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RESEARCH ARTICLE

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

Yue Jin¹°, Haolu Wang^{2,3}°, Xiaowei Ma⁴, Xiaowen Liang³, Xin Liu³, Yu Wang¹*

1 Department of Gynecology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University Shanghai, China, 2 Department of Biliary-Pancreatic Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China, 3 Therapeutics Research Centre, Princess Alexandra Hospital, School of Medicine, The University of Queensland, Brisbane, Australia, 4 Department of Clinical Laboratory, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

• These authors contributed equally to this work.

* renjiwangyu@gmail.com

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-1 α 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-1 α was associated with the clinicopathological characteristics of gynecological cancer. The expression of HIF-1 α 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). The expression of HIF-1 α in III IV stage or lymph node metastasis was significantly higher than that in I II stage or that without lymph node metastasis, respectively (OR=2.66, 95% (CI): 1.87,3.79, *p*<0.00001; OR= 3.98, 95% (CI): 2.10,12.89, *p*<0.0001). HIF-1 α was associated with histological grade of cancer (Grade 3 vs. Grade 1: OR=3.77, 95% (CI): 2.76,5.16, *p*<0.00001; 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,

p<0.00001),5-years disease free survival (DFS) rates (OR=2.93, 95% (CI):1.43,6.01, *p*=0.001) and 5-years overall survival (OS) rates (OR=5.53, 95% (CI): 2.48,12.31, *p*<0.0001).

Conclusion

HIF-1 α 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-1 α is regulated by the oxygen level [3]. Under normoxic conditions, HIF-1 α 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-1 α . On the contrary, in hypoxic conditions, the degradation of HIF-1 α is suppressed and the expression of HIF-1 α would increase. Over-expression of HIF-1 α 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-1 α may play a vital role in tumor progression [<u>4–6</u>].

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-1 α 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-1 α was a facilitator of premalignant progression. Acs et al. [9] and Birner et al. [10] found a consistent correlation between tumor stage and HIF-1 α expression. Moreover, Seeber *et al.* [11], Bachtiary et al. [12] and Shimogai et al. [13] proposed HIF-1 α as a predictor of poor prognosis and response to therapy. However, results of studies on HIF-1 α in gynecological cancer are not always consistent. We carried out the first meta-analysis to assess the potential association between HIF-1 α and the clinicopathological parameters of gynecological cancer. Cancers of the vulva and vagina are relatively rare. No study on HIF-1 α 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 (<u>S1 PRISMA Checklist</u>).

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-1 α ", 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-1 α expression should be detected with immunohistochemistry (IHC); and (3) the association between clinicopathologic variables and HIF-1 α 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-1 α 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-1 α expression (HIF-1 α expression score \geq +), which was measured by semi-quantitatively assessing the percentage of tumor cells expressing HIF-1 α , 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-1 α 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-1a expression and pathological variables

All 59 studies including 6612 patients explored the association between HIF-1 α expression and clinicopathological variables of gynecological cancer. We performed pooled analyses with available data on the association between HIF-1 α expression and pathological type, FIGO stage, histological type, and lymph node metastasis. <u>Table 2</u> summarized the evaluations of association between HIF-1 α 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 <u>6–8</u>, 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-1 α 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-1 α expression and 5-year DFS rate, 5-year OS rate

The estimated pooled OR for 14 studies on the prognostic value of HIF-1 α expression showed the positive expression of HIF-1 α were associated with lower 5-year DFS and OS

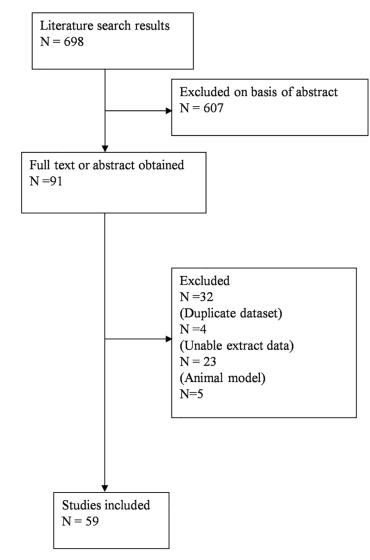


Fig 1. Flowchart of study selection. Sixty independent studies were included in the final review.

rate (<5 years vs. \geq 5 years, Figs <u>10</u> and <u>11</u>, *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, <u>Fig 10</u>, *p* = 0.55, OS: OR, 3.67; 95% CI, 0.52–25.63, <u>Fig 11</u>, *p* = 0.19) and ovarian cancer (DFS: OR, 2.42; 95% CI, 0.80–7.36, <u>Fig 11</u>, *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

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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				(cancer/ borderline/ benign)	(serous/clear cell/others)	(I–II/ III–IV)	(G1/G2/G3)	(yes/no)	(<5/≥5)	(<5/≥5)
Daponte ¹⁴	120	2008(Greece)	61(59)	78/22/20	-	-	-	-	-	-
Shimogai ¹³	66	2008 (Japan)	11(55)	66/-/-	48/5/13	22/44	-	25/41	24/42	11/55
Yu ¹⁵	117	2012 (China)	59(58)	87/-/30	75/12*	45/44	-	42/45	53/34	-
Birner ¹⁰	172	2001(Austria)	116(56)	102/50/20	64/8/30	-	-	-	-	-
Osada ¹⁶	107	2007 (Japan)	82(25)	72/17/18	-	48/24	32/30/10	-	-	-
Shen ¹⁷	63	2013 (China)	55(8)	63/-/-	-	44/19	19/17/16	-	-	-
Su ¹⁸	81	2011 (China)	40(41)	35/22/24	-	13/22	4/17/14	-	-	-
Yu ¹⁹	30	2009 (China)	26(4)	30/-/-	18/2/10	12/18	10/10/8	-	-	-
Liu ²⁰	171	2012 (China)	80(91)	96/-/45	45/8/43	30/66	24/40/32	-	-	-
Chen ²¹	62	2011 (China)	29(33)	62/-/-	40/22*	26/36	25/37 △	36/26	44/18	-
Fu ²²	119	2008 (China)	70(49)	101/-/-	51/9/41	53/48	-	-	-	-
Guo ²³	108	2010 (China)	39(66)	58/-/30	-	20/38	18/28/12	27/31	-	-
Naka ²⁶	52	2007 (Japan)	36(16)	52/-/-	29/9/14	-/52	19/14/10	-	-	-
Ji ²⁵	116	2013 (China)	70(46)	41/20/27	-	20/21	-	27/14	-	-
Nakayama ²⁶	60	2002 (Japan)	30(30)	60/-/-	29/17/14 [#]	23/37	17/16/22	-	-	-
lida ²⁷	102	2008 (Japan)	91(11)	39/32/31	-	-	-	-	-	-
Chen ²⁸	164	2012 (China)	62(102)	124/-/-	80/44▲	53/71	49/75 △	50/74	-	-
Li ²⁹	141	2011(China)	66(75)	60/21/30	40/20*	19/41	23/37	36/24	-	-
Wong ³⁰	53	2003(USA)	22(31)	37/-/16	29/2/6	-/37	-	-	-	-
Luo ³¹	308	2005(China)	208(100)	238/19/38	148/20/70	77/ 161	53/101/84	-	-	-
Wang ³²	145	2008(China)	86(79)	112/9/18	58/33/31 [#]	46/76	24/48/38	-	-	-
Tong ³⁴	31	2008(China)	26(5)	31/-/-	31/-/-	-	-	21/10	-	21/10
Li ³³	73	2009(China)	35(38)	37/19/-	-	13/24	12/25 ^{\$}	27/10	-	-
Miyazawa ³⁵	36	2009(Japan)	21(2)	23/2/11	5/7/11	-	-	-	-	-
Yasuda ³⁶	74	2008(Japan)	69(5)	74/-/-	21/18/35	-	-	-	-	-
Cervical cancer				(cancer/CIN/ normal)	(squamous/ others)	(I−II/ III−IV)	(G1/G2/G3)	(yes/no)	(<5/≥5)	(<5/≥5)
Cheng ³⁷	158	2013(China)	63(35)	98/32/28	98/-	57/ 41 [@]	42/35/21	39/59	-	-
Kim ³⁸	745	2013(Korea)	60(91)	179/209/357	144/35	174/5	-	-	17/134	31/120
Huang ³⁹	74	2014(China)	39(35)	74/-/-	58/16	35/ 39 ^{\$}	38/36 △	17/57	-	-
Dellas ⁴⁰	44	2008 (Germany)	32(12)	44/-/-	-	9/35	-	-	19/25	-
Birner ⁸	106	2000(Austria)	20(71)	91/10/5	-	91/-	-	-	17/74	28/63
Bachtiary ¹²	67	2003(Austria)	32(35)	67/-/-	59/8	40/27	7/34/17	21/46	-	-
Li ⁴¹	120	2010(China)	90(30)	40/40/40	40/-	40/-	10/21/9	10/30	-	-
Guo ⁴²	189	2008(China)	93(96)	79/90/20	79/-	54/25	17/36/26	-	-	-
Liu ⁴³	93	2008(China)	26(19)	45/28/20	45/-	45/-	29/16 △	-	-	-
Zhang ⁴⁴	54	2009(China)	28(26)	34/10/10	23/11	34/-	13/21 ^{\$}	19/15	-	-
Acs ⁴⁵	170	2003(USA)	143(27)	15/70/85	15/-	15/-	-	-	-	-

Table 1. Characteristics of studies included in this meta-analysis.

(Continued)

Table 1. (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 ⁴⁶	99	2004(United Kingdom)	68(31)	99/-/-	-	57/42	17/57/14	-	-	-
No ⁴⁷	116	2009(Korea)	40(76)	36/39/41		-	-	11/25	-	-
Ishikawa ⁴⁸	38	2004(Japan)	20(18)	38/-/-	38/-	-/38	-	-	-	17/21
Haugland ⁴⁹	101	2002 (Canada)	23(22)	45/-/-	33/12	30/15	-	11/34	-	-
Burri ⁵⁰	91	2003 (Switzerland)	46(32)	78/-/-	63/15	9/43/ 26 ^{&}	-	30/47	-	-
Markowska ⁵¹	106	2007(Poland)	81(25)	106/-/-	106/-	-	29/46/31	-	-	-
Endometrial cancer				(cancer/ borderline/ normal)	(type 1/ type 2)	(I–II/ III–IV)	(G1/G2/G3)	(yes/no)	(<5/≥5)	(<5/≥5)
Ozbudak ⁵²	100	2008(Turkey)	45(55)	100/-/-	100/-	69/31	60/25/15	-	-	-
Feng ⁵³	187	2013(China)	100(87)	124/28/35	124/-	101/ 23	57/41/26	31/93	-	-
Espinosa ⁵⁴	64	2010(Italy)	17(32)	64/-/-	64/-	24/25	14/22/28	-	-	-
Seeber ⁶⁹	108	2010 (Netherlands)	54(39)	93/-/-	75/18	75/18	28/47/18	-	-	18/72
Pijnenborg ⁵⁵	65	2007 (Netherlands)	14(51)	65/-/-	65/-	60/5	20/29/16	-	-	40/25
Acs ⁹	166	2004(USA)	79(28)	107/-/59	74/33	65/42	36/20/51	-	-	-
Pansare ⁵⁶	149	2007(USA)	54(90)	149/-/-	80/41	114/ 30	42/66 ^{\$}	-	-	-
Horrée ⁵⁷	79	2007 (Netherlands)	48(31)	39/23/17	39/-	23/16	6/21/12	-	-	-
Koda ⁵⁸	85	2007(Poland)	55(30)	60/-/25	-	29/31	8/44/8	-	-	-
Aybatli ⁵⁹	94	2011(Turkey)	28(66)	94/-/-	76/18	64/30	36/30/28	34/60	-	9/85
Yeramian ⁶⁰	93	2011(Spain and USA)	26(55)	93/-/-	93/-	-	26/35/21	-	-	9/72
Li ⁶¹	54	2008(China)	20(34)	42/-/12	36/6	21/21	8/34 ^{\$}	32/10	-	-
Zhai ⁶²	62	2007(China)	25(37)	42/-/20	42/-	28/14	25/17 [△]	16/26	-	-
Pan ⁶³	93	2011(China)	51(42)	52/23/18	52/-	32/20	17/17/18	11/41	-	-
Song ⁶⁴	40	2009(China)	26(14)	30/10/-	20/10	27/3	-	-	-	-
Sivridis ²	106	2002(Greece)	40(41)	81/-/25	81/-	81/-	50/31 ^{\$}	-	10/71	-
Wang ⁶⁵	125	2010(China)	65(33)	105/-/20	105/-	92/13	53/40/12	-	12/86	-

*: serous/mucinous;

#: serous/mucinous/others;

▲: serous/others;

 $^{\bigtriangleup}$: G₁-G₂/G₃;

^{\$}: G₁/G₂-G₃;

[@]: la_1 -IIa/IIb-IIIb; \$: la_2 -Ib_1/Ib₂-IIb; &: Ib-IIa/IIb-IIIa/IIIb-IVa

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Variables	Number of patients	Test of a	ssociatio	on	Test	of heterog	eneity	Meta-analysis mode
		OR (95% CI)	Z test	p value	Q	p value	l ² (%)	
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	0.0001	21.59	0.003	68	Random
Ovarian cancer	1401	9.73[4.90,19.32]	6.51	<0.00001	44.90	<0.0001	73	Random
Total	2371	9.59[5.97,15.39]	9.36	<0.00001	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	<0.00001	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	<0.00001	39.80	0.0008	60	Random
Total	2474	2.66[1.87,3.79]	5.42	<0.00001	83.78	<0.0001	63	Random
Histological type								
G3 vs G1								
Endometrial cancer	301	2.65[1.53,4.59]	3.49	0.0005	7.35	0.20	32	Fixed
Cervical cancer	240	4.29[2.26,8.14]	4.46	< 0.00001	10.76	0.06	54	Fixed
Ovarian cancer	466	4.52[2.79,7.31]	6.13	<0.00001	16.50	0.06	45	Fixed
Total	1007	3.77[2.76,5.16]	8.32	< 0.00001	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	1210	1.02[1.20,2.10]	0.11	0.002	2	0.20	10	- Mou
Endometrial cancer	410	2.19[1.43,3.37]	3.58	0.0003	8.23	0.14	39	Fixed
Cervical cancer	351	2.40[1.46,3.93]	3.46	0.0005	3.68	0.60	0	Fixed
Ovarian cancer	541	2.43[1.65,3.59]	4.48	< 0.00001	10.41	0.32	14	Fixed
Total	1302	2.34[1.82,3.00]	6.68	< 0.00001	22.43	0.38	6	Fixed
Lymph node metastasis	1002	2.0 [[1.02,0.00]	0.00	0.00001	22.10	0.00	U	T MOU
Endometrial cancer	454	4.02[1.32,12.26]	2.44	0.01	10.75	0.03	63	Random
Cervical cancer	471	2.94[1.19,7329]	2.44	0.01	24.73	0.0008	72	Random
Ovarian cancer	566	5.20[2.10,12.89]	3.56	0.02	33.87	< 0.0003	76	Random
Total	1391	3.98[2.10,12.89]	5.00	<0.0004	3.98	<0.0001	70	Random
5-years desease free survival rate	1091	3.30[2.10,12.09]	5.00	~0.000T	3.90	~0.000T	71	nanuom
Endometrial cancer	220	1 5610 26 6 921	0.60	0.55	11 00	0.009	75	Pandom
	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	<0.00001	1.91	0.38	0	Fixed

1.56

2.42[0.80,7.36]

0.12

0.36

0.55

0

Fixed

PLOS ONE

(Continued)

Ovarian cancer

97

Table 2. (Continued)

Variables	Number of patients	Test of as	ssociatio	on	Test	of heterog	Meta-analysis model	
		OR (95% CI)	Z test	p value	Q	p value	l ² (%)	
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

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	Cance		Border			Odds Ratio	Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.9.1 Endometrial Car		404	4.0		C 000	0.00 // 14 7.00	
eng 2013	81	124	10	28	5.9%	3.39 [1.44, 7.99]	
Horrée 2007	34	39	14	23	4.7%	4.37 [1.24, 15.38]	
Pan 2011	38	52	9	23	5.3%	4.22 [1.50, 11.92]	
Bong 2009 Subtatal (05% CI)	24	30 245	2	10 84	3.5%	16.00 [2.67, 95.75]	
Subtotal (95% CI)	4 7 7	240	25	84	19.4%	4.41 [2.53, 7.69]	-
Fotal events	177		35		01.17 0.00	,	
Heterogeneity: Tau² = Fest for overall effect: :				P = 0.5	0); 1-= 0%	0	
rest for overall effect.	2 = 5.23 (P < U.L	0001)				
3.9.2 Cervical Cancer							
Acs 2004	12	15	59	70	4.3%	0.75 [0.18, 3.08]	
Birner 2000	20	91	2	10	3.8%	1.13 [0.22, 5.73]	
Guo 2008	62	79	30	90	6.3%	7.29 [3.65, 14.58]	
_i 2010	36	40	30	40	4.7%	3.00 [0.85, 10.54]	
iu 2008	19	33	19	40	5.7%	1.50 [0.59, 3.80]	
No 2009	16	36	17	39	5.7%	1.04 [0.42, 2.58]	
Zhang 2009	25	34	3	10	4.0%	6.48 [1.37, 30.61]	
Subtotal (95% CI)		328		299	34.5%	2.18 [1.03, 4.64]	
Total events	190		160				
Heterogeneity: Tau ² =	0.67; Chi	² = 19.1	15, df = 6	(P = 0.	004); I ^z =	69%	
Fest for overall effect: .	Z = 2.03 (P = 0.0	(4)				
3.9.3 Ovarian Cancer							
Birner 2001	70	102	44	50	5.6%	0.30 [0.12, 0.77]	
Daponte 2008	47	78	12	22	5.6%	1.26 [0.49, 3.28]	
ida 2008	39	39	29	32	1.8%	9.37 [0.47, 188.51]	
Ji 2013	36	41	18	20	3.6%	0.80 [0.14, 4.53]	
_i 2009	31	37	4	19	4.3%	19.38 [4.74, 79.15]	
.i 2011	39	60	12	21	5.4%	1.39 [0.51, 3.84]	
uo 2005	195	238	8	19	5.5%	6.24 [2.37, 16.43]	
Osada 2007	57	72	11	17	5.0%	2.07 [0.66, 6.52]	
Gu 2011	29	35	10	22	4.8%	5.80 [1.72, 19.55]	
Vang 2008	79	112	5	9	4.4%	1.92 [0.48, 7.58]	
Subtotal (95% CI)		814		231	46.1%	2.31 [1.04, 5.09]	
Total events	622		153				
Heterogeneity: Tau ² =	1.17; Chi	² = 37.1	29, df = 9	(P < 0.	0001); l² =	= 76%	
Fest for overall effect: .	Z=2.07 (P = 0.0	14)				
fotal (95% CI)		1387		614	100.0%	2.61 [1.65, 4.11]	•
Fotal events	989		348	014	.00.070	2.01 [1.00, 4.11]	-
Heterogeneity: Tau ² =		- 6A		0/P < 1	000043	12 - 60%	
fest for overall effect: .			•	- v · · ·			0.01 0.1 1 10 100

Fig 2. Forest plot of the expression of HIF-1 α in cancer versus that in borderline tissue. ($l^2 = 69\%$).

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	Canc	er	Norm	al		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
3.8.1 Endometrial Ca	ncer						
Feng 2013	81	124	9	35	5.4%	5.44 [2.34, 12.65	1 –
Horrée 2007	34	39	0	17	1.8%	219.55 [11.47, 4201.54	-
Koda 2007	47	60	8	25	5.0%	7.68 [2.71, 21.75	
Li 2008	20	42	0	12	1.9%	22.78 [1.27, 409.58	i
Pan 2011	38	52	4	18	4.5%	9.50 [2.67, 33.79	-
Qu 2007	25	42	0	20	1.9%	59.74 [3.39, 1054.34	
Subtotal (95% CI)		359		127	20.5%	11.42 [4.92, 26.48	i 🔰 🔶
Total events	245		21				
Heterogeneity: Tau ² =	0.42; Ch	i ² = 8.73	3, df = 5 (P = 0.1	2); l ² = 43	%	
Test for overall effect:	Z= 5.67	(P < 0.0	0001)				
3.8.2 Cervical Cance	r						
Acs 2004	12	15	72	85	4.2%	0.72 [0.18, 2.92]
Birner 2000	20	91	0	5	1.8%	3.15 [0.17, 59.44	j <u> </u>
Guo 2008	62	79	1	20	2.9%	69.29 [8.65, 555.35	
Li 2010	36	40	24	40	4.6%	6.00 [1.79, 20.15	-
Liu 2008	19	33	5	20	4.6%	4.07 [1.20, 13.86	
No 2009	16	36	7	41	5.0%	3.89 [1.37, 11.06	·
Zhang 2009	25	34	0	10	1.9%	56.37 [3.00, 1059.05	-
Subtotal (95% CI)		328		221	24.9%	5.53 [1.99, 15.33	
Total events	190		109			,	
Heterogeneity: Tau ² =		$i^2 = 17^{-1}$		(P = 0	009) [,] I ² =	65%	
Test for overall effect:				ų v.			
	- 0.20		,				
3.8.3 Ovarian Cancer	r						
Birner 2001	70	102	2	20	3.9%	19.69 [4.31, 89.98	ı
Daponte 2008	47	78	3	20	4.4%	8.59 [2.32, 31.79	
Guo 2010	37	57	2	30	3.9%	25.90 [5.58, 120.12	
lida 2008	39	39	23	31	1.9%	28.57 [1.58, 518.03	· · · · · · · · · · · · · · · · · · ·
Ji 2013	36	41	11	27	4.6%	10.47 [3.12, 35.12	
Li 2011	39	60	8	30	5.2%	5.11 [1.94, 13.44	-
Liu 2012	70	96	10	45	5.5%	9.42 [4.09, 21.71	
Luo 2005	195	238	5	38	5.1%	29.93 [11.05, 81.10	
Osada 2007	57	72	14	18	4.5%	1.09 [0.31, 3.78	
Su 2011	29	35	1	24	2.7%	111.17 [12.48, 989.92	-
Wang 2008	79	112	2	18	3.9%	19.15 [4.17, 88.01	
Wong 2003	20	37	2	16	3.7%	8.24 [1.64, 41.47	
Yu 2012	46	87	13	30	5.5%	1.47 [0.64, 3.38	
Subtotal (95% CI)		1054		347	54.6%	9.73 [4.90, 19.32	
Total events	764		96		-		
Heterogeneity: Tau ² =		$i^2 = 44$		2 (P < 1	1 00011 [.] P	² = 73%	
Test for overall effect:							
. Sotion overall effect.	2 - 0.01						
Total (95% CI)		1741		695	100.0%	8.86 [5.53, 14.19	1
Total events	1199	00.51	226			,	-
Heterogeneity: Tau ² =		i ² = 73.0		5 (P < 1	0.000011:	I² = 66%	
Test for overall effect:							0.01 0.1 1 10 100
			,				Favours experimental Favours control
							-

Fig 3. Forest plot of the expression of HIF-1 α in cancer versus that in nomal tissue. ($l^2 = 66\%$).

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time. Statistically similar results were obtained by this procedure, indicating the stability of this meat-analysis (data not shown).

Discussion

HIF-1 α 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



	Border	line	Norm	al		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.6.1 Endometrial Ca	ncer						
Feng 2013	10	28	9	35	7.1%	1.60 [0.54, 4.74]	_ -
Horrée 2007	14	23	0	17	2.4%	53.42 [2.86, 998.20]	│ ——→
Pan 2011	9	23	4	18	5.9%	2.25 [0.56, 9.05]	
Subtotal (95% CI)		74		70	15.3%	3.48 [0.75, 16.15]	
Total events	33		13				
Heterogeneity: Tau ² =				P = 0.0	7); l² = 63	%	
Test for overall effect:	Z=1.59 ((P = 0.1	1)				
	_						
3.6.2 Cervical Cance			70		7.000		
Acs 2004	59	70	72	85	7.9%	0.97 [0.40, 2.32]	
Birner 2000	2	10	0	5	2.1%	3.24 [0.13, 80.99]	
Guo 2008	30	90	1	20	3.9%	9.50 [1.21, 74.39]	
Li 2010	30	40	24	40	7.6%	2.00 [0.77, 5.20]	
Liu 2008	19	40	5	20	6.6%	2.71 [0.83, 8.90]	
No 2009	17	39	7	41	7.3%	3.75 [1.34, 10.52]	
Zhang 2009	3	10	0	10	2.2%	9.80 [0.44, 219.25]	
Subtotal (95% CI)		299		221	37.5%	2.36 [1.34, 4.13]	-
Total events	160		109			~	
Heterogeneity: Tau ² =				² = 0.2	(); i* = 21	%	
Test for overall effect:	Z = 2.99 ((P = 0.0	03)				
3.6.3 Ovarian Cancer							
Birner 2001	44	50	2	20	4.9%	66.00 [12.16, 358.28]	
Daponte 2008	12	22	3	20	5.5%	6.80 [1.54, 30.08]	
lida 2008	29	32	23	31	5.7%	3.36 [0.80, 14.13]	
Ji 2013	18	20	11	27	5.0%	13.09 [2.51, 68.18]	· · · · · · · · · · · · · · · · · · ·
Li 2011	12	21	8	30	6.6%	3.67 [1.12, 11.98]	
Luo 2005	8	19	5	38	6.2%	4.80 [1.30, 17.78]	
Osada 2007	11	17	14	18	5.5%	0.52 [0.12, 2.33]	
Su 2011	10	22	1	24	3.6%	19.17 [2.19, 168.02]	
Wang 2008	5	9	2	18	4.1%	10.00 [1.39, 71.86]	
Subtotal (95% CI)		212		226	47.2%	6.29 [2.69, 14.73]	
Total events	149		69				
Heterogeneity: Tau ² =	1.04; Chi	r = 21.5	57, df = 8	(P = 0.	006); I ² =	63%	
Test for overall effect:	Z= 4.24 ((P < 0.0	001)				
Total (95% CI)		585		517	100.0%	4.08 [2.44, 6.85]	•
Total events	342	505	191	517	100.070	4.00 [2.44, 0.05]	•
Heterogeneity: Tau ² =		2 - 11 0		8 (P = 0	001\-	- 57%	
Test for overall effect:				5(1-0			0.01 0.1 i 10 100
restion overall effect.	2 - 5.54 (, - 0.0	0001)			F	avours experimental Favours control



a key role in hypoxic conditions that occur during tumor angiogenesis, invasion and metastasis [67, 68]. In gynecological cancer, HIF-1 α 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-1 α expression and clinicopathological variables.

We demonstrated that the expression of HIF-1 α 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-1 α 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 inconsistence may result from a relatively small number of included studies (only three studies were in the subgroup analysis).

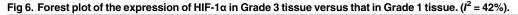
	III - IV	/	I - II			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.1.1 Endometrial Ca	ncer						
Aybatl 2011	9	30	19	64	3.9%	1.02 [0.39, 2.62]	_ _
Espinosa 2010	6	25	11	24	3.3%	0.37 [0.11, 1.26]	
Feng 2013	19	23	62	101	3.5%	2.99 [0.95, 9.44]	
Koda 2007	25	31	22	29	3.3%	1.33 [0.39, 4.54]	_
Li 2008	13	21	7	21	3.2%	3.25 [0.92, 11.51]	
Ozbudak 2008	31	31	14	69	1.2%	241.14 [13.91, 4180.83]	
Pan 2011	18	20	20	32	2.5%	5.40 [1.06, 27.47]	
Pansare 2007	25	30	29	114	3.7%	14.66 [5.14, 41.82]	
Qu 2007	10	14	15	28	3.0%	2.17 [0.55, 8.59]	
Seeber 2010	12	18	42	75	3.6%	1.57 [0.53, 4.63]	
Song 2009	3	3	21	27	1.1%	2.12 [0.10, 46.53]	
Subtotal (95% CI)		246		584	32.4%	2.76 [1.25, 6.09]	◆
Total events	171		262				
Heterogeneity: Tau ² =	1.24; Chi	i ² = 38	44. df = 1	0 (P < (0.0001); P	²= 74%	
Test for overall effect:							
3.1.2 Cervical Cancer	r						
Bachtiary 2003	14	27	18	40	3.9%	1.32 [0.49, 3.50]	- +
Guo 2008	23	25	39	54	2.7%	4.42 [0.93, 21.11]	
Haugland 2002	7	15	16	30	3.3%	0.77 [0.22, 2.65]	
Hutchison 2004	33	42	35	57	4.0%	2.30 [0.93, 5.72]	
Subtotal (95% CI)		109		181	13.8%	1.69 [0.90, 3.15]	◆
Total events	77		108				
Heterogeneity: Tau ² =	0.08; Chi	i ² = 3.7-	4, df = 3 (P = 0.2	9); I ² = 20	%	
Test for overall effect:	Z = 1.65 ((P = 0.1	0)				
3.1.3 Ovarian Cancer							
Chen 2011	21	36	8	26	3.7%	3.15 [1.09, 9.13]	
Chen 2012	44	71	16	53	4.4%	3.77 [1.77, 8.04]	
Fu 2008	35	48	30	53	4.2%	2.06 [0.89, 4.77]	—
Guo 2010	28	38	9	20	3.5%	3.42 [1.10, 10.69]	
Ji 2013	21	21	19	20	1.0%	3.31 [0.13, 86.06]	
Li 2009	23	24	8	13	1.7%	14.38 [1.45, 142.35]	
Li 2011	31	41	8	19	3.5%	4.26 [1.34, 13.55]	
Liu 2012	58	66	12	30	3.7%	10.88 [3.85, 30.74]	
Luo 2005	133	161	62	77	4.5%	1.15 [0.57, 2.30]	
Nakayama 2002	19	37	11	23	3.7%	1.15 [0.41, 3.26]	
Osada 2007	20	24	37	48	3.2%	1.49 [0.42, 5.28]	
Shen 2013	18	19	37	44	1.8%	3.41 [0.39, 29.82]	
Shimogai 2008	7	44	4	22	3.0%	0.85 [0.22, 3.29]	
Su 2011	19	22	10	13	2.3%	1.90 [0.32, 11.20]	
Wang 2008	56	76	23	46	4.4%	2.80 [1.29, 6.05]	
Yu 2009	16	18	10	12	1.9%	1.60 [0.19, 13.24]	
Yu 2012	39	44	9	45	3.4%	31.20 [9.55, 101.88]	
Subtotal (95% CI)		790		564	53.8%	3.01 [1.92, 4.74]	▼
Total events	588	_	313				
Heterogeneity: Tau ² =				6 (P = 1	0.0008); P	²= 60%	
Test for overall effect:	Z= 4.78 ((P < 0.0	10001)				
Total (05% Ch		4445		4220	100.00	2 66 14 07 2 201	
Total (95% CI)	000	1145	600	1529	100.0%	2.66 [1.87, 3.79]	▼
Total events	836	2 - 02	683 70 46 - 0	4 (0	000045	17 - 6000	
Heterogeneity: Tau ² =				1 (P < 1	J.00001);	17 = 03%	0.005 0.1 1 10 200
Test for overall effect:	∠= 5.42 (۲ < ۵.0	10001)			F	avours experimental Favours control
5		41 a m 1-					(1 ² cos())



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



	G3		G1			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
3.10.1 Endometrial C	ancer						
Aybatl 2011	3	10	7	36	5.0%	1.78 [0.36, 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, 40.98]	
Seeber 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: Chi ² =	7.35, df=	5 (P =	0.20); I ² =	: 32%			
Test for overall effect:	Z= 3.49	(P = 0.0)	005)				
3.10.2 Cervical Canc	er						
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, 25.82]	
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]	
Li 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: Chi ² =	10.76, df	= 5 (P =	= 0.06); l ²	= 54%			
Test for overall effect:	Z=4.46	(P < 0.0	0001)				
3.10.3 Ovarian Cance			_				
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: Chi ² =		-		= 45%			
Test for overall effect:	Z= 6.13	(P < 0.0	10001)				
Total (95% CI)		459		548	100.0%	3.77 [2.76, 5.16]	◆
Total events	376		287				
Heterogeneity: Chi ² =		= 21 (F		$ ^{2} = 42^{\circ}$	%		
Test for overall effect:						_	0.01 0.1 1 10 100
Test for subaroup diff		•				F	avours experimental Favours control
. setter cabaroas an	2.0.000.						



revealed that HIF-1 α 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-1 α is related to many critical aspects of gynecological cancer biology. HIF-1 α synthesis could be increased by several growth factors, cytokines and other signaling molecules responsible for stimulating phosphatidylinositol 3-kinase (PI3K) or mitogenactivated protein kinase (MAPK) pathways [38]. The regulated markers of HIF-1 α , 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-1 α also regulates many



	G3		G2			Odds Ratio	Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
3.11.1 Endometrial C	ancer						
Aybatl 2011	3	10	14	30	7.1%	0.49 [0.11, 2.26]	
Feng 2013	22	26	29	41	5.0%	2.28 [0.65, 8.02]	
Koda 2007	6	8	34	44	3.8%	0.88 [0.15, 5.07]	
Ozbudak 2008	7	15	11	25	6.4%	1.11 [0.31, 4.03]	
Pan 2011	16	18	13	17	2.2%	2.46 [0.39, 15.63]	
Seeber 2010	12	18	33	47	8.8%	0.85 [0.27, 2.71]	
Subtotal (95% CI)		95		204	33.2%	1.15 [0.65, 2.01]	•
Total events	66		134				
Heterogeneity: Chi ² =	3.33, df=	5 (P =	0.65); l² =	= 0%			
Test for overall effect:	Z = 0.48 ((P = 0.8	i3)				
3.11.2 Cervical Canc	er						
Bachtiary 2003	8	17	17	34	8.7%	0.89 [0.28, 2.85]	
Cheng 2013	18	21	25	34	3.9%	2.40 [0.58, 9.98]	
Guo 2008	26	26	23	36	0.6%	15.81 [0.87, 287.51]	
Hutchison 2004	20	14	40	57	8.2%	0.77 [0.22, 2.62]	
Li 2010	8	9	40	21	1.8%	0.84 [0.07, 10.66]	
Markowska 2007	28	31	37	46	4.2%	2.27 [0.56, 9.17]	
Subtotal (95% CI)	20	118	57	229	27.4%	1.62 [0.91, 2.90]	
Total events	97	110	166	225	21.470	1.02 [0.0 1, 2.00]	Ŧ
Heterogeneity: Chi ² =		5 (P -		- 11%			
Test for overall effect:				- 11 /0			
restion overall ellect.	2 - 1.001	(1 - 0.1	0)				
3.11.3 Ovarian Cance							
Guo 2010	11	12	20	28	1.4%	4.40 [0.49, 39.92]	
Liu 2012	25	32	30	40	8.4%	1.19 [0.40, 3.58]	
Luo 2005	81	84	82	101	3.9%	6.26 [1.78, 21.96]	
Nakai 2007	6	10	10	14	4.8%	0.60 [0.11, 3.34]	
Nakayama 2002	13	22	11	16	7.5%	0.66 [0.17, 2.55]	
Osada 2007	8	10	25	30	3.6%	0.80 [0.13, 4.95]	
Shen 2013	14	16	16	17	2.8%	0.44 [0.04, 5.36]	
Su 2011	14	14	12	17	0.5%	12.76 [0.64, 254.31]	
Wang 2008	33	38	34	48	5.7%	2.72 [0.88, 8.39]	
Yu 2009	8	8	7	10	0.5%	7.93 [0.35, 179.96]	
Subtotal (95% CI)		246		321	39.4%	2.02 [1.27, 3.19]	-
Total events	213		247				
Heterogeneity: Chi ² =		•		= 35%	Ē.		
Test for overall effect:	Z= 2.99 ((P = 0.0	103)				
Total (95% CI)		459		754	100.0%	1.62 [1.20, 2.19]	◆
Total events	376		547				
Heterogeneity: Chi ² =	24.17, df	= 21 (F	= 0.29);	l ² = 139	%		
Test for overall effect:							Favours experimental Favours control
Test for subaroup dif	ferences:	Not ap	olicable				avours experimental ravours control



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-1 α 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 inconsistence. For example, type I endometrial cancer is often characterized by



	G2		G1			Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl			
3.4.1 Endometrial Ca	псег									
Aybatl 2011	14	30	7	36	4.3%	3.63 [1.21, 10.82]				
Feng 2013	29	41	30	57	9.2%	2.17 [0.93, 5.09]				
Koda 2007	34	44	7	8	3.4%	0.49 [0.05, 4.43]				
Ozbudak 2008	11	25	27	60	11.2%	0.96 [0.38, 2.46]				
Pan 2011	13	17	9	17	2.7%	2.89 [0.66, 12.57]				
Seeber 2010	33	47	9	28	4.2%	4.98 [1.81, 13.66]				
Subtotal (95% CI)		204		206	34.9%	2.19 [1.43, 3.37]	•			
Total events	134		89							
Heterogeneity: Chi ² =				= 39%						
Test for overall effect:	Z = 3.58	(P = 0.0	0003)							
3.4.2 Cervical Cance										
	17	24	2	7	2.104	2 50 10 42 14 741				
Bachtiary 2003	25	34 35	2 20	7 42	2.1% 6.5%	2.50 [0.42, 14.71]				
Cheng 2013						2.75 [1.06, 7.12]				
Guo 2008	28	36	8	17	3.0%	3.94 [1.15, 13.53]				
Hutchison 2004	40	57 21	12 9	17	6.9%	0.98 [0.30, 3.21]				
Li 2010 Markawaka 2007	19		-	10	1.5%	1.06 [0.08, 13.23]				
Markowska 2007 Subtotal (05% CI)	37	46 229	16	29 122	4.8% 24.8%	3.34 [1.19, 9.38]				
Subtotal (95% CI) Total events	166	229	67	122	24.070	2.40 [1.46, 3.93]	-			
Heterogeneity: Chi ² =		6 /D -		- 0%						
Test for overall effect:		•		- 0 %						
restion overall ellect.	2 - 3.40	(1 - 0.0	,000,							
3.4.3 Ovarian Cancer										
Guo 2010	20	28	6	18	2.6%	5.00 [1.39, 17.94]				
Liu 2012	30	40	15	24	5.9%	1.80 [0.60, 5.37]				
Luo 2005	82	101	32	53	9.9%	2.83 [1.35, 5.95]				
Nakai 2007	10	14	13	19	4.0%	1.15 [0.25, 5.22]				
Nakayama 2002	11	16	3	17		10.27 [2.00, 52.65]				
Osada 2007	25	30	24	32	4.9%	1.67 [0.48, 5.82]				
Shen 2013	16	17	14	19	1.0%	5.71 [0.59, 54.96]				
Su 2011	12	17	3	4	1.8%	0.80 [0.07, 9.67]				
Wang 2008	34	48	12	24	5.9%	2.43 [0.88, 6.69]				
Yu 2009	7	10	9	10	3.4%	0.26 [0.02, 3.06]				
Subtotal (95% CI)		321		220	40.3%	2.43 [1.65, 3.59]				
Total events	247		131							
Heterogeneity: Chi ² =	•	•		ʻ=14%						
Test for overall effect:	Z= 4.48	(P < 0.0	00001)							
Total (95% CI)		754		548	100.0%	2.34 [1.82, 3.00]	•			
Total events	547		287							
Heterogeneity: Chi ² =	22.43, df	= 21 (F	e = 0.38);	l ² = 6%						
Test for overall effect:	Z = 6.68	(P < 0.0	00001)							
Test for subaroup diff	Test for subgroup differences: Not applicable Favours experimental Favours control									

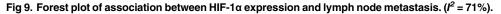


mutations in tumor suppressor PTEN, while type II endometrial cancer generally contains the mutation of another tumor suppressor p53 [71–74]. In cervical cancer, the overexpression of human papillomavirus (HPV) and the loss of p53 promote tumor invasion and metastasis [75]. Thus, further studies included both HIF-1 α 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



	YES		NO			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.2.1 Endometrial Ca	ncer						
Aybatl 2011	10	34	18	60	5.8%	0.97 [0.39, 2.44]	_
Feng 2013	26	31	55	93	5.6%	3.59 [1.27, 10.19]	—•—
Li 2008	18	32	2	10	4.1%	5.14 [0.94, 28.14]	
Pan 2011	11	11	27	41	2.3%	12.13 [0.67, 220.84]	↓ →
Qu 2007	15	16	10	26	3.3%	24.00 [2.73, 210.82]	
Subtotal (95% CI)		124		230	21.1%	4.02 [1.32, 12.26]	
Total events	80		112				
Heterogeneity: Tau ² =	0.92; Chi	² = 10.7	75, df = 4	(P = 0.	03); I ² = 6	33%	
Test for overall effect:							
3.2.2 Cervical Cancer	r						
Bachtiary 2003	12	21	20	46	5.6%	1.73 [0.61, 4.92]	- -
Burri 2003	20	30	26	47	5.7%	1.62 [0.62, 4.19]	- +
Cheng 2013	37	39	25	59	4.5%	25.16 [5.54, 114.31]	
Haugland 2002	5	11	18	34	4.8%	0.74 [0.19, 2.90]	
Huang 2014	10	17	29	57	5.4%	1.38 [0.46, 4.13]	_ -
Li 2010	10	10	4	30	2.2%	123.67 [6.11, 2503.58]	
No 2009	5	11	11	25	4.7%	1.06 [0.25, 4.41]	
Zhang 2009	17	19	8	15	4.0%	7.44 [1.25, 44.19]	
Subtotal (95% CI)		158		313	37.0%	2.94 [1.19, 7.29]	
Total events	116		141				
Heterogeneity: Tau ² =	1.16; Chi	² = 24.3	73. df = 7	(P = 0.	0008); I ² :	= 72%	
Test for overall effect:							
			,				
3.2.3 Ovarian Cancer							
Chen 2011	25	36	4	26	5.0%	12.50 [3.48, 44.95]	
Chen 2012	34	50	26	74	6.1%	3.92 [1.83, 8.41]	
Guo 2010	14	27	21	31	5.5%	0.51 [0.18, 1.49]	
Ji 2013	26	27	10	14	3.1%	10.40 [1.03, 104.72]	
Li 2009	26	27	5	10	3.0%	26.00 [2.48, 272.82]	→
Li 2011	29	36	10	24	5.3%	5.80 [1.82, 18.46]	
Shimogai 2008	5	25	6	41	5.0%	1.46 [0.39, 5.39]	-
Tong 2008	19	21	7	10	3.6%	4.07 [0.56, 29.73]	
Yu 2012	37	42	9	45	5.2%	29.60 [9.04, 96.87]	
Subtotal (95% CI)		291		275	41.9%	5.20 [2.10, 12.89]	
Total events	215		98				
Heterogeneity: Tau ² =	1.37; Chi	² = 33.8	87, df = 8	(P < 0.	0001); l ^a :	= 76%	
Test for overall effect:							
Total (95% CI)		573		Q10	100.0%	3.98 [2.31, 6.83]	
Total events	411	515	351	010	100.0%	5.50 [2.51, 0.05]	•
Heterogeneity: Tau ² =		Z = 72 -		1 /0 ~ 1	000043	12 - 71 %	
				I (F < I	5.00001);		0.01 0.1 i 10 100
Test for overall effect:	∠ = 0.00 (۳ ۹ ۵.۵	0001)			F	avours experimental Favours control



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-1 α 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



Study or Subgroup Events Total Weight M.H. Random, 95% Cl M.H. Random, 95% Cl 3.3.1 Endometrial Cancer 1 9 27 85 7.1% 0.27 [0.03, 2.26] Pijnenborg 2007 7 40 7 25 12.5% 0.55 [0.17, 1.80] Seeber 2010 14 18 37 72 12.5% 3.31 [0.99, 11.03] Yeramian 2011 7 9 19 72 9.5% 9.76 [1.86, 51.17] Subtotal (95% Cl) 76 254 41.6% 1.56 [0.36, 6.83] 1.5% Test for overall effect: $Z = 0.60 (P = 0.55)$ 3.3.2 Cervical cancer 8.50 [1.54, 27.49] 4.650 [1.54, 27.49] Kim 2013 20 31 40 120 15.3% 3.64 [1.59, 8.32] Subtotal (95% Cl) 76 204 39.1% 5.33 [2.91, 9.75] 5.33 [2.91, 9.75] Total events 47 53 4.07 [0.56, 29.73] 4.07 [0.56, 29.73] 4.07 [0.56, 29.73] Subtotal (95% Cl) 32 65 19.3% 2.45 [0.81, 7.45]		<5 years		>=5 years		Odds Ratio		Odds Ratio				
Ayball 2011 1 9 27 85 7.1% 0.27 [0.03, 2.26] Pijnenborg 2007 7 40 7 25 12.5% 0.55 [0.17, 1.80] Seeber 2010 14 18 37 72 12.5% 3.31 [0.99, 11.03] Yeramian 2011 7 9 19 72 9.5% 9.76 [1.86, 51.17] Subtotal (95% Cl) 76 254 41.6% 1.56 [0.36, 6.83] 1.56 [0.36, 6.83] Total events 29 90 90 90 14 28 6 63 13.1% 9.50 [3.10, 29.14] Ishikawa 2004 13 17 7 21 10.8% 6.50 [1.54, 27.49] Kim 2013 20 31 40 120 15.3% 3.64 [1.59, 8.32] Subtotal (95% Cl) 76 204 39.1% 5.33 [2.91, 9.75] 7.44] Total events 47 53 1.95 [0.51, 7.44] 7.10 7.8% 4.07 [0.56, 29.73] Subtotal (95% Cl) 32 65 19.3% 2.45 [0.81, 7.45] 1.41 1.41 1.41 1.41 1.41	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl				
Pijnenborg 2007 7 40 7 25 12.5% 0.55 [0.17, 1.80] Seeber 2010 14 18 37 72 12.5% 3.31 [0.99, 11.03] Yeramian 2011 7 9 19 72 9.5% 9.76 [1.86, 51.17] Subtotal (95% CI) 76 254 41.6% 1.56 [0.36, 6.83] Total events 29 90 Heterogeneity: Tau ² = 1.64; Chi ² = 11.80, df = 3 (P = 0.008); I ² = 75% Test for overall effect: $Z = 0.60$ (P = 0.55) 3.3.2 Cervical cancer Bimer 2000 14 28 6 63 13.1% 9.50 [3.10, 29.14] Ishikawa 2004 13 17 7 21 10.8% 6.50 [1.54, 27.49] Kim 2013 20 31 40 120 15.3% 3.64 [1.59, 8.32] Subtotal (95% CI) 76 204 39.1% 5.33 [2.91, 9.75] Total events 47 53 Heterogeneity: Tau ² = 0.00; Chi ² = 1.91, df = 2 (P = 0.38); I ² = 0% Test for overall effect: $Z = 5.42$ (P < 0.00001) 3.3.3 Ovarian Cancer Shimogal 2008 7 11 26 55 11.5% 1.95 [0.51, 7.44] Tong 2008 19 21 7 10 7.8% 4.07 [0.56, 29.73] Subtotal (95% CI) 32 65 19.3% 2.45 [0.81, 7.45] Total events 26 33 Heterogeneity: Tau ² = 0.00; Chi ² = 0.36, df = 1 (P = 0.55); I ² = 0% Test for overall effect: $Z = 1.59$ (P = 0.11) Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 0.37, df = 8 (P = 0.008); I ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 2.71, df = 8 (P = 0.008); I ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 2.071, df = 8 (P = 0.008); I ² = 61%	3.3.1 Endometrial Cancer											
Seeber 2010 14 18 37 72 12.5% 3.31 [0.99, 11.03] Yeramian 2011 7 9 19 72 9.5% 9.76 [1.86, 51.17] Subtotal (95% CI) 76 254 41.6% 1.56 [0.36, 6.83] Total events 29 90 Heterogeneity: Tau ² = 1.64; Ch ² = 11.80, df = 3 (P = 0.008); I ² = 75% Test for overall effect $Z = 0.60$ (P = 0.55) 3.3.2 Cervical cancer Birner 2000 14 28 6 63 13.1% 9.50 [3.10, 29.14] Ishikawa 2004 13 17 7 21 10.8% 6.50 [1.54, 27.49] Kim 2013 20 31 40 120 15.3% 3.64 (1.59, 8.32] Subtotal (95% CI) 76 204 39.1% 5.33 [2.91, 9.75] Total events 47 53 Heterogeneity: Tau ² = 0.00; Chi ² = 1.91, df = 2 (P = 0.38); I ² = 0% Test for overall effect $Z = 5.42$ (P < 0.00001) 3.3.3 Ovarian Cancer Shimogai 2008 7 11 26 55 11.5% 1.95 [0.51, 7.44] Total events 26 33 Heterogeneity: Tau ² = 0.00; Chi ² = 0.36, df = 1 (P = 0.55); I ² = 0% Test for overall effect $Z = 1.59$ (P = 0.11) Total events 26 33 Heterogeneity: Tau ² = 0.00; Chi ² = 0.38, df = 1 (P = 0.55); I ² = 0% Test for overall effect $Z = 1.59$ (P = 0.11) Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 20.71, df = 8 (P = 0.008); I ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 20.71, df = 8 (P = 0.008); I ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 20.71, df = 8 (P = 0.008); I ² = 61%	Aybatl 2011	1	9	27	85	7.1%	0.27 [0.03, 2.26]					
Yeramian 2011 7 9 19 72 9.5% 9.76 [1.86, 51.17] Subtotal (95% Cl) 76 254 41.6% 1.56 [0.36, 6.83] Total events 29 90 Heterogeneity: Tau ² = 1.64; Chi ² = 11.80, df = 3 (P = 0.008); I ² = 75% Test for overall effect $Z = 0.60$ (P = 0.55) 3.3.2 Cervical cancer Birner 2000 14 28 6 63 13.1% 9.50 [3.10, 29.14] Ishikawa 2004 13 17 7 21 10.8% 6.50 [1.54, 27.49] Kim 2013 20 31 40 120 15.3% 3.64 [1.59, 8.32] Subtotal (95% Cl) 76 204 39.1% 5.33 [2.91, 9.75] Total events 47 53 Heterogeneity: Tau ² = 0.00; Chi ² = 1.91, df = 2 (P = 0.38); I ² = 0% Test for overall effect $Z = 5.42$ (P < 0.00001) 3.3.3 Ovarian Cancer Shimogai 2008 7 11 26 55 11.5% 1.95 [0.51, 7.44] Total events 26 33 Heterogeneity: Tau ² = 0.00; Chi ² = 0.36, df = 1 (P = 0.55); I ² = 0% Test for overall effect $Z = 1.59$ (P = 0.11) Total events 102 176 Heterogeneity: Tau ² = 0.07; Chi ² = 20.71, df = 8 (P = 0.008); I ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 2.07.1, df = 8 (P = 0.008); I ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 2.07.1, df = 8 (P = 0.008); I ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 0.002)	Pijnenborg 2007	7	40	7	25	12.5%	0.55 [0.17, 1.80]					
Subtotal (95% CI) 76 254 41.6% 1.56 [0.36, 6.83] Total events 29 90 Heterogeneity: Tau ² = 1.64; Chi ² = 11.80, df = 3 (P = 0.008); l ² = 75% Test for overall effect: $Z = 0.60$ (P = 0.55) 3.3.2 Cervical cancer Birner 2000 14 28 6 63 13.1% 9.50 [3.10, 29.14] Ishikawa 2004 13 17 7 21 10.8% 6.50 [1.54, 27.49] Kim 2013 20 31 40 120 15.3% 3.64 [1.59, 8.32] Subtotal (95% CI) 76 204 39.1% 5.33 [2.91, 9.75] Total events 47 53 Heterogeneity: Tau ² = 0.00; Chi ² = 1.91, df = 2 (P = 0.38); l ² = 0% Test for overall effect: $Z = 5.42$ (P < 0.00001) 3.3.3 Ovarian Cancer Shimogai 2008 7 11 26 55 11.5% 1.95 [0.51, 7.44] Total events 26 33 Heterogeneity: Tau ² = 0.00; Chi ² = 0.36, df = 1 (P = 0.55); l ² = 0% Test for overall effect: $Z = 1.59$ (P = 0.11) Total events 26 33 Heterogeneity: Tau ² = 0.00; Chi ² = 20.71, df = 8 (P = 0.008); l ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 20.71, df = 8 (P = 0.008); l ² = 61% Total events 7 = 2 2.20 (P = 0.002)	Seeber 2010	14	18	37	72	12.5%	3.31 [0.99, 11.03]					
Total events 29 90 Heterogeneity: Tau ² = 1.64; Chi ² = 11.80, df = 3 (P = 0.008); l ² = 75% Test for overall effect: $Z = 0.60$ (P = 0.55) 3.3.2 Cervical cancer Birner 2000 14 28 6 63 13.1% 9.50 [3.10, 29.14] Ishikawa 2004 13 17 7 21 10.8% 6.50 [1.54, 27.49] Kim 2013 20 31 40 120 15.3% 3.64 [1.59, 8.32] Subtotal (95% CI) 76 204 39.1% 5.33 [2.91, 9.75] Total events 47 53 Heterogeneity: Tau ² = 0.00; Chi ² = 1.91, df = 2 (P = 0.38); l ² = 0% Test for overall effect: $Z = 5.42$ (P < 0.00001) 3.3.3 Ovarian Cancer Shimogai 2008 7 11 26 55 11.5% 1.95 [0.51, 7.44] Total events 26 33 Heterogeneity: Tau ² = 0.00; Chi ² = 0.36, df = 1 (P = 0.55); l ² = 0% Test for overall effect: $Z = 1.59$ (P = 0.11) Total (95% CI) 184 523 100.0% 2.93 [1.43, 6.01] Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 20.71, df = 8 (P = 0.008); l ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 20.71, df = 8 (P = 0.008); l ² = 61% Total events 102 176 Heterogeneity: Tau ² = 0.70; Chi ² = 20.71, df = 8 (P = 0.008); l ² = 61%		7	-	19								
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Eavours lexperimentally Eavours Icontroll			· · · · ·	/			F	avours [experimental] Favours [control]				
Test for subaroup differences: Chi ² = 3.16. df = 2 (P = 0.21). I ² = 36.7%												



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-1 α 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-1 α is emerging as an important factor in the carcinogenesis of gynecological cancer. HIF-1 α 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-1 α may serve as a reliable tool for early and accurate prediction of cancer and may be a potential therapeutic target for gynecological cancer.

	<5 years		>=5 years		Odds Ratio		Odds Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% Cl					
3.12.1 Endometrial Cancer												
Sivridis 2002	9	10	31	71	8.6%	11.61 [1.40, 96.61						
Wang 2010	9	12	56	86	13.2%	1.61 (0.40, 6.39						
Subtotal (95% CI)		22		157	21.8%	3.67 [0.52, 25.63						
Total events	18		87									
Heterogeneity: Tau ² = 1.19; Chi ² = 2.43, df = 1 (P = 0.12); l ² = 59%												
Test for overall effect: Z = 1.31 (P = 0.19)												
3.12.2 Cervical Canc	er											
Birner 2000	5	17	15	74	14.7%	1.64 [0.50, 5.37]					
Dellas 2008	18	19	14	25	8.4%	14.14 [1.63, 123.00]					
Kim 2013	11	17	49	134	15.8%	3.18 [1.11, 9.13						
Subtotal (95% CI)		53		233	38.8%	3.14 [1.19, 8.27						
Total events	34		78									
Heterogeneity: Tau ² =	0.26; Ch	i ² = 3.0	7, df = 2 (P = 0.2	2); I ² = 35	i%						
Test for overall effect:	Z = 2.32	(P = 0.0	12)									
3.12.3 Ovarian Cance	er											
Chen 2011	27	44	2	18	11.7%	12.71 [2.59, 62.33]					
Shimogai 2008	7	24	4	42		3.91 [1.01, 15.17						
Yu 2012	42	53	4	34	14.3%	28.64 [8.32, 98.62						
Subtotal (95% CI)		121		94	39.4%	11.46 [3.43, 38.29						
Total events	76		10									
Heterogeneity: Tau ² = 0.63; Chi ² = 4.54, df = 2 (P = 0.10); l ² = 56%												
Test for overall effect:	Z = 3.96	(P < 0.0	1001)									
Total (95% CI)		196		484	100.0%	5.53 [2.48, 12.31						
Total events	128		175									
Heterogeneity: Tau ² =	0.77; Ch	i ² = 17.	46, df = 7	(P = 0.	.01); I ² = 6	i0%						
Test for overall effect:	Z = 4.19	(P < 0.0	1001)				Favours experimental Favours control					
							ravours experimental ravours control					

Fig 11. Forest plot of association between HIF-1 α expression and 5-years overall survival rate. ($l^2 = 60\%$).

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Supporting Information

S1 PRISMA Checklist. PRISMA Checklist. (DOC)

S1 Table. Quality assessments of included studies. (DOC)

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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