

Supplementary Data and Methods

Immunohistochemical staining: IHC staining was performed on 5 µm sections from each TMA. Tissue sections were deparaffinized using xylene and graded alcohols. Antigen retrieval was performed in Target Retrieval Solution, pH 6.1 (Dako, Inc., Carpinteria, CA, USA) at 95°C for 30 minutes. After cooling at room temperature, slides were rinsed in Tris buffered saline (TBS), pH 7.5 (0.02 M Tris/Tris HCl and 0.15 M NaCl). Endogenous peroxidase was quenched with peroxidase blocking reagent (Dako, Inc.) for 10 minutes. After rinsing with TBS, blocking solution was applied for 30 min at room temperature and then the primary antibody solution was applied. IHC conditions for the primary antibodies were previously described (1). Slides were washed three times with TBS-T (0.1% Tween 20), then incubated with the appropriate secondary antibody (EnVision™+ Kits, Dako, Inc.). After 3× washes with TBS-T, slides were incubated with Diaminobenzidine chromogen solution. Slides were rinsed with water and counterstained with hematoxylin, dehydrated through graded alcohols, absolute ethanol, and xylene, then cover slipped with mounting medium. Positive control and negative control tissue slides were stained in parallel for all IHC staining assays.

For ER-alpha and PR, nuclear staining was scored as the staining intensity and the percentage of cells that stained positive. For the IR, the percentage of nuclear cells that stained positive (<50%, ≥50%) as well as the cytoplasmic and overall staining intensity were scored. For the IGF1R and pIGF1R/pIR, we recorded the percentage of cells with positive membranous staining (<50%, >50%) and the cytoplasmic and overall staining intensities. No nuclear staining was observed for IGF1R and pIGF1R/pIR. For ER and PR, the percentage of cells that stained positive was multiplied by the intensity value [0 (none), 1 (weak), 2 (moderate) or 3 (strong)] to calculate the histological score (H-score) with a maximum value of 300. A clinical cut-off (H-score ≥75) was used to differentiate positive and negative ER and PR staining.

Quantitative real time reverse transcription PCR (qPCR): We assessed gene expression levels of *IGF1*, *IGF2*, *IGFBP1* and *IGFBP3* using investigator-validated primers for the target genes (1, 2). To extract RNA, whole frozen tissues were pulverized in a tissueTUBE bag (Covaris, Woburn, MA, USA) using a Covaris CryoPrep and then homogenized in Buffer RLT (Qiagen, Valencia, CA, USA) using a Covaris adaptive focused acoustics tissue disrupter. The Qiagen AllPrep kit was used following the manufacturer's instructions for isolation of RNA and DNA. The RNA concentration and purity was measured using a Nanodrop spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA), and RNA integrity was evaluated with the Agilent Bioanalyzer (Agilent, Santa Clara, CA, USA). RNA quality met the following criteria; Nanodrop, 260/280 ratio>1.8. qPCR analysis was carried out on 97% of the fresh frozen tissue samples; 11 samples (3%) were not subjected to cDNA synthesis and qPCR due to the low RNA yield/concentration. Following RNA extraction and purification, complementary DNA was synthesized from 1µg of total RNA using the SuperScript VILO cDNA Synthesis Kit (Life Technologies, Grand Island, NY, USA). qPCR reactions were carried out using primers and PowerSYBR Green (Life Technologies) detection following the manufacturer's recommendations. The reaction scale was adjusted for use in 384-well plates on the Applied Biosystems 7900HT Fast Real-Time PCR System (Life Technologies). Target gene expression was internally normalized to the expression of the housekeeping gene *peptidylprolyl isomerase B (PPIB)* and each reaction was run in triplicate on the same plate. Each assay plate included two reactions that omitted either the mRNA template or the reverse transcriptase enzyme to exclude the possibility of contamination. RNA concentrations were provided as raw Ct values and expression scores were calculated using $2^{(-\Delta Ct)} * 1000$ [arbitrary units/scaling factor] (3).

Serology assays: Concentrations of the insulin, total IGF-I, IGFBP-3 serologic biomarkers were carried out in the laboratory of Dr. Herbert Yu. Insulin was measured using an immunoassay kit from Diagnostic Systems Laboratories (DSL, Webster, Texas, USA). Concentrations of total IGF-I and IGFBP-3 serologic biomarkers were determined by Quantikine ELISAs (R&D Systems, Minneapolis, MN, USA). Serum concentrations of estrone and SHBG were measured in the GCRC Analytic Core Laboratory at the Albert Einstein College of Medicine using ELISAs from ALPCO (Salem, NH, USA). Levels of serologic estradiol were measured in the

Einstein Department of Pathology laboratory using the Electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA).

References

1. Merritt MA, Strickler HD, Einstein MH, Yang HP, Sherman ME, Wentzensen N, et al. Insulin/IGF and sex hormone axes in human endometrium and associations with endometrial cancer risk factors. *Cancer Causes Control*. 2016;27(6):737-48.
2. Brouwer-Visser J, Lee J, McCullagh K, Cossio MJ, Wang Y, Huang GS. Insulin-like growth factor 2 silencing restores taxol sensitivity in drug resistant ovarian cancer. *PLoS One*. 2014;9(6):e100165.
3. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the $2^{-\Delta\Delta C(T)}$ Method. *Methods*. 2001;25(4):402-8.

Table S1: Adjusted hazard ratios (95% CI) for the associations between immunohistochemical staining of insulin/IGF and sex hormone axis factors in endometrial cancer in relation to progression-free survival

	Total N ^a	Recurrent N	Recurrent %	HR ^b	95% CI ^b	95% CI ^b
ER (gland) negative	351	130	37.0	1.00 (Ref)		
ER (gland) positive	171	45	26.3	0.67	0.47	0.95
ER (stroma) negative	500	170	34.0	1.00 (Ref)		
ER (stroma) positive	22	5	22.7	0.73	0.30	1.81
PR (gland) negative	241	96	39.8	1.00 (Ref)		
PR (gland) positive	283	80	28.3	0.81	0.59	1.11
PR (stroma) negative	483	167	34.6	1.00 (Ref)		
PR (stroma) positive	41	9	22.0	0.79	0.40	1.56
ER negative/PR negative ^c	206	83	40.3	1.00 (Ref)		
ER negative/PR positive ^c	144	46	31.9	0.94	0.64	1.39
ER positive/PR negative ^c	34	13	38.2	0.83	0.45	1.51
ER positive/PR positive ^c	136	32	23.5	0.61	0.40	0.94
IR-cyto negative	23	12	52.2	1.00 (Ref)		
IR-cyto weak	412	137	33.3	0.51	0.28	0.94
IR-cyto moderate/strong	82	25	30.5	0.47	0.23	0.93
IR-nucl negative	84	35	41.7	1.00 (Ref)		
IR-nucl <50% positive	130	46	35.4	0.67	0.43	1.04
IR-nucl ≥50% positive	303	93	30.7	0.62	0.42	0.92
IR-overall negative	24	12	50.0	1.00 (Ref)		
IR-overall weak	252	85	33.7	0.53	0.28	0.97
IR-overall moderate/strong	241	77	32.0	0.53	0.29	0.98
pIGF1R/pIR-cyto negative	352	111	31.5	1.00 (Ref)		
pIGF1R/pIR-cyto positive ^d	136	51	37.5	1.24	0.89	1.74
pIGF1R/pIR-overall negative	325	98	30.2	1.00 (Ref)		
pIGF1R/pIR-overall positive ^e	163	64	39.3	1.40	1.02	1.92
pIGF1R/pIR-memb negative	356	113	31.7	1.00 (Ref)		
pIGF1R/pIR-memb <50% positive	121	45	37.2	1.22	0.86	1.72
pIGF1R/pIR-memb ≥50% positive	11	4	36.4	0.77	0.28	2.11
IGF1R-cyto negative	113	46	40.7	1.00 (Ref)		
IGF1R-cyto positive ^d	383	121	31.6	0.78	0.56	1.10
IGF1R-overall negative	113	46	40.7	1.00 (Ref)		
IGF1R-overall weak	301	98	32.6	0.79	0.56	1.12
IGF1R-overall moderate/strong	80	22	27.5	0.75	0.45	1.26
IGF1R-memb negative	239	80	33.5	1.00 (Ref)		
IGF1R-memb <50% positive	170	61	35.9	1.17	0.84	1.64
IGF1R-memb ≥50% positive	87	26	29.9	0.90	0.57	1.40

^aCase numbers may not sum to 524 due to missing data.

^bModels were adjusted for age at enrollment (continuous), FIGO stage (II [Ref], III, IV) and grade (1, 2, 3 [Ref]).

^cThe combined ER/PR staining refers to glandular cell staining only.

^dOnly weak staining was observed.

^eThis category refers to weak/moderate staining.

Abbreviations: CI confidence interval, cyto cytoplasmic, ER estrogen receptor alpha, HR hazard ratio, IGF1R insulin-like growth factor 1 receptor, IR insulin receptor, memb membranous, nucl nuclear, pIGF1R/pIR phosphorylated IGF1R/insulin receptor, PR, progesterone receptor.

Table S2. Gene expression^a of IGF axis genes in endometrial cancer tissues in relation to progression-free survival

	Total N	Recurrent N	Recurrent %	HR ^b	95% CI ^b	95% CI ^b
IGF1						
<50th pctl	179	64	36	1.00 (Ref)		
≥50th pctl	179	58	32	0.98	0.68	1.40
IGF2						
<50th pctl	179	74	41	1.00 (Ref)		
≥50th pctl	179	48	27	0.75	0.52	1.08
IGFBP1						
<50th pctl	179	62	35	1.00 (Ref)		
≥50th pctl	179	60	34	1.10	0.77	1.57
IGFBP3						
<50th pctl	179	67	37	1.00 (Ref)		
≥50th pctl	179	55	31	1.00	0.69	1.43

^aGene expression values (normalized to *PPIB*) as detected by qPCR.

^bModels were adjusted for age at enrollment (continuous) and FIGO stage (II [Ref], III, IV).

Abbreviations: CI confidence interval, HR hazard ratio, *IGF1* insulin-like growth factor 1, *IGF2* insulin-like growth factor 2, *IGFBP1* *IGFBP3* insulin-like growth factor binding proteins 1 and 3, respectively; qPCR quantitative real time reverse transcription PCR.

Table S3: Adjusted hazard ratios (95% CI) for the associations of preoperative circulating levels of insulin/IGF and sex hormone axis components in relation to endometrioid adenocarcinoma progression-free survival

	Quantile 1	Quantile 2	Quantile 3	Quantile 4	<i>P</i> -trend ^a
IGFBP-3					
Quartile cut points (ng/ml)	<2046.2	≥2046.2-<2529.6	≥2529.6-<3127.4	≥3127.4	
Total <i>N</i>	202	202	202	202	
Recurrent <i>N</i> (%)	88 (43.6)	62 (30.7)	62 (30.7)	68 (33.7)	
HR (95% CI) ^b	1.00 (Ref)	0.73 (0.52-1.01)	0.69 (0.50-0.96)	0.78 (0.57-1.08)	0.09
IGF-I					
Quartile cut points (ng/ml)	<84.4	≥84.4-<109.6	≥109.6-<137.8	≥137.8	
Total <i>N</i>	201	202	201	203	
Recurrent <i>N</i> (%)	83 (41.3)	76 (37.6)	65 (32.3)	56 (27.6)	
HR (95% CI) ^b	1.00 (Ref)	0.93 (0.68-1.27)	0.82 (0.60-1.14)	0.66 (0.47-0.92)	0.01
Insulin^c					
Tertile cut points (uU/ml)	<3.9	≥3.9-<9.2	≥9.2		
Total <i>N</i>	52	52	53		
Recurrent <i>N</i> (%)	20 (38.5)	18 (34.6)	19 (35.9)		
HR (95% CI) ^b	1.00 (Ref)	0.83 (0.44-1.59)	1.25 (0.63-2.45)	N/A	0.01^d
Estradiol^e					
Tertile cut points (pg/ml)	<14.5	≥14.5-<24.5	≥24.5		
Total <i>N</i>	124	128	131		
Recurrent <i>N</i> (%)	48 (38.7)	49 (38.3)	49 (37.4)		
HR (95% CI) ^b	1.00 (Ref)	1.15 (0.77-1.73)	1.55 (1.02-2.36)	N/A	0.69
Estrone^e					
Tertile cut points (pg/ml)	<40.5	≥40.5-<84.0	≥84.0		
Total <i>N</i>	128	129	129		
Recurrent <i>N</i> (%)	47 (36.7)	53 (41.1)	49 (38.0)		
HR (95% CI) ^b	1.00 (Ref)	1.61 (1.08-2.39)	1.21 (0.80-1.83)	N/A	0.68
SHBG^e					
Tertile cut points (nmol/L)	<412.1	≥412.1-<639.5	≥639.5		
Total <i>N</i>	130	131	131		
Recurrent <i>N</i> (%)	44 (33.9)	58 (44.3)	49 (37.4)		
HR (95% CI) ^b	1.00 (Ref)	1.12 (0.75-1.68)	0.85 (0.56-1.29)	N/A	0.50

^a*P*-trend based on a continuous variable.

^bModels were adjusted for age at enrollment (continuous), FIGO stage (II [Ref], III, IV) and grade (1, 2, 3 [Ref]).

^cRestricted to fasting cases.

^dFollowing log transformation, the *P*-trend for circulating insulin was no longer significant.

^eRestricted to postmenopausal women who were not using hormones.

Abbreviations: BMI body mass index, CI confidence interval, E2 estradiol, IGF-I insulin-like growth factor-I, IGFBP-3 insulin-like growth factor binding protein-3, HR hazard ratio, SHBG sex hormone-binding globulin.

Table S4: Adjusted hazard ratios (95% CI) for the associations between immunohistochemical staining of insulin/IGF and sex hormone axis factors in endometrial cancer in relation to progression-free survival (overall and stratified by stage)

	Total N ^a	All cases (N=524)			SII cases (N=186)			SII/III cases (N=472)			SIII/IV cases (N=345)			
		Recurrent N	HR ^b	95% CI ^b	95% CI ^b	HR ^b	95% CI ^b	95% CI ^b	HR ^b	95% CI ^b	95% CI ^b	HR ^b	95% CI ^b	95% CI ^b
ER (gland) negative	351	130	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
ER (gland) positive	171	45	0.67	0.47	0.95	0.60	0.30	1.21	0.64	0.43	0.94	0.71	0.47	1.07
ER (stroma) negative	500	170	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
ER (stroma) positive	22	5	0.73	0.30	1.81	NA	NA	NA	0.49	0.15	1.54	1.04	0.42	2.59
PR (gland) negative	241	96	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
PR (gland) positive	283	80	0.81	0.59	1.11	1.08	0.54	2.18	0.77	0.54	1.10	0.70	0.48	1.00
PR (stroma) negative	483	167	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
PR (stroma) positive	41	9	0.79	0.40	1.56	0.50	0.12	2.10	0.65	0.30	1.41	0.84	0.39	1.81
ER negative/PR negative ^c	206	83	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
ER negative/PR positive ^c	144	46	0.94	0.64	1.39	1.42	0.63	3.22	0.91	0.59	1.41	0.80	0.51	1.24
ER positive/PR negative ^c	34	13	0.83	0.45	1.51	0.60	0.08	4.77	0.79	0.37	1.66	0.95	0.51	1.78
ER positive/PR positive ^c	136	32	0.61	0.40	0.94	0.77	0.33	1.79	0.59	0.37	0.94	0.55	0.33	0.92
IR-cyto negative	23	12	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
IR-cyto weak	412	137	0.51	0.28	0.94	0.31	0.11	0.88	0.48	0.26	0.88	0.73	0.35	1.50
IR-cyto moderate/strong	82	25	0.47	0.23	0.93	0.19	0.05	0.77	0.48	0.24	0.96	0.64	0.28	1.45
IR-nucl negative	84	35	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
IR-nucl <50% positive	130	46	0.67	0.43	1.04	0.90	0.28	2.83	0.66	0.40	1.07	0.71	0.44	1.15
IR-nucl ≥50% positive	303	93	0.62	0.42	0.92	1.01	0.41	2.45	0.55	0.36	0.84	0.60	0.38	0.93
IR-overall negative	24	12	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
IR-overall weak	252	85	0.53	0.28	0.97	0.19	0.06	0.61	0.47	0.25	0.88	0.81	0.39	1.69
IR-overall moderate/strong	241	77	0.53	0.29	0.98	0.37	0.13	1.07	0.52	0.28	0.97	0.69	0.33	1.46
pIGF1R/pIR-cyto negative	352	111	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
pIGF1R/pIR-cyto positive ^d	136	51	1.24	0.89	1.74	1.18	0.57	2.46	1.35	0.93	1.95	1.28	0.88	1.86
pIGF1R/pIR-overall negative	325	98	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
pIGF1R/pIR-overall positive ^e	163	64	1.40	1.02	1.92	1.23	0.60	2.52	1.45	1.02	2.07	1.48	1.04	2.11
pIGF1R/pIR-memb negative	356	113	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
pIGF1R/pIR-memb <50% positive	121	45	1.22	0.86	1.72	1.29	0.60	2.77	1.30	0.88	1.90	1.22	0.82	1.80
pIGF1R/pIR-memb ≥50% positive	11	4	0.77	0.28	2.11	NA	NA	NA	1.77	0.55	5.65	1.23	0.45	3.35

^aCase numbers may not sum to total due to missing data.

^bModels (all cases) were adjusted for age at enrollment (continuous), FIGO stage (II [Ref], III, IV) and grade (1, 2, 3 [Ref]). Models stratified by stage were adjusted for age and grade only.

^cThe combined ER/PR staining refers to glandular cell staining only.

^dOnly weak staining was observed.

^eThis category refers to weak/moderate staining.

Table S4 (continued): Adjusted hazard ratios (95% CI) for the associations between immunohistochemical staining of insulin/IGF and sex hormone axis factors in endometrial cancer in relation to progression-free survival (overall and stratified by stage)

	Total N ^a	All cases (N=524)			SII cases (N=186)			SII/III cases (N=472)			SIII/IV cases (N=345)			
		Recurrent N	HR ^b	95% CI ^b	95% CI ^b	HR ^b	95% CI ^b	95% CI ^b	HR ^b	95% CI ^b	95% CI ^b	HR ^b	95% CI ^b	95% CI ^b
IGF1R-cyto negative	113	46	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
IGF1R-cyto positive ^d	383	121	0.78	0.56	1.10	0.63	0.31	1.27	0.85	0.57	1.25	0.91	0.62	1.35
IGF1R-overall negative	113	46	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
IGF1R-overall weak	301	98	0.79	0.56	1.12	0.58	0.28	1.22	0.87	0.58	1.31	0.96	0.64	1.43
IGF1R-overall moderate/strong	80	22	0.75	0.45	1.26	0.80	0.32	2.03	0.74	0.41	1.31	0.72	0.38	1.34
IGF1R-memb negative	239	80	1.00 (Ref)			1.00 (Ref)			1.00 (Ref)			1.00 (Ref)		
IGF1R-memb <50% positive	170	61	1.17	0.84	1.64	0.90	0.44	1.86	1.24	0.85	1.82	1.34	0.92	1.96
IGF1R-memb ≥50% positive	87	26	0.90	0.57	1.40	1.17	0.50	2.77	1.13	0.69	1.86	0.91	0.54	1.54

^aCase numbers may not sum to total due to missing data.

^bModels (all cases) were adjusted for age at enrollment (continuous), FIGO stage (II [Ref], III, IV) and grade (1, 2, 3 [Ref]). Models stratified by stage were adjusted for age and grade only.

^cThe combined ER/PR staining refers to glandular cell staining only.

^dOnly weak staining was observed.

^eThis category refers to weak/moderate staining.

Abbreviations: CI confidence interval, cyto cytoplasmic, ER estrogen receptor alpha, HR hazard ratio, IGF1R insulin-like growth factor 1 receptor, IR insulin receptor, memb membranous, NA not available, nucl nuclear, pIGF1R/pIR phosphorylated IGF1R/insulin receptor, PR, progesterone receptor.

Table S5: Adjusted hazard ratios (95% CI) for the associations of preoperative circulating levels of insulin/IGF and sex hormone axis components in relation to endometrioid adenocarcinoma progression-free survival (overall and stratified by stage)

	Total N	All cases		SII cases	SII/III cases	SIII/IV cases
		Recurrent N	HR (95% CI) ^b	HR (95% CI) ^b	HR (95% CI) ^b	HR (95% CI) ^b
IGFBP-3						
Quantile 1	202	88	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Quantile 2	202	62	0.73 (0.52-1.01)	0.66 (0.33-1.33)	0.71 (0.49-1.02)	0.70 (0.49-1.01)
Quantile 3	202	62	0.69 (0.50-0.96)	0.53 (0.25-1.13)	0.71 (0.49-1.03)	0.76 (0.53-1.09)
Quantile 4	202	68	0.78 (0.57-1.08)	0.34 (0.15-0.77)	0.71 (0.49-1.02)	0.76 (0.53-1.09)
P-trend ^a			0.09	0.005	0.02	0.26
IGF-I						
Quantile 1	201	83	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Quantile 2	202	76	0.93 (0.68-1.27)	1.13 (0.56-2.28)	1.05 (0.73-1.49)	0.87 (0.62-1.24)
Quantile 3	201	65	0.82 (0.60-1.14)	0.80 (0.38-1.66)	0.84 (0.58-1.21)	0.81 (0.56-1.16)
Quantile 4	203	56	0.66 (0.47-0.92)	0.44 (0.19-1.04)	0.66 (0.45-0.98)	0.69 (0.47-1.00)
P-trend ^a			0.01	0.02	0.01	0.047
Insulin^c						
Quantile 1	52	20	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Quantile 2	52	18	0.83 (0.44-1.59)	0.26 (0.02-2.99)	0.72 (0.33-1.58)	1.09 (0.55-2.14)
Quantile 3	53	19	1.25 (0.63-2.45)	6.89 (0.69-68.83)	1.30 (0.61-2.77)	1.03 (0.48-2.20)
P-trend ^d				0.21	0.22	0.32
Estradiol^e						
Quantile 1	124	48	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Quantile 2	128	49	1.15 (0.77-1.73)	1.39 (0.53-3.60)	1.02 (0.65-1.60)	1.20 (0.76-1.89)
Quantile 3	131	49	1.55 (1.02-2.36)	2.28 (0.86-6.07)	1.42 (0.89-2.28)	1.72 (1.07-2.78)
P-trend ^a			0.69	0.41	0.67	0.71
Estrone^e						
Quantile 1	128	47	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Quantile 2	129	53	1.61 (1.08-2.39)	1.16 (0.48-2.79)	1.49 (0.96-2.32)	1.50 (0.96-2.33)
Quantile 3	129	49	1.21 (0.80-1.83)	1.73 (0.74-4.06)	1.20 (0.75-1.92)	1.16 (0.73-1.85)
P-trend ^a			0.68	0.90	0.53	0.32
SHBG^e						
Quantile 1	130	44	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Quantile 2	131	58	1.12 (0.75-1.68)	2.37 (0.93-6.06)	1.24 (0.80-1.92)	1.05 (0.67-1.62)
Quantile 3	131	49	0.85 (0.56-1.29)	1.88 (0.72-4.94)	0.86 (0.54-1.38)	0.84 (0.53-1.33)
P-trend ^a			0.50	0.85	0.45	0.65

^aP-trend based on a continuous variable.

^bModels (all cases) were adjusted for age at enrollment (continuous), FIGO stage (II [Ref], III, IV) and grade (1, 2, 3 [Ref]). Models stratified by stage were adjusted for age and grade only.

^cRestricted to fasting cases.

^dP-trend for circulating insulin refers to the log transformed data.

^eRestricted to postmenopausal women who were not using hormones.

Abbreviations: BMI body mass index, CI confidence interval, E2 estradiol, IGF-I insulin-like growth factor-I, IGFBP-3 insulin-like growth factor binding protein-3, HR hazard ratio, SHBG sex hormone-binding globulin.

Table S6: Pearson's correlation coefficients for serologic insulin/IGF and sex hormone axis factors and tumor IGF-axis gene expression levels for 357 women with advanced stage endometrioid adenocarcinoma

Serologic factors	Tumor gene expression (normalized <i>PPIB</i>)			
	<i>IGF1</i>	<i>IGF2</i>	<i>IGFBP1</i>	<i>IGFBP3</i>
IGF-I, ρ	-0.02538	0.07628	-0.04179	-0.03672
IGF-I, p-value	0.6332	0.1509	0.4319	0.4898
IGFBP-3, ρ	-0.07751	-0.00586	-0.09221	-0.01351
IGFBP-3, p-value	0.1438	0.9121	0.0819	0.7991
Insulin ^a , ρ	-0.04833	-0.06717	-0.11305	-0.09723
Insulin ^a , p-value	0.7068	0.6009	0.3777	0.4484
Estradiol ^b , ρ	-0.06450	-0.05333	-0.04691	-0.07375
Estradiol ^b , p-value	0.3992	0.4859	0.5400	0.3349
Estrone ^b , ρ	-0.05259	-0.02919	-0.04590	-0.03967
Estrone ^b , p-value	0.4820	0.6965	0.5395	0.5960
SHBG ^b , ρ	0.10031	0.08870	0.04918	-0.02331
SHBG ^b , P-value	0.1791	0.2351	0.5109	0.7554

^aRestricted to individuals (N=63) who were fasting.

^bRestricted to individuals (N=181) who were postmenopausal and non-users of hormone therapy.

ρ is the Pearson's correlation coefficient.

P-value is for the probability of observing this correlation coefficient or one more extreme under the null hypothesis (H_0) that the correlation (ρ) is 0.

Table S7: Pearson's correlation coefficients for insulin/IGF and sex hormone axis serologic and tumor immunohistochemical staining in 523 women with advanced stage endometrioid adenocarcinoma

Tumor proteins	Serologic factors					
	IGF-I	IGFBP-3	Insulin ^a	Estradiol ^b	Estrone ^b	SHBG ^b
ER (gland) H-score, ρ	0.04422	0.06972	-0.07296	-0.07468	0.01427	-0.03890
ER (gland) H-score, p-value	0.3142	0.1119	0.4595	0.2319	0.8179	0.5275
ER (stroma) H-score, ρ	0.08221	0.07478	0.08124	-0.00656	0.04562	-0.02286
ER (stroma) H-score, p-value	0.0610	0.0881	0.4100	0.9165	0.4613	0.7105
PR (gland) H-score, ρ	-0.03571	-0.01402	-0.01337	0.17932	0.16104	-0.19431
PR (gland) H-score, p-value	0.4155	0.7490	0.8918	0.0039	0.0089	0.0014
PR (stroma) H-score, ρ	0.01116	-0.00381	0.03026	0.06660	0.04708	-0.07085
PR (stroma) H-score, p-value	0.7991	0.9307	0.7581	0.2866	0.4471	0.2495
IR-cyto, ρ	0.03129	-0.00149	0.15406	0.02816	0.06781	-0.02213
IR-cyto, p-value	0.4787	0.9730	0.1184	0.6551	0.2769	0.7220
IR-nucl, ρ	0.00183	0.03991	-0.04498	-0.13378	0.01926	0.11814
IR-nucl, p-value	0.9670	0.3656	0.6503	0.0331	0.7577	0.0566
IR-overall, ρ	-0.00575	-0.01309	-0.15414	-0.02032	-0.04221	0.08762
IR-overall, p-value	0.8964	0.7667	0.1182	0.7473	0.4988	0.1581
pIGF1R/pIR-cyto, ρ	-0.04791	-0.04915	-0.09418	-0.04008	-0.04282	0.08603
pIGF1R/pIR-cyto, p-value	0.2919	0.2790	0.3563	0.5299	0.4995	0.1717
pIGF1R/pIR-overall, ρ	0.00636	-0.01590	-0.06299	-0.05134	-0.05165	0.12794
pIGF1R/pIR-overall, p-value	0.8888	0.7263	0.5378	0.4208	0.4152	0.0416
pIGF1R/pIR-memb, ρ	0.00991	0.01455	-0.03813	-0.06813	-0.04553	0.13227
pIGF1R/pIR-memb, p-value	0.8275	0.7488	0.7094	0.2852	0.4726	0.0351
IGF1R-cyto, ρ	0.06978	0.01867	0.11662	0.02091	0.05623	0.03461
IGF1R-cyto, p-value	0.1214	0.6787	0.2407	0.7462	0.3799	0.5867
IGF1R-overall, ρ	0.05384	-0.01833	0.06442	0.02832	0.05664	-0.00470
IGF1R-overall, p-value	0.2333	0.6848	0.5179	0.6618	0.3773	0.9412
IGF1R-memb, ρ	0.05230	-0.02157	0.10340	0.03885	0.07566	0.04238
IGF1R-memb, p-value	0.2459	0.6321	0.2986	0.5475	0.2371	0.5057

^aRestricted to individuals (N=106) who were fasting.

^bRestricted to individuals (N=266) who were postmenopausal and non-users of hormone therapy.

ρ is the Pearson's correlation coefficient.

P-value is for the probability of observing this correlation coefficient or one more extreme under the null hypothesis (H0) that the correlation (Rho) is 0.

Table S8: Pearson's correlation coefficients for insulin/IGF and sex hormone axis tumor gene expression levels and immunohistochemical staining in 279 women with advanced stage endometrioid adenocarcinoma

IHC staining	Gene expression (normalized <i>PPIB</i>)			
	<i>IGF1</i>	<i>IGF2</i>	<i>IGFBP1</i>	<i>IGFBP3</i>
ER (gland) H-score, ρ	0.06309	-0.00119	-0.05642	0.05686
ER (gland) H-score, p-value	0.2937	0.9843	0.3478	0.3440
ER (stroma) H-score, ρ	0.01286	-0.00835	0.04226	0.05816
ER (stroma) H-score, p-value	0.8306	0.8895	0.4821	0.3331
PR (gland) H-score, ρ	0.02492	-0.00329	-0.11773	-0.01318
PR (gland) H-score, p-value	0.6791	0.9565	0.0499	0.8268
PR (stroma) H-score, ρ	0.02682	-0.01218	-0.00725	0.00245
PR (stroma) H-score, p-value	0.6561	0.8398	0.9042	0.9676
IR-cyto, ρ	0.03507	-0.05188	0.00829	-0.00756
IR-cyto, p-value	0.5626	0.3914	0.8912	0.9007
IR-nucl, ρ	0.09983	-0.04015	0.09223	0.03893
IR-nucl, p-value	0.0985	0.5073	0.1271	0.5203
IR-overall, ρ	0.13209	0.03540	0.04748	0.08148
IR-overall, p-value	0.0285	0.5589	0.4329	0.1779
pIGF1R/pIR-cyto, ρ	-0.06088	-0.06035	-0.01100	-0.04026
pIGF1R/pIR-cyto, p-value	0.3310	0.3352	0.8608	0.5205
pIGF1R/pIR-overall, ρ	-0.06882	-0.06899	-0.03497	-0.02763
pIGF1R/pIR-overall, p-value	0.2717	0.2705	0.5768	0.6593
pIGF1R/pIR-memb, ρ	-0.06305	-0.06119	-0.06527	-0.02388
pIGF1R/pIR-memb, p-value	0.3140	0.3285	0.2972	0.7032
IGF1R-cyto, ρ	0.14067	-0.08557	0.05005	0.05005
IGF1R-cyto, p-value	0.0215	0.1633	0.4154	0.4154
IGF1R-overall, ρ	0.11433	-0.07402	0.05394	0.05394
IGF1R-overall, p-value	0.0626	0.2289	0.3809	0.3809
IGF1R-memb, ρ	0.05146	-0.03200	-0.00347	-0.00347
IGF1R-memb, p-value	0.4023	0.6027	0.9550	0.9550

ρ is the Pearson's correlation coefficient.

P-value is for the probability of observing this correlation coefficient or one more extreme under the null hypothesis (H_0) that the correlation (Rho) is 0.

Table S9a: Pearson's correlation coefficients for serologic factors, age and BMI in 808 women with advanced stage endometrioid adenocarcinoma

	Age	BMI	IGF-I	IGFBP-3	Insulin ^a	Estradiol ^b	Estrone ^b	SHBG ^b
Age, y, ρ	1.00							
Age, y, p-value	-							
BMI (kg/m ²), ρ	-0.15347	1.00						
BMI (kg/m ²), p-value	<.0001	-						
IGF-I, ρ	-0.10147	-0.12132	1.00					
IGF-I, p-value	0.0039	0.0006	-					
IGFBP-3, ρ	0.04010	-0.13482	0.56436	1.00				
IGFBP-3, p-value	0.2549	0.0001	<.0001	-				
Insulin ^a , ρ	-0.10328	0.18644	0.14824	0.02659	1.00			
Insulin ^a , p-value	0.1980	0.0194	0.0639	0.7409	-			
Estradiol ^b , ρ	-0.32857	0.02522	0.11298	-0.04048	-0.06361	1.00		
Estradiol ^b , p-value	<.0001	0.6227	0.0272	0.4295	0.5929	-		
Estrone ^b , ρ	-0.12989	0.08746	-0.02623	-0.12417	-0.10754	0.28788	1.00	
Estrone ^b , p-value	0.0106	0.0862	0.6079	0.0146	0.2384	<.0001	-	
SHBG ^b , ρ	0.09143	-0.25571	-0.05992	-0.00386	0.13621	0.02503	-0.03996	1.00
SHBG ^b , P-value	0.0706	<.0001	0.2365	0.9393	0.2439	0.6258	0.4343	-

^aRestricted to individuals (N=157) who were fasting.

^bRestricted to individuals (N=393) who were postmenopausal and non-users of hormone therapy, or women who were also fasting women for measurements of insulin (N=75).

ρ is the Pearson's correlation coefficient. Correlation coefficients ≥ 0.50 are highlighted.

P-value is for the probability of observing this correlation coefficient or one more extreme under the null hypothesis (H0) that the correlation (Rho) is 0.

Table S9b: Pearson's correlation coefficients for serologic factors, age and BMI in 193 women with advanced stage endometrioid adenocarcinoma restricting to cases who were non-diabetic, postmenopausal and non-users of hormone therapy

	Age	BMI	IGF-I	IGFBP-3	Insulin ^a	Estradiol ^b	Estrone ^b	SHBG ^b
Age, y, ρ	1.00							
Age, y, p-value	-							
BMI (kg/m ²), ρ	-0.05554	1.00						
BMI (kg/m ²), p-value	0.4418	-						
IGF-I, ρ	-0.16160	-0.11222	1.00					
IGF-I, p-value	0.0251	0.1212	-					
IGFBP-3, ρ	0.03910	-0.13684	0.54351	1.00				
IGFBP-3, p-value	0.5893	0.0577	<.0001	-				
Insulin ^a , ρ	-0.07395	0.18419	0.06094	-0.00612	1.00			
Insulin ^a , p-value	0.4512	0.0587	0.5349	0.9503	-			
Estradiol, ρ	-0.31215	0.20745	0.02134	-0.22937	-0.02773	1.00		
Estradiol, p-value	<.0001	0.0043	0.7719	0.0015	0.7799	-		
Estrone, ρ	-0.17731	0.11394	-0.11061	-0.19306	-0.03058	0.34678	1.00	
Estrone, p-value	0.0141	0.1165	0.1287	0.0075	0.7568	<.0001	-	
SHBG, ρ	0.02847	-0.27519	-0.07704	0.02573	-0.15543	0.06367	-0.02706	1.00
SHBG, P-value	0.6951	0.0001	0.2882	0.7232	0.1116	0.3867	0.7109	-

^aRestricted to individuals (N=106) who were fasting.

ρ is the Pearson's correlation coefficient. Correlation coefficients ≥ 0.50 are highlighted.

P-value is for the probability of observing this correlation coefficient or one more extreme under the null hypothesis (H0) that the correlation (Rho) is 0.

Table S10: Pearson's correlation coefficients for insulin/IGF and sex hormone axis tumor gene expression in 365 women with advanced stage endometrioid adenocarcinoma

	Gene expression (normalized <i>PPIB</i>)			
	<i>IGF1</i>	<i>IGF2</i>	<i>IGFBP1</i>	<i>IGFBP3</i>
<i>IGF1</i> , ρ	1.00			
<i>IGF1</i> , p-value	-			
<i>IGF2</i> , ρ	0.18405	1.00		
<i>IGF2</i> , p-value	0.0004	-		
<i>IGFBP1</i> , ρ	0.12112	0.04037	1.00	
<i>IGFBP1</i> , p-value	0.0206	0.4419	-	
<i>IGFBP3</i> , ρ	0.15683	0.15683	0.43548	1.00
<i>IGFBP3</i> , p-value	0.0027	0.0027	<.0001	-

ρ is the Pearson's correlation coefficient.

P-value is for the probability of observing this correlation coefficient or one more extreme under the null hypothesis (H_0) that the correlation (Rho) is 0.

Table S11a: Pearson's correlation coefficients for insulin/IGF and sex hormone axis tumor proteins in 524 women with advanced stage endometrioid adenocarcinoma

	Age	BMI	ER (gland) H-score	ER (stroma) H- score	PR (gland) H-score	PR (stroma) H- score	IR-cyto	IR-nucl	IR-overall	pIGF1R/pIR -cyto	pIGF1R/pIR -overall
Age, y, ρ	1.00										
Age, y, p-value	-										
BMI (kg/m ²), ρ	-0.15347	1.00									
BMI (kg/m ²), p-value	<.0001	-									
ER (gland) H-score, ρ	0.14520	0.02786	1.00								
ER (gland) H-score, p-value	0.0009	0.5253	-								
ER (stroma) H-score, ρ	0.06232	0.01642	0.28941	1.00							
ER (stroma) H-score, p-value	0.1550	0.7082	<.0001	-							
PR (gland) H-score, ρ	-0.00269	0.23243	0.51715	0.11116	1.00						
PR (gland) H-score, p-value	0.9510	<.0001	<.0001	0.0112	-						
PR (stroma) H-score, ρ	-0.02196	0.13421	0.22554	0.71590	0.20479	1.00					
PR (stroma) H-score, p-value	0.6160	0.0021	<.0001	<.0001	<.0001	-					
IR-cyto, ρ	-0.07394	-0.05449	0.06615	0.08142	0.01686	0.09515	1.00				
IR-cyto, p-value	0.0931	0.2161	0.1342	0.0651	0.7025	0.0307	-				
IR-nucl, ρ	0.00409	-0.03110	0.24805	0.12405	0.12860	0.10177	0.25881	1.00			
IR-nucl, p-value	0.9261	0.4804	<.0001	0.0049	0.0034	0.0208	<.0001	-			
IR-overall, ρ	-0.03867	-0.02119	0.16037	0.15300	0.05433	0.11993	0.61375	0.55293	1.00		
IR-overall, p-value	0.3803	0.6307	0.0003	0.0005	0.2179	0.0064	<.0001	<.0001	-		
pIGF1R/pIR-cyto, ρ	0.06414	-0.03066	0.13584	0.04439	-0.00863	-0.01810	0.09084	0.12897	0.12550	1.00	
pIGF1R/pIR-cyto, p-value	0.1571	0.4992	0.0027	0.3288	0.8495	0.6907	0.0460	0.0045	0.0057	-	
pIGF1R/pIR-overall, ρ	0.04603	-0.03576	0.15398	0.06193	0.15398	-0.02822	0.06558	0.15986	0.11751	0.87770	1.00
pIGF1R/pIR-overall, p-value	0.3102	0.4306	0.0007	0.1729	0.0007	0.5348	0.1501	0.0004	0.0097	<.0001	-

Table S11a continued: Pearson's correlation coefficients for insulin/IGF and sex hormone axis tumor proteins in 524 women with advanced stage endometrioid adenocarcinoma

	Age	BMI	ER (gland) H-score	ER (stroma) H- score	PR (gland) H-score	PR (stroma) H- score	IR-cyto	IR-nucl	IR-overall	pIGF1R/pIR -cyto	pIGF1R/pIR -overall
pIGF1R/pIR-memb, ρ	0.07752	-0.05500	0.22759	0.11355	0.02637	0.00330	0.10171	0.21842	0.14794	0.69295	0.82386
pIGF1R/pIR-memb, p-value	0.0871	0.2252	<.0001	0.0122	0.5620	0.9421	0.0254	<.0001	0.0011	<.0001	<.0001
IGF1R-cyto, ρ	-0.09024	0.04625	0.14095	0.08873	0.14014	0.06504	0.09308	0.12062	0.17205	0.09228	0.07377
IGF1R-cyto, p-value	0.0446	0.3040	0.0017	0.0485	0.0018	0.1480	0.0394	0.0075	0.0001	0.0477	0.1137
IGF1R-overall, ρ	0.3040	0.10478	0.10192	0.05859	0.18274	0.05034	0.22649	0.15398	0.26308	0.04715	0.04425
IGF1R-overall, p-value	0.0013	0.0198	0.0236	0.1940	<.0001	0.2641	<.0001	0.0006	<.0001	0.3134	0.3442
IGF1R-memb, ρ	-0.08466	0.09201	0.07765	0.08396	0.14284	0.03650	0.03650	0.05870	0.14582	0.07861	0.10447
IGF1R-memb, p-value	0.0595	0.0405	0.0844	0.0619	0.0014	0.4172	0.4172	0.1946	0.0012	0.0918	0.0249

Table S11b: Pearson's correlation coefficients for insulin/IGF and sex hormone axis proteins in 524 women with advanced stage endometrioid adenocarcinoma

	pIGF1R/pIR-memb	IGF1R-cyto	IGF1R-overall	IGF1R-memb
pIGF1R/pIR-memb, ρ	1.00			
pIGF1R/pIR-memb, p-value	-			
IGF1R-cyto, ρ	0.09398	1.00		
IGF1R-cyto, p-value	0.0437	-		
IGF1R-overall, ρ	0.05877	0.81777	1.00	
IGF1R-overall, p-value	0.2088	<.0001	-	
IGF1R-memb, ρ	0.13073	0.50191	0.68728	1.00
IGF1R-memb, p-value	0.0049	<.0001	<.0001	-

ρ is the Pearson's correlation coefficient. Correlation coefficients ≥ 0.50 are highlighted.

P-value is for the probability of observing this correlation coefficient or one more extreme under the null hypothesis (H_0) that the correlation (Rho) is 0.