RESEARCH ARTICLE

# Correlations Between Serum IL33 and Tumor Development: a Meta-analysis

**Xiang-Jun Chen[1], Ying-De Huang[1], Nian Li[1], Min Chen[1], Fang Liu[1], Dan Pu[2], Tao-You Zhou[3]***

## Abstract

**Background: Interleukin-33 (IL-33) has recently been implicated in tumor development. Methods: Data was obtained from PubMed, EMBASE, Clinical trial, Cochrane Library, Web of Science, CNKI and Wanfang databases. After quality assessment and data extraction, a meta-analysis was performed using Review Manager 5. 2 software. Results: There were eight documents included in this meta-analysis. The results showed IL33 levels to be higher in tumor patients than that in health people, but no correlations tumor stage, metastasis and survival time of tumor patients were evident. Conclusion: IL33 may be useful as an alarm factor in tumor detection and prognosis.**

**Keywords:** IL33 - tumor - meta-analysis

*Asian Pac J Cancer Prev,* **15 (8)**, 3503-3505

## Introduction

Interleukin-33 (IL-33). is a novel cytokine belonging to the IL-1 family which was found in 2005 (Schmitz et al., 2005). It is found in various cells included fibroblasts, bronchial and epithelial cells, endothelial cells, and some immune cells, including macrophages and dendritic cells (Kakkar and Lee 2008). IL-33 is a multifunctional cytokine in immune regulation that activates Th1 cells, Th2 cells, CD8+T cells and NK cells (Chackerian et al., 2007; Bourgeois et al., 2009; Liew, et al., 2010; Bonilla et al., 2012). Accumulated data also demonstrated that immune cells play important role in tumor progress and prognosis (Dobrzanski et al., 2006; Williams and Bevan 2007). Moreover, IL-33 participates in many diseases with dual, proinflammatory or protective roles depending on the cellular and cytokine context, including infection-related diseases (such as parasitic and viral infection). (Walzl et al., 2001; Humphreys et al., 2008; Liew et al., 2010). However, the role of IL-33 in tumor progress and prognosis is unclear.

In this paper, we were attempt to reveal the role of IL-33 in tumor progress and prognosis by a meta analysis.

## Materials and Methods

A computerized literature search was conducted using Pubmed, MEDLINE, EMBASE and Chinese databases (including CNKI and WanFang database). from 1 January 2000 through 31 October 2013. The search strategy used medical subject heading (MeSH). terms and keywords "interleukin-33" or "IL-33"; "cancer", "tumor" or "neoplasm (s)" and "randomized controlled trials". We also manually reviewed the reference lists to identify additional relevant studies. No language restrictions were imposed.

*Data Extraction*

Two investigators independently performed the data extraction. When discrepancies were found, a third investigator would make the definitive decision for data extraction. The extracted information included: the first author's last name, publication year, study location, participant characteristics (age and sex), sample size, follow-up (yes or no), variables adjusted in the analysis.

*Statistical analysis*

The main outcomes were analyzed by using RveMan 5. 1 software. Chi-square and I-square tests were used to assess heterogeneity amongst the RCTs, when the results were $P>0.1$ and $I^2<50\%$, it mains there were no heterogeneity, and then fixed-effect model was analyzed; when $P<0.1$ and $I^2>50\%$, there were significant heterogeneity exist, we used random-effects statistical model.

## Results

*Generally data*

We first found 723 studies which met inclusion criteria,

*[1]Department of Medical Quality Control, [2]Clinical Skill Experiment Teaching Center, [3]Department of Infectious Disease, West China Hospital, Sichuan University, Chengdu, China *For correspondence: drchan_hxyy@mcwcums. com*

**Table 1. The General Data**

| First Author | Publishing year | Methohodogical quality | | | | | | Intervention | |
|---|---|---|---|---|---|---|---|---|---|
| | | Study design | Randomized method | Allocation concalment | Double -blind | Withdraw | Jaded score | Baseline | Outcomes |
| Sun | 2001 | RCT | Unclear | Unclear | Yes | Yes | 3 | Similar | RIT; TM; TS; TST |
| Naumnik | 2012 | RCT | Unclear | Unclear | Yes | Yes | 3 | Similar | RIT |
| Zhang | 2012 | RCT | Unclear | Unclear | No | Yes | 3 | Similar | RIT; TM |
| Bergis | 2013 | RCT | Unclear | Unclear | Yes | Yes | 2 | Similar | RIT; TS |
| Chen | 2013 | RCT | Unclear | Unclear | No | Yes | 3 | Similar | RIT |
| Gangemi | 2013 | RCT | Unclear | Unclear | No | Yes | 2 | Similar | RIT |
| Hu | 2013 | RCT | Unclear | Unclear | Yes | Yes | 3 | Similar | RIT; TS; TST |
| Santulli | 2013 | RCT | Unclear | Unclear | Yes | Yes | 3 | | RIT |

TS, tumor stage; TM: tumor metastasis; TST, tumor survival time; RIT, Relation between IL33 level and tumor

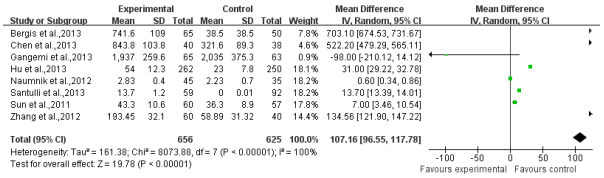


**Figure 1. The Meta-analysis Result of IL33 Level in Tumor**

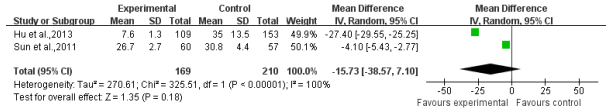


**Figure 2. The Meta-analysis Result of Relation between IL33 and Survival Time**

after reviewing carefully, all of the eight papers (Sun et al., 2011; Naumnik et al., 2012; Zhang et al., 2012; Bergis et al., 2013; Chen et al., 2013; Gangemi et al., 2013; Hu et al., 2013; Santulli et al., 2013). were included into this meta-analysis. The publication dates ranged from Jan 1, 1989 to Dec 31, 2013 (Figure 1).

*Methodological quality*

The characteristics of the included studies and Jadad score are shown in Table 1. No studies described randomized methods and allocation concealment. Five studies adopted double-blind, and the baseline of all researches was similar. All articles used the intent-to-treat analysis. The outcomes included the correlation between IL33 level and tumor, survival time, the correlation between IL33 level and tumor stage, the correlation between IL33 level and tumor metastasis.

*The meta-analysis results*

The correlation between IL33 expression level and lots of tumor: All of the eight included papers (Sun et al., 2011; Naumnik et al., 2012; Zhang et al., 2012; Bergis et al., 2013; Chen et al., 2013; Gangemi et al., 2013; Hu et al., 2013; Santulli et al., 2013). reported the correlation between IL33 expression level and tumors, there were 656 patients with tumors and 625 healthy people. The meta-analysis results shown that IL33 level in tumors patients is higher than that in healthy people ($P$<0.00001, 95%CI (96. 55, 117. 78))

The survival time: In here, two papers (Sun et al., 2011;

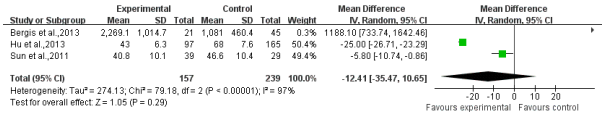


**Figure 3. The Meta-analysis Result of Relation between IL33 and Tumor Stage**

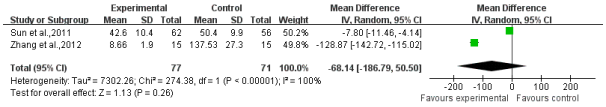


**Figure 4. The Meta-analysis Result of Relation between IL33 and Tumor Metastasis**

Hu et al., 2013). reported the correlation between IL33 expression level and survival time in tumors cases. The meta-analysis results shown there were not significantly differences between IL33 level and survival time ($P$=0.18, 95%CI (-38. 57, 7. 10)).

The correlation between IL-33 level and tumor stage: There were three researches (Sun et al., 2011; Bergis et al., 2013; Hu et al., 2013). described the correlation between IL33 level and tumor stage. The meta-analysis results shown that the IL33 level in I-II stage is not higher than III-IV stage ($P$=0.29, 95%CI (-35.47, 10.65)).

The correlation between IL33 expression level and tumor metastasis: There were two researches (Sun et al., 2011; Zhang et al., 2012). reported the correlation between IL33 level and tumor metastasis. The meta-analysis results shown that there were not significant differences between IL33 level and tumor metastasis ($P$=0.26, 95%CI (-186.79, 50.50)).

## Discussion

In this meta-analysis paper, we reported the IL-33 expression level is higher in tumor patients than that in healthy people, however, there are not significant differences between IL-33 expression level and survival time, tumor stage and tumor metastasis.

Interleukin-33 (IL-33). is a recently finding cytokine with lots of functions. IL-33 has been reported as a potent inducer of Th2 immune responses as well as “alarmin” cytokine released from necrotic cells (Arshad et al., 2012; Lopetuso et al., 2012; Roy et al., 2014). Recently, some

researches reported that IL-33 is play important role in tumorigenesis and tumor progress (Chen et al., 2013; Jovanovic et al., 2014)Serum IL-33 may be a useful indicator for prognosis of tumor (Sun et al., 2011). In here, our meta-analysis included eight papers results shown that IL33 expression level is higher in tumor patients that in healthy people, so, there is a clinical value that IL-33 can be as a potential diagnostic for tumor patient. Therefore, cumulative meta-analysis showed an increased accuracy with larger samples aggregated for the correlation in the estimate of the effects in IL-33 cytokine. However, there were not significant difference between IL-33 expression level and survival time, tumor stage and tumor metastasis, perhaps because less papers were included into this paper. Therefore, more reporting correlation between two should be needed.

IL-33 signaling is mediated via its receptor ST2L. The role of IL-33/ST2 axis has recently been implicated in cancer, but with limited data. The Bergis et al., (Bergis et al., 2013). reported the ST2 level is higher in tumor patients than in healthy people (1079. 6±310.1 vs 218. 6±45. 8, $P<0.05$). High ST2 levels have been found in malignant patients with lung cancer (Oshikawa et al., 2002). Moreover, it has been demonstrated that a lack of ST2 in ST-/- mice is associated with suppressed breast cancer prooression and metastasis (Jovanovic et al., 2011). However, there were limited documents describing the relation between ST2 and tumor. So, the correlation between ST2 level and tumor was not included into this meta-analysis.

In conclusion, this meta-analysis suggest that the IL33 level is higher in tumor patients than health people. However, there were not correlation between IL33 level and survival time, metastasis and stage of tumor. Moreover, more related documents should be supplemented.

## References

Arshad MI, Piquet-Pellorce C, Samson M (2012). IL-33 and HMGB1 alarmins: sensors of cellular death and their involvement in liver pathology. *Liver Int*, **32**, 1200-10.

Bergis D, Kassis V, Ranglack A, et al (2013). High serum levels of the interleukin-33 receptor soluble ST2 as a negative prognostic factor in hepatocellular carcinoma. *Transl Oncol*, **6**, 311-8.

Bonilla WV, Frohlich A, Senn K, et al (2012). The alarmin interleukin-33 drives protective antiviral CD8 (+). T cell responses. *Science*, **335**, 984–9.

Bourgeois E, Van LP, Samson M, et al (2009). The pro-Th2 cytokine IL-33 directly interacts with invariant NKT and NK cells to induce IFN-gamma production. *Eur J Immunol*, **39**, 1046–55.

Chackerian AA, Oldham ER, Murphy EE, et al (2007). IL-1 receptor accessory protein and ST2 comprise the IL-33 receptor complex. *J Immunol*, **179**, 2551–5.

Chen SF, Nieh S, Jao SW, et al (2013). The paracrine effect of cancer-associated fibroblast-induced interleukin-33 regulates the invasiveness of head and neck squamous cell carcinoma. *J Pathol*, **231**, 180-9.

Dobrzanski MJ, Reome JB, Hylind JC, et al (2006). CD8-mediated type 1 antitumor responses selectively modulate endogenous differentiated and nondifferentiated T cell localization, activation, and function in progressive breast cancer. *J Immunol*, **177**, 8191-201.

Gangemi S, Allegra A, Profita M, et al (2013). Decreased plasma levels of IL-33 could contribute to the altered function of Th2 lymphocytes in patients with polycythemia vera and essential thrombocythemia. *Cancer Invest*, **31**, 212-3.

Hu LA, Fu Y, Zhang DN, et al (2013). Serum IL-33 as a diagnostic and prognostic marker in non- small cell lung cancer. *Asian Pac J Cancer Prev*, **14**, 2563-6.

Humphreys NE, Xu D, Hepworth MR, et al (2008). IL-33, a potent inducer of adaptive immunity to intestinal nematodes. *J Immunol*, **180**, 2443-9.

Jovanovic IP, Pejnovic NN, Radosavljevic GD, et al (2014). Interleukin-33/ST2 axis promotes breast cancer growth and metastases by facilitating intratumoral accumulation of immunosuppressive and innate lymphoid cells. *Int J Cancer*, **134**, 1669-82.

Jovanovic I, Radosavljevic G, Mitrovic M, et al (2011). ST2 deletion enhances innate and acquired immunity to murine mammary carcinoma. *Eur J Immuno*, **l41**, 1902-12.

Kakkar R and Lee RT (2008). The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov*, **7**, 827–40.

Liew FY, Pitman N, McInnes IB (2010). Disease-associated functions of IL-33: the new kid in the IL-1 family, *Nat Rev Immunol*, **10**, 103–10.

Lopetuso LR, Scaldaferri F, Pizarro TT (2012). Emerging role of the interleukin (IL)-33/ST2 axis in gut mucosal wound healing and fibrosis. *Fibrogenesis Tissue Repair*, 5, 18.

Naumnik W, Naumnik B, Niewiarowska K, et al (2012). Novel cytokines: IL-27, IL-29, IL-31 and IL-33. Can they be useful in clinical practice at the time diagnosis of lung cancer?*Exp Oncol*, **34**, 348-53.

Oshikawa K, Yanagisawa K, Ohno S, et al (2002). Expression of ST2 in helper T lymphocytes of malignant pleural effusions. *Am J Respir Crit Care Med*, **165**, 1005-9.

Roy A, Ganesh G, Sippola H, et al (2014). Mast Cell Chymase Degrades the Alarmins Heat Shock Protein 70, Biglycan, HMGB1, and Interleukin-33 (IL-33). and Limits Danger-induced Inflammation. *J Biol Chem*, **289**, 237-50.

Santulli P, Even M, Chouzenoux S, et al (2013). Profibrotic interleukin-33 is correlated with uterine leiomyoma tumour burden. *Hum Reprod*, **28**, 2126-33.

Schmitz J, Owyang A, Oldham E, et al (2005). IL-33, an interleukin-1-likecytokine that signals via the IL-1 receptor-related protein ST2 and induces Thelper type 2-associated cytokines. *Immunity*, **23**, 479–90.

Sun P, Ben Q, Tu S, et al (2011). Serum interleukin-33 levels in patients with gastric cancer. *Dig Dis Sci*, **56**, 3596-601.

Walzl G, Matthews S, Kendall S, et al (2001). Inhibition of T1/ST2 during respiratory syncytial virus infection prevents T helper cell type 2 (Th2)-but not Th1-driven immunopathology. *J Exp Med*, **193**, 785-92.

Williams MA, Bevan MJ (2007). Effector and memory CTL differentiation, *Annu Rev Immunol*, **25**, 171-92.

Zhang P, Liu XK, Chu Z, et al (2012). Detection of interleukin-33 in serum and carcinoma tissue from patients with hepatocellular carcinoma and its clinical implications. *J Int Med Res*, **40**, 1654-61.