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在线全文

肥胖相关蛋白在女性乳腺癌发病中的交互作用初探*

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【摘要】 目的 探讨女性乳腺癌发病过程中肥胖相关蛋白可能存在的交互作用。**方法** 采用病例对照研究设计，于2014年4月–2015年5月序贯收集279例原发性女性乳腺癌病例，按年龄频数匹配收集260例同期健康对照。通过文献循证筛选肥胖-乳腺癌病因链上较受关注的蛋白，运用酶联免疫吸附法测定研究对象血浆中相关蛋白水平。按照绝经状态分层后，采用多因素logistic回归和广义多因子降维法（generalized multifactor dimensionality reduction, GMDR）相结合的分析策略，探讨肥胖相关蛋白在乳腺癌发病风险影响中的可能相互作用。**结果** 绝经前亚组中，胰岛素样生长因子1（IGF-1）、胰岛素样生长因子结合蛋白3（IGFBP3）、C反应蛋白（CRP）、抵抗素（RETN）、可溶性瘦素受体（sOB-R）、脂联素（ADP）存在边际高阶交互作用（测试集平衡准确度59.01%，交叉验证一致性10/10，置换检验P=0.05）。绝经后亚组中，瘦素（LEP）、sOB-R、ADP、CRP、IGFBP3、内脂素（VF）存在高阶交互作用（测试集平衡准确度67.31%，交叉验证一致性10/10，置换检验P=0.01）。随着肥胖相关蛋白暴露数目的增多，绝经前后乳腺癌发病风险逐渐增大（$OR_{绝经前}$=2.18，95%*CI*：1.69~2.82；$OR_{绝经后}$=2.41，95%*CI*：1.75~3.32）。**结论** 肥胖相关蛋白在对绝经前后乳腺癌发病影响上均存在高阶交互作用，未来的研究应密切关注这些蛋白在联合用作预测因子或构建乳腺癌风险评分时可能存在的交互作用。

【关键词】 乳腺癌 肥胖 肥胖相关蛋白 交互作用

Effect of Interactions Among Obesity-Related Proteins on Breast Cancer Risk: A Preliminary Study

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【Abstract】 Objective To explore the potential interactions among obesity-related proteins in the pathogenic process of breast cancer (BC) in women. **Methods** We conducted a case-control study, enrolling 279 primary breast cancer cases and 260 age-frequency-matched healthy women between April 2014 and May 2015. Based on the evidence of previous published literature on obesity-related proteins and BC risks, we selected proteins that received more attention and measured the plasma levels of these proteins by enzyme-linked immunosorbent assay (ELISA). After stratification of the subjects according to their menopausal status, an analytic strategy combining multivariate logistic regression and generalized multifactor dimensionality reduction (GMDR) was used to explore the effect of the possible interactions of these proteins on BC risk. **Results** There were marginal high-order interactions among insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), C-reactive protein (CRP), resistin (RETN), soluble leptin receptor (sOB-R), and adiponectin (ADP) in premenopausal women (with the balanced accuracy for the testing set being 59.01%, cross-validation consistency being 10/10, and permutation test P=0.05). There were high-order interactions among leptin (LEP), sOB-R, ADP, CRP, IGFBP3 and visfatin (VF) in postmenopausal women (with the balanced accuracy for the testing set being 67.31%, cross-validation consistency being 10/10, and permutation test P=0.01). Along with an increase in the number of obesity-related proteins to which the subjects were exposed, the risk of developing breast cancer gradually increased in both pre- and postmenopausal women (OR_{pre}=2.18, 95% *CI*: 1.69-2.82; OR_{post}=2.41, 95% *CI*: 1.75-3.32). **Conclusions** This preliminary study suggested high-order interactions among obesity-related proteins on BC risk in both pre- and postmenopausal women. In future studies, close attention should be given to these potential interactions when these proteins are used jointly as predictors, as well as in developing a comprehensive risk scoring system for BC.

【Key words】 Breast cancer Obesity Obesity-related proteins Interaction

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研究显示，肥胖是女性乳腺癌的发病危险因素。肥胖可能通过促进雌激素分泌[1]、伴发胰岛素抵抗[2-3]、促进

脂肪因子及炎性因子分泌[4-6],即改变相关蛋白或激素的水平,从而影响乳腺癌的发生与进展。国内外开展了大量的研究以探讨肥胖相关蛋白与乳腺癌发病风险关联。但目前的研究大多仅独立分析单个指标的效应或简单将众多指标放入一个模型[7-8],未考虑到蛋白指标间复杂的生物学机制关联,从而忽略了在对乳腺癌发病影响中各蛋白指标间可能存在的交互作用。因此,本研究拟采用病例对照研究设计,初步探究不同绝经状态下,肥胖相关蛋白对女性乳腺癌发病影响上可能存在的交互作用,为提示未来相关乳腺癌预测研究关注蛋白间复杂关联提供真实有据的参考。

1 对象与方法

1.1 研究对象

乳腺癌组序贯收集2014年4月–2015年4月就诊于四川省肿瘤医院及四川大学华西医院经病理确诊的原发乳腺癌病例,排除转移性乳腺癌以及其他有精神或内分泌疾病的患者。对照组按照年龄频数匹配,序贯收集同期来源于四川省人民医院体检中心或成都市双流区农村乳腺癌筛查点的健康女性,排除有其他恶性肿瘤或精神、内分泌疾病的患者。本研究经四川大学华西公共卫生学院/四川大学华西第四医院伦理委员会批准(scuhx4h2013003),研究对象均签订知情同意书。

1.2 蛋白筛选

本研究基于目前较公认的4条肥胖与乳腺癌关联通路(雌激素通路、胰岛素抵抗通路、脂肪因子通路和炎症通路),通过文献循证筛选出对乳腺癌发病风险有阳性影响的蛋白。具体筛选标准及流程已在前期文章中详细介绍[9]。最终,本研究纳入了9种肥胖相关蛋白:雌激素通路的雌二醇(estradiol, E2);脂肪因子通路的瘦素(leptin, LEP)、可溶性瘦素受体(soluble leptin receptor, sOB-R)、脂联素(adiponectin, ADP)、抵抗素(resistin, RETN)、内脂素(visfatin, VF);炎性因子通路的C反应蛋白(C-reactive protein, CRP);以及胰岛素抵抗通路的胰岛素样生长因子1(insulin-like growth factor 1, IGF-1)、胰岛素样生长因子结合蛋白3(insulin-like growth factor binding protein 3, IGFBP-3)。由于雌激素与绝经前乳腺癌发病风险的关联尚不明确,且绝经前雌激素主要来自于卵巢而非脂肪组织[10],因此本研究仅在绝经后亚组中检测雌激素指标。

1.3 资料收集

采用统一编制的调查表收集研究对象的基本人口学特征、生殖生育史、生活行为方式、良性疾病史及肿瘤家族史,并在问卷调查现场测量对象的体质量、身高。采用医院的电子病历系统核实病例的确诊信息。

1.4 实验室检测

采用EDTA抗凝管采集研究对象空腹静脉血5 mL,病例采血时间在临床治疗之前。血液采集后4 h内,将全血离心,分离上层血浆并分装保存于–80 ℃冰箱内。采用酶联免疫吸附试验测定血浆中肥胖相关蛋白的水平。本次实验所需的试验试剂盒均购自武汉伊莱瑞特生物科技有限公司。

1.5 统计学方法

将研究对象按照绝经状态分层,采用多因素logistic回归筛选对乳腺癌发病风险有阳性影响的蛋白。以低风险的蛋白水平为非暴露水平,采用分层分析估计任意两阳性蛋白单独及协同暴露的效应值比值比(odds ratio, *OR*),筛选联合暴露效应高于单独暴露的蛋白,采用广义多因子降维法(generalized multifactor dimensionality reduction, GMDR)分析蛋白间高阶交互作用。最后,按照蛋白暴露数量将高阶交互变量进行组合,采用多因素logistic回归模型估计交互组合变量对乳腺癌发病风险的联合效应。

本研究分别分析了总LEP、游离LEP(FLI=LEP/sOB-R),以及总IGF1和游离IGF1(IGF-1/IGFBP3)与乳腺癌发生风险的关联,由于游离变量为原始变量的比值指标,为避免结果混淆,不再对游离LEP与sOB-R、游离IGF1与IGFBP3进行联合效应分析。并且在高阶交互作用分析时,比值指标一律以原指标纳入模型。本研究采用SAS 9.4软件进行统计学分析,双侧检验水准 α=0.05。

2 结果

2.1 绝经前后病例与对照组基本特征以及各蛋白水平的分布

本研究共纳入539例研究对象,其中绝经前316例,绝经后223例。绝经前亚组中,原发乳腺癌患者167例,对照149例,中位年龄均为44岁,平均体质指数(BMI)分别为(23.03±2.93) kg/m^2、(23.15 ±3.06) kg/m^2。绝经后亚组中,原发乳腺癌患者112例,对照111例,中位年龄分别为57.5、56岁,平均BMI分别为(23.26±2.70) kg/m^2、(23.78±2.94) kg/m^2。组间基本特征及各蛋白水平分布的差异检验结果见表1。

2.2 血浆肥胖相关蛋白对女性乳腺癌发生风险影响的主效应

logistic回归结果显示,血浆高水平的IGF-1、RETN、CRP,以及低水平的IGFBP3、sOB-R、ADP可增大绝经前女性乳腺癌发病风险(P<0.05);血浆低水平的IGFBP3、VF、sOB-R、ADP以及高水平的CRP、游离瘦素指数

表 1　绝经前后乳腺癌组与对照组基本特征以及各蛋白水平的分布与比较

Table 1　Characteristics of pre- and postmenopausal breast cancer cases and controls and the distribution of the obesity-related protein levels

Variable	Premenopausal (n=316)				Postmenopausal (n=223)			
	Breast cancer group (n=167)	Control group (n=149)	χ^2/Z	P	Breast cancer group (n=112)	Control group (n=111)	χ^2/Z	P
Age/yr., median (Q1, Q3)	44 (41, 47)	44 (41, 47)	−0.18	0.86	57.5 (53, 62)	56 (52, 62)	−1.18	0.24
Residence/case (%)			3.94	0.047			0.36	0.55
Urban	96 (57.49)	69 (46.31)			61 (54.46)	56 (50.45)		
Rural	71 (42.51)	80 (53.69)			51 (45.54)	55 (49.55)		
Occupation/case (%)			12.28	0.02			15.91	<0.01
Unemployed	40 (23.95)	23 (15.44)			15 (13.39)	25 (22.52)		
Government, enterprises, and public institutions	36 (21.56)	50 (33.56)			29 (25.89)	42 (37.84)		
Manufacturing worker	29 (17.37)	15 (10.07)			19 (16.96)	4 (3.60)		
Commercial services	44 (26.35)	36 (24.16)			15 (13.39)	10 (9.01)		
Agriculture	18 (10.78)	25 (16.78)			34 (30.36)	30 (27.03)		
Total annual household income/case (%)			1.71	0.43			8.53	0.01
<￥30 000	66 (39.52)	66 (44.30)			54 (48.21)	46 (41.44)		
￥30 000-50 000	45 (26.95)	31 (20.81)			33 (29.46)	21 (18.92)		
≥￥50 000	56 (33.53)	52 (34.90)			25 (22.32)	44 (39.64)		
Menarche age/yr., median (Q1, Q3)	13 (12, 14)	14 (13, 15)	1.98	0.047	15 (13, 16)	14 (13, 16)	−1.46	0.14
Number of live birth(s)/case (%)			<0.01	<0.01			<0.01	<0.01
0	3 (1.80)	4 (2.68)			4 (3.57)	1 (0.90)		
1	112 (67.07)	125 (83.89)			59 (52.68)	81 (72.97)		
2	47 (28.14)	19 (12.75)			34 (30.36)	23 (20.72)		
≥3	5 (2.99)	1 (0.67)			15 (13.39)	6 (5.41)		
Family history of cancer/case (%)			0.10	0.75			7.95	<0.01
No	139 (83.23)	122 (81.88)			85 (75.89)	100 (90.09)		
Yes	28 (16.77)	27 (18.12)			27 (24.11)	11 (9.91)		
BMI/(kg/m^2), $\bar{x}\pm s$	23.03±2.93	23.15±3.06	0.14	0.71	23.26±2.70	23.78±2.94	1.91	0.17
E2/(pg/mL), median (Q1, Q3)	–	–	–	–	10.95 (8.14, 13.11)	10.09 (6.40, 12.88)	−1.35	0.18
RETN/(μg/L), median (Q1, Q3)	20.00 (9.69, 40.42)	12.55 (4.97, 24.30)	−3.74	<0.01	53.21 (31.65, 103.78)	44.10 (24.45, 71.45)	−2.08	0.04
VF/(μg/L), median (Q1, Q3)	6.76 (3.59, 11.70)	7.72 (4.35, 12.92)	1.27	0.20	5.34 (2.92, 12.77)	6.77 (3.47, 15.02)	1.06	0.29
LEP/(μg/L), median (Q1, Q3)	8.34 (4.00, 14.11)	8.82 (4.68, 14.06)	0.78	0.44	7.98 (4.72, 12.54)	8.22 (4.38, 13.76)	0.05	0.96
sOB-R/(ng/mL), median (Q1, Q3)	24.55 (13.15, 38.80)	30.10 (19.48, 43.80)	2.55	0.01	22.49 (13.42, 34.81)	31.57 (18.40, 41.80)	2.39	0.02
FLI (median [Q1, Q3])	0.37 (0.23, 0.48)	0.30 (0.21, 0.41)	−2.71	<0.01	0.36 (0.23, 0.47)	0.27 (0.18, 0.36)	−3.19	<0.01
ADP/(μg/mL), median (Q1, Q3)	10.68 (7.21, 14.90)	13.83 (9.04, 17.66)	3.69	<0.01	12.01 (9.18, 16.61)	19.57 (10.07, 27.57)	4.71	<0.01
CRP/(mg/L), median (Q1, Q3)	2.51 (0.83, 7.02)	1.45 (0.61, 4.04)	−2.37	0.02	4.32 (1.72, 10.32)	1.98 (0.77, 5.93)	−3.08	<0.01
IGF-1/(ng/mL), median (Q1, Q3)	86.92 (60.67, 171.77)	99.51 (48.10, 199.69)	0.14	0.89	89.60 (60.59, 195.98)	128.91 (61.61, 257.98)	1.28	0.20
IGFBP3/(ng/mL), median (Q1, Q3)	277.45 (161.77, 481.44)	355.15 (230.81, 514.54)	2.42	0.02	316.88 (185.30, 464.73)	330.55 (232.19, 505.60)	1.41	0.16
IGF-1/IGFBP3 ratio (median [Q1, Q3])	0.34 (0.15, 0.83)	0.30 (0.13, 0.66)	−1.08	0.28	0.30 (0.16, 0.67)	0.36 (0.15, 0.80)	0.38	0.70

E2: estradiol; RETN: resistin; VF: visfatin; LEP: leptin; sOB-R: soluble leptin receptor; FLI: free leptin index, i.e., LEP/sOB-R ratio; ADP: adiponectin; CRP: C-reactive protein; IGF-1: insulin-like growth factor 1; IGFBP3: insulin-like growth factor binding protein 3.

(FLI)可增大绝经后女性乳腺癌发病风险(P<0.05)。见表2。

2.3　肥胖相关蛋白对乳腺癌发病影响中可能存在的交互作用

在绝经前亚组中，蛋白联合暴露效应结果提示，IGF-1、IGFBP3、CRP、RETN、sOB-R、ADP 6个蛋白指标在任意两两联合暴露时的风险均高于单暴露，在对乳腺癌发病的影响上可能存在联合作用。进一步的高阶交互作用

表 2 肥胖相关蛋白指标与乳腺癌发病风险关联

Table 2 The association between obesity-related proteins and the risk of breast cancer

Premenopausal (*n*=316)			Postmenopausal (*n*=223)		
Protein variable	Breast cancer cases/Controls	*OR* (95% *CI*)[a]	Protein variable	Breast cancer cases/Controls	*OR* (95% *CI*)[b]
E2			E2		
–	–	–	<10.09 pg/mL	47/57	1.00
–	–	–	⩾10.09 pg/mL	65/54	1.79 (0.98-3.26)
IGF-1*			IGF-1		
<48.10 ng/mL	23/37	1.00	<128.91 ng/mL	69/55	1.00
⩾48.10 ng/mL	144/112	2.38 (1.25-4.55)	⩾128.91 ng/mL	43/56	0.66 (0.37-1.19)
IGFBP3			IGFBP3*		
<355.15 ng/mL	105/74	1.00	<232.19 ng/mL	43/27	1.00
⩾355.15 ng/mL	62/75	0.58 (0.35-0.96)	⩾232.19 ng/mL	69/84	0.45 (0.23-0.86)
IGF-1/IGFBP3 ratio			IGF-1/IGFBP3 ratio		
<0.30	80/74	1.00	<0.36	61/56	1.00
⩾0.30	87/75	0.99 (0.76-1.28)	⩾0.36	51/55	0.94 (0.52-1.68)
VF			VF		
<7.72 ng/mL	92/74	1.00	<6.77 ng/mL	69/55	1.00
⩾7.72 ng/mL	75/75	0.81 (0.50-1.32)	⩾6.77 ng/mL	43/56	0.46 (0.25-0.84)
RETN*			RETN		
<4.97 ng/mL	19/36	1.00	<44.10 ng/mL	47/55	1.00
⩾4.97 ng/mL	148/113	3.30 (1.64-6.66)	⩾44.10 ng/mL	65/56	1.33 (0.63-2.78)
LEP			LEP		
<8.82 ng/mL	88/74	1.00	<8.22 ng/mL	60/55	1.00
⩾8.82 ng/mL	79/75	0.77 (0.47-1.26)	⩾8.22 ng/mL	52/56	0.70 (0.38-1.29)
sOB-R*			sOB-R		
<19.48 ng/mL	67/37	1.00	<31.57 ng/mL	77/55	1.00
⩾19.48 ng/mL	100/112	0.39 (0.23-0.67)	⩾31.57 ng/mL	35/56	0.39 (0.21-0.75)
FLI			FLI		
<0.30	63/75	1.00	<0.27	34/56	1.00
⩾0.30	104/74	1.42 (0.86-2.33]	⩾0.27	78/55	2.30 (1.21-4.37)
ADP			ADP		
<13.83 μg/mL	111/74	1.00	<19.57 μg/mL	96/55	1.00
⩾13.83 μg/mL	56/75	0.47 (0.28-0.78)	⩾19.57 μg/mL	16/56	0.14 (0.06-0.29)
CRP			CRP		
<1.45 mg/L	61/74	1.00	<1.98 mg/L	36/55	1.00
⩾1.45 mg/L	106/75	1.65 (1.01-2.70)	⩾1.98 mg/L	76/56	2.16 (1.17-3.98)

The abbreviations are explained in the note to Table 1. [a] Adjusted for residence, occupation, menarche age, and number of live birth(s); [b] adjusted for occupation, total annual household income, number of live birth(s), and family history of cancer; * The variables are classified according to the lower quartile of the control, and the rest is classified according to the median of the control.

分析结果显示，IGF-1、IGFBP3、CRP、RETN、sOB-R、ADP间存在边际高阶交互作用(测试集平衡检验准确度为59.01%，交叉验证一致性为10/10，置换检验P=0.05)，见表3。

在绝经后亚组中，蛋白联合暴露效应结果提示，FLI、sOB-R、ADP、CRP、IGFBP3、VF 6个蛋白指标在任意两两联合暴露时的风险均高于单暴露。采用LEP代替FLI纳入高阶交互作用分析，结果显示，LEP、sOB-R、ADP、CRP、IGFBP3、VF间存在高阶交互作用(测试集平衡检验准确度67.31%，交叉验证一致性10/10，置换检验P=0.01)，见表3。

2.4 具有交互作用的肥胖相关蛋白对乳腺癌发病风险的联合影响

由表4可见，绝经前后亚组中，与低暴露组(蛋白暴露数目⩽3)相比，暴露蛋白数>3的女性乳腺癌发病风险更高($OR_{绝经前}$=3.86, 95%CI: 2.29~6.52, $OR_{绝经后}$=3.20, 95%CI:

表 3　GMDR模型构建的最佳交互作用组合

Table 3　The best interaction models obtained by GMDR

Best model	Testing accuracy/%	Prediction accuracy/%	*P* for sign test	Cross validation
Premenopausal (*n*=316)[a]				
IGFBP3, ADP	62.25	57.06	0.17	8/10
sOB-R, RETN, CRP	63.66	56.43	0.17	4/10
sOB-R, RETN, CRP, ADP	66.12	56.34	0.17	5/10
sOB-R, RETN, CRP, ADP, IGF1	68.10	55.69	0.01	5/10
sOB-R, RETN, CRP, ADP, IGF1, IGFBP3	69.83	59.01	0.05	10/10
Postmenopausal (*n*=223)[b]				
sOB-R, ADP	70.70	64.84	0.001	8/10
sOB-R, ADP, CRP	73.19	67.56	0.01	7/10
sOB-R, ADP, LEP, IGFBP3	74.12	64.99	0.001	3/10
sOB-R, ADP, LEP, IGFBP3,VF	76.11	66.43	0.001	6/10
sOB-R, ADP, LEP, IGFBP3,VF,CRP	77.48	67.31	0.01	10/10

The abbreviations are explained in the note to Table 1. [a] Adjusted for residence, occupation, menarche age, and number of live birth(s); [b] adjusted for occupation, total annual household income, number of live birth(s), and family history of cancer.

表 4　GMDR发现的交互项对乳腺癌发生风险的效应估计

Table 4　Estimated effects of obesity-related proteins with interactive effect identified by GMDR on the risk of breast cancer

Number of exposure proteins	Premenopausal (*n*=316)		Postmenopausal (n=223)	
	Breast cancer cases/controls	*OR* (95% *CI*)[a]	Breast cancercases/controls	*OR* (95% *CI*)[b]
⩽3	48/86	1.00	53/79	1.00
>3	119/63	3.86 (2.29-6.52)	59/32	3.20 (1.69-6.06)
Per 1 exposure protein		2.18 (1.69-2.82)		2.41 (1.75-3.32)

[a] Adjusted for residence, occupation, menarche age, and number of live birth(s) for premenopausal models; [b] adjusted for occupation, total annual household income, number of live birth(s), and family history of cancer for postmenopausal models.

1.69~6.06)。并且每增加一种蛋白暴露,绝经前后乳腺癌发病风险分别增加118%和 141%($OR_{绝经前}$=2.18, 95%*CI*: 1.69~2.82, $OR_{绝经后}$=2.41, 95%*CI*: 1.75~3.32)。

3　讨论

本研究基于回顾性病例对照设计,广泛探究不同绝经状态下肥胖相关蛋白对乳腺癌发病影响上可能存在的交互作用。结果显示,绝经前亚组中,IGF-1、IGFBP3、CRP、RETN、sOB-R、ADP存在边际高阶交互作用,绝经后亚组中,LEP、sOB-R、ADP、CRP、IGFBP3、VF存在高阶交互作用。

既往研究提示,本研究关注的蛋白间存在以下生物学关联,可能致使其表现出统计学交互作用: ①影响彼此表达水平,如ADP与CRP[10]; ②影响信号转导或生理效应,如CRP与LEP[11], ADP与LEP[12], 以及 IGF-1与ADP[13]; ③诱导蛋白受体磷酸化,如LEP与IGF-1[14]。此外,sOB-R和IGFBP3分别是LEP和IGF-1的主要结合蛋白,可以通过LEP和IGF-1的生物学活性来影响他们与其他蛋白的生物学关联。另外,本研究所关注的肥胖相关蛋白存在部分相同的信号转导通路,也可能导致其生物学关联。CHRISTODOULATOS等[15]的综述总结了脂肪因子与乳腺癌关联的潜在机制,结果显示,LEP、ADP、VF均可作用于JAK、STAT3信号通路,LEP、VF、RETN均可作用于PI3K、Akt、MAPK、ERK信号通路,ADP与RETN均可作用于NF-κB通路的信号转导,LEP与ADP均可作用于AMPK途径的信号转导。此外,胰岛素通路的IGF-1与细胞表面的受体特异性结合后,也可激活PI3K/Akt以及MAPK信号通路,促进肿瘤细胞的增殖[16]。炎症通路的CRP可通过ERK信号通路促进MMP-9表达,从而促进乳腺肿瘤的侵袭[17],也可通过激活MEK/ERK和PI3K/AKT信号通路刺激癌细胞迁移和侵袭[18]。

本研究在探究交互作用的蛋白对乳腺癌发病风险的联合影响时,观察到了明显的剂量反应关系,提示不能只关注某一种蛋白,而应该从整体角度关注肥胖相关蛋白的风险。未来的研究应该发展综合的评估方法,比如建立综合的蛋白评分系统[19]以充分反映肥胖相关蛋白对乳

腺癌发生风险的联合影响。

本研究首次从人群流行病学角度出发，基于对四大肥胖-乳腺癌病因链上的蛋白开展文献循证，共纳入九种蛋白，较为全面地呈现了肥胖相关蛋白指标在乳腺癌发病影响上的交互作用，为提示未来乳腺癌风险预测研究应关注蛋白间复杂的关联提供了真实有据的参考。同时，本研究基于联合效应分析结果筛选进入高阶交互作用分析的蛋白，避免盲目将所有蛋白纳入高阶交互作用模型造成结果不易解释。虽然本研究属于回顾性病例对照研究，病例的血样采集在诊断之后，但本研究纳入的蛋白基本均基于前瞻性研究证据。本研究基于回顾性的样本及资料开展探究，样本量有限，可能会影响交互作用分析的检验效能，未来仍需要大样本前瞻性研究的证据。但通过小样本的初探，仍然发现肥胖相关蛋白对乳腺癌发生影响中存在高阶交互作用，可见肥胖相关蛋白间存在的复杂生物学关联对乳腺癌风险效应评估造成的影响不可忽视。未来的研究应重视蛋白间交互作用的存在，并采用合理的方法评估蛋白对乳腺癌发病风险的联合效应。

* * *

利益冲突 所有作者均声明不存在利益冲突

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