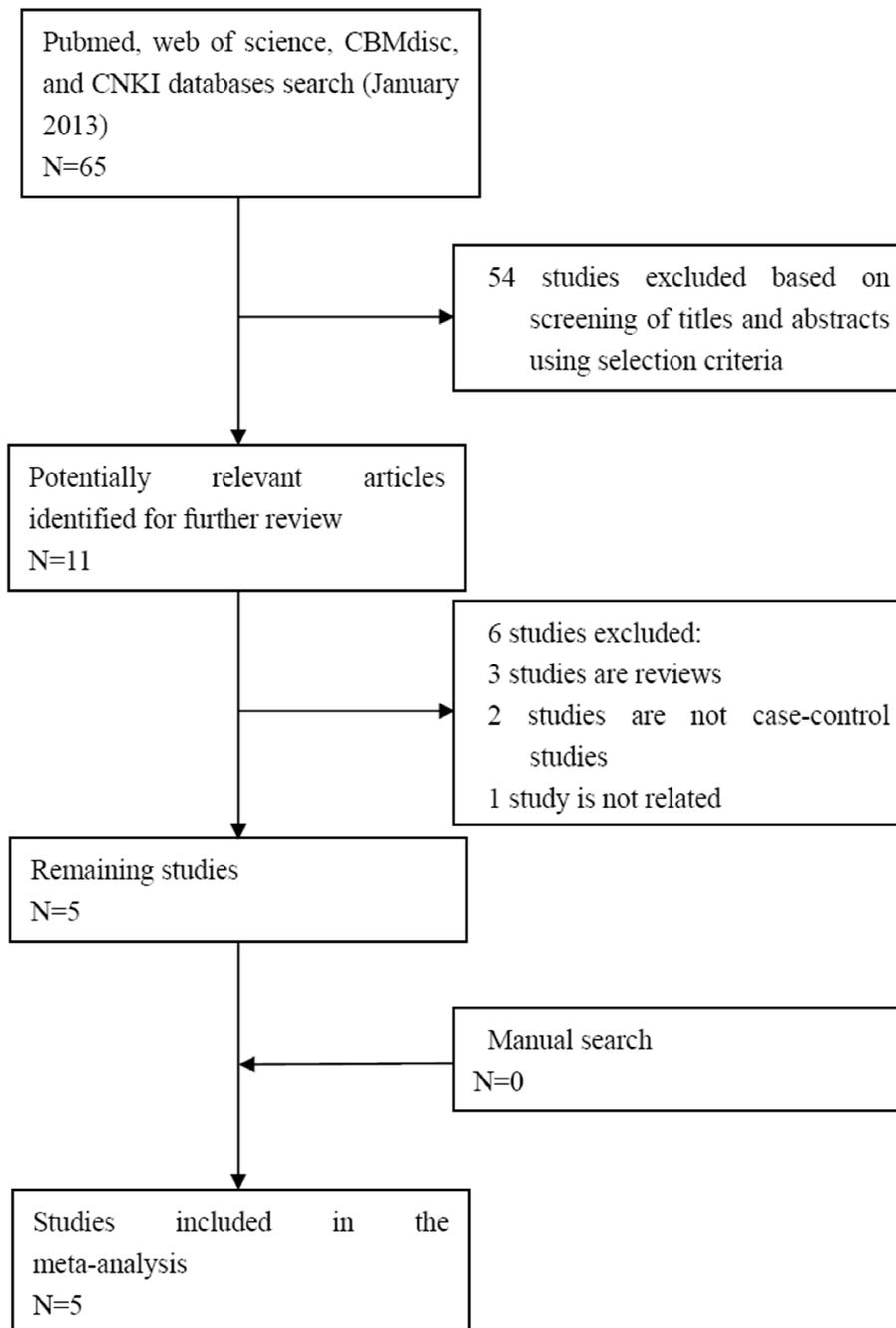


Figure 1. Literature search for meta-analysis

(Table 1) (Barber et al., 1999; Beranek et al., 2003; Duell et al., 2006; Talar-Wojnarowska et al., 2009; Wu et al., 2010). The countries of these five studies included United Kingdom, Germany, United States and Poland, which were almost Caucasian population. All the controls of five studies were population-based and the genotyping samples were from blood.

Meta-analysis of TNF- α -308G/A polymorphism and pancreatic cancer risk

When those five studies were included into the meta-analysis, there was not obvious heterogeneity between the individual studies using five genetic models ($P > 0.05$). Overall, TNF- α -308G/A polymorphism was not

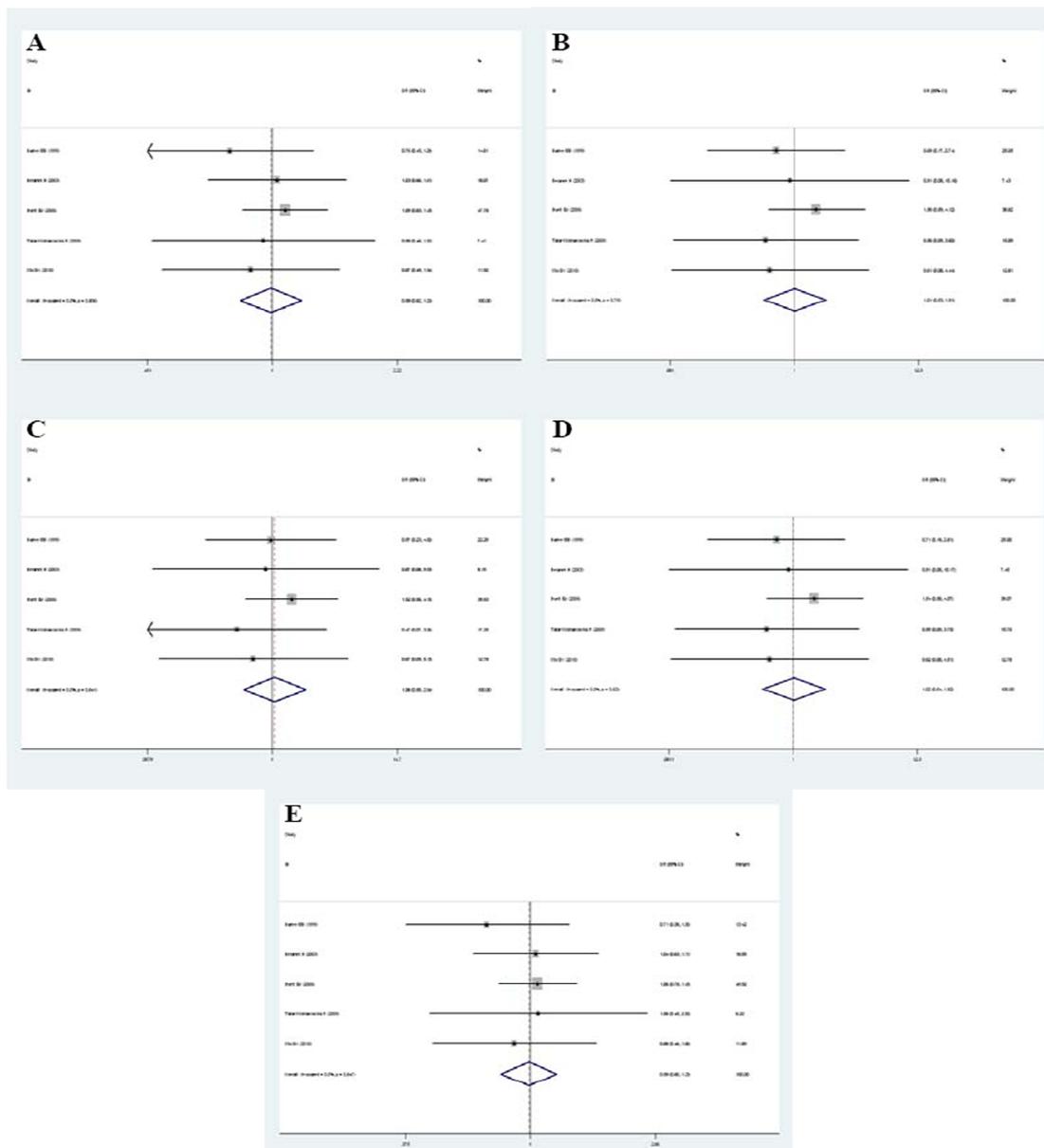


Figure 2. Forest plot for TNF- α -308G/A polymorphism and pancreatic cancer susceptibility in five genetic models. A Allelic model: G versus A; B Additive model: GG versus AA; C Co-dominant model: GA versus AA; D Dominant model: GG + GA versus AA; E Recessive model: GG versus GA + AA.

associated with pancreatic cancer risk when all studies were pooled into the meta-analysis using five genetic models (for G vs A: OR=0.993, 95% CI=0.820-1.202, $P=0.940$; for GG vs AA: OR=1.011, 95% CI=0.535-1.912, $P=0.973$; for GA vs AA: OR=1.055, 95% CI=0.546-2.038, $P=0.873$; for GG + GA vs AA: OR=1.018, 95% CI=0.538-1.924, $P=0.957$; for GG vs GA + AA: OR=0.988, 95% CI=0.795-1.227, $P=0.911$). The detailed evaluation of the association between TNF- α -308G/A polymorphism

and pancreatic cancer risk is shown in Table 2, and the forest plots are shown in Figure 2. Moreover, the five studies possessed highly homogeneity in all five genetic models ($P_{\text{heterogeneity}} > 0.05$, Table 2, Figure 2). In addition, all five studies were almost Caucasians descendants (one study with 89.5% Caucasians and other four studies were all Caucasians) and population-based. Considering the above information, we did not perform subgroup analysis.

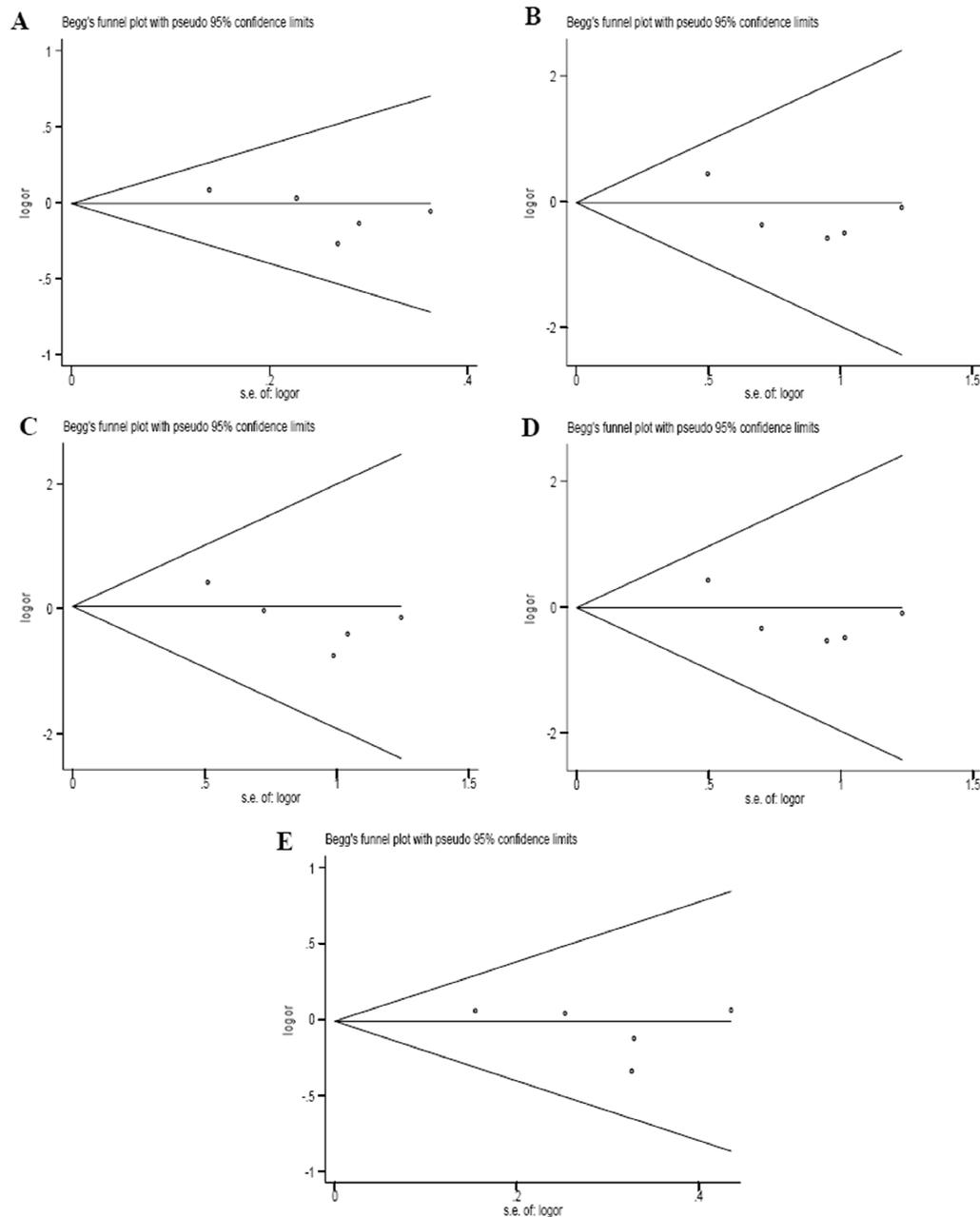


Figure 3. Begg's funnel plot for assessing the publication bias risk. A: Begg's funnel plot for TNF- α -308G/A G versus A, $P_{\text{egger}}=0.147$; B: Begg's funnel plot for TNF- α -308G/A GG versus AA, $P_{\text{egger}}=0.135$; C: Begg's funnel plot for TNF- α -308G/A GA versus AA, $P_{\text{egger}}=0.074$; D: Begg's funnel plot for TNF- α -308G/A GG + GA versus AA $P_{\text{egger}}=0.131$; E: Begg's funnel plot for TNF- α -308G/A GG versus GA + AA, $P_{\text{egger}}=0.342$.

Publication bias

A funnel plot of these five included studies was symmetrical and didn't suggest a possibility of publication bias (Figure 3). The statistical results from Egger's test

still did not show publication bias in these five studies using five genetic models (for G versus A, $P_{\text{egger}}=0.147$; for GG versus AA, $P_{\text{egger}}=0.135$; for GA versus AA, $P_{\text{egger}}=0.074$; for GG + GA versus AA $P_{\text{egger}}=0.131$; for GG versus GA + AA, $P_{\text{egger}}=0.342$).

DISCUSSION

Pancreatic cancer is a highly malignancy for which only a small number of risk factors have been identified. And there are much number of genetic syndromes contributes to increase the risk of pancreatic cancer, but little has been absolutely known about. TNF- α is a classic inflammatory factor with strong immunostimulatory activity and plays a pivotal role in the inflammatory etiology of pancreatic cancer. It has reported that the TNF- α have been shown to be elevated with more advanced disease stage in cancer patients (Aderka et al, 1991). Polymorphisms of TNF- α gene have been related to TNF- α production and outcome in malignant diseases (Lu et al., 2010; Wang et al., 2011; Yin et al., 2012). Pro-inflammatory cytokines and the inflammatory state then affect outcome of pancreatic cancer. Accumulated studies have explored the association between TNF- α 308G/A polymorphism and risk of pancreatic cancer (Barber et al., 1999; Beranek et al., 2003; Duell et al., 2006; Reyes-Gibby et al., 2009; Talar-Wojnarowska et al., 2009; Wu et al., 2010; Zhang et al., 2012), however, the conclusion remains unclear yet.

In the present study, we investigated the association between TNF- α 308G/A polymorphism and pancreatic cancer susceptibility by included five studies involving a total of 689 cases and 1331 controls. From our pooled data, we found no evidence of correlation between TNF- α 308G/A polymorphism and pancreatic cancer susceptibility in Caucasian population. Moreover, these five studies were highly homogenous although performed in different countries, and publish bias analysis also showed that there was no publish bias existed in the five studies, further supporting our conclusion.

There are some limitations needed to be considered in our study. Firstly, we did not evaluate the pancreatic cancer susceptibility of this polymorphism in other than Caucasian population due to lack of sufficient data on TNF- α 308G/A polymorphism and pancreatic cancer risk in Asian population and other population. Secondly, every study in this meta-analysis was strictly selected and performed, but some other related factors not considered yet may affect our meta-analysis results. Finally, the study size was relatively limited in our meta-analysis especially in populations other than Caucasian descents, therefore, more studies with larger sample size were greatly needed to confirm the TNF- α 308G/A polymorphism and pancreatic cancer susceptibility.

In conclusion, the present study is the first meta-analysis to exam the association between TNF- α 308G/A polymorphism and pancreatic cancer risk. The result indicated that the TNF- α 308G/A polymorphism may be have no association with pancreatic cancer susceptibility in Caucasian population.

REFERENCES

- Aderka D, Englemann H, Hornik V et al (1991). Increased serum levels of soluble receptors for tumor necrosis factor in cancer patients. *Cancer Res.* 51: 5602-07.
- Barber MD, Powell JJ, Lynch SF, et al (1999). Two polymorphisms of the tumour necrosis factor gene do not influence survival in pancreatic cancer. *Clin. Exp. Immunol.* 117: 425-29.
- Beranek H, Teich N, Witt H, et al (2003). Analysis of tumour necrosis factor alpha and interleukin 10 promoter variants in patients with chronic pancreatitis. *Eur. J. Gastroenterol. Hepatol.* 15: 1223-27.
- Capurso G, Festa S, Valente R, et al (2012). Molecular pathology and genetics of pancreatic endocrine tumours. *J. Mol. Endocrinol.* 49: R37-50.
- Duell EJ, Casella DP, Burk RD, et al (2006). Inflammation, genetic polymorphisms in proinflammatory genes TNF-A, RANTES, and CCR5, and risk of pancreatic adenocarcinoma. *Cancer Epidemiol. Biomarkers Prev.* 15: 726-731.
- Feig C, Gopinathan A, Neesse A, et al (2012). The pancreas cancer microenvironment. *Clin. Cancer Res.* 18: 4266-4276.
- Lu PH, Tang Y, Li C, et al (2010). [Meta-analysis of association of tumor necrosis factor alpha-308 gene promoter polymorphism with gastric cancer]. *Zhonghua Yu Fang Yi Xue Za Zhi* 44: 209-14.
- Mazaki T, Masuda H, Takayama T (2011). Polymorphisms and pancreatic cancer risk: a meta-analysis. *Eur. J. Cancer Prev.* 20: 169-83.
- Melton SD, Genta RM, Souza RF (2010). Biomarkers and molecular diagnosis of gastrointestinal and pancreatic neoplasms. *Nat. Rev. Gastroenterol. Hepatol.* 7: 620-628.
- Reyes-Gibby CC, Shete S, Yennurajalingam S, et al (2009). Genetic and nongenetic covariates of pain severity in patients with adenocarcinoma of the pancreas: assessing the influence of cytokine genes. *J. Pain Symptom Manage.* 38: 894-902.
- Talar-Wojnarowska R, Gasiorowska A, Smolarz B, et al (2009). Tumor necrosis factor alpha and interferon gamma genes polymorphisms and serum levels in pancreatic adenocarcinoma. *Neoplasma.* 56: 56-62.
- Wang J, Cao C, Luo H, et al (2011). Tumour necrosis factor alpha -308G/A polymorphism and risk of the four most frequent cancers: a meta-analysis. *Int. J. Immunogenet.* 38: 311-20.
- Wang J, Jin X, Wang H et al. (2013). The -308G/A polymorphism of the tumor necrosis factor-alpha gene is associated with the risk of upper aerodigestive tract cancer: a meta-analysis. *Tohoku J. Exp. Med.* 229: 245-54.
- Wu GY, Lu Q, Hasenberg T, et al (2010). Association between EGF, TGF- β 1, TNF- α gene polymorphisms and cancer of the pancreatic head. *Anticancer Res.* 30: 5257-5261.
- Yin YW, Hu AM, Sun QQ et al. (2012). Association between tumor necrosis factor-alpha gene -308A/G polymorphism and the risk of acute pancreatitis: a meta-analysis. *J. Surg. Res.* 178: 409-414.
- Zhang HL, Zhang YJ (2013). A systemic assessment of the association between tumor necrosis factor alpha 308 G/A polymorphism and risk of cervical cancer. *Tumour Biol.* 34: 1659-1665.
- Zhang L, Wu G, Herrle F, et al. (2012). Single nucleotide polymorphisms of genes for EGF, TGF-beta and TNF-alpha in patients with pancreatic carcinoma. *Cancer Genomics Proteomics* 9: 287-295.