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**Original Paper**

# Circulating Insulin-Like Growth Factor-1 Level and Ovarian Cancer Risk

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**Key Words**
Ovarian cancer • Meta-analysis • Insulin-like growth factor-1

## Abstract

**Background/Aims:** Insulin-like growth factor-1 (IGF-1) has an important role in cells' proliferation, differentiation and apoptosis, and it may be involved in carcinogenesis. Several epidemiological studies assessed the association between circulating IGF-1 level and ovarian cancer risk, but there was still no conclusive finding. **Methods:** A meta-analysis of published studies was performed to assess the association between circulating IGF-1 level and ovarian cancer risk. The summary odds ratio (OR) with 95% confidence interval (95%CI) was calculated through meta-analysis to evaluate the strength of the association. **Results:** Five eligible studies were included into the meta-analysis, which involved a total of 2,028 cases of ovarian cancer and 4,625 controls. Meta-analysis of total 5 studies showed that high circulating IGF-1 level was correlated with decreased risk of ovarian cancer (OR = 0.84, 95%CI 0.74-0.97, P = 0.013). After adjusting for heterogeneity, high circulating IGF-1 level was still correlated with decreased risk of ovarian cancer (OR = 0.83, 95%CI 0.72-0.95, P = 0.007). Subgroup analysis by age showed that circulating IGF-1 level was not correlated with ovarian cancer risk in women both less than 55 years and more than 55 years. However, after adjusting for heterogeneity, high circulating IGF-1 level was correlated with decreased ovarian cancer risk in women less than 55 years (OR = 0.82, 95%CI 0.72-0.94, P = 0.004). **Conclusion:** Our meta-analysis suggests that high circulating IGF-1 level may be correlated with decreased ovarian cancer risk, especially in women less than 55 years. More studies are needed to further assess the association between circulating IGF-1 level and ovarian cancer risk in the future.

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**Cellular Physiology and Biochemistry**

Cell Physiol Biochem 2016;38:589-597

DOI: 10.1159/000438652
Published online: February 05, 2016

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## Introduction

Ovarian cancer is the most prevalent gynecological malignancy in the world, and its incidence is increasing in both developed and developing countries [1, 2]. Despite several medical advancements in the treatment of ovarian cancer, the survival rate has not improved significantly [3]. Many studies have been published to achieve the identification of effective biomarkers for ovarian cancer, such as carbohydrate antigen 125 (CA125) [4-7]. Identification of biomarkers for ovarian cancer not only can help us get a better understanding of the mechanism of ovarian cancer, but also can help us find some diagnostic biomarkers. Insulin-like growth factor-1 (IGF-1) has an important role in cells' proliferation, differentiation and apoptosis, and it may be involved in carcinogenesis [8-11]. Previous studies have shown that IGF-1 and its receptor are involved in cell's malignant transformation, and thereby the IGF system may be involved in the development or progression of ovarian cancer. Previous epidemiological studies have provided some evidence for the associations of circulating IGF-1 level with colorectal cancer, prostate cancer, and breast cancer [12-14]. However, other studies have found that circulating IGF-1 level is not associated with lung cancer risk [15]. There were also several epidemiological studies performed to assess the association between circulating IGF-1 level and ovarian cancer risk, but there was still no conclusive finding [16-23]. We thus performed a systematic review and meta-analysis of published epidemiological studies to evaluate the association between circulating IGF-1 level and ovarian cancer risk. We carried out the meta-analysis according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [24].

## Materials and Methods

### Data sources

A systematic literature search of all published studies on the association between circulating IGF-1 level and ovarian cancer risk was performed. We searched Pubmed (1980-2015), Embase (1980-2015), and Web of Science (1980-2015) up to June 26 2015. The following search strategy was used: (Ovarian cancer or ovarian carcinoma) AND (IGF1, IGF-1, insulin-like growth factor 1, insulin-like growth factor I, or IGF-I). We also searched the reference lists of relevant reviews on the subject. No language limitation was used in the literature search.

### Selection criteria

To be included into the meta-analysis, studies had to meet the following criteria: 1) prospective or retrospective cohort studies, nested case-control studies, or case-control studies; 2) Assessed the association between circulating IGF-1 level and ovarian cancer risk; 3) Reported risk estimates for the association between circulating IGF-1 level and ovarian cancer risk, such as odds ratio (OR) or relative risk (RR) with 95% confidence interval (95%CI); 4) Reported risk estimates adjusted for possible confounding factors. Case-only studies were excluded, and case reports or reviews were also excluded. When two or more studies appeared to be from one research, we included the most recent publication, or the one containing the largest number of cases. Studies without usable data were also excluded.

### Data extraction

Two investigators of the investigation teem performed the data extraction independently. They used a standardized data extraction form and extracted data from each included study, and disagreements were resolved by discussion. Data were extracted on first author, study design, time of follow-up, inclusion of cases, mean age of participants, control groups, matched factors, confounding factors, and risk estimates. The OR for highest vs. lowest group analysis was used in the meta-analysis.

### Quality assessment

The quality of included studies was assessed using the Newcastle Ottawa scale (NOS), which was recommended by the Cochrane Non-Randomized Studies Methods Working Group [25]. There was a

maximum of nine points for each included study, namely four points in the selection of participants, two points in the comparability of participants, and three points in the ascertainment of outcomes. Studies with 7-9 points were assigned to have excellent quality, studies with 4-6 points were assigned to have good quality, and studies with 0-3 points were assigned to have low quality.

*Statistical analysis*

To assess the association between circulating IGF-1 level and ovarian cancer risk, the summary OR with 95%CI was calculated through meta-analysis. As shown in the data extraction, the OR for highest vs. lowest group analysis was used in the meta-analysis. We used random-effect or fixed-effect meta-analysis to calculate the summary OR [26, 27]. The between-study heterogeneity was assessed using Cochran's Q statistic and the $I^2$ statistic [28, 29]. For the existence of obvious between-study heterogeneity (P< 0.10 for Cochran's Q statistic, or $I^2$ > 50%), random-effect model (DerSimonian and Laird model) was used [27]. When there was no obvious between-study heterogeneity (P> 0.10 for Cochran's Q statistic, or $I^2$ < 50%), the fixed-effect model (Mantel-Haenszel method) was used [26]. To test the credibility of the summary OR, single study was excluded by turns and the change in the pooled estimates was evaluated in the sensitivity analysis. Subgroup analyses were performed by study design and age. Publication bias was assessed by the inspection of funnel plot and computation of Egger's and Begg's tests. All statistical analyses were carried out using Stata statistical software (version 11.0. College Station, TX: Stata, 2010).

## Results

*Study selection and characteristics*

The literature search in Pubmed, Embase, and Web of Science yielded a total of 659 references (Fig. 1). After reviewing titles and abstracts, most studies were excluded and only 10 papers were selected as potentially relevant studies, which were further assessed for eligibility by reading full-text [16-23, 30, 31]. Three studies were further excluded for case-only studies [18, 21, 30], and two studies were excluded for containing overlapping data [19, 20]. Finally, five studies were included into the meta-analysis [16, 17, 22, 23, 31]. Table 1 showed the main characteristics of those 5 studies (Table 1). Four of those included studies were nested case-control studies, and the other one was case-control study (Table 1). The total number of ovarian cancer cases in each included study ranged from 59 to 1045, and the number of controls ranged from 108 to 2,058 (Table 1). There were a total of 2028 cases of ovarian cancer and 4625 controls in the meta-analysis. Those 5 studies were published

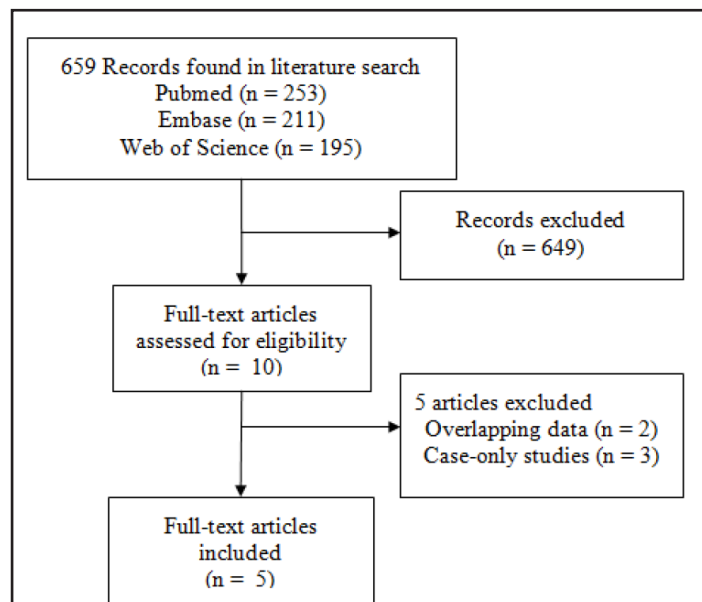**Fig. 1.** Flow chart showing the study selection in the meta-analysis.

**Cellular Physiology and Biochemistry**

Cell Physiol Biochem 2016;38:589-597

DOI: 10.1159/000438652
Published online: February 05, 2016

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**Table 1.** Characteristics of five included studies in the meta-analysis (H vs. L, Higher level of IGF-1 vs. low level of IGF-1)

| Study | Design | Country (Recruitment period) | Subjects | Adjustment | Comparison | Quality scores |
|---|---|---|---|---|---|---|
| Lukanova et al. 2002 [23] | Nested case-control | NYUWHS (New York, USA; 1985–1991); NSHDS (Umea, Sweden; 1986–2001); ORDET (Milan, Italy; 1987–1992) | 132 women with primary invasive epithelial ovarian cancer diagnosed at least 1 year after blood donation were case subjects, and 263 matched control subjects | Yes | H vs. L | 7 |
| Dal Maso et al. 2004 [22] | Case-control | Pordenone province, Italy (1999-2003) | 59 women with ovarian cancer and 108 non-neoplastic controls admitted to the same hospital network as cases | Yes | H vs. L | 6 |
| Tworoger et al. 2007 [31] | Nested case-control | NHS/NHSII (USA; 1996-2003); WHS (USA; 1992-2004) | 222 cases and 599 matched controls | Yes | H vs. L | 8 |
| Ose et al. 2015 [16] | Nested case-control | Denmark, France, Germany, Greece, Italy, Netherlands, Spain, and UK (1999-2003) | 565 ovarian cancer cases and 1097 matched controls | Yes | H vs. L | 9 |
| Schock et al. 2014 [17] | Nested case-control | Finnish Maternity Cohort (FMC), Finland (1983-2011) and NSMC, Sweden (1987-2013) | 1,045 ovarian cancer cases and 2,658 individually matched controls | Yes | H vs. L | 9 |

**Fig. 2.** Meta-analysis of the association between circulating IGF-1 level and ovarian cancer risk.
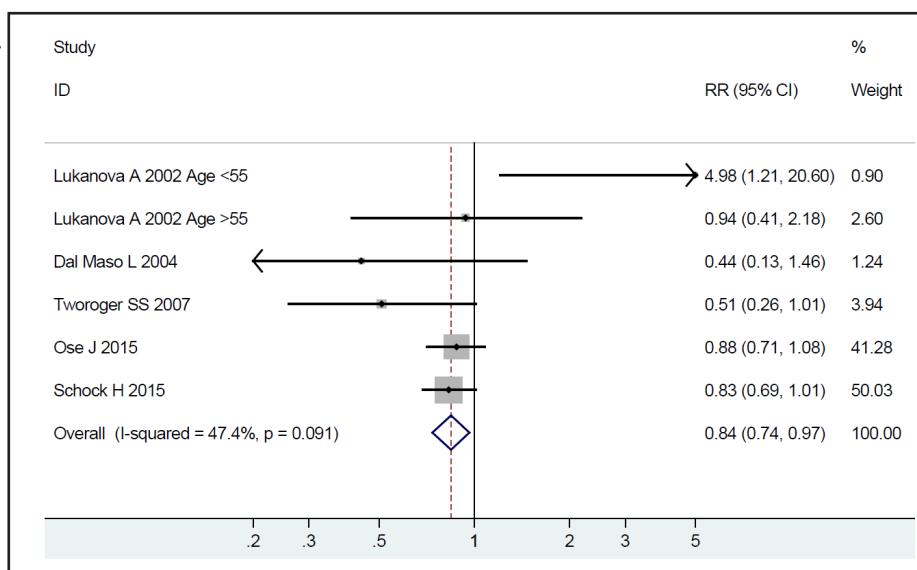


from 2002 to 2015, and all studies were performed in European countries or USA. Most controls in those included studies were healthy controls, and were matched to cases by age. All studies reported adjusted risk estimates, but the confounding factors were different from each other (Table 1). According to the quality scale, four studies had excellent quality with 7-9 stars, and one study had good quality (Table 1).

*Meta-analysis*

There was obvious between-study heterogeneity in the meta-analysis of total included studies (P = 0.09). Meta-analysis of total 5 studies showed that high circulating IGF-1 level was correlated with decreased risk of ovarian cancer (OR = 0.84, 95%CI 0.74-0.97, P = 0.013) (Fig. 2). When using sensitivity analysis, the summary ORs were changed obviously by excluding single study by turns. When performing sensitivity analysis, we also observed the change of between-study heterogeneity. When performing sensitivity analysis by excluding Lukanova's study, there was obvious decrease in the between-study heterogeneity (from 47% to 10%), and there was no statistically significant between-study heterogeneity (P =

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**Fig. 3.** Meta-analysis of the association between circulating IGF-1 level and ovarian cancer risk after adjusting heterogeneity.
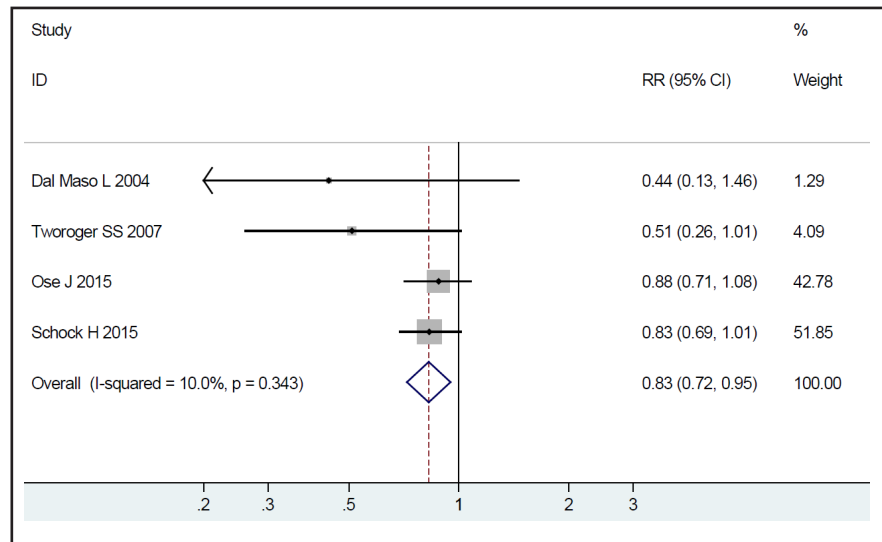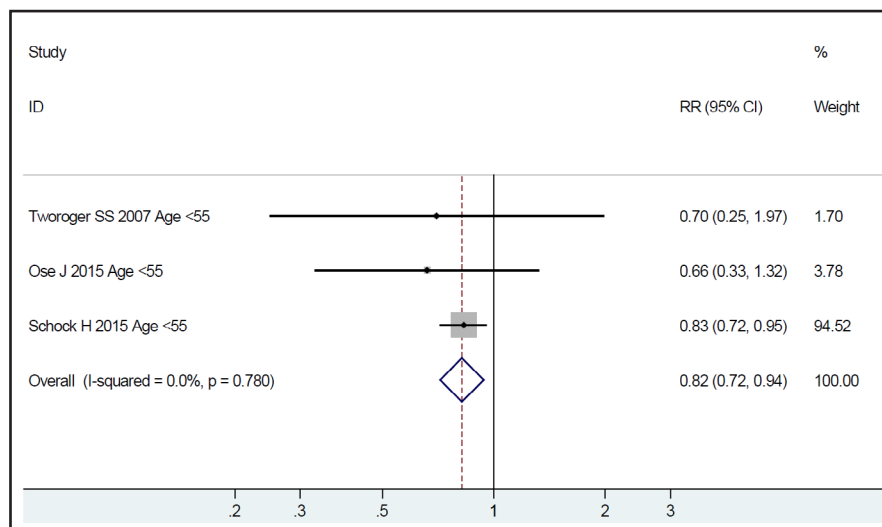


**Fig. 4.** High circulating IGF-1 level was correlated with decreased ovarian cancer risk in women less than 55 years.



0.34). After adjusting for heterogeneity by excluding Lukanova's study, high circulating IGF-1 level was still correlated with decreased ovarian cancer risk (OR = 0.83, 95%CI 0.72-0.95, P = 0.007) (Fig. 3).

In the subgroup analysis by study design, meta-analysis of 4 nested case-control studies showed that circulating IGF-1 level was not correlated with ovarian cancer risk (OR = 0.86, 95%CI 0.66-1.12, P = 0.26). Subgroup analysis by age showed that circulating IGF-1 level was not correlated with ovarian cancer risk in women both less than 55 years and more than 55 years. However, after adjusting for heterogeneity by excluding Lukanova's study, high circulating IGF-1 level was correlated with decreased ovarian cancer risk in women less than 55 years (OR = 0.82, 95%CI 0.72-0.94, P = 0.004) (Fig. 4). In addition, when using sensitivity analysis, the summary ORs were changed obviously by excluding single study by turns.

There was no indication of asymmetry in the funnel plot (Fig. 5), which was further supported by the results from the Egger's test (P = 0.86) and Begg's test (P = 0.71).

## Discussion

In present study, we performed a systematic review and meta-analysis of published studies to evaluate the association between circulating IGF-1 level and ovarian cancer risk.

**Fig. 5.** There was no indication of asymmetry in the funnel plot.
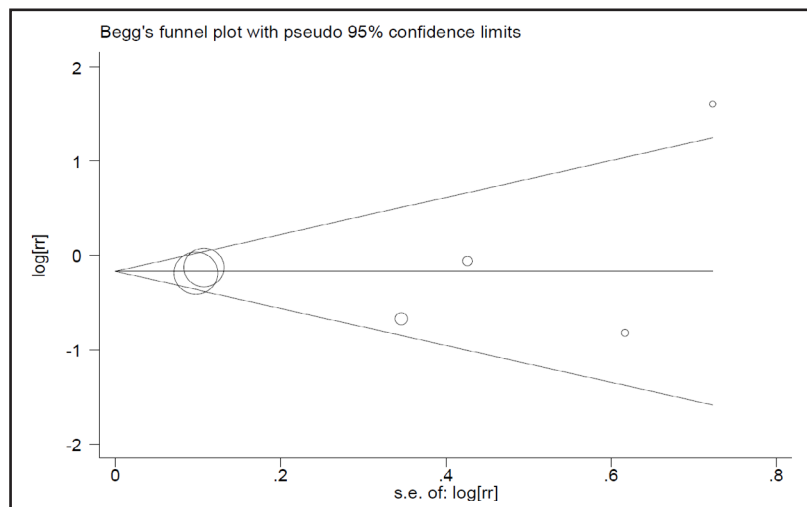


There were a total of 2028 cases of ovarian cancer and 4625 controls in the meta-analysis, which could help us to get a more appropriate evaluation on the association between circulating IGF-1 level and ovarian cancer risk. Meta-analysis of total 5 studies showed that high circulating IGF-1 level was correlated with decreased ovarian cancer risk (OR = 0.84, 95%CI 0.74-0.97, P = 0.013). After adjusting for heterogeneity, high circulating IGF-1 level was still correlated with decreased ovarian cancer risk (OR = 0.83, 95%CI 0.72-0.95, P = 0.007). After adjusting for heterogeneity, high circulating IGF-1 level was correlated with decreased ovarian cancer risk in women less than 55 years (OR = 0.82, 95%CI 0.72-0.94, P = 0.004). Therefore, our meta-analysis suggests that high circulating IGF-1 level may be correlated with decreased ovarian cancer risk, especially in women less than 55 years.

IGF-1 has important roles in promoting body growth, and it also has many other biological functions in different organs [32]. High circulating IGF-1 levels are also associated with various diseases, such as acromegaly [33, 34]. In addition, circulating IGF-1 has direct effects on cell's growth and proliferation, and high IGF-1 bioactivity may contribute to carcinogenesis and neoplastic progression [12-14]. High levels of serum IGF-1 has been identified to be associated with increased risk of colorectal cancer, prostate cancer, and breast cancer [12-14]. Besides, some agents targeting IGF-1 signaling are also promising in the treatment of some cancers [13, 35, 36]. Other factors in the IGF system are also likely to be potential therapeutic targets, and anticancer therapies aiming to target those factors are currently under investigation [13, 35, 36].

High levels of serum IGF-1 are associated with increased risk of colorectal cancer, prostate cancer, and breast cancer [12-14], which also prove that IGF-1 is intensively involved in the carcinogenesis of common cancers [37, 38]. It also has been proposed that IGF-1 may be involved in the carcinogenesis of ovarian cancer, and several epidemiological studies have been performed to assess the association between circulating IGF-1 level and ovarian cancer risk. Unfortunately, those studies failed to find a consistent finding on the association between circulating IGF-1 level and ovarian cancer risk. At present, there is still lack of compressive assessment for the impact of circulating IGF-1 level on ovarian cancer. In present, we showed a compressive assessment of the association between circulating IGF-1 level and ovarian cancer risk. The finding in the meta-analysis supports an obvious association between circulating IGF-1 level and ovarian cancer risk.

The meta-analysis suggests that higher levels of IGF-1 correlate with lower risk of ovarian cancer. However, previous studies have found a correlation between higher levels of IGF-1 and higher risk of colon cancer or breast cancer. It has been well accepted that IGF-1 may exert a direct effect by increasing cell's proliferation and inhibition of apoptosis, and experimental studies have shown that the malignant transformation of ovarian cells can be induced by overexpression of the IGF-1 receptor, which is IGF-I receptor-dependent pathway and has also been found in other types of cancers [39]. However, IGF-I may be involved in

**Cellular Physiology and Biochemistry**

Cell Physiol Biochem 2016;38:589-597

DOI: 10.1159/000438652
Published online: February 05, 2016

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ovarian carcinogenesis through other mechanisms, which may be different from other types of cancers [39]. For example, IGF-I may influence ovarian cancer risk through the modulation of the bioavailability of sex steroid hormones, which have been implicated in the etiology of ovarian cancer. IGF-I has high affinity for both the IGF-I receptor and the estrogen receptors, and IGF-I is also a powerful negative regulator of estrogen bioavailability [40]. The above estrogen receptor-dependent pathway may explain the discrepancy on the correlations of IGF-1 with ovarian cancer and other types of cancers. However, more studies are needed to further explain this discrepancy.

Several limitations in the meta-analysis should also be acknowledged. Firstly, heterogeneity is an important factor that can influence the credibility of the pooled results in meta-analyses. In the present meta-analysis, we observed obvious between-study heterogeneity. There was obvious difference in the study design, which could result in the difference in the effect size reported from those included studies. In addition, owing to the lack of usable information, further subgroup analysis by types of ovarian cancer was not performed. Secondly, the circulating IGF-1 level changes obviously after menopause [41, 42]. In addition, IGF-1 levels also decreases significantly with age [43]. The association between circulating IGF-1 level and ovarian cancer may be different between premenopausal and postmenopausal women. In present meta-analysis, subgroup analysis by age showed that circulating IGF-1 level was not correlated with ovarian cancer risk in women both less than 55 years and more than 55 years. However, after adjusting for heterogeneity, high circulating IGF-1 level was correlated with decreased ovarian cancer risk in women less than 55 years (OR = 0.82, 95%CI 0.72-0.94, P = 0.004) (Fig. 4). More studies are needed to explore the association between circulating IGF-1 level and ovarian cancer risk with different ages. Finally, even though we observed an obvious association between circulating IGF-1 level and ovarian cancer risk, current literature was unable to provide a conclusive finding owing to the limited number of included studies. The sample size in the meta-analysis was still not large enough to help us get a confidential estimation. More future prospective studies with large sample size are needed to clarify the association between circulating IGF-1 level and ovarian cancer risk.

In summary, our meta-analysis suggests that high circulating IGF-1 level may be correlated with decreased ovarian cancer risk, especially in women less than 55 years. More prospective studies with large sample size are needed to further assess the association between circulating IGF-1 level and ovarian cancer risk in the future.

### Acknowledgments

### Disclosure Statement

The authors report no conflicts of interest in this work.

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**Cellular Physiology and Biochemistry**

Cell Physiol Biochem 2016;38:589-597

DOI: 10.1159/000438652
Published online: February 05, 2016

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**Cellular Physiology and Biochemistry**

Cell Physiol Biochem 2016;38:589-597

DOI: 10.1159/000438652
Published online: February 05, 2016

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