Pre-diagnosis insulin-like growth factor-I and risk of epithelial invasive ovarian cancer by histological subtypes: A collaborative re-analysis from the Ovarian Cancer Cohort Consortium

Jennifer Ose[1,2], Helena Schock[1], Elizabeth M. Poole[3], Matti Lehtinen[4], Kala Visvanathan[5], Kathy Helzlsouer[5], Julie E. Buring[6,7], I-Min Lee[6,7], Anne Tjønneland[8], Marie-Christine Boutron-Ruault[9,10], Antonia Trichopoulou[11,12], Amalia Mattiello[13], N. Charlotte Onland-Moret[14], Elisabete Weiderpass[15,16,17,18], María-José Sánchez[19,20], Annika Idahl[21], Ruth C. Travis[22], Sabina Rinaldi[23], Melissa A. Merritt[24], Nicolas Wentzensen[25], Shelley S. Tworoger[3,7], Rudolf Kaaks[1], Renée T. Fortner[1]

[1]Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Baden-Württemberg, Germany
[2]Department of Population Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA
[3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[4]Karolinska Institutet, Department of Laboratory Medicine, Huddinge, Sweden
[5]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
[6]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[7]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[8]Unit of Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark
[9] Université Paris-Saclay, Université Paris-Sud, UVSQ, CESP, INSERM, Villejuif, France
[10]Gustave Roussy, F-94805, Villejuif, France
[11]Hellenic Health Foundation, Athens, Greece
[12]WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Dept. of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Greece
[13] Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy
[14] Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[15]Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway.
[16]Department of Research, Cancer Registry of Norway, Oslo, Norway
[17]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[18]Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland
[19]Escuela Andaluza de Salud Pública. Instituto de Investigación Biosanitaria ibs.GRANADA. Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain
[20]CIBER de Epidemiología y Salud Pública (CIBERESP), Spain
[21]Department of Clinical Sciences, Obstetrics and Gynecology, Umea University, Umea, Sweden
[22]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[23]Section of Nutrition and Metabolism, International Agency for Research on Cancer (IARC), Lyon, France
[24]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK
[25]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

Corresponding author: Renée T. Fortner, Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany. Phone: + 49 (0) 6221 42 2241; Fax: + 49 (0) 6221 42 2203; E-mail: r.fortner@dkfz-heidelberg.de

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Abstract

Purpose: Biologic evidence suggests that the Insulin-like growth factor (IGF)-family may be involved in the etiology of epithelial invasive ovarian cancer (EOC). However, prospective studies investigating the role of IGF-I in ovarian carcinogenesis have yielded conflicting results.

Methods: We pooled and harmonized data from 6 case-control studies nested within the Ovarian Cancer Cohort Consortium to investigate the association between pre-diagnosis IGF-I concentrations and subsequent risk of EOC. We evaluated IGF-I concentrations and risk of EOC overall and by tumor subtype (defined by histology, grade, stage) in 1,270 cases and 2,907 matched controls. Multivariable conditional logistic regression models were used to calculate Odds Ratios (OR) and 95% Confidence Intervals (CI).

Results: Doubling of IGF-I concentration was associated with significantly lower risk of overall EOC [OR_{log2}=0.82; CI: 0.72-0.93]. We observed no heterogeneity by tumor characteristics (e.g., histology, p_{het}=0.62), menopausal status at blood collection (p_{het}=0.79), or age at diagnosis (p_{het}=0.60).

Conclusions: These results suggest that IGF-I concentrations are inversely associated with EOC risk, independent of histological phenotype. Future prospective research should consider potential mechanisms for this association, including considering other members of the IGF-family to better characterize the role of IGF-signaling in the etiology of EOC.

Introduction

Insulin-like growth factor (IGF) signalling has been implicated in the development of various epithelial cancers (e.g., breast and prostate), supported by evidence from *in vitro* and *in vivo* studies (as reviewed in: (1)). Data from mechanistic studies demonstrate a role for IGF-I in cellular proliferation, invasion, and angiogenesis of ovarian cancer cells (2, 3). Thus, a role for IGF-I in the development of epithelial invasive ovarian cancer (EOC) has been hypothesized.

Prospective studies evaluating circulating concentrations of IGF-I and EOC risk have yielded inconclusive results (4-8). Emerging data support different etiologies for the main EOC histologic subtypes (e.g., serous, endometrioid, mucinous and clear cell tumors) (9), which can be categorized using the hypothesized dualistic model of ovarian carcinogenesis (i.e., type I, predominantly low grade serous and endometrioid histologies, as well as mucinous and clear cell tumors; and type II, predominantly higher grade serous and endometrioid) (10). However, in prior research evaluating circulating IGF-I and risk, EOC was predominantly investigated as a composite outcome due to limited power. To date, two studies evaluated differences in IGF-I associations across histologies and by developmental pathways with no clear heterogeneity (7, 8).

In the present study, we pooled available data from 6 prospective cohort studies within the Ovarian Cancer Cohort Consortium (OC3) to investigate the association between pre-diagnosis IGF-I and EOC risk among 1,270 invasive EOC cases and 2,907 matched controls. We investigated overall EOC risk, as well as heterogeneity by EOC subtypes (e.g., histology, grade, stage) and developmental pathways (i.e., type I vs. type II).

Materials and Methods

Study populations

The OC3 has been described previously (9). For this investigation, eligible cohorts were required to have data on a defined set of *a priori* selected covariates (e.g., menopausal status at blood donation, oral contraceptive use at blood donation, parity) and pre-diagnosis measurements of circulating IGF-I. Data from the following OC3 studies were included in the current study: "Give Us a Clue to Cancer and Heart Disease" (CLUE II), the European Prospective Investigation into Cancer and Nutrition (EPIC) (7), the Harvard Women's Health Study (WHS) (5), and the Nurses' Health Studies (NHS and NHSII) (5). In addition to the OC3 cohorts, the Finnish Maternity Cohort (FMC) (8), a cohort of women pregnant at blood collection, contributed data to this investigation (for additional information on contributing cohorts, see **Table S1**). Available biomarker and questionnaire data from each cohort were centrally collated and harmonized.

Ascertainment of cases

Eligible cases included women diagnosed with incident epithelial invasive ovarian cancer (International Classification of Disease (ICD) codes: ICD9 codes 183 and 158; ICD10 codes C56) ascertained by self-report with medical record confirmation and/or linkage to cancer registries. Cases were individually matched to two or three controls on age, date, menopausal status and day or phase of menstrual cycle in premenopausal women, with exception of the FMC, which was restricted to currently pregnant women. Cases and controls in the FMC were matched on age and date at blood collection and parity at blood collection and diagnosis (or reference date for controls) (**Table S1**). Histologic classification was as follows: 50% of tumors were of serous histology (n=630), 13% endometrioid (n=163), 15% mucinous

(n=186), 4% clear cell (n=57) and 18% other (including “not otherwise specified” (NOS), malignant neoplasms, carcinoma, mixed Mullerian, mixed mesodermal or malignant Brenner tumors; n=234). The majority of cases had data on stage at diagnosis (n=1,044; 82%). Information on grade was available for 34% of the cases (missing for all FMC cases). Well-differentiated tumors (i.e., grade 1) were classified as “low grade”, whereas moderately, poorly, and undifferentiated tumors (i.e., grades 2-4) were classified as “high grade”; well differentiated tumors had a district risk factor profile relative to moderately and poorly differentiated tumors in a previous study in the OC3, whereas moderately and poorly differentiated tumors clustered together (9). Data on histology and grade were used to classify tumors into developmental pathways. Low-grade serous and endometrioid, and all mucinous and clear cell cases were classified as Type I (49%, n=277); high-grade serous and endometrioid were classified as type II (51%, n=284) (10). Mucinous and clear cell cases from the FMC were characterized as Type I; however, all serous and endometrioid tumors from the FMC were excluded from Type I/Type II analyses given no data on grade were available. After excluding participants from FMC, we observed a type I / type II distribution as expected from the literature (type I: 28% vs. type II: 72%) (10).

Laboratory methods

Case-control sets from all cohorts were measured in the same batch and technicians performing the assays were blinded to case-control status and quality control samples. With the exception of EPIC and the FMC, which used serum, IGF-I was measured in plasma samples (**Table S2**). All studies, with exception of the FMC, used an enzyme-linked immunosorbent assay (ELISA); the FMC used a chemiluminescent immunoradiometric assay. Coefficients of variation ranged from 2% (NHS, NHSII, WHS) to 14.6% (FMC). To account for differences in study-specific mean concentrations and a different case-control ratio between studies (1:2 vs. 1:3), IGF-I concentrations were standardized based on the cohort-

specific mean concentrations in controls (i.e., for each cohort, standardized concentration = original concentration – mean concentration in controls).

Statistical analyses

Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). The association between IGF-I concentrations and EOC risk was evaluated on the log2-transformed continuous scale and in tertiles; quintiles were evaluated in a secondary analysis. Quantiles were defined based on the distribution in controls. Results from models considering study-specific quantiles vs. across-study quantiles based on the standardized IGF-I concentrations were similar. Therefore, only results from across-study quantiles are presented. In order to account for potential differences in assay distribution between cohorts, a continuous probit score was used to test for trend across tertiles (generating a rank for each participant in each cohort by hormone concentration). Multivariable models were adjusted for parity (never, ever) and OC use ((never, ever, missing (48%); missing excluding FMC (0.3%)). We evaluated the impact of adjustment for body mass index (BMI; kg/m^2) among the subset of the study population with this data available (686 cases and 1,442 controls).

Statistical analyses were conducted using a two-stage approach. First, the log2 relative risks were calculated within each cohort and pooled using DerSimonian and Laird random effects meta-analysis models (11). Heterogeneity between cohort-specific effect estimates was tested by DerSimonian and Lairds Q statistic (11). Second, effect estimates based on pooled individual participant data were calculated. We observed no significant between-study heterogeneity in the meta-analysis, therefore, we present results based on the pooled participant data.

The assumption of linearity was tested using restricted cubic splines; no significant deviations from linearity were observed (data not shown). Statistical heterogeneity of associations across subtypes was assessed via a likelihood ratio test comparing a model allowing the association for the risk factor of interest to vary by subtype versus one assuming the same association across subtypes using polytomous conditional logistic regression (12). We evaluated heterogeneity by menopausal status at blood collection and age at diagnosis by including a multiplicative interaction term in the models and evaluating the Wald p value. The FMC (pregnant at blood collection) was excluded in a sensitivity analysis. Given the potential influence of IGF-I in early phases of carcinogenesis we evaluated risk associations excluding women diagnosed within 2 years after blood donation.

SAS Statistical Software, version 9.3 (SAS Institute, Cary NC, USA) was used for all statistical analyses. P-values<0.05 were considered as statistically significant; all statistical tests and p-values were two-sided.

Results

In total, 1,270 cases and 2,907 matched controls were included; the number of cases and controls contributed from each of the participating studies ranged from 15 cases / 44 controls (NHS II) up to 575 cases / 1,427 controls (FMC) (**Table 1**). Women who were postmenopausal at blood collection accounted for 42% of the cases and 39% of the controls, and the majority of women (91% cases, 95% controls) were parous. The median duration of follow-up was 9.1 (SD: 6.1) years among incident cancer cases, ranging from 2.7 (SD: 1.9) years for NHS II to 12.3 (SD: 6.8) years for the FMC. Overall, mean age at diagnosis was 54.6 (SD: 12.5) years with youngest cases in FMC (mean: 44.7 (SD: 8.1) years) and oldest cases in CLUE II (mean: 67.4 (SD: 13.0) years) (**Table S3**).

Higher IGF-I concentrations were associated with lower EOC risk (all cases: OR_{log2}=0.82; [0.72-0.93]; **Table 2**). The ORs from analyses considering extreme tertiles vs. quintiles were

similar (Tertile 3 vs. 1, OR=0.75 [0.62-0.90]; Quintile 5 vs. 1, OR=0.74 [0.59-0.93]). We observed no between-study heterogeneity (p_{het}=0.81; **Figure 1**), and results from the meta-analysis were comparable to those of the pooled analysis (OR_{log2}=0.82 [0.73-0.94]). The association between IGF and EOC did not differ significantly across histological subtypes (p_{het}=0.62) or for Type I vs. Type II disease (p_{het}=0.67). We observed no significant heterogeneity by disease stage at diagnosis (local disease: OR_{log2}: 0.79 [0.59-1.06]; regional/metastatic disease, OR_{log2}: 0.84 [0.71-0.98]; p_{het}: 0.79) or tumor grade (low grade: OR_{log2}: 1.25 [0.52-3.03]; high grade: OR_{log2}: 0.82 [0.63-1.07]; p_{het}: 0.43); however, the number of low grade tumors was limited (n=49).

Additional adjustment for BMI did not impact the associations (e.g., overall EOC among women with data on BMI: without adjusting for BMI: OR_{log2}: 0.89; [0.78-1.03] vs. adjusting for BMI OR_{log2}: 0.91; [0.79-1.04]). Results were similar by menopausal status at blood collection (p_{het}=0.79) and age at diagnosis (p_{het}=0.60). Exclusion of women from the FMC (after exclusion, OR_{log2}: 0.81 [0.67-0.98]) or women diagnosed within 2 years after blood donation (after exclusion, OR_{log2}: 0.86 [0.75-0.98] did not impact the results.

Discussion

We present the largest and most comprehensive study to date on the relationship between pre-diagnosis IGF-I and risk of EOC, including 1,270 cases and 2,907 matched controls. In this collaborative re-analysis of 6 nested case-control studies, we observed an 18% risk reduction for overall EOC risk with a doubling of IGF-I concentration. We observed no heterogeneity between histological subtypes or by other tumor characteristics (e.g., stage, grade, type I/II).

To date, 5 published prospective studies (n cases, range: 132 to 1,052), all of which are included in this pooled analysis, have addressed the association between IGF-I and EOC risk (4-8). Two of these investigations reported inverse associations overall (7, 8), whereas the others observed significant associations only in subgroups defined by age at diagnosis (4-6).

In the current study, we observed an inverse association between IGF-I and EOC risk overall, with no heterogeneity by age at diagnosis. To date, data on the role of IGF-I in the development of different EOC subtypes are sparse and generally did not support a heterogeneous association (7, 8). Consistent with those findings, we observed no heterogeneity by EOC subtype in this pooled re-analysis.

IGF-I has well established mitogenic and anti-apoptotic properties (as reviewed in (1)), which are believed to underlie its association with a number of epithelial cancers. We therefore hypothesized a positive association between IGF-I and EOC risk. The observed inverse association is not in line with this hypothesis. The biological pathways underlying the inverse association observed in this study remain to be fully elucidated. One potential explanation for the observed inverse association may be the anti-inflammatory effects of IGF-I (13). Serum IGF-I is inversely correlated with C-reactive protein [CRP; (14)]. Recent nested case-control studies have shown a consistent positive association between high CRP concentrations (CRP > 10 mg/L) and subsequent risk of EOC (15-19) , although we were unable to adjust for CRP levels in this analysis. Clearly, additional research is needed to understand the potential biological mechanisms underlying the apparent inverse association between IGF-I and EOC risk.

Given the large sample size, our study was powered to investigate risk associations overall, as well as for less common tumors (e.g., mucinous) and by the dualistic model of ovarian carcinogenesis. However, our study also has limitations. Data on tumor characteristics (e.g., missing data on grade: 66%, type I / type II: 56%) and potential confounders (e.g., BMI: 49%) was incomplete for some subgroup and sensitivity analyses. A general limitation of pooled analyses is between-cohort differences in data on covariates, biospecimen collection, and laboratory methods. Data from each cohort were centrally compiled and harmonized, and differences in absolute biomarker concentrations were addressed through (I) standardizing of

hormone measurement using study-specific mean concentrations and (II) using study-specific tertiles. IGF-I standardization was carried out under the assumption that between-study differences in IGF-I concentrations were due to differences in collection and/or laboratory methods, and not due to true underlying differences in concentrations between cohorts. Results were similar in analyses using meta-analysis and calculating OR from the pooling of individual data and we did not observe between-study heterogeneity. Limited covariate data were available for statistical adjustment. However, data from previous studies included in our pooled analysis do not suggest strong confounding of the association between IGF-I and EOC by lifestyle or reproductive factors (5, 7). Further, we included a cohort of women pregnant at blood collection (FMC) in this study. IGF-I concentrations decrease in early pregnancy, relative to pre-conception concentrations, with a subsequent increase in concentrations in mid-to late pregnancy until delivery (20). FMC blood samples were collected at a mean 10.4 (controls) – 10.7 (cases) weeks gestation. Pre- and early pregnancy concentrations are modestly correlated (8 weeks gestation: $r = 0.32$; 16 weeks gestation: $r = 0.15$) (20).We excluded the FMC in sensitivity analyses, and observed similar results. An additional limitation is the quantification of circulation IGF-I in a single blood sample. However, the stability of IGF-I measurements over a 5 year period and its utility as epidemiologic biomarker has been shown previously (intra-class coefficient of variation: 0.74 (95% CI, 0.55–0.93)) (21). Finally, IGF signaling is exceptionally complex as the distinct members of the IGF-family activate different downstream signaling pathways. This investigation only evaluated one member of the IGF-I family and EOC risk. Finally, it is unclear if circulating measures of IGF-I are related to exposure in the peritoneal cavity.

In conclusion, our investigation does not support the hypothesis that elevated IGF-I concentrations increase risk of EOC overall or for specific disease subtypes. In contrast, in this large, pooled analysis, we observed a significant inverse association and no heterogeneity

by subtype. To more fully characterize the function of the IGF-pathway in ovarian carcinogenesis future investigations should consider other growth factors and binding proteins (e.g., IGF-II or Insulin-like factor III, IGFBP2, IGFBP3).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these data.

Authors' Contributions

Conception and design: RTF, RK, SST

Development of methodology: JO, EMP, HS, ML, KV, KH, I-ML, AT, LD, AT, GM, NCMO, EW, EJD, AI, RCT, SR, MAM, NW, SST, RK, RTF

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): JO, EMP, HS, ML, KV, KH, I-ML, AT, LD, AT, GM, NCMO, EW, EJD, AI, RCT, SR, MAM, NW, SST, RK, RTF

Writing, review, and/or revision of the manuscript: JO, RTF, EMP, HS, HMS, KV, KH, I-ML, AT, LD, AT, GM, NCMO, EW, EJD, AI, RCT, SR, MAM, NW, SST, RK

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): JO, RTF, EMP, SST

Study supervision: RTF, RK

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Table 1. Case and control characteristics by cohort in pooled analysis of prospective data on circulating IGF-I and EOC risk: the Ovarian Cancer Cohort Consortium (OC3)

Cohort	Reference		No	Mean age, at blood donation years (SD)	Nulliparous %[1]	Ever OC use, %[2]	Postmenopausal, %	Mean BMI (SD)
Clue II	≠	Case	46	60.8 (13.0)	19	20	85	26.3 (5.8)
	≠	Control	90	60.9 (12.9)	13	13	86	25.3 (4.7)
EPIC	Ose et al. 2015	Case	450	55.9 (8.5)	17	37	77	26.8 (4.9)
		Control	864	55.9 (8.6)	12	45	77	26.3 (4.8)
FMC	Schock et al. 2015	Case	575	32.5 (4.8)	0	##	0	##
		Control	1,427	32.5 (4.7)	0	##	0	##
NHS	Tworoger et al. 2007	Case	121	57.9 (6.5)	8	41	80	24.8 (4.8)
		Control	360	57.8 (6.5)	4	47	80	24.7 (4.0)
NHS II	Tworoger et al. 2007	Case	15	46.1 (4.4)	20	93	20	29.6 (9.8)
		Control	44	45.8 (4.2)	23	86	18	25.9 (5.9)
WHS	Tworoger et al. 2007	Case	63	55.7 (7.2)	25	65	75	24.5 (3.9)
		Control	122	55.5 (7.0)	15	71	70	25.1 (4.4)
Total		Case	1,270	45.5 (13.9)	9	40	42	26.3 (5.1)
		Control	2,907	44.6 (13.8)	5	47	39	25.8 (4.6)

[1]Among women with data: parity 2.2% missing; OC use 48% missing (excluding FMC: 0.3% missing)

[2]Percentage presented for women with data: n=2,168

BMI = body mass index; CLUE = Washington County, MD Study 'Give us a clue to cancer and heart disease'; EPIC = European Prospective Investigation into Cancer and Nutrition; FMC = Finish Maternity Cohort; NHS = Nurses' Health Study; WHS = Women's Health Study;

≠ Data from Clue II have not been published.

Information on BMI and OC use was not collected in the FMC

Table 2: Odds ratios (95% CI) for tertiles and doubling of IGF-I and EOC risk overall and IGF-I doubling and EOC risk by tumor characteristics, menopausal status at blood donation and age at diagnosis: the Ovarian Cancer Cohort Consortium (OC3) [1]

	Sets	OR (95%CI)	p_{trend}[2]
Overall EOC			
Tertile 1	460	ref	
Tertile 2	441	0.93 (0.78 - 1.09)	
Tertile 3	369	0.75 (0.62 - 0.90)	<0.01[2]
Doubling	1,270	0.82 (0.72 - 0.93)	<0.01
ORs for Doubling			
Histology			
Serous	630	0.89 (0.74 - 1.06)	0.19
Endometriod	163	0.82 (0.56 - 1.20)	0.32
Mucinous	186	0.81 (0.58 - 1.12)	0.21
Clear Cell	57	0.50 (0.26 - 0.99)	0.04
phet[3]			0.62
Grade			
Low grade	49	1.25 (0.52 - 3.03)	0.62
High grade	377	0.82 (0.63 - 1.07)	0.15
phet[3]			0.43
Dualistic Pathway[4]			
Type I	277	0.78 (0.59 - 1.03)	0.08
Type II	284	0.87 (0.64 - 1.18)	0.35
phet[3]			0.67
Disease Stage			
Local	246	0.79 (0.59 - 1.06)	0.12
Regional/metastatic	802	0.84 (0.71 - 0.98)	0.03
phet[3]			0.79
Menopausal Status at Blood Collection			
Premenopausal	738	0.84 (0.71 - 0.98)	0.03
Postmenopausal	532	0.80 (0.65 - 0.99)	0.04
phet[3]			0.79
Age at Diagnosis			
Age < 55	665	0.80 (0.67 - 0.94)	0.01
Age ≥ 55	605	0.86 (0.71 - 1.04)	0.12
phet[3]			0.60

[1]ORs from conditional logistic regression models adjusted for OC use (never/ever/missing) and parity (never/ever/missing). Tertiles cutpoints based on all study controls using IGF-I concentrations standardized to mean=0 ng/mL: T1: ≤ -0.20, T2: > -0.20 to 0.26; T3: >0.26.

[2]The p value for trend across tertiles is based on a continuous probit score (generating a rank for each person in each cohort by hormone level); p_{trend} for doubling of hormone concentrations was estimated on $\log_2$ scale.

[3]P for heterogeneity from likelihood ratio test comparing a model allowing the association to vary by subtype versus one assuming the same association across subtype using polytomous conditional logistic regression; for age at diagnosis, Wald p-value from interaction term

[4] Type I: Low-grade serous and endometrioid, and all mucinous and clear cell cases; Type II: high-grade serous and endometrioid cases

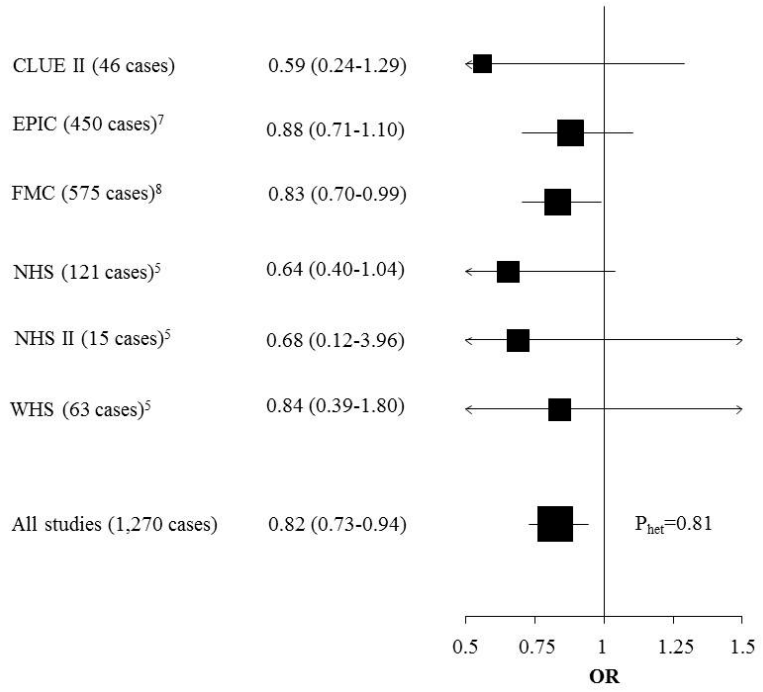

Figure 1. OR (95% CI) for the association between circulating IGF-I and overall EOC risk for each of the cohorts included in the pooled re-analysis, and results from meta-analysis: the Ovarian Cancer Cohort Consortium (OC3)

Table S1: Basic information on the participating cohort studies for the pooled analysis within the OC3 consortium

Cohort (cases)	Population	Recruitment period	Fasting status	Storage	Matching criteria					
					Controls per case	Age at blood donation	Date of blood sample	Day of cycle	Menopausal status	Other criteria
Clue II (46)	Residents of Washington Country, USA	1989	Non-fasting	-70°C	1:2	± 1 years	± 14 days	± 1 day	Menopausal status at blood collection	Current OC / HRT use
EPIC (451)	Volunteers in Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden and UK	1992-2000	Matched	-196°C[1]	1:2	± 6 months	No (incidence density sampling)	5 phases	Menopausal status at blood collection	Recruitment center, Time of the day of blood collection,
FMC (576)	Population based maternity cohort	1986-2007	Not available	-25°C	1:3	± 6 months	± 3 months	Not available	Not available	Parity (1,2,>2), parity at diagnosis (1,2,>2)
NHS and II[2] (138)	Registered nurses in the USA	1996-99	Matched	-130°C	1:3	± 2 years	± 2 months	± 1 day for luteal blood sample[3]	Menopausal status at baseline and diagnosis	Time of day, use of postmenopausal hormones at blood collection
WHS (63)	US female health professionals; RCT[4]	1992-1995	Matched	-170°C	1:2	± 1 year	± 3 months	Not available	Menopausal status at baseline / diagnosis	Postmenopausal hormones at baseline /diagnosis, time since randomization (± 6 months)

CLUE II = Campaign against Cancer and Heart Disease study. EPIC= European Prospective Investigation into Cancer and Nutrition. FMC= Finnish Maternity Cohort. NHS= Nurses' Health Study. NYU WHS = New York University Women's Health Study. [1]Most samples were stored in liquid nitrogen at -196°C, apart from Denmark and Sweden were samples were stored locally at -150°C and -70°C. [2]NHS phase 1 (1999-2003 follow-up cycles and phase 2 (2005-09 follow-up cycles). [3]Patients were asked to provide follicular sample at 3-5 days and luteal sample at 7-9 days before anticipated start of the next cycle. [4] RCT = Randomised Controlled Trial; RCT only from 1992-2004; currently an observational cohort study.

Table S2: Laboratory assays and Intra- and Interbatch CV's for IGF-I measurements in the participating cohorts

Biomarker	Sample	Assay	Intra-Batch CV (%)	Inter-Batch CV (%)
CLUE II	Plasma	ELISA[1]	2.8	3.2
EPIC phase 1	Serum	ELISA[1]	2.5	12.2
EPIC phase 2		ELISA[2]	9.4	8.9
FMC	Serum	Chemiluminescent immunoradiometric[3]	14.6	13.2
WHS*	Plasma	ELISA	range*	-
NHS*	Plasma	ELISA	from	-
NHS II*	Plasma	ELISA	2 to 10	-

[1]Enzyme-linked immunosorbent assay (ELISA); DSL, Webster, Texas, USA; [2]Immunodiagnostics Systems, Germany. [3]Quantified on the Immulite 2000 Siemens analyzer, a solid-phase enzyme-labeled chemiluminescent immunometric assay, using reagents from Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA
*Analyzed together; average intra-batch coefficient from NHS / NHS II and WHS

Table S3. Tumor characteristics by cohort in pooled analysis of prospective data on IGF-I and EOC risk: OC3

	Clue II	**EPIC**	**FMC**	**NHS**	**NHS II**	**WHS**	**Total**
References	≠	Ose et al. 2014	Schock et al. 2014	Tworoger et al. 2008	Tworoger et al. 2008	Tworoger et al. 2008	
No	46	450	575	121	15	63	1,270
Age at dx, yrs [1]	67.4 (13.0)	62.5 (8.9)	44.7 (8.1)	65.0 (7.3)	48.8 (3.8)	60.1 (8.0)	54.6 (12.5)
Lag time, yrs [1]	6.6 (3.0)	6.6 (3.6)	12.3 (6.8)	7.1 (4.0)	2.7 (1.9)	4.3 (2.6)	9.1 (6.1)
Histology							
Serous	19 (41%)	237 (53%)	263 (46%)	64 (53%)	5 (33%)	42 (67%)	630 (50%)
Endometrioid	5 (11%)	45 (10%)	92 (16%)	12 (10%)	4 (27%)	5 (8%)	163 (13%)
Mucinous	2 (4%)	30 (7%)	142 (25%)	9 (7%)	1 (7%)	2 (3%)	186 (15%)
Clear cell	2 (4%)	25 (5%)	23 (4%)	5 (4%)	2 (13%)	-	57 (4%)
Others	18 (39%)	113 (25%)	55 (10%)	31 (26%)	3 (20%)	14 (22%)	234 (18%)
Grade [2]							
Low grade	1 (4%)	31 (12%)	-	11 (12%)	3 (25%)	3 (7%)	49 (12%)
High grade	24 (96%)	220 (88%)	-	82 (88%)	9 (75%)	42 (93%)	377 (88%)
Stage [2]							
Low stage	3 (9%)	57 (14%)	150 (31%)	29 (24%)	7 (47%)	-	246 (24%)
High stage	29 (91%)	340 (86%)	331 (69%)	90 (76%)	8 (53%)	-	798 (76%)
Type [2]							
Type I	5 (24%)	76 (32%)	165 (100%)	21 (24%)	6 (55%)	4 (11%)	277 (49%)
Type II	16 (76%)	163 (68%)	-	68 (74%)	5 (45%)	32 (89%)	284 (51%)

[1]presented as mean (±std)

[2]Among cases with data. Grade missing for 66%, stage missing for 18%, Type I/II missing for 56%

≠ Data from Clue II have not been previously published.