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Supplementary webappendix

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Insulin-like growth factor-I (IGF-I), IGF binding protein-3 (IGFBP-3), and breast cancer risk: reanalysis of seventeen prospective studies

Endogenous Hormones and Breast Cancer Collaborative Group

Factor and subset	n	opriate, age at blo Mean* (95% CI)	P values [#]	Relative mean⁺ & 95% C
Are at blood callestion@				
Age at blood collection [@] under 45	2318	129 (126-131)	0.006	
45-49	1477			X
		128 (125-130)	(0.001)	
50-54	1301	129 (127-131)		
55-59	1621	125 (123-127)		
60-64	1546	125 (123-127)		
65 and over	1626	122 (120-125)		•
Height (cm)				
<155`	1294	125 (123-127)	0.701	•
155-159	2072	127 (125-128)	(0.781)	•
160-164	2628	127 (125-128)		•
165-169	1893	126 (125-128)		•
170+	1120	126 (124-128)		•
				7
Body mass index (kg/m ²)		105 (400 400)	0.105	4
<22.5	2071	125 (123-126)	0.105	X
22.5-24.9	2316	126 (124-127)	(0.055)	.
25.0-27.4	1808	128 (126-130)		_
27.5-29.9	1261	127 (125-129)		T
30.0+	1631	127 (125-128)		
Smoking status				
never	5203	127 (126-128)	0.487	•
previous	2262	126 (125-128)	0.101	Ě.
current	1320	125 (123-127)		ě.
		125 (125 127)		
Usual alcohol consumpt				
none	3079	124 (122-125)	<0.0001	
<10 g/d	2694	127 (126-129)	(0.0001)	•
10-19 g/d	1103	129 (127-132)		
20+ g/d	823	129 (126-131)		
Nother or sister with bre	ast cancer®			
no	3718	126 (125 120)	0.370	
	582	126 (125-128) 125 (122-128)	0.370	
yes	302	125 (122-126)		
Age at menarche				
under 12	1471	129 (128-131)	<0.0001	
12-13	4325	127 (126-128)	(<0.0001)	•
14 and over	3105	124 (123-125)		•
lumber of full term prog	nanolog	. ,		
Number of full-term preg	1248	125 (122 127)	0.768	
none		125 (123-127)		
one	1091	126 (123-128)	(0.331)	
two	2896	127 (125-128)		X
three	1977	126 (125-128)		T T
four or more	1527	127 (125-128)		—
Age at first full-term preg	nancy			
under 20	605	124 (121-127)	0.420	•
20-24	3160	126 (125-127)	(0.238)	Č.
25-29	2691	127 (125-128)	(ě
30 and over	1089	127 (124-129)		ě
				Ţ
Type of menopause (pos	unenopausa		0.070	_
natural	4058	127 (126-128)	0.072	
hysterectomy	705	124 (122-127)		
bilateral ovariectomy	273	122 (118-127)		-
fears since menopause	(natural post	menopausal womer	only)	
0-4	733	124 (121-128)	0.464	
5-14	2160	127 (125-128)	(0.385)	
15+	1222	127 (124-129)	(0.000)	Ă
		(Ţ
Use of hormonal contrac		100 // 0 / 100		÷
never	3861	126 (124-127)	0.163	
past	3895	127 (126-128)		•
Use of hormone therapy	(natural post	menopausal womer	n only)®	
never	2966	126 (124-127)	0.067	<u></u>
past	746	129 (126-131)	0.007	1
puor	740	123(120-131)		

* means are scaled to the overall geometric mean concentration
P values for tests of heterogeneity and, where applicable and in parenthesis, linear trend
* values are depicted as a proportion of the overall geometric mean concentration (dotted line)
® P<0.05 for test of interaction with study

Webfigure 1. Geometric mean IGFBP-3 concentrations (nmol/l with 95% confidence intervals) among controls by selected factors. Adjusted for study and age at blood collection, as appropriate.

Supplementary Fig. 2a.

Association of breast cancer risk with IGFBP-3 concentration among premenopausal women, by study

Ratio of median concentrations:					
Study	Cases/ Controls	top-bottom fifth	OR (95% CI)	Odds ratio & 95% Cl	
CLUE I & CLUE II, USA ¹⁷	87/87	1.5	0.80 (0.31-2.03)	e	
EPIC, Europe ¹⁶	392/742	2.5	1.24 (0.64-2.41)		
Guernsey, UK ¹³	70/203	1.6	0.53 (0.24-1.19)		
Janus Biobank, Norway ²⁰	323/635	1.8	0.88 (0.59-1.33)		
KP-OFAS, USA ⁹	89/89	2.0	1.33 (0.56-3.15)		
Malmo-Umea, Sweden ⁸	141/256	1.6	0.96 (0.51-1.78)	#	
MCCS, Australia ¹⁹	154/562	1.6	0.67 (0.40-1.11)		
Nurses' Health Study, USA ^{6,15}	194/262	1.9	1.31 (0.69-2.48)	_	
Nurses' Health Study II, USA ¹	⁸ 231/454	1.5	1.04 (0.65-1.67)		
NYU WHS, USA ⁷	172/483	1.8	1.35 (0.79-2.32)		
ORDET, Italy ¹⁰	62/239	1.7	1.79 (0.70-4.58)		
All studies	1915/4012		0.99 (0.83-1.19)	\diamond	
Test of significance (all studies): χ Test of heterogeneity between stu			0.2	5 0.5 1 2	

Test of heterogeneity between studies: $\chi^2_{10} = 9.73$; P=0.464

The odds ratio is the estimate of the linear trend for IGFBP-3 concentration obtained using a variable that was scored 0, 0.25, 0.5, 0.75, and 1, corresponding to the fifths of concentration.

Webfigure 2a. Odds ratios (ORs) for breast cancer associated with an increase in IGFBP-3 concentration among women who were premenopausal at blood collection. The OR is the estimate of the linear trend for IGFBP-3 obtained by replacing the categorical variables representing the fifths of concentration among controls by a continuous variable scored as 0, 0.25, 0.5, 0.75 and 1. The black squares indicate the ORs and the horizontal lines show the 95% confidence intervals. The area of each square is proportional to the amount of statistical information (inverse of the variance of the logarithm of the OR). The diamond indicates the OR and 95% CI for all studies combined. Estimates are from conditional logistic regression on case-control sets matched within each study.

Supplementary Fig. 2b.

Association of breast cancer risk with IGFBP-3 concentration among postmenopausal women, by study

	C	atio of media		
Study	Cases/ Controls	top-bottom fifth	OR (95% CI)	Odds ratio & 95% Cl
CLUE I & CLUE II, USA ¹⁷	73/73	1.5	1.99 (0.79-4.99)	
EPIC, Europe ¹⁶	647/1205	2.6	1.74 (1.13-2.67)	∎
Guernsey, UK ¹³	47/139	1.7	1.21 (0.44-3.32)	
KKH, Denmark ¹²	195/195	1.6	1.78 (0.89-3.55)	
KP-OFAS, USA ⁹	27/27	2.1	1.17 (0.25-5.54)	
Malmo-Umea, Sweden ⁸	222/401	2.4	1.10 (0.64-1.89)	
MCCS, Australia ¹⁹	252/956	1.8	1.60 (1.07-2.39)	
Nurses' Health Study, USA ^{6,15}	239/470	2.0	0.62 (0.37-1.05)	
NYU WHS, USA ⁷	98/171	1.9	1.37 (0.63-2.99)	_
ORDET, Italy ¹⁰	60/220	1.8	0.83 (0.36-1.89)	
PLCO, USA ²²	386/468	1.6	1.12 (0.76-1.65)	
PPHV, Netherlands ¹¹	77/167	1.5	2.48 (1.06-5.84)	
Prospect-EPIC, Netherlands ¹¹	15/35	1.5	0.94 (0.16-5.33)	
SOF, USA ²⁶	101/235	1.7	1.17 (0.59-2.32)	
WHI-OS, USA ²¹	377/434	1.6	0.85 (0.57-1.26)	
All studies	2816/5196		1.21 (1.04-1.41)	\diamond
Test of significance (all studies): $\chi_1^2 = 6.30$; P=0.0120.250.512Test of heterogeneity between studies: $\chi_{14}^2 = 20.59$; P=0.1130.250.512				

The odds ratio is the estimate of the linear trend for IGFBP-3 concentration obtained using a variable that was scored 0, 0.25, 0.5, 0.75, and 1, corresponding to the fifths of concentration.

Webfigure 2b. Odds ratios (ORs) for breast cancer associated with an increase in IGFBP-3 concentration among women who were postmenopausal at blood collection. The OR is the estimate of the linear trend for IGFBP-3 obtained by replacing the categorical variables representing the fifths of concentration among controls by a continuous variable scored as 0, 0.25, 0.5, 0.75 and 1. The black squares indicate the ORs and the horizontal lines show the 95% confidence intervals. The area of each square is proportional to the amount of statistical information (inverse of the variance of the logarithm of the OR). The diamond indicates the OR and 95% CI for all studies combined. Estimates are from conditional logistic regression on case-control sets matched within each study.

Supplementary Fig. 3.

Factor and subset	Cases/Controls		Odds ratio & 95% CI
All studies	4731/9208	1.12 (0.99-1.25)	
Menopausal status	1015/1010		
premenopausal	1915/4012 2816/5196	0.99 (0.83-1.19)	
postmenopausal	2010/0190	1.21 (1.04-1.41) χ^2_1 het = 2.82; P=0.093	
Age at diagnosis		λη ποι = 2.02, η =0.000	
<50	1055/2232	1.01 (0.79-1.28)	
≥50	3676/6976	1.15 (1.01-1.31)	
Years from blood collectio	n to diagnosis	χ^2_1 het = 0.91; P=0.339	
	2599/4982	1.11 (0.94-1.30)	
≥4	2132/4226	1.13 (0.95-1.33)	
		χ^2_1 het = 0.03; P=0.870	
Stage of disease			
in situ	393/736	1.62 (1.07-2.46)	
invasive	3582/7036	1.06 (0.93-1.21)	
Oostrogon recontors		χ^2_1 het = 3.67; P=0.055	
Oestrogen receptors positive	1405/2654	1.15 (0.95-1.40)	+ i
negative	477/938	0.77 (0.55-1.07)	
		χ^2_1 het = 4.27; P=0.039	
Body mass index			
<25 kg/m ²	1902/4032	1.08 (0.91-1.28)	-8
≥25 kg/m²	2368/4339	1.15 (0.98-1.35)	⊢ ₽ ₽
Smoking		χ^2_1 het = 0.36; P=0.547	
Smoking never or past smoker	3499/6819	1.13 (0.99-1.29)	
current smoker	650/1198	1.20 (0.90-1.59)	
		χ^2_1 het = 0.16; P=0.689	
Usual alcohol consumption			
<10 g ethanol per day	2578/5248	1.09 (0.93-1.27)	
≥10 g ethanol per day	988/1770	1.13 (0.89-1.45)	
Mother or sister with breas	t concor	χ^2_1 het = 0.09; P=0.770	
no	1689/3365	1.03 (0.86-1.23)	
yes	389/495	1.35 (0.92-1.99)	
,		χ^2_1 het = 1.68; P=0.195	
Age at menarche			
<14 years	2775/5286	1.06 (0.91-1.22) 1.27 (1.04-1.55)	- # -
≥14 years	1330/2846	1.27 (1.04-1.55)	
Parity		χ^2_1 het = 2.46; P=0.117	
Parity nulliparous	633/1135	1.14 (0.85-1.52)	_
parous	3444/6768	1.12 (0.98-1.28)	
		χ^2_1 het = 0.01; P=0.906	
Age at first birth			L
<25 years	1513/2866	1.06 (0.88-1.29)	- H -
≥25 years	1723/2887	1.21 (1.00-1.46)	
Type of menopause		χ^2_1 het = 1.07; P=0.301	
natural	2229/4089	1.17 (0.99-1.39)	, im −
other	516/952	1.34 (0.98-1.85)	↓ ¯ ∎
		χ^2_1 het = 0.58; P=0.447	
OC use		4 4 4 10 00 4 0 1	
never user	2008/3913	1.11 (0.93-1.31)	+₽
past user	1594/3430	1.25 (1.03-1.52)	
HRT use among natural po	stmenonausal wom	χ^2_1 het = 0.99; P=0.319	
never user	1434/2498	1.16 (0.94-1.44)	+ i
past user	379/575	1.18 (0.80-1.74)	
		χ^2_1 het = 0.00; P=0.946	
		0.2	5 0.5 1 2 4
		0.23	J U.J I Z 4

Webfigure 3. Odds ratios (ORs) for breast cancer associated with IGFBP-3 concentration, according to menopausal status at blood collection and other factors. The OR is the estimate of the linear trend obtained by replacing the categorical variables representing the fifths of IGFBP-3 concentration among controls by a continuous variable scored as 0, 0.25, 0.5, 0.75 and 1. Black squares indicate the OR and the horizontal lines show the 95% confidence intervals. The area of each square is proportional to the amount of statistical information (inverse of the variance of the logarithm of the OR). The vertical dotted line indicates the OR for all studies. Tests for heterogeneity are for the difference in the association of IGFBP-3 with breast cancer risk between subgroups. Estimates are from conditional logistic regression on case-control sets matched within each study.

	Thirds of IGF-I							
Thirds of IGFBP-3	Low		Medium		High			
	Cases/controls	RR (95% CI)	Cases/controls	RR (95% CI)	Cases/controls	RR (95% CI)		
Low	825/1730	1.00 (ref)	518/988	1.12 (0.97-1.28)	223/427	1.15 (0.95-1.40)		
Medium	408/847	0.99 (0.86-1.15)	592/1194	1.06 (0.93-1.21)	572/1018	1.22 (1.06-1.40)		
High	239/505	0.91 (0.75-1.11)	464/896	1.05 (0.90-1.22)	886/1591	1.18 (1.04-1.34)		
	Test of interaction: χ^2_4 =1.15, P=0.887							

Webtable 1: Relationships of IGF-I with breast cancer risk among all women, according to plasma concentrations of IGFBP-3