RESEARCH ARTICLE

Clinicopathological Characteristics of Gynecological Cancer Associated with Hypoxia-Inducible Factor 1α Expression: A Meta-Analysis Including 6,612 Subjects

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Abstract

Background

Gynecological cancer is characterized by tumor hypoxia. However, the role of hypoxia-inducible factor 1α (HIF-1α) in gynecological cancer remains unclear.

Method

Electronic databases including Cochrane Library, PUBMED, Web of Knowledge and clinical trial registries were searched from inception through October 2014 for published, case-control studies assessing the association between HIF-1α and the clinicopathological characteristics of gynecological cancer. We pooled results from 59 studies using fixed or random-effects models and present results as odds ratios (ORs) following the PRISMA guidelines.

Results

Our meta-analysis, which included 6,612 women, demonstrated that the expression of HIF-1α was associated with the clinicopathological characteristics of gynecological cancer. The expression of HIF-1α in cancer or borderline tissue was significantly higher than that in normal tissue (cancer vs. normal: odds ratio (OR) =9.59, 95% confidence interval (CI): 5.97, 15.39, p<0.00001; borderline vs. normal: OR=4.13, 95% (CI): 2.43, 7.02, p<0.00001; cancer vs. borderline: OR=2.70, 95% (CI): 1.69, 4.31, p<0.0001). HIF-1α was associated with histological grade of cancer (Grade 3 vs. Grade 1: OR=3.77, 95% (CI): 2.76, 5.16, p<0.0001; Grade 3 vs. Grade 2: OR=1.62, 95% (CI): 1.20, 2.19, p=0.002; Grade 2 vs. Grade 1: OR=2.34, 95% (CI): 1.82, 3.00,
Conclusion

HIF-1α is associated with the malignant degree, FIGO stage, histological grade, lymph node metastasis, 5-years survival rate and recurrence rate of gynecological cancer. It may play an important role in clinical treatment and prognostic evaluation.

Introduction

Solid tumors outgrow their own vasculature beyond the size of several cubic millimeters, resulting in hypoxia. HIF-1 regulates cellular oxygen homeostasis, and plays a key role in hypoxic conditions that occur during tumor angiogenesis, invasion and metastasis [1, 2]. HIF-1 is a heterodimeric transcription factor that consists of α and β subunits. The β subunit is constitutively expressed, while the expression of HIF-1α is regulated by the oxygen level [3]. Under normoxic conditions, HIF-1α would be degraded due to targeted ubiquitination and degradation by the proteasome. This process is mediated by direct binding of von Hippel—Lindau tumor suppressor protein (pVHL), a component of the E3 ubiquitin—protein ligase complex, with the minimal N-terminal transactivation domain (N-TAD) located within the oxygen-dependent degradation domain of HIF-1α. On the contrary, in hypoxic conditions, the degradation of HIF-1α is suppressed and the expression of HIF-1α would increase. Over-expression of HIF-1α has been reported in many types of malignancies, including lung, prostate, breast, colon and rectum carcinoma, and in both regional and distant metastases, implying that HIF-1α may play a vital role in tumor progression [4–6].

Gynecological malignancies, including cancers of endometrium, cervix, ovary, vulva and vagina, account for 11.7% of all new cancers in women. The American Cancer Society estimates that 94,990 women will have been diagnosed with, and 28,790 women will have died of, cancer of the female genital tract in 2014 in the USA [7]. Thus, it is important to understand the mechanisms of carcinogenesis and progression in gynecological cancer. HIF-1α is a key cellular survival protein during hypoxia, and is associated with tumor progression and metastasis in various solid tumors. In gynecological malignancies, Birner et al. [8] suggested that HIF-1α was a facilitator of premalignant progression. Acs et al. [9] and Birner et al. [10] found a consistent correlation between tumor stage and HIF-1α expression. Moreover, Seeber et al. [11], Bachtiary et al. [12] and Shimogai et al. [13] proposed HIF-1α as a predictor of poor prognosis and response to therapy. However, results of studies on HIF-1α in gynecological cancer are not always consistent. We carried out the first meta-analysis to assess the potential association between HIF-1α and the clinicopathological parameters of gynecological cancer. Cancers of the vulva and vagina are relatively rare. No study on HIF-1α and the clinicopathological characteristics of these malignancies has been published. Cancers of endometrium, cervix and ovary were included as subgroups in the final analysis.

Materials and Methods

Search strategy

We conducted the literature searches and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (S1 PRISMA Checklist).
The electronic databases including Cochrane Library, PUBMED, Web of Knowledge and clinical trial registries, were used for systematic literature searches. Eligibility was restricted to studies published from inception to October 2014 with abstract or full text available. No language restrictions were made. We employed “hypoxia-inducible factor”, “HIF-1α”, or “HIF-1”, concatenated with “gynecological”, “endometrial”, “cervical”, “ovarian”, “vulva”, “vagina” and “tumor”, “cancer”, “carcinoma”, or “malignancy” as search terms. A comprehensive search of reference lists of all review articles and original studies retrieved by this method was performed to identify additional reports.

Criteria for inclusion and exclusion

The inclusion criteria for primary studies were as follows: (1) primary gynecological cancer should be pathologically proven; and (2) HIF-1α expression should be detected with immunohistochemistry (IHC); and (3) the association between clinicopathologic variables and HIF-1α expression should be described; or (4) provides information on survival data; and (5) laboratory methodology of IHC: (5.1) the staining of protein should be described (nuclear, cytoplasm); and (5.2) tissue sample conservation (fixation in formalin, alcohol or paraffin); and (5.3) description of the revelation test procedure of the biological factors with the first antibody type, clone identification, second antibody type, reaction characteristics, coloration method and epitope unmasking method; and (5.4) description of the negative and positive control; and (5.5) definition of the level of positivity of the test; or (5.6) the pathologist evaluating the IHC outcome was double-blind (or random) to patient clinicopathologic data and outcome. When studies were retrospective, the pathologist blinding was simple-blind.

Exclusion criteria for primary studies were as follows: (1) review, abstract, case report, animal or cell studies; or (2) not possible to extract the exact data (the association between clinicopathologic variables and HIF-1α expression); or (3) patients received chemotherapy, radiotherapy, targeted therapy before operation; and (4) laboratory methodology of IHC: (4.1) the study design was not defined; or (4.2) was unclear and no detailed description of standard laboratory methodology about IHC; or (4.3) the pathologist blinding was unblinded.

Review procedure and data extraction

Titles and abstracts were studied to assess inclusion criteria and examined independently for eligibility by two reviewers (Y. Jin and H. Wang). Disagreements were resolved by consulting a third reviewer (Y. Wang). The study characteristics were recorded as follows: (1) the first author, the nationality of included patients, article publication year; (2) the number of patients, cancer cases, borderline cases and controls for positive HIF-1α expression (HIF-1α expression score ≥ +), which was measured by semi-quantitatively assessing the percentage of tumor cells expressing HIF-1α, intensity of cell staining and extent of staining; (3) the number of test cases (FIGO III–IV stage, lymph nodes metastasis) and control cases (FIGO I–II, no lymph nodes metastasis) for positive HIF-1α expression; (4) the number of test cases (Grade 3 or Grade 2) and control cases (Grade 1); (5) the hazard ratio of 5-year disease free survival (DFS) and OS.

Quality assessments

Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality of the included case-control studies. A study can be awarded 1 point for each numbered item in nine of NOS. Studies with scores of 0–4 are considered as low-quality, while 5–9 as high-quality.
Statistical analysis

We estimated the odds ratio (OR) for clinicopathologic variables (FIGO III–IV vs. FIGO I–II; lymph nodes metastasis vs. no lymph nodes metastasis; Grade 3 or Grade 2 vs. Grade 1), 5-year DFS and 5-year overall survival (OS). Statistical heterogeneity assumption among studies was checked using the X²-based Q-test. When $I^2$ was less than 50%, pooled odds ratios, relative risk and 95% confidence intervals (CIs) were calculated using Mantel-Haenszel method with fixed effect models. Whereas significant heterogeneity among the studies was detected ($I^2>50%$), a random-effect model was adopted. If necessary, a sensitive analysis was also performed to evaluate the influence of individual studies on the final effect. All p-values were two-sided. A $p$-value < 0.05 was considered significant. All the statistical analyses were performed using RevMan 5.0 software (The Cochrane Collaboration, Oxford, United Kingdom).

Results

Description and quality assessments of included studies

The bibliographical search yielded a total of 698 studies and full text or abstract was obtained for 91 studies. Thirty-two of these studies did not meet the inclusion criteria: four studies referred to a duplicate dataset, twenty-three studies did not present exact data to extract, and five was animal studies. Finally, fifty-nine independent studies [2, 8–65] were included in the final review. The processes of study selection were summarized in the flow diagram (Fig 1). The main characteristics of the eligible studies were shown in Table 1, and the quality assessments of the included studies were summarized in S1 Table.

HIF-1α expression and pathological variables

All 59 studies including 6612 patients explored the association between HIF-1α expression and clinicopathological variables of gynecological cancer. We performed pooled analyses with available data on the association between HIF-1α expression and pathological type, FIGO stage, histological type, and lymph node metastasis. Table 2 summarized the evaluations of association between HIF-1α expression and clinicopathological variables of gynecological cancer.

The estimated pooled OR for all studies showed a significantly increased risk of malignant progression (cancer vs. borderline: OR, 2.70; 95% CI, 1.69–4.31, cancer vs. normal: OR, 9.59; 95% CI, 5.97–15.39, borderline vs. normal: OR, 4.13; 95% CI, 2.43–7.02, Figs 2–4, all $p<0.05$), higher FIGO stage (III–IV vs. I–II: OR, 2.66; 95% CI, 1.87–3.79, Fig 5, $p<0.05$), higher grade type (Grade 3 vs. Grade 1: OR, 3.77; 95% CI, 2.76–5.16, Grade 3 vs. Grade 2: OR, 1.62; 95% CI, 1.20–2.19, Grade 2 vs. Grade 1: OR, 2.34; 95% CI, 1.82–3.00, Figs 6–8, all $p<0.05$) and lymph node metastasis (yes vs. no: OR, 3.98; 95% CI, 2.10–12.89, Fig 9, $p<0.05$) in patients with positive HIF-1α expression. To explore potential sources of heterogeneity, we conducted subgroup analyses considering tumor types of gynecological cancer including endometrial, cervical and ovarian cancer. Almost all subgroup analyses maintained the positive association except the analysis of endometrial (borderline vs. normal: OR, 3.48; 95% CI, 0.75–16.15, Fig 4, $p = 0.11$), Grade 3 vs. Grade 2: OR, 1.15; 95% CI, 0.65–2.01, Fig 7, $p = 0.63$.) and cervical cancer (Grade 3 vs. Grade 2: OR, 1.62; 95% CI, 0.91–2.90, Fig 3, $p = 0.10$).

HIF-1α expression and 5-year DFS rate, 5-year OS rate

The estimated pooled OR for 14 studies on the prognostic value of HIF-1α expression showed the positive expression of HIF-1α were associated with lower 5-year DFS and OS
rate (<5 years vs. ≥5 years, Figs 10 and 11, $p<0.05$), the OR (95% CI) was 2.93 (1.43, 6.01), 5.53 (2.48, 12.31), respectively. To explore potential sources of heterogeneity, we conducted subgroup analyses. However, the subgroup of endometrial (DFS: OR, 1.56; 95% CI, 0.36–6.83, Fig 10, $p = 0.55$, OS: OR, 3.67; 95% CI, 0.52–25.63, Fig 11, $p = 0.19$) and ovarian cancer (DFS: OR, 2.42; 95% CI, 0.80–7.36, Fig 11, $p = 0.12$) did not maintain the positive association.

**Sensitivity analysis**

Sensitivity analysis was performed to explore the influence of an individual study on the pooled results by repeating the meta-analysis while omitting some obviously different studies at the
Table 1. Characteristics of studies included in this meta-analysis.

| Author       | Number of patients | Year (country) | HIF-1α positive (negative) | Pathological type | Histological type | FIGO stage | Histological grade | Lymph node metastasis | 5-years overall survival rate | 5-years disease free survival rate |
|--------------|--------------------|----------------|-----------------------------|-------------------|-------------------|------------|-------------------|------------------------|----------------------------------|----------------------------------|
| **Ovarian cancer** | | | | | | | | | | | |
| Daponte14     | 120                | 2008 (Greece)  | 61 (59)                     | 78/22/20          | -                 | -          | -                 | -                      | -                               | -                               |
| Shimogai13    | 66                 | 2008 (Japan)   | 11 (55)                     | 48/5/13           | 22/44             | -          | 25/41             | 24/42                  | 11/55                            | -                               |
| Yu15          | 117                | 2012 (China)   | 59 (58)                     | 87/2/5            | 45/44             | -          | 42/45             | -                      | -                               | 53/34                            |
| Birner10      | 172                | 2001 (Austria) | 116 (56)                    | 102/50/20         | 64/8/30           | -          | -                 | -                      | -                               | -                               |
| Osada16       | 107                | 2007 (Japan)   | 82 (25)                     | 72/17/18          | -                 | 48/24      | 32/30             | -                      | -                               | -                               |
| Shen17        | 63                 | 2013 (China)   | 55 (8)                      | -                 | 63/23             | -          | -                 | 53/34                  | -                               | -                               |
| Su18          | 81                 | 2011 (China)   | 40 (41)                     | 35/22/24          | -                 | 13/22      | 4/17              | -                      | -                               | -                               |
| Yu19          | 30                 | 2009 (China)   | 26 (4)                      | 30/20             | -                 | 12/18      | 10/18             | -                      | -                               | -                               |
| Liu20         | 170                | 2012 (China)   | 80 (81)                     | 96/4/45           | 45/8/3            | 30/66      | 24/40             | -                      | -                               | -                               |
| Chen11        | 62                 | 2011 (China)   | 29 (33)                     | 62/2/2            | 40/22             | 26/36      | 25/37             | -                      | 36/26                            | 44/18                            |
| Fu22          | 119                | 2008 (China)   | 70 (49)                     | 101/7             | 51/9/41           | 53/48      | -                 | -                      | -                               | -                               |
| Guo23         | 108                | 2010 (China)   | 39 (66)                     | 58/30             | -                 | 20/38      | 18/28/2             | 27/31                  | -                               | -                               |
| Naka26        | 52                 | 2007 (Japan)   | 36 (16)                     | 52/3/2            | 29/9/14           | 5/2        | 19/14             | -                      | -                               | -                               |
| Ji25          | 116                | 2013 (China)   | 70 (46)                     | 41/20/7           | -                 | 20/21      | 27/14             | -                      | -                               | -                               |
| Nakayama26    | 60                 | 2002 (Japan)   | 30 (30)                     | 60/-              | 29/17/2           | 33/26      | 17/16             | 22/2                   | -                               | -                               |
| Iida27        | 102                | 2008 (Japan)   | 91 (11)                     | 39/32/23          | -                 | -          | -                 | -                      | -                               | -                               |
| Chen28        | 164                | 2012 (China)   | 62 (102)                    | 124/4             | 80/44             | 53/71      | 49/75             | -                      | 50/74                            | -                               |
| Li29          | 141                | 2011 (China)   | 66 (75)                     | 60/23/30          | 40/20             | 15/41      | 23/6              | 36/24                  | -                               | -                               |
| Wong30        | 53                 | 2003 (USA)     | 22 (31)                     | 37/16             | 29/2/6            | <3/7       | -                 | -                      | -                               | -                               |
| Luo31         | 308                | 2005 (China)   | 208 (100)                   | 238/19/38         | 148/20/70        | 77/161     | 53/101           | 84/2                    | -                               | -                               |
| Wang32        | 145                | 2008 (China)   | 86 (79)                     | 112/9/18          | 58/33/31          | 46/76      | 24/48             | 38/8                   | -                               | -                               |
| Tong34        | 31                 | 2008 (China)   | 26 (5)                      | 31/-              | 31/1/-            | -          | 21/10             | -                      | 21/10                            | -                               |
| Li33          | 73                 | 2009 (China)   | 35 (38)                     | 37/19/-           | -                 | 13/24      | 12/5/2           | -                      | 27/10                            | -                               |
| Miyazawa35    | 36                 | 2009 (Japan)   | 21 (2)                      | 23/2/11           | 5/7/11           | -          | -                 | -                      | -                               | -                               |
| Yasuda36      | 74                 | 2008 (Japan)   | 69 (5)                      | 74/-              | 21/18/35         | -          | -                 | -                      | -                               | -                               |
| **Cervical cancer** | | | | | | | | | | | |
| Cheng37       | 158                | 2013 (China)   | 63 (35)                     | 98/32/28          | 98/-              | 57/41*     | 42/35/21         | 39/59                  | -                               | -                               |
| Kim38         | 745                | 2013 (Korea)   | 60 (91)                     | 179/209/357       | 144/35           | 174/5      | -                 | -                      | 17/34                           | 31/120                          |
| Huang39       | 74                 | 2014 (China)   | 39 (35)                     | 74/-              | 58/16            | 35/39*     | 38/36*            | 17/57                  | -                               | -                               |
| Dallas40      | 44                 | 2008 (Germany) | 32 (12)                     | 44/-              | -                 | 9/35       | -                 | 19/25                  | -                               | -                               |
| Birner8       | 106                | 2000 (Austria) | 20 (71)                     | -                 | 91/-             | -          | -                 | 17/74                  | 28/63                            | -                               |
| Bachtiany12   | 67                 | 2003 (Austria) | 32 (35)                     | 67/-              | -                 | 9/10/5     | -                 | 17/45                  | -                               | -                               |
| Li51          | 120                | 2010 (China)   | 90 (30)                     | 40/40/40          | 40/-             | -          | -                 | -                      | 10/21/9                         | 10/30                            |
| Guo42         | 189                | 2008 (China)   | 93 (96)                     | 79/90/20          | 79/-             | 54/25      | 15/36/2           | -                      | -                               | -                               |
| Liu43         | 93                 | 2008 (China)   | 26 (19)                     | 45/28/20          | 45/-             | 45/-       | 29/16             | -                      | -                               | -                               |
| Zhang44       | 54                 | 2009 (China)   | 28 (26)                     | 34/10/10          | 23/11            | 34/-       | 13/21             | 19/15                  | -                               | -                               |
| Acs45         | 170                | 2003 (USA)     | 143 (27)                    | 15/70/85          | 15/-             | 15/-       | -                 | -                      | -                               | -                               |

(Continued)
| Author       | Number of patients | Year (country)       | HIF-1α positive (negative) | Pathological type | Histological type | FIGO stage | Histological grade | Lymph node metastasis | 5-years overall survival rate | 5-years disease free survival rate |
|--------------|--------------------|----------------------|-----------------------------|-------------------|-------------------|-------------|-------------------|------------------------|-------------------------------|-------------------------------|
| Hutchison    | 99                 | 2004 (United Kingdom)| 68(31)                     | 99/-/-            | -                 | 57/42       | 17/57/14         | -                      | -                             | -                             |
| No           | 116                | 2009 (Korea)         | 40(76)                     | 36/39/41          | -                 | -           | -                 | 11/25                  | -                             | -                             |
| Ishikawa     | 38                 | 2004 (Japan)         | 20(18)                     | 38/-/-            | 38/-              | -/38        | -                 | -                      | -                             | -                             |
| Haugland     | 101                | 2002 (Canada)        | 23(22)                     | 45/-/-            | 33/12             | 30/15       | -                 | 11/34                  | -                             | -                             |
| Burri        | 91                 | 2003 (Switzerland)   | 46(32)                     | 78/-/-            | 63/15             | 9/43/26     | -                 | 30/47                  | -                             | -                             |
| Markowska    | 106                | 2007 (Poland)        | 81(25)                     | 106/-/-           | -                 | 29/46/31    | -                 | -                      | -                             | -                             |
| Ozbudak      | 100                | 2008 (Turkey)        | 45(55)                     | 100/-/-           | 100/-             | 69/31       | 60/25/15         | -                      | -                             | -                             |
| Feng         | 187                | 2013 (China)         | 100(87)                    | 124/28/35         | 124/-             | 101/23      | 57/41/26         | 31/93                  | -                             | -                             |
| Espinosa     | 64                 | 2010 (Italy)         | 17(32)                     | 64/-/-            | 64/-              | 24/25       | 14/22/28         | -                      | -                             | -                             |
| Seebauer     | 108                | 2010 (Netherlands)   | 54(39)                     | 93/-/-            | 75/18             | 75/18       | 28/47/18         | -                      | -                             | 18/72                         |
| Pijnenborg   | 65                 | 2007 (Netherlands)   | 14(51)                     | 65/-/-            | 65/-              | 60/5        | 20/29/16         | -                      | 40/25                         |
| Acs          | 166                | 2004 (USA)           | 79(28)                     | 107/-/-/59        | 74/33             | 65/42       | 36/20/51         | -                      | -                             | -                             |
| Pansare      | 149                | 2007 (USA)           | 54(90)                     | 149/-/-           | 80/41             | 114/30      | 42/66^           | -                      | -                             | -                             |
| Horrée       | 79                 | 2007 (Netherlands)   | 48(31)                     | 39/23/17          | 39/-              | 23/16       | 6/21/12          | -                      | -                             | -                             |
| Koda         | 85                 | 2007 (Poland)        | 55(30)                     | 60/-/-/25         | -                 | 29/31       | 8/44/8           | -                      | -                             | -                             |
| Aybali       | 94                 | 2011 (Turkey)        | 28(66)                     | 94/-/-            | 76/18             | 64/30       | 36/30/28         | 34/60                  | 9/85                          |
| Yeramian     | 93                 | 2011 (Spain and USA) | 26(55)                     | 93/-/-            | 93/-              | -           | 26/35/21         | -                      | 9/72                          |
| Li           | 54                 | 2008 (China)         | 20(34)                     | 42/-/12           | 36/6              | 21/21       | 8/34^            | 32/10                  | -                             | -                             |
| Zhai         | 62                 | 2007 (China)         | 25(37)                     | 42/-/20           | 42/-              | 28/14       | 25/17^           | 16/26                  | -                             | -                             |
| Pan          | 93                 | 2011 (China)         | 51(42)                     | 52/23/18          | 52/-              | 32/20       | 17/17/18         | 11/41                  | -                             | -                             |
| Song         | 40                 | 2009 (China)         | 26(14)                     | 30/10/-           | 20/10             | 27/3        | -                | -                      | -                             | -                             |
| Sivridis     | 106                | 2002 (Greece)        | 40(41)                     | 81/-/25           | 81/-              | 81/-        | 50/31^           | 10/71                  | -                             | -                             |
| Wang         | 125                | 2010 (China)         | 65(33)                     | 105/-/20          | 105/-             | 92/13       | 53/40/12         | 12/86                  | -                             | -                             |

*: serous/mucinous;  
^a: serous/mucinous/others;  
Δ: serous/others;  
^b: G1/G2/G3;  
^c: G1/G2-G3;  
^d: G1/G2-G3;  
^e: Ia1-Ila/IIb-IIIb;  
^f: Ia2-IIb-IIIb-IIib-IVa  
^g: Ia2-IIb-IIIb-IIib-IVa  
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Table 2. Quantitative analyses of HIF-1α expression and clinicopathological variables of gynecological cancer.

| Variables                   | Number of patients | Test of association | Test of heterogeneity | Meta-analysis model |
|-----------------------------|--------------------|---------------------|-----------------------|--------------------|
|                             |                    | OR (95% CI)         | Z test | p value | Q | p value | I² (%) |
| Pathological type           |                    |                     |                     |                    |
| Cancer vs Borderline        |                    |                     |                     |                    |
| Endometrial cancer          | 212                | 4.45[2.57,7.71]     | 5.33 | <0.00001 | 2.36 | 0.50 | 0 Fixed |
| Cervical cancer             | 328                | 2.36[1.04,5.38]     | 2.05 | 0.04     | 18.09 | 0.003 | 72 Random |
| Ovarian cancer              | 1045               | 2.31[1.04,5.09]     | 2.07 | 0.04     | 63.13 | <0.0001 | 76 Random |
| Total                       | 1900               | 2.70[1.69,4.31]     | 4.15 | <0.0001 | 63.13 | <0.0001 | 70 Random |
| Cancer vs Normal            |                    |                     |                     |                    |
| Endometrial cancer          | 486                | 11.03[6.55,18.58]   | 9.02 | <0.00001 | 8.73 | 0.12 | 43 Fixed |
| Cervical cancer             | 484                | 8.17[2.80,23.85]    | 3.85 | 0.001    | 21.59 | 0.003 | 68 Random |
| Ovarian cancer              | 1401               | 9.73[4.90,19.32]    | 6.51 | <0.0001  | 44.90 | <0.0001 | 73 Random |
| Total                       | 2371               | 9.59[5.97,15.39]    | 9.36 | <0.0001  | 76.80 | <0.0001 | 66 Random |
| Borderline vs Normal        |                    |                     |                     |                    |
| Endometrial cancer          | 144                | 3.48[0.75,16.15]    | 1.59 | 0.11     | 5.43 | 0.07 | 63 Random |
| Cervical cancer             | 520                | 2.40[1.52,3.78]     | 3.78 | 0.0002   | 7.59 | 0.27 | 21 Fixed |
| Ovarian cancer              | 438                | 6.29[2.69,14.73]    | 4.24 | <0.0001  | 21.57 | 0.0006 | 63 Random |
| Total                       | 1087               | 4.13[2.43,7.02]     | 5.24 | <0.0001  | 41.82 | 0.0007 | 59 Random |
| FIGO stage                  |                    |                     |                     |                    |
| Endometrial cancer          | 830                | 2.76[1.25,6.09]     | 2.50 | 0.01     | 38.44 | <0.0001 | 74 Random |
| Cervical cancer             | 290                | 1.76[1.03,2.99]     | 2.08 | 0.04     | 3.74 | 0.29 | 20 Fixed |
| Ovarian cancer              | 1354               | 3.01[1.92,4.74]     | 4.78 | <0.0001  | 39.80 | 0.0008 | 60 Random |
| Total                       | 2474               | 2.66[1.87,3.79]     | 5.42 | <0.0001  | 83.78 | <0.0001 | 63 Random |
| Histological type           |                    |                     |                     |                    |
| G3 vs G1                    |                    |                     |                     |                    |
| Endometrial cancer          | 301                | 2.65[1.53,4.59]     | 3.49 | 0.005    | 7.35 | 0.20 | 32 Fixed |
| Cervical cancer             | 240                | 4.29[2.68,14.14]    | 4.46 | <0.0001  | 10.76 | 0.06 | 54 Fixed |
| Ovarian cancer              | 466                | 4.52[2.79,7.31]     | 6.13 | <0.0001  | 16.50 | 0.06 | 45 Fixed |
| Total                       | 1007               | 3.77[2.76,5.16]     | 8.32 | <0.0001  | 36.18 | 0.02 | 42 Fixed |
| G3 vs G2                    |                    |                     |                     |                    |
| Endometrial cancer          | 299                | 1.15[0.65,2.01]     | 0.48 | 0.63     | 3.33 | 0.65 | 0 Fixed |
| Cervical cancer             | 347                | 1.62[0.91,2.90]     | 1.65 | 0.10     | 5.59 | 0.35 | 11 Fixed |
| Ovarian cancer              | 567                | 2.02[1.27,3.19]     | 2.99 | 0.003    | 13.91 | 0.13 | 35 Fixed |
| Total                       | 1213               | 1.62[1.20,2.19]     | 3.14 | 0.002    | 24.17 | 0.29 | 13 Fixed |
| G2 vs G1                    |                    |                     |                     |                    |
| Endometrial cancer          | 410                | 2.19[1.43,3.37]     | 3.58 | 0.003    | 8.23 | 0.14 | 39 Fixed |
| Cervical cancer             | 351                | 2.40[1.46,3.93]     | 3.46 | 0.005    | 3.68 | 0.60 | 0 Fixed |
| Ovarian cancer              | 541                | 2.43[1.65,3.59]     | 4.48 | <0.0001  | 10.41 | 0.32 | 14 Fixed |
| Total                       | 1302               | 2.34[1.82,3.00]     | 6.68 | <0.0001  | 22.43 | 0.38 | 6 Fixed |
| Lymph node metastasis       |                    |                     |                     |                    |
| Endometrial cancer          | 454                | 4.02[1.32,12.26]    | 2.44 | 0.01     | 10.75 | 0.03 | 63 Random |
| Cervical cancer             | 471                | 2.94[1.19,7.329]    | 2.33 | 0.02     | 24.73 | 0.0008 | 72 Random |
| Ovarian cancer              | 566                | 5.20[2.10,12.89]    | 3.56 | 0.004  | 33.87 | <0.0001 | 76 Random |
| Total                       | 1391               | 3.98[2.10,12.89]    | 5.00 | <0.0001  | 3.98 | <0.0001 | 71 Random |
| 5-years disease free survival rate |       |                     |                     |                    |
| Endometrial cancer          | 330                | 1.56[0.36,6.83]     | 0.60 | 0.55     | 11.80 | 0.008 | 75 Random |
| Cervical cancer             | 280                | 5.28[2.90,9.63]     | 5.43 | <0.0001  | 1.91 | 0.38 | 0 Fixed |
| Ovarian cancer              | 97                 | 2.42[0.80,7.36]     | 1.56 | 0.12     | 0.36 | 0.55 | 0 Fixed |

(Continued)
### Table 2. (Continued)

| Variables                     | Number of patients | OR (95% CI) | Z test | p value | Q     | p value | I² (%) | Meta-analysis model |
|-------------------------------|--------------------|-------------|--------|---------|-------|---------|--------|---------------------|
| **Total**                     | 707                | 2.93[1.43,6.01] | 2.93   | 0.003   | 20.71 | 0.008   | 61     | Random              |
| **5-years overall survival rate** |                    |             |        |         |       |         |        |                     |
| Endometrial cancer            | 179                | 3.67[0.52,25.63] | 1.31   | 0.19    | 2.43  | 0.12    | 59     | Random              |
| Cervical cancer               | 286                | 3.28[1.63,6.60] | 3.34   | 0.008   | 3.07  | 0.22    | 35     | Fixed               |
| Ovarian cancer                | 215                | 11.46[3.43,38.29] | 3.96   | <0.0001 | 4.54  | 0.10    | 56     | Random              |
| **Total**                     | 680                | 5.53[2.48,12.31] | 4.19   | <0.0001 | 17.46 | 0.01    | 60     | Random              |

![Fig 2. Forest plot of the expression of HIF-1α in cancer versus that in borderline tissue. (I² = 69%).](https://doi.org/10.1371/journal.pone.0127229.g002)
time. Statistically similar results were obtained by this procedure, indicating the stability of this meat-analysis (data not shown).

Discussion

HIF-1α is a key transcription factor that regulates cellular reaction to hypoxia. It is over-expressed in many types of malignancies in response to low oxygen concentration [66], and plays
a key role in hypoxic conditions that occur during tumor angiogenesis, invasion and metastasis [67, 68]. In gynecological cancer, HIF-1α has been suggested as an adverse prognostic factor, but conflicting findings do exist [69]. Thus, pooled analysis was performed with available data on the association between HIF-1α expression and clinicopathological variables.

We demonstrated that the expression of HIF-1α in normal tissue was lower than that in borderline or cancer tissue in gynecological cancer, which is in agreement with previous findings from different studies [2, 8, 9, 16, 27, 30, 52, 57, 70]. HIF-1α may be a facilitator of premalignant progression in gynecological cancer. This positive association maintained in most subgroup analyses except in the "borderline vs. normal" of endometrial cancer. This inconsistency may result from a relatively small number of included studies (only three studies were in the subgroup analysis).
Clinicopathologic features including pathological type, tumor stage, and lymph node metastasis are the major facts related to cancer-related prognosis. In our meta-analysis, higher HIF-1α expression was found to be associated with increased risk of lymph node metastasis, higher FIGO stage, higher histological grade, and lower 5-year OS and DFS rate. These findings...
revealed that HIF-1α could be considered as a hallmark of tumour progression, and a prognostic factor for gynecological cancer. To reveal the mechanisms, several included studies of this meta-analysis reported that HIF-1α is related to many critical aspects of gynecological cancer biology. HIF-1α synthesis could be increased by several growth factors, cytokines and other signaling molecules responsible for stimulating phosphatidylinositol 3-kinase (PI3K) or mitogen-activated protein kinase (MAPK) pathways [38]. The regulated markers of HIF-1α, such as glucose transporter type 1 (GLUT1), carbonic anhydrase 9 (CA9) and c-Met, have been found to be highly associated with poor prognosis in various cancers [38]. HIF-1α also regulates many

| Study or Subgroup | G3 Events | G3 Total | Weight | Odds Ratio M-H Fixed, 95% CI | Odds Ratio M-H Fixed, 95% CI |
|-------------------|-----------|----------|--------|----------------------------|----------------------------|
| 3.10.1 Endometrial Cancer | Ayebli 2011 | 3 10 | 7 36 | 5.0% | 1.78 [0.38, 8.66] |
|                   | Feng 2013 | 22 26 | 30 57 | 6.7% | 4.95 [1.51, 16.20] |
|                   | Koda 2007 | 6 8 | 7 8 | 4.1% | 0.43 [0.03, 5.98] |
|                   | Ozbudak 2008 | 7 15 | 27 60 | 13.4% | 1.07 [0.34, 3.33] |
|                   | Pan 2011 | 16 18 | 9 17 | 2.4% | 7.11 [1.23, 40.90] |
|                   | Seeberg 2010 | 12 18 | 9 28 | 5.5% | 4.22 [1.20, 14.90] |
| Subtotal (95% CI) | 95 | 206 | 37.1% | 2.65 [1.53, 4.59] |
| Total events | 66 | 89 | |
| Heterogeneity: Chi² = 7.35, df = 5 (P = 0.20); I² = 32% |
| Test for overall effect: Z = 3.49 (P = 0.0005) |

| Study or Subgroup | G3 Events | G3 Total | Weight | Odds Ratio M-H Fixed, 95% CI | Odds Ratio M-H Fixed, 95% CI |
|-------------------|-----------|----------|--------|----------------------------|----------------------------|
| 3.10.2 Cervical Cancer | Bachtiary 2003 | 8 17 | 2 7 | 3.5% | 2.22 [0.33, 14.80] |
|                   | Cheng 2013 | 18 21 | 20 42 | 4.4% | 6.60 [1.69, 25.62] |
|                   | Guo 2008 | 26 26 | 8 17 | 0.4% | 59.24 [3.11, 1128.24] |
|                   | Hutchison 2004 | 9 14 | 12 17 | 9.0% | 0.75 [0.17, 3.40] |
|                   | Liu 2010 | 8 9 | 9 10 | 2.2% | 0.89 [0.05, 16.66] |
|                   | Markowska 2007 | 28 31 | 16 29 | 3.7% | 7.58 [1.87, 30.68] |
| Subtotal (95% CI) | 118 | 122 | 23.3% | 4.29 [2.26, 8.14] |
| Total events | 97 | 67 | |
| Heterogeneity: Chi² = 10.76, df = 5 (P = 0.06); I² = 54% |
| Test for overall effect: Z = 4.46 (P < 0.00001) |

| Study or Subgroup | G3 Events | G3 Total | Weight | Odds Ratio M-H Fixed, 95% CI | Odds Ratio M-H Fixed, 95% CI |
|-------------------|-----------|----------|--------|----------------------------|----------------------------|
| 3.10.3 Ovarian Cancer | Guo 2010 | 11 12 | 6 18 | 0.9% | 22.00 [2.27, 212.86] |
|                   | Liu 2012 | 25 32 | 15 24 | 8.7% | 2.14 [0.66, 6.95] |
|                   | Luo 2005 | 81 84 | 32 53 | 3.3% | 17.72 [4.94, 63.54] |
|                   | Nakai 2007 | 6 10 | 13 19 | 8.4% | 0.69 [0.14, 3.40] |
|                   | Nakayama 2002 | 13 22 | 3 17 | 3.2% | 6.74 [1.49, 30.48] |
|                   | Osada 2007 | 8 10 | 24 32 | 5.3% | 1.33 [0.23, 7.63] |
|                   | Shen 2013 | 14 16 | 14 19 | 3.7% | 2.50 [0.41, 15.11] |
|                   | Su 2011 | 14 14 | 3 4 | 0.4% | 12.43 [0.41, 374.96] |
|                   | Wang 2008 | 33 38 | 12 24 | 4.5% | 6.60 [1.92, 22.69] |
|                   | Yu 2009 | 8 8 | 9 10 | 1.1% | 2.68 [0.10, 75.12] |
| Subtotal (95% CI) | 246 | 220 | 39.6% | 4.52 [2.79, 7.31] |
| Total events | 213 | 131 | |
| Heterogeneity: Chi² = 16.50, df = 9 (P = 0.06); I² = 45% |
| Test for overall effect: Z = 6.13 (P < 0.00001) |

| Study or Subgroup | G3 Events | G3 Total | Weight | Odds Ratio M-H Fixed, 95% CI | Odds Ratio M-H Fixed, 95% CI |
|-------------------|-----------|----------|--------|----------------------------|----------------------------|
|                   | 459 | 548 | 100.0% | 3.77 [2.76, 5.16] |
| Total events | 376 | 287 | |
| Heterogeneity: Chi² = 36.18, df = 21 (P = 0.02); I² = 42% |
| Test for overall effect: Z = 8.32 (P < 0.00001) |
| Test for subgroup differences: Not applicable |

Fig 6. Forest plot of the expression of HIF-1α in Grade 3 tissue versus that in Grade 1 tissue. (I² = 42%).

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cancer signaling pathways, including PI3K/AKT/mTOR, Notch, and Myc, to mediate tumor proliferation, invasion and migration [2, 8, 9, 16, 27, 30, 52, 57, 70].

However, the association between HIF-1α and the clinicopathologic features was not observed in subgroup analyses of “Grade 3 vs. Grade 2” in endometrial and cervical cancers. When stratified by cancer type, results of survival analysis were not statistically significant in the “endometrial and ovarian cancer” subgroup. We suggested that besides the heterogeneity of included studies, other factors related to clinicopathologic features of gynecological cancer might contribute to this inconsistency. For example, type I endometrial cancer is often characterized by

cancer signaling pathways, including PI3K/AKT/mTOR, Notch, and Myc, to mediate tumor proliferation, invasion and migration [2, 8, 9, 16, 27, 30, 52, 57, 70].

However, the association between HIF-1α and the clinicopathologic features was not observed in subgroup analyses of “Grade 3 vs. Grade 2” in endometrial and cervical cancers. When stratified by cancer type, results of survival analysis were not statistically significant in the “endometrial and ovarian cancer” subgroup. We suggested that besides the heterogeneity of included studies, other factors related to clinicopathologic features of gynecological cancer might contribute to this inconsistency. For example, type I endometrial cancer is often characterized by

Fig 7. Forest plot of the expression of HIF-1α in Grade 3 tissue versus that in Grade 2 tissue. (I² = 13%).

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mutations in tumor suppressor PTEN, while type II endometrial cancer generally contains the mutation of another tumor suppressor p53 [71–74]. In cervical cancer, the overexpression of human papillomavirus (HPV) and the loss of p53 promote tumor invasion and metastasis [75]. Thus, further studies included both HIF-1α and other factors are warranted to validate our findings, and to unravel the mechanism of carcinogenesis and progression in gynecological cancer.

Some limitations should be acknowledged. First, immunohistochemistry was a semiquantitative method, and this may affect the precision of the result. In this meta-analysis, no
subgroup survival analysis was performed for different histological subtypes. Differences in primary antibodies, immunohistochemistry staining protocols, evaluation standards, and cut-off values for high HIF-1α expression might contribute to heterogeneity. However, this meta-analysis pooled series of studies and had higher statistical power to make up for this disadvantage to some extent. Further multicenter researches using standardized and quantitative methods are encouraged. Second, this meta-analysis included studies published in between 2001 and 2014. During those 13 years, improved surgical techniques and better perioperative care were developed at more specialized centers. The time-varying therapeutic regimen would be the major source of heterogeneity in cancer-related prognosis. For example, in the survival analysis

![Fig 9. Forest plot of association between HIF-1α expression and lymph node metastasis. (I² = 71%).](doi:10.1371/journal.pone.0127229.g009)
of the “endometrial and ovarian cancer” subgroup, three studies reported postoperative adjuvant chemotherapy, fourteen studies reported postoperative adjuvant radiotherapy, while others did not provide any information about postoperative adjuvant therapy. Thus, the results of the prognosis analyses should be interpreted with caution. Third, more than half of included studies in this meta-analysis are from Asia. Because of this population bias, our results might not fully reveal the association of HIF-1α and clinicopathological characteristics of patients all over the world. Therefore, patients from a variety of countries should be studied to improve the reliability of our analysis in the near future.

Conclusions

Despite the limitations of this meta-analysis, we confirmed that HIF-1α is emerging as an important factor in the carcinogenesis of gynecological cancer. HIF-1α is associated with the malignant degree, FIGO stage, histological grade, lymph node metastasis, 5-years survival rate and recurrence rate of gynecological cancer. We expect that HIF-1α may serve as a reliable tool for early and accurate prediction of cancer and may be a potential therapeutic target for gynecological cancer.
Supporting Information

S1 PRISMA Checklist. PRISMA Checklist.

(SDOC)

S1 Table. Quality assessments of included studies.

(SDOC)

Author Contributions

Conceived and designed the experiments: YJ HLW. Performed the experiments: YJ HLW. Analyzed the data: YJ HLW XWM. Contributed reagents/materials/analysis tools: YW. Wrote the paper: YJ HLW XWM XWL XL YW.

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