

## RESEARCH ARTICLE

# Influence of Propofol, Isoflurane and Enflurance on Levels of Serum Interleukin-8 and Interleukin-10 in Cancer Patients

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## Abstract

**Objective:** To observe the influence of propofol, isoflurane and enflurance on interleukin-8 (IL-8) and IL-10 levels in cancer patients. **Methods:** Ninety cancer patients with selective operation from March 2011 to May 2014 were randomly divided into group A (34 cases), group B (28 cases) and group C (28 cases). Intramuscular injections of scopolamine hydrochloride and phenobarbital sodium were routinely conducted to 3 groups. After general anesthesia was induced, tracheal intubations were given. During the maintenance of anesthesia, 0.5~1.0 mg/kg propofol was intravenously injected to group A discontinuously, while continuous suction of isoflurane and enflurance were subsequently performed to group B and C correspondingly. Clinical outcomes, postoperative complications as well as serum IL-8 and IL-10 levels before operation (T0), at the time of skin incision (T1), 3 h after the beginning of the operation (T2) and 24 h (T3) and 72 h (T4) after the operation were observed among 3 groups. **Results:** Operations in all groups were successfully completed. The rates of surgery associated complications were 8.82% (3/34), 7.14% (2/28) and 7.14% (2/28) in group A, B and C, respectively, and there were no significant differences ( $P>0.05$ ). Serum IL-8 and IL-10 levels increased gradually from the beginning of the operation and reached the peak at T3, and were evidently higher at each time point than at T0 ( $P<0.01$ ). At T1, serum IL-8 and IL-10 levels had no significant differences among 3 groups ( $P>0.05$ ), but the differences were significant at T2, T3 and T4 ( $P<0.05$ ). Moreover, correlation analysis suggested that serum IL-8 level was in positive relation with IL-10 level ( $r=0.952, P<0.01$ ). **Conclusions:** Propofol, which is better in inhibiting serum IL-8 secretion and improving IL-10 secretion than isoflurane and enflurance, can be regarded as a preferable anesthetic agent in inhibiting traumatic inflammatory responses.

**Keywords:** Propofol - isoflurane - enflurance - tumor - traumatic inflammation - cytokines - interleukin-8 - interleukin-10

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## Introduction

Pro-inflammatory cytokine and anti-inflammatory cytokine, maintaining a certain balance in healthy population, often expressed disorderly in cancer patients, and the surgery induced traumatic inflammation could aggravate their imbalance and disorder (Ziebell et al., 2010; Jawa et al., 2011; Marik et al., 2012). Studies have shown that anesthetic agents have certain impact on the secretion of isolated cytokine, but their effects on the expressions of isolated cytokine in vivo are still controversial (Hofstetter et al., 2005; Ward et al., 2011; Mawhinney et al., 2012). This study mainly observed the influence of propofol, isoflurane and enflurance on the expressions of interleukin-8 (IL-8) and IL-10 in cancer patients.

## Materials and Methods

### General data

Ninety cancer patients with selective operations in our hospital from March 2011 to May 2014 were diagnosed

pathologically at degree I~II according to American Society Of Anesthesiologists (ASA), and received no radio- or/and chemotherapy before the operations. All patients were randomly divided into group A (34 cases), group B (28 cases) and group C (28 cases). In group A, there were 20 males and 14 females, aged 31~65 years, with average age being (59.23±2.41) years. In group B, there were 13 males and 15 females, aged 30~65 years, with average age being (59.48±2.57) years. And in group C, there were 14 males and 14 females, aged 30~64 years, with average age being (59.53±2.39) years. Three groups are comparable as there were no significant differences in the general data, such as gender and age ( $P>0.05$ ).

### Methods

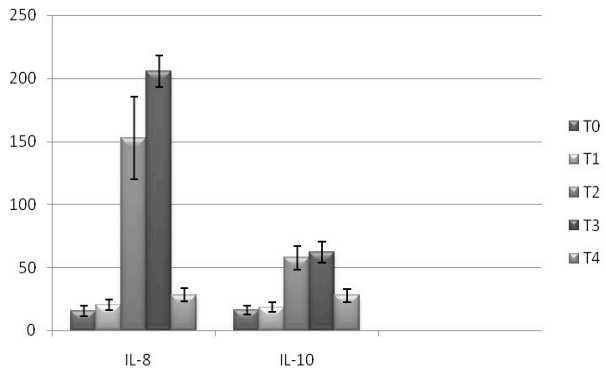
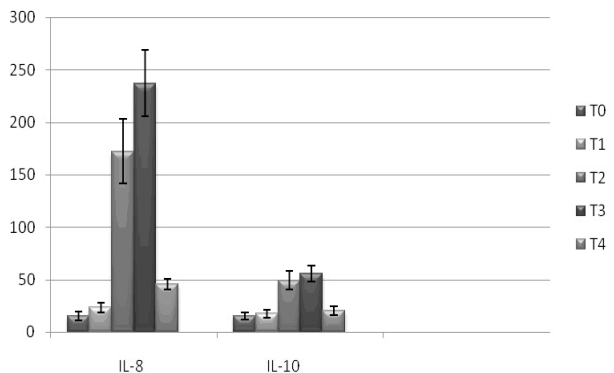
Anesthetic methods: 30 min before operation, intramuscular injection of 0.3 mg scopolamine hydrochloride and 100 mg phenobarbital sodium were routinely given, followed by induced anesthesia with induced drugs including 0.1 mg/kg midazolam, 3~5 g/kg fentanyl and 1~1.5 mg/kg succinylcholine chloride. After tracheal intubation, anesthesia machine was connected to conduct

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**Table 1. Serum IL-8 and IL-10 Expression Changes before and after Operations among 3 Groups ( $\bar{x}\pm s$ ) pg/mL**

Detecting time	IL-8			IL-10		
	A group (n=34)	B group (n=28)	C group (n=28)	A group (n=34)	B group (n=28)	C group (n=28)
T <sub>0</sub>	15.34±4.17	14.67±4.28	15.29±4.27	16.24±3.27	15.83±4.17	15.34±3.56
T <sub>1</sub>	20.33±4.36**	21.49±3.75**	23.35±4.68**	18.54±3.66**	18.46±3.52*	17.49±4.11*
T <sub>2</sub>	152.37±32.75** <sup>#</sup> △	180.31±20.65**	172.33±30.49**	57.76±9.41** <sup>#</sup> △	50.14±6.43**	49.36±8.74**
T <sub>3</sub>	205.48±12.38** <sup>#</sup> △	234.38±39.71**	237.16±31.48**	62.35±8.37** <sup>#</sup> △	57.47±7.09**	55.82±7.69
T <sub>4</sub>	28.36±5.17** <sup>#</sup> △	54.06±4.28** <sup>#</sup> △	45.69±4.75**	27.94±5.33** <sup>#</sup> △	22.93±4.67** <sup>#</sup> △	20.46±4.23**

Compared with T<sub>0</sub>, \*P<0.05, \*\*P<0.01; Compared with B group, #P<0.05; Compared with C group, △P<0.05

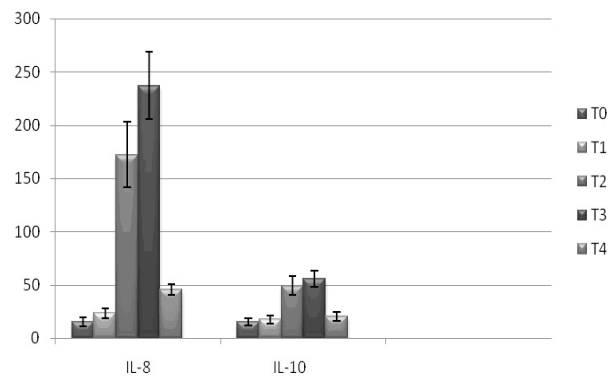
**Figure 1. Serum IL-8 and IL-10 Expression Changes at Different Time Points in Group A****Figure 2. Serum IL-8 and IL-10 Expression Changes at Different Time Points in Group B**

mechanical ventilation, with tidal volume, respiratory frequency and respiratory time ratio being 10 mL/kg, 13 times/min and 1:2, respectively. Discontinuous intravenous injections of fentanyl and vecuronium bromide were performed. During the maintenance of anesthesia, 0.5~1.0 mg/kg propofol was intravenously injected to group A discontinuously, while continuous suction of isoflurane and enflurane were subsequently performed to group B and C correspondingly, with volume fraction being 0.6%~1.0%.

Detecting methods: 3 mL venous blood was collected at each time point from all people. Kits were provided by French Immun Otech Company. The expressions of serum IL-8 and IL-10 were detected by enzyme-linked immunosorbent assay (ELLSA), with sensitivities being 31 pg/mL and 15 pg/mL respectively, which had strong specificity without cross reaction with other cytokines. The above operations were conducted strictly according to the instructions.

#### Observational indexes

Clinical outcomes, postoperative complications as

**Figure 3. Serum IL-8 and IL-10 Expression Changes at Different Time Points in Group C**

well as the levels of serum IL-8 and IL-10 before the operation (T<sub>0</sub>), at the time of skin incision (T<sub>1</sub>), 3 h after the beginning of the operation (T<sub>2</sub>) and 24 h (T<sub>3</sub>) and 72 h (T<sub>4</sub>) after the operation were observed among 3 groups.

#### Statistical data analysis

SPSS19.0 software was applied for all data analysis. Enumeration data was expressed by % and analyzed by X<sup>2</sup> test, while measurement data was expressed by mean±standard deviation ( $\bar{x}\pm s$ ) and analyzed by t test. Comparisons among groups were analyzed by variance analysis. P<0.05 was considered to be significantly different.

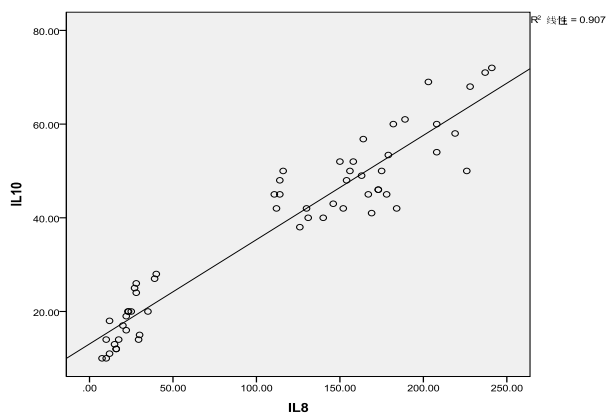
## Results

#### Clinical outcomes and postoperative complications in 3 groups

Operations were all successfully completed. The average hospital stays were (16.25±3.37) d, (15.72±3.24) d and (16.41±3.35) d, and the complication rates were 8.82% (3/34), 7.14% (2/28) and 7.14% (2/28) in groups A, B and C, respectively, and there were no significant differences (P>0.05).

#### Serum IL-8 and IL-10 expression changes before and after treatment among 3 groups

The levels of serum IL-8 and IL-10 had no significant difference among 3 groups before the operation (P>0.05). After the operation, serum IL-8 and IL-10 levels increased gradually and reached the peak at T<sub>3</sub>, and were evidently higher at each time point than at T<sub>0</sub> (P<0.01). Variance analysis indicated that at T<sub>1</sub>, serum IL-8 and IL-10 levels had no significant differences among 3 groups (P>0.05), but the level of IL-8 was obviously lower and the level of IL-10 was evidently higher at T<sub>2</sub> and T<sub>3</sub> in group A than



**Figure 4. Correlation Analysis of IL-8 and IL-10 Expressions**

in the other 2 groups ( $P < 0.05$ ). However, the difference was not significant between group B and C ( $P > 0.05$ ). Additionally, the levels of serum IL-8 and IL-10 had significant differences among 3 groups at T4 ( $P < 0.05$ ). Relevance analysis suggested that the level of serum IL-8 was in positive relation with IL-10 level ( $r = 0.952$ ,  $P < 0.01$ ). As shown in Table 1 and Figures 1~3.

#### Correlation analysis of IL-8 and IL-10 expressions

As shown in Figure 4, the levels of serum IL-8 and IL-10 showed similar increasing and decreasing trends after operation and Pearson correlation analysis demonstrated that the level of IL-8 was in positive association with IL-10 level in all groups ( $r = 0.952$ ,  $P < 0.01$ ).

## Discussion

Immunological dysfunction, which is common in cancer patients and can be aggravated by surgery-induced traumatic inflammation, becomes one of the important risk factors for cancer (Franca et al., 2013; Yu et al., 2014). With the development of molecular biology, cytokine has received more and more attentions due to its critical role in traumatic inflammatory responses. During the surgery, inflammatory mediators, like C-reactive protein, cortisol hormone and cytokines, are released in large abundance, which activate the inflammatory cells and constantly exacerbate the inflammatory responses. A researcher proposed that the balance between pro-inflammatory cytokines (IL-8 and tumor necrosis factor- $\alpha$ ) and anti-inflammatory cytokines (IL-4 and IL-10) was beneficial to eliminating the adverse impacts result from traumatic inflammatory responses and promoting the recovery of diseases (Allahtavakoli et al., 2011; de Lima et al., 2011; Sun et al., 2011; Gabel et al., 2013; Shen et al., 2013; Verit et al., 2013; Yang et al., 2013; Zhao et al., 2013; Guo et al., 2014; Kma et al., 2014; Lu et al., 2014; Pandurangan et al., 2014; Soliman et al., 2014).

IL-8 is a kind of inflammatory cytokine produced by mononuclear macrophages and vascular endothelial cells with stronger chemotaxis. It can improve the aggregation of neutrophils on inflammatory locations and induce their degeneration and degranulation and the release of elastase. Therefore, it can produce active oxygen species that may directly damage histocytes. Abundant researches suggested

that serum IL-8 expression increased significantly during surgery of cancer patients (Tylman et al., 2011; Veenhof et al., 2011). IL-10 is an anti-inflammatory cytokine that has immune-regulating function in cellular immunity, which can inhibit monocytes from secreting pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6 and IL-8, and reduce major histocompatibility complex II (MHCII) on antigen-presenting cells. In addition, it can promote the release of anti-inflammatory mediators like TNF soluble receptor I and II and IL-1 receptor antagonist, etc..

The influences of different anesthetic agents on serum cytokine expressions of surgical patients have become a hot-topic in recent researches (Schilling et al., 2011; Lisowska et al., 2013). Multiple studies found that anesthetic agents had significant influence on serum cytokines in patients who underwent surgeries (Dermitzaki et al., 2009; Reikeras et al., 2010). Propofol, as one of the anesthetic agents commonly used in clinic, has favorable sedation, anti-inflammatory responses and anti-oxidation characteristics (Cavalca et al., 2008; Gonzalez-Correa et al., 2008). A report revealed that during septicopyemia, propofol could effectively suppress the release of pro-inflammatory cytokines TNF- $\alpha$ , IL-6 and IL-8 and alleviate the lung infiltration of neutrophils and acidosis (Taniguchi et al., 2002), which was predicated to be closely associated with the action of propofol on the calcium ion ( $Ca^{+}$ ) pathway in cell membrane due to the important role of  $Ca^{+}$  pathway played in the cytokine secretion process. Some scholars used propofol and sevoflurane to 2 groups respectively and found that patients in sevoflurane secreted more inflammatory cytokines TNF- $\alpha$ , IL-6 and IL-10 and led to more severe damage on lung function, indicating that propofol could reduce the release of pro-inflammatory cytokines (Jin et al., 2013). However, Tylman (Tylman et al., 2011) et al believed that these 2 anesthetic agents had similar impact on patients' immunological responses. Baki (Baki et al., 2013) et al randomly divided 40 patients with coronary artery diseases underwent selective operations into 2 groups and treated with propofol and desflurane respectively, and the results demonstrated that serum IL-6 and IL-8 levels in propofol group were evidently higher than those in desflurane group. Inhalation anesthesia of isoflurane or enflurance is commonly used in clinic, whose effect on organic cytokine expressions has become the research focus of abundant scholars (Kumakura et al., 2013). Experimental study suggested that isoflurane might trigger cell damage by bringing about the increase of pro-inflammatory cytokines (TNF- $\alpha$ ) in rats in vivo (Lin et al., 2011; Lopez-Astacio et al., 2012). Inhalation of isoflurane or enflurance under mechanical ventilation may aggravate the pro-inflammatory cytokine induced injury on human bodies by increasing the transcription of TNF- $\alpha$  mRNA to increase the plasma expression level. Additionally, most researchers presented that propofol could better improve the release of anti-inflammatory cytokines and inhibit pro-inflammatory cytokines than other anesthetic agents such as isoflurane and enflurance, etc. (Abdulsalam et al., 2013; Erol et al., 2014; Kusku et al., 2014).

This study compared the influence of propofol, isoflurane and enflurance on the levels of serum pro-inflammatory cytokine IL-8 and anti-inflammatory

cytokine IL-10 in cancer patients, which discovered that the levels of serum IL-8 and IL-10 showed synchronous variation trend and group A was apparently higher in the level of IL-10 but had relevantly lower ascending range of IL-8 level than other 2 groups, demonstrating that propofol had more remarkable anti-inflammatory response than isoflurane and enflurance and could better reduce the traumatic inflammatory response. Meanwhile, this study also found that the level of serum IL-10 ascended almost synchronously with IL-8 level and there was positive association, suggesting that cytokine secretion in vivo was similar to network, marked by compensatory increase of IL-10 secretion due to the ascending IL-8 level so as to maintain the balance of pro- and anti-inflammatory cytokines, which was consistent with relevant report (Lisowska et al., 2013). Though the influence of propofol on cytokines proved in this study, no unfavorable prognosis (sepsis and multiple organ failure) was observed in all patients in the following clinical observation, indicating that the selection of anesthetic agents that influenced the balance of cytokines had played no effect on immune homeostasis of human body. However, as to high risk patients who need long-term anesthetic agents for sedation or analgesia, the agents should be strictly selected in order to promote cytokines in maintaining balanced state.

## References

- Allahtavakoli M, Jarrott B (2011). Sigma-1 receptor ligand PRE-084 reduced infarct volume, neurological deficits, pro-inflammatory cytokines and enhanced anti-inflammatory cytokines after embolic stroke in rats. *Brain Res Bull*, **85**, 219-24.
- Baki ED, Aldemir M, Kokulu S, et al (2013). Comparison of the effects of desflurane and propofol anesthesia on the inflammatory response and S100 $\beta$  protein during coronary artery bypass grafting. *Inflammation*, **36**, 1327-33.
- Cavalca V, Colli S, Veglia F, et al (2008). Anesthetic propofol enhances plasma  $\gamma$ -tocopherol levels in patients undergoing cardiac surgery. *Anesthesiology*, **108**, 988-97.
- de Lima FM, Villaverde AB, Albertini R, et al (2011). Dual Effect of low-level laser therapy (LLLT) on the acute lung inflammation induced by intestinal ischemia and reperfusion: Action on anti- and pro-inflammatory cytokines. *Lasers Surg Med*, **43**, 410-20.
- Dermitzaki E, Staikou C, Petropoulos G, et al (2009). A randomized study of maternal serum cytokine levels following cesarean section under general or neuraxial anesthesia. *Int J Obstet Anesth*, **18**, 33-7.
- Ekin A, Donmez F, Taspinar V, Dikmen B (2013). Patient-controlled sedation in orthopedic surgery under regional anesthesia: a new approach in procedural sedation. *Rev Bras Anesthesiol*, **63**, 410-4.
- Erol İM, Özdoğan L, Örnek D, et al (2014). Effect of Ketamine on the Quality of Anesthesia and Postoperative Analgesia in Epidural Anesthesia. *J Exp Clin Med*, **6**, 83-9.
- Franca EL, Franca-Botelho Ado C, Franca JL, et al (2013). Repercussions of breastfeeding by diabetic women for breast cancer. *Asian Pac J Cancer Prev*, **14**, 6233-9.
- Gäbel J, Westerberg M, Bengtsson A, et al (2013). Cell salvage of cardiomyotomy suction blood improves the balance between pro- and anti-inflammatory cytokines after cardiac surgery. *Eur J Cardiothorac Surg*, **44**, 506-11.
- Guo JR, Xu F, Jin XJ, et al (2014). Impact of allogenic and autologous transfusion on immune function in patients with tumors. *Asian Pac J Cancer Prev*, **15**, 467-74.
- Gonzalez-Correa JA, Cruz-Andreotti E, Arrebola MM, et al (2008). Effects of propofol on the leukocyte nitric oxide pathway: in vitro and ex vivo studies in surgical patients. *Naunyn Schmiedebergs Arch Pharmacol*, **376**, 331-9.
- Hofstetter C, Flondor M, Boost KA, et al (2005). A brief exposure to isoflurane (50 s) significantly impacts on plasma cytokine levels in endotoxemic rats. *Int Immunopharmacol*, **5**, 1519-22.
- Jawa RS, Anillo S, Huntoon K, et al (2011). Analytic review: interleukin-6 in surgery, trauma, and critical care: part I: basic science. *J Intensive Care Med*, **26**, 3-12.
- Jin Y, Zhao X, Li H, et al (2013). Effects of sevoflurane and propofol on the inflammatory response and pulmonary function of perioperative patients with one-lung ventilation. *Exp Ther Med*, **6**, 781.
- Kusku A, Demir G, Cukurova Z, et al (2014). Monitorization of the effects of spinal anaesthesia on cerebral oxygen saturation in elder patients using near-infrared spectroscopy. *Braz J Anesthesiol*, **64**, 241-6.
- Kma L (2014). Plant extracts and plant-derived compounds: promising players in a countermeasure strategy against radiological exposure. *Asian Pac J Cancer Prev*, **15**, 2405-25.
- Kumakura S, Yamaguchi K, Sugasawa Y, et al (2013). Effects of nitrous oxide on the production of cytokines and chemokines by the airway epithelium during anesthesia with sevoflurane and propofol. *Mol Med Rep*, **8**, 1643-8.
- Lin D, Zuo Z (2011). Isoflurane induces hippocampal cell injury and cognitive impairments in adult rats. *Neuropharmacology*, **61**, 1354-9.
- Lisowska B, Szymańska M, Nowacka E, et al (2013). Anesthesiology and the cytokine network. *Postepy Hig Med Dosw (Online)*, **67**, 761-9.
- Lopez-Astacio RA, Jimenez E, Hernandez A, et al (2012). Isoflurane-induced impairments in rodents exposed to a novel object recognition task. *FASEB J*, **2012**, lb835.
- Lu K, Song XL, Han SL, et al (2014). Potential study perspectives on mechanisms and correlations between adiposity and malignancy. *Asian Pac J Cancer Prev*, **15**, 1057-60.
- Marik PE, Flemmer M (2012). The immune response to surgery and trauma: Implications for treatment. *J Trauma Acute Care Surg*, **73**, 801-8.
- Mawhinney LJ, de Rivero Vaccari JP, Alonso OF, et al (2012). Isoflurane/nitrous oxide anesthesia induces increases in NMDA receptor subunit NR2B protein expression in the aged rat brain. *Brain Res*, **1431**, 23-34.
- Pandurangan AK, Esa NM (2014). Signal transducer and activator of transcription 3 - a promising target in colitis-associated cancer. *Asian Pac J Cancer Prev*, **15**, 551-60.
- Reikerås O (2010). Immune depression in musculoskeletal trauma. *Inflamm Res*, **59**, 409-14.
- Schilling T, Kozian A, Senturk M, et al (2011). Effects of volatile and intravenous anesthesia on the alveolar and systemic inflammatory response in thoracic surgical patients. *Anesthesiology*, **115**, 65-74.
- Shen B, Zheng MQ, Lu JW, et al (2013). CXCL12-CXCR4 promotes proliferation and invasion of pancreatic cancer cells. *Asian Pac J Cancer Prev*, **14**, 5403-8.
- Soliman NA, Zineldeen DH, El-Khadrawy OH (2014). Effect of NUCKS-1 overexpression on cytokine profiling in obese women with breast cancer. *Asian Pac J Cancer Prev*, **15**, 837-45.
- Sun T, Wang X, Liu Z, et al (2011). Plasma concentrations of pro- and anti-inflammatory cytokines and outcome prediction

- in elderly hip fracture patients. *Injury*, **42**, 707-13.
- Taniguchi T, Kankura H, Yamato K (2013). Effects of posttreatment with propofol on mortality and cytokine responses to endotoxin-induced shock in rat. *Crit Care Med*, **30**, 904-7.
- Tylman M, Sarbinowski R, Bengtson JP, et al (2011). Inflammatory response in patients undergoing colorectal cancer surgery: the effect of two different anesthetic techniques. *Minerva Anestesiol*, **77**, 275-82.
- Veenhof A, Sietses C, von Blomberg BME, et al (2011). The surgical stress response and postoperative immune function after laparoscopic or conventional total mesorectal excision in rectal cancer: a randomized trial. *Int J Colorectal Dis*, **26**, 53-9.
- Verit FF, Yucel O (2013). Endometriosis, leiomyoma and adenomyosis: the risk of gynecologic malignancy. *Asian Pac J Cancer Prev*, **14**, 5589-97.
- Ward JL, Harting MT, Cox Jr CS, et al (2011). Effects of ketamine on endotoxin and traumatic brain injury induced cytokine production in the rat. *J Trauma*, **70**, 1471.
- Yang L, Sun MJ, Liu JW, et al (2013). IL-6-6331 (T/C, rs10499563) is associated with decreased risk of gastric cancer in Northern Chinese. *Asian Pac J Cancer Prev*, **14**, 7467-72.
- Yu DP, Han Y, Zhao QY, et al (2014). CD3+ CD4+ and CD3+ CD8+ lymphocyte subgroups and their surface receptors NKG2D and NKG2A in patients with non-small cell lung cancer. *Asian Pac J Cancer Prev*, **15**, 2685-8.
- Zhao YH, Wang T, Yu GF, et al (2013). Anti-proliferation effects of interferon-gamma on gastric cancer cells. *Asian Pac J Cancer Prev*, **14**, 5513-8.
- Ziebell JM, Morganti-Kossmann MC (2010). Involvement of pro- and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. *Neurotherapeutics*, **7**, 22-30.