FULL PAPER

BJC

British Journal of Cancer (2015) 112, 162–166 | doi: 10.1038/bjc.2014.566

Keywords: IGF-I; ovarian cancer; histological subtypes; carcinogenesis; type I/type II; dualistic pathway

Insulin-like growth factor I and risk of epithelial invasive ovarian cancer by tumour characteristics: results from the EPIC cohort

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Received 28 May 2014; revised 24 September 2014; accepted 8 October 2014; published online 4 November 2014

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Background: Prospective studies on insulin-like growth factor I (IGF-I) and epithelial ovarian cancer (EOC) risk are inconclusive. Data suggest risk associations vary by tumour characteristics.

Methods: We conducted a nested case–control study in the European Prospective Investigation into Cancer and Nutrition (EPIC) to evaluate IGF-I concentrations and EOC risk by tumour characteristics ($n = 565$ cases). Multivariable conditional logistic regression models were used to estimate associations.

Results: We observed no association between IGF-I and EOC overall or by tumour characteristics.

Conclusions: In the largest prospective study to date was no association between IGF-I and EOC risk. Pre-diagnostic serum IGF-I concentrations may not influence EOC risk.

Insulin-like growth factor I (IGF-I)-related signalling pathways are implicated in the aetiology of epithelial cancer at various sites (e.g., prostate, colon and breast cancer), including ovarian cancer (reviewed in Bruchim and Werner, 2013; Singh *et al*, 2014). Insulin-like growth factor I drives cellular proliferation in several cell lines of epithelial neoplasms (reviewed in Pollak, 2008) and is additionally associated with invasion and angiogenesis in epithelial ovarian cancer cells (reviewed in Beauchamp *et al*, 2010). Recently, IGF-I was shown to be overexpressed in low-grade, but not high-grade, serous ovarian cancer cell lines, suggesting IGF-I may be differentially associated with risk across ovarian cancer subtypes (King *et al*, 2011). Further, low-grade ovarian cancer cells expressing IGF-I were more responsive to IGF-I stimulation and IGF-I receptor (IGF-IR) inhibition compared with high-grade serous ovarian cancer cells (King *et al*, 2011).

Prior prospective studies on the association between pre-diagnostic circulating IGF-I and epithelial invasive ovarian cancer (EOC) were inconclusive and evaluated EOC as a single disease entity, without addressing associations in EOC subgroups (i.e., histologic subtype, dualistic model of ovarian carcinogenesis) (Lukanova *et al*, 2002; Peeters *et al*, 2007; Tworoger *et al*, 2007). This is the largest prospective study to date ($n = 565$ cases; 1097 controls) investigating the role of IGF-I and EOC risk, and the first prospective investigation to assess IGF-I and EOC by tumour characteristics (histology, grade, stage and type I/II status).

MATERIALS AND METHODS

Study population. The European Prospective Investigation into Cancer and Nutrition (EPIC) is an ongoing multicentre prospective cohort study. Descriptions of study design, population and baseline data collection of the cohort (Riboli *et al*, 2002) and this nested case–control study (Ose *et al*, 2014) have been reported in detail. Briefly, 519 978 participants (366 521 women) aged 25–70 years were enrolled from 1992 to 2000 in 10 European countries. Data on diet, reproductive factors, use of exogenous hormones (oral contraceptives (OC) and hormone replacement therapy (HRT)), disease history and anthropometric measures were collected at baseline. A total of 226 673 women provided a baseline blood sample.

Women not using exogenous hormones at blood donation and with no history of cancer at recruitment (with the exception of non-melanoma skin cancer) were eligible for this study.

A total of 565 eligible cases with biological samples and incident epithelial invasive ovarian, fallopian tube or primary peritoneal cancer were 1:2 matched to 1097 controls. An incidence density sampling protocol was used. We included 201 cases and 372 matched controls from a prior analysis in EPIC (phase 1; Peeters *et al*, 2007) and additional 364 cases (725 matched controls) subsequently diagnosed during follow-up (phase 2).

Information on tumour characteristics (histologic subtype (serous, endometrioid, clear cell, mucinous and not otherwise specified (NOS)), grade (well, moderately or poorly/undifferentiated) and stage (local, regional and metastatic)) was available from pathology reports and from cancer registries. Tumours were classified on the basis of histology and the proposed dualistic pathway of ovarian carcinogenesis (type I/II; Kurman and Shih, 2011). Clear cell carcinomas ($n = 28$) were excluded from type I/II analyses as they show unique clinical behaviour (Penson *et al*, 2013). All participants gave written informed consent. The Ethical Review Board of the International Agency for Research on Cancer and the Institutional Review Board of each EPIC centre approved these analyses.

Laboratory assays. Pre-diagnostic concentrations of IGF-I ($nmol\,l^{-1}$) were analysed with enzyme-linked immunosorbent assays at IARC (phase 1 (Peeters *et al*, 2007): DSL, Webster, TX, USA) and at the Division of Cancer Epidemiology at the German Cancer Research Center (phase 2: Immunodiagnostics Systems, Frankfurt, Germany). Cases and matched controls were analysed within the same analytical batch by laboratory technicians blinded to case–control status and identity of quality control samples. Intra- and inter-batch coefficients of variation from replicate quality control (QC) samples were 2.50% and 12.20% (phase 1: triplicate QCs), and 9.42% and 8.93% (phase 2: duplicate QCs).

Statistical analyses. Insulin-like growth factor I values were log2 transformed and centred to a mean value of zero in each phase. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression. Insulin-like growth factor I was examined continuously on the log2 scale and in tertiles with phase-specific cut-offs based on the distribution in controls.

The final model included full-term pregnancy (never/ever), as other covariates (BMI, height, smoking, physical activity, diabetes, alcohol, age at menarche, age at first birth, number of births, age at menopause, OC use and HRT use) did not change the OR by $>10\%$ (i.e., by a factor 1.10 or its reciprocal; Maldonado and Greenland, 1993).

Heterogeneity in the associations between IGF-I and EOC by tumour characteristics was assessed using likelihood ratio tests comparing logistic regression models with and without corresponding interaction terms (Rothman *et al*, 2008).

Sensitivity analyses included stratification by menopausal status at blood donation and age at diagnosis (<55 and ⩾55 years); exclusion of women providing a blood sample <2 years before diagnosis (to ensure any observed associations were not due to cancers influencing circulating concentrations of IGF-I, but not yet diagnosed) and women who had a prior hysterectomy.

All statistical tests were two-tailed and significant at the $P<0.05$ level. SAS 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analysis.

RESULTS

Cases and controls were similar with respect to most characteristics, except for established reproductive risk factors (e.g., cases were less likely to be parous, $P<0.01$ or to use OCs, $P<0.01$; Table 1). We observed no case–control differences in IGF-I concentrations overall or by study phase.

There was no association between EOC and IGF-I concentrations for doubling of hormone concentrations or comparing top to bottom tertiles in overall analyses (all histological subtypes combined ($OR_{log2}=0.88$; 95% CI 0.71–1.08)). A similar pattern was observed in subgroup analyses by tumour characteristics (e.g., serous tumours: $OR_{log2}=0.98$; 95% CI 0.74–1.30; Table 2). We did not observe heterogeneity between risk associations by tumour characteristics (e.g., P_{het} for histological subtypes = 0.12). Overall, risk estimates were similar when analyses were restricted to study phase 2 (data not shown).

Results were similar in sensitivity analyses by age at diagnosis (<55 *vs* ⩾55) and menopausal status at blood donation (pre- *vs* postmenopausal at blood donation). Excluding women with unilateral oophorectomy/hysterectomy ($n=116$) or women diagnosed within 2 years after blood donation ($n=84$) led to results comparable to overall results (data not shown).

DISCUSSION

This is the largest prospective study on the relationship between IGF-I and EOC to date and the first to assess risk associations by tumour characteristics. We observed no association between IGF-I and EOC overall. The same pattern was observed in analyses stratified by tumour characteristics, age at diagnosis or menopausal status at blood donation.

Three prospective studies (range: 132 cases (Lukanova *et al*, 2002) to 222 cases (Tworoger *et al*, 2007)) have evaluated this association previously. Two of these studies observed a positive association between IGF-I and EOC in women <55 at diagnosis (Lukanova *et al*, 2002; Peeters *et al*, 2007); however, sample size in these subgroups was limited ($n\leqslant66$ younger than 55 at diagnosis) and confidence intervals were wide (i.e., $OR_{Q3\text{-}Q1}=5.10$; 95% CI 1.50–18.20 (Peeters *et al*, 2007)). In a US-based study, no association was observed in women diagnosed before the age of 55, but there was an inverse association in women diagnosed after the age of 55 ($OR_{Q4\text{-}Q1}=0.52$; 95% CI 0.28–0.95 (Tworoger *et al*, 2007)). Slightly different exclusion criteria might contribute to inconsistent results across studies (e.g., exclusion of: cases diagnosed within 1 year after blood donation (Lukanova *et al*, 2002), fallopian tube cancers (Tworoger *et al*, 2007), unilateral oophorectomy/hysterectomy (EPIC phase 1; Peeters *et al*, 2007). In the current study including 565 EOC cases, we observed no association between IGF-I and ovarian cancer risk regardless of the age at diagnosis.

Table 1. Selected baseline characteristics of EOC cases and matched controls at enrolment in the EPIC study

	Cases ($n=565$)[a]	Controls ($n=1097$)[a]	*P*-value[b]
Age at blood donation[c]	57.0 (33.6–80.7)	56.9 (33.6–79.3)	
Age at diagnosis	63.6 (37.4–86.5)		
Lag time between blood donation and diagnosis	6.7 (0–16)		
Menopausal status at blood donation[b]			
Pre	112 (20%)	219 (20%)	
Post	453 (80%)	878 (80%)	
Age at menopause[d]	50 (32–60)	50 (30–59)	**0.03**
Ever full-term pregnancy			**<0.01**
No	95 (17%)	124 (12%)	
Yes	448 (83%)	935 (88%)	
OC use			**< 0.01**
Never	349 (62%)	594 (54%)	
Ever	214 (38%)	498 (46%)	
HRT use[b]			0.57
Never	452 (87%)	867 (86%)	
Ever	69 (13%)	145 (14%)	
Histology			
Serous	302 (53%)		
Mucinous	41 (7%)		
Endometrioid	66 (12%)		
Clear Cell	28 (5%)		
NOS	99 (18%)		
Other	29 (5%)		
Grade[e,f]			
Low grade	35 (10%)		
High grade	308 (90%)		
Stage[e,g]			
Low stage	76 (15%)		
High stage	420 (85%)		
Type I/II[e]			
Type I	67 (22%)		
Type II	242 (78%)		
IGF-I (nmol l^{-1}) [h]	13.98 (13.39–14.6)	14.06 (13.63–14.5)	0.26

Abbreviations: EOC = epithelial ovarian cancer; EPIC = European Prospective Investigation into Cancer and Nutrition; HRT = hormone replacement therapy; IGF-I = insulin-like growth factor I. Values are shown as median (range) or number (percentage).

[a]Cases and controls in both study phases were matched on: study recruitment centre, age at blood donation (±6 months), time of the day of blood collection (±1 h), fasting status (<3 h, 3–6 h, >6 h) and menopausal status at blood collection (premenopausal, perimenopausal and postmenopausal), as well as menstrual cycle phase for premenopausal women ('early follicular' (days 0–7 of the cycle), 'late follicular' (days 8–11), 'peri-ovulatory' (days 12–16), 'mid-luteal' (days 20–24) and 'other luteal' (days 17–19 or days 25–40). Cases missing data on the phase of menstrual cycle were matched to controls with missing information on menstrual cycle phase.

[b]Among postmenopausal women only.

[c]Matching factor.

[d]Differences between cases and matched controls based on conditional logistic regression.

[e]Percentages presented among women with data on tumour characteristics. Percentage of missing data: grade (39%), stage (12%) and type I/II status (45%).

[f]Low-grade tumours: well differentiated tumours; high-grade tumours: moderately, poorly or undifferentiated tumours.

[g]Low-stage tumours: localised tumours; high-grade tumours: regional metastatic or distant metastatic tumours.

[h]Differences in IGF-I concentrations between cases and matched controls based on geometric mean (95% confidence interval); values from each study phase are standardised to a mean of 0 for analyses.

Elevated IGF-I concentrations may lead to the development of a malignant cell rather than to apoptotic cell death in the early phases of carcinogenesis (reviewed in Pollak, 2008). Insulin-like growth factor I signalling is predominantly mediated by the IGF-IR; higher IGF-IR expression is associated with development of epithelial neoplasms through anti-apoptotic and mitogenic

Table 2. OR (95% CI) for ovarian cancer by tertiles and for doubling of IGF-I by tumour characteristics and menopausal status[a]

		Tertiles[b]					
		1	2	3	OR_{log2} (95% CI)	P_{trend}[c]	P_{het}[d]
Overall	565 sets	ref.	0.93 (0.72–1.20)	0.92 (0.70–1.20)	0.88 (0.71–1.08)	0.21	
Histology							
Serous	302 sets	ref.	1.02 (0.72–1.46)	1.03 (0.71–1.48)	0.98 (0.74–1.30)	0.90	
Mucinous	41 sets	ref.	1.07 (0.42–2.73)	0.60 (0.20–1.82)	0.59 (0.24–1.42)	0.24	
Endometrioid	66 sets	ref.	1.01 (0.43–2.34)	0.93 (0.37–2.32)	0.73 (0.34–1.56)	0.42	
Clear cell	28 sets	ref.	1.52 (0.43–5.36)	0.99 (0.29–3.40)	0.89 (0.37–2.13)	0.80	
NOS	99 sets	ref.	0.63 (0.36–1.12)	0.67 (0.36–1.24)	0.75 (0.48–1.17)	0.21	
Other	29 sets	ref.	0.89 (0.28–2.78)	1.71 (0.42–6.87)	1.07 (0.40–2.83)	0.89	0.12
Grade							
Low grade	35 sets	ref.	0.24 (0.06–1.08)	0.56 (0.15–2.00)	0.87 (0.34–2.24)	0.78	
High grade	306 sets	ref.	0.95 (0.68–1.34)	1.01 (0.70–1.47)	0.96 (0.72–1.28)	0.79	0.89
Stage							
Low stage	76 sets	ref.	1.23 (0.57–2.67)	1.39 (0.65–3.01)	1.02 (0.56–1.85)	0.95	
High stage	419 sets	ref.	0.98 (0.73–1.31)	0.87 (0.64–1.19)	0.86 (0.68–1.09)	0.21	0.52
Type I/II							
Type I	67 sets	ref.	0.69 (0.31–1.54)	0.72 (0.32–1.62)	0.84 (0.43–1.64)	0.61	
Type II	242 sets	ref.	1.04 (0.70–1.54)	1.16 (0.76–1.78)	1.02 (0.73–1.42)	0.90	0.71
Menopausal status							
Premenopausal	112 sets	ref.	0.56 (0.27–1.16)	0.69 (0.34–1.40)	0.93 (0.55–1.58)	0.80	
Postmenopausal	452 sets	ref.	1.01 (0.77–1.32)	0.93 (0.70–1.26)	0.87 (0.69–1.08)	0.21	0.69
Age at diagnosis							
<55 years	105 sets	ref.	0.46 (0.22–0.95)	0.66 (0.33–1.32)	0.91 (0.55–1.50)	0.70	
≥ 55 years	459 sets	ref.	1.04 (0.79–1.36)	0.95 (0.71–1.28)	0.87 (0.70–1.09)	0.23	0.83

Abbreviations: CI = confidence interval; IGF-I = insulin-like growth factor I; OR = odds ratio.

[a]Matched for study centre, age at blood donation, menopausal status, time of day of blood collection, fasting status and phase of the menstrual cycle and additionally adjusted for ever full-term pregnancy (never/ever).

[b]Phase-specific cut-offs; raw data IGF-I (nmol l^{-1}) for phase 1: first tertile 16.30–23.61; second tertile 23.62–33.95; third tertile: >33.95. Phase 2: first tertile 8.05–10.95; second tertile 10.96–15.10; third tertile >15.10.

[c]Linear trends for OR estimated on $\log_2$ continuous scale.

[d]Statistical tests for heterogeneity were based on likelihood ratio test, comparing the model fit for logistic regression models with and without corresponding interaction term.

activities and its role in oncogenic transformation (reviewed in Pollak, 2008). We hypothesised that circulating IGF-I would be differentially associated with ovarian cancer subtypes given the differential expression of IGF-I in low- and high-grade serous tumours. Insulin-like growth factor I has been shown to be overexpressed in low-grade serous ovarian cancer cell lines (i.e., type I), which were more responsive to IGF-I stimulation and IGF-IR inhibition compared with high-grade serous ovarian cancer cell lines (i.e., type II) (King *et al*, 2011). We did not observe the hypothesised associations; however, we had small sample size in some subgroups (i.e., low-grade serous tumours, $n = 35$).

Our study has important strengths and limitations. We investigated pre-diagnostic serum IGF-I and EOC risk in a large, well-characterised nested case–control study. However, circulating IGF-I may not be reflective of IGF-I exposure in the ovary. Although the data on this association are mixed (Rabinovici *et al*, 1990; Thierry van Dessel *et al*, 1996), there is evidence to suggest that follicular fluid concentrations are well correlated with serum concentrations ($r = 0.77$, $P < 0.001$; Dorn *et al*, 2003). In addition, the current analysis is based on a single biomarker in the IGF signalling axis. However, data to date suggest IGF-I and the IGF-IR are the most relevant members of the IGF family for ovarian carcinogenesis (reviewed in Beauchamp *et al*, 2010). In line with other epidemiologic studies, a single measurement was used to evaluate risk associations. However, relatively high intra-individual reproducibility of IGF-I measurements has been consistently shown (2–3 years; premenopausal women: ICC = 0.86 (Missmer *et al*, 2006), up to 5 years; pre- and postmenopausal women: ICC = 0.71 (Borofsky *et al*, 2002)).

The sample size for subgroup analyses by tumour characteristics (e.g., histology, grade or type I/type II) may have been too small to detect an association, with the exception of the group of serous tumours (cases $n = 302$). For subgroup analyses by grade as well as type I/type II classification a considerable proportion of data was missing ($>39\%$), further limiting sample size in those subgroups.

Despite evidence suggesting that IGF-I could be involved in EOC development (reviewed in Bruchim and Werner, 2013; Singh *et al*, 2014), our study shows no association between circulating IGF-I and EOC risk. Larger, pooled prospective studies are needed to confirm our results and to address the associations in small subgroups with more statistical power and assess risk associations with expression of IGF receptors.

ACKNOWLEDGEMENTS

We thank all the EPIC participants for their invaluable contribution to the study. The German Cancer Research Center, Division of Cancer Epidemiology (Principal Investigator: Rudolf Kaaks) funded the analysis of IGF-I for this study. The European Prospective Investigation into Cancer and Nutrition is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); Deutsche Krebshilfe (70-2488), Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany; Grant 01-EA-9401); Hellenic Health Foundation (Greece) and the Stavros Niarchos Foundation; Italian Association for Research on Cancer

(AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); ERC-2009-AdG 232997 and Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health. (Norway); Health Research Fund (FIS) of the Spanish Ministry of health (Exp 96/0032), Regional Governments of Andalucía, Asturias, Basque Country, Murcia (no. 6236) and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skåne and Västerbotten (Sweden); Cancer Research UK, Medical Research Council (United Kingdom).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The sponsors had no role in the study design, data collection, and analysis, interpretation of results or writing of the paper.

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