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牛瑞洁, 曾军, 李宙童, 汪成, 蒋金全

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·短篇论著·

心血管疾病危险因素与乳腺癌之间的相关性分析

牛瑞洁[1]，曾 军[2*]，李宙童[2]，汪 成[1]，蒋金全[2]
1. 上海交通大学医学院附属第九人民医院黄浦分院乳腺外科, 上海 200011
2. 上海交通大学医学院附属第九人民医院黄浦分院心内科, 上海 200011

［摘要］ **目的** 探讨心血管疾病危险因素与乳腺癌之间的相关性。**方法** 连续选择2023年1月至2023年6月在上海交通大学医学院附属第九人民医院黄浦分院乳腺外科就诊并接受手术的300例确诊为乳腺癌和300例确诊为乳腺良性疾病的患者。比较两组患者相关心血管疾病危险因素。按照绝经与否进行分层，比较两组不同月经状态患者相关心血管疾病危险因素。采用logistic回归分析乳腺癌相关心血管疾病危险因素。**结果** 两组患者临床及实验室指标差异均有统计学意义（$P<0.01$）。多因素logistic回归分析显示，年龄（OR=1.03, $P=0.029$）、三酰甘油（TG；OR=1.94，$P=0.025$）、C反应蛋白（OR=2.73, $P<0.001$）、D-二聚体（OR=61.19, $P<0.001$）和同型半胱氨酸（OR=2.10，$P<0.001$）是乳腺癌发生独立相关因素。分层分析结果显示，绝经前及绝经后，年龄、TG、C反应蛋白、D-二聚体和同型半胱氨酸均与乳腺癌发生独立相关（$P<0.05$）。**结论** 心血管疾病危险因素中，年龄增加，TG、C反应蛋白、D-二聚体和同型半胱氨酸水平升高可能导致乳腺癌发生风险增加，有助于筛查乳腺癌高危患者。

［关键词］ 乳腺癌；心血管疾病；肿瘤心脏病学；危险因素
［中图分类号］ R 737.9 ［文献标志码］ A

Analysis of associations between risk factors for cardiovascular disease and breast cancer

NIU Ruijie[1], ZENG Jun[2*], LI Zhoutong[2], WANG Cheng[1], JIANG Jinquan[2]
1. Department of Breast Surgery, Huangpu Branch, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China
2. Department of Cardiology, Huangpu Branch, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

［**Abstract**］ **Objective** To explore the associations between risk factors for cardiovascular disease and breast cancer. **Methods** A total of 300 patients with breast cancer and 300 with benign breast diseases diagnosed by postoperative pathology were included in the Department of Breast Surgery, Huangpu Branch of the Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine from January 2023 to June 2023. The main cardiovascular risk factors in patients between the two groups were compared. Stratification was performed according to menstrual status, and the main cardiovascular risk factors in patients with different menstrual status between the two groups were compared. The logistic regression correlation analysis was used to analyze the risk factors related to cardiovascular disease for breast cancer. **Results** There were statistically significant differences in clinical data and laboratory indicators between the two groups ($P<0.01$) . Multivariate logistic regression analysis showed that age (OR=1.03, $P=0.029$), triglyceride (TG; OR=1.94, $P=0.025$), C-reactive protein (CRP; OR=2.73, $P<0.001$), D-dimer (OR=61.19, $P<0.001$), and homocysteine (Hcy; OR=2.10, $P<0.001$) were independently associated with breast cancer. The stratified analysis showed age, TG, CRP, D-dimer, and Hcy were independently associated with breast cancer in both premenopausal and postmenopausal patients ($P<0.05$). **Conclusions** Among risk factors for cardiovascular disease, advanced age, increased TG, CRP, D-dimer, and Hcy might increase breast cancer risk, which are helpful of screening high-risk individuals for breast cancer.

［**Key Words**］ breast cancer; cardiovascular disease; cardio-oncology; risk factor

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［作者简介］ 牛瑞洁，硕士，主治医师. E-mail：twinkleniu@163.com
*通信作者 (Corresponding author). Tel: 021-23308990，E-mail：zengjun76@163.com

乳腺癌是女性癌症死亡的第一大原因。2020年乳腺癌新确诊患者估计226万例，女性乳腺癌死亡68万例，分别占女性癌症新确诊人数的24.5%和女性癌症死亡人数的15.5%[1]。以手术为主的综合治疗（化疗、靶向治疗、内分泌治疗、免疫治疗及放疗等）显著延长了乳腺癌患者生存期。然而，各种抗肿瘤治疗均可导致或加重心血管疾病（cardiovascular disease，CVD）[2]。乳腺癌合并CVD患者死亡率常高于同分类同分期单一乳腺癌患者，两种疾病之间可能存在直接联系[3]。因此，早期筛选出乳腺癌合并CVD危险因素的高危人群并及时进行干预是提高这类患者生存率的关键。

乳腺癌危险因素很多，发病机制仍未明确，目前针对乳腺癌的一级预防措施也有限。而CVD的发病因素和预防措施更确切。美国心脏协会（AHA）心血管健康评估指南[4]指出，体质量指数、胆固醇、血糖、血压为CVD相关因素。C反应蛋白（CRP）[5]、D-二聚体[6]、同型半胱氨酸（Hcy）[7]等也与CVD发生显著相关。目前，降脂药物已成为预防动脉粥样硬化性CVD（ASCVD）的主要手段[8]。肥胖也是影响CVD发生以及预后的重要因素[9]。

上述CVD危险因素易监测和预防。本研究探讨这些因素与乳腺癌发病的相关性，希望发现这2种疾病交叉危险因素，为建立早期乳腺癌并发CVD风险预测模式和分级筛查策略，有效延缓或避免同时罹患这2种疾病提供参考。

1　资料与方法

1.1　一般资料　连续选择2023年1月至2023年6月于上海交通大学医学院附属第九人民医院黄浦分院乳腺外科住院并接受手术的女性患者，根据术后病理诊断结果，纳入300例乳腺癌和300例乳腺良性疾病患者。排除标准：（1）缺乏病理诊断；（2）乳腺炎患者；（3）再次入院患者。

1.2　资料收集　通过我院电子病例系统和检验系统收集患者的相关指标。（1）临床指标：年龄、身高、体质量、合并症（高血压、糖尿病）；（2）实验室指标：空腹血糖（FPG）、三酰甘油（TG）、总胆固醇（TC）、低密度脂蛋白胆固醇（LDL-C)、高密度脂蛋白胆固醇（HDL-C）、CRP、D-二聚体、Hcy；（3）病理结果。

1.3　统计学处理　采用R 4.3.0进行统计分析，计数资料以n(%)表示，组间比较采用χ^2检验。对计量资料进行正态检验，符合正态分布时以$\bar{x}\pm s$表示，组间比较采用t检验；不符合正态分布时以$M(P_{25}, P_{75})$表示，组间比较采用非参数检验。筛选单因素分析中差异有统计学意义的指标，进行多因素logistic回归分析。进一步根据患者绝经与否，进行分层分析。检验水准（α）为0.05。

2　结　果

2.1　两组患者的一般临床特征比较　结果（表1）显示，乳腺癌组和乳腺良性病变组年龄、合并症、FPG、血脂、CRP、D-二聚体、Hcy差异均有统计学意义（P<0.01）。

表1　两组患者临床、实验室指标比较

Table 1　Comparison of clinical and laboratorial indices between the two groups

n=300

Index	Breast cancer group	Benign breast disease group	P
Age/year	61.0(51.00, 67.00)	42.00(35.00, 52.00)	<0.001
Diabetes n(%)	37(12.3)	7(2.3)	<0.001
Hypertension n(%)	135(45.0)	39(13.1)	<0.001
BMI/(kg•m^{-2})	23.5(21.48, 26.04)	21.60(19.99, 23.35)	<0.001
FPG/(mmol•L^{-1})	5.19(4.70, 5.86)	4.68(4.31, 5.10)	<0.001
TG/(mmol•L^{-1})	1.44(1.03, 1.95)	1.03(0.74, 1.28)	<0.001
TC/(mmol•L^{-1})	5.10(4.40, 5.70)	4.50(4.00, 5.10)	<0.001
LDL-C/(mmol•L^{-1})	2.95(2.38, 3.58)	2.34(1.98, 2.84)	<0.001

Continued table 1

Index	Breast cancer group	Benign breast disease group	*P*
HDL-C/(mmol•L^{-1})	1.32(1.03, 1.55)	1.40(1.14, 1.61)	0.006
CRP/(mg•L^{-1})	1.02(0.5, 3.54)	0.50(0.0, 0.58)	＜0.001
D-dimer/(mg•L^{-1})	0.49(0.29, 0.82)	0.19(0.14, 0.29)	＜0.001
Hcy/(μmol•L^{-1})	9.10(7.60, 11.0)	6.05(4.90, 7.10)	＜0.001

BMI: body mass index; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; Hcy: homocysteine.

2.2 乳腺癌相关 CVD 危险因素 将上述指标纳入 logistic 回归分析，结果（表 2）显示：上述指标均与乳腺癌相关，其中年龄、TG、CRP、D-二聚体和 Hcy 为乳腺癌独立相关因素（*P*＜0.05）。

表 2 心血管疾病危险因素与乳腺癌关系的 logistic 回归分析

Table 2 Logistic regression analysis of associations between cardiovascular risk factors and breast cancer

Variable	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P*	OR(95%CI)	*P*
Age	1.10(1.08-1.12)	＜0.001	1.03(1.00-1.06)	0.029
Diabetes	5.89(2.58-13.43)	＜0.001	1.48(0.31-6.94)	0.622
Hypertension	5.48(3.65-8.22)	＜0.001	1.01(0.46-2.25)	0.972
BMI	1.25(1.17-1.32)	＜0.001	0.30(0.06-1.61)	0.162
FPG	2.82(2.16-3.68)	＜0.001	1.36(0.86-2.17)	0.187
TG	2.77(2.07-3.69)	＜0.001	1.94(1.08-3.46)	0.025
TC	2.15(1.75-2.63)	＜0.001	0.96(0.42-2.22)	0.927
LDL-C	2.19(1.76-2.72)	＜0.001	1.70(0.73-3.97)	0.216
HDL-C	0.60(0.39-0.92)	0.021	2.19(0.68-7.07)	0.189
CRP	3.48(2.52-4.79)	＜0.001	2.73(1.74-4.28)	＜0.001
D-dimer	371.80(117.33-1 178.17)	＜0.001	61.19(13.97-267.99)	＜0.001
Hcy	2.19(1.91-2.51)	＜0.001	2.10(1.74-2.53)	＜0.001

BMI: body mass index; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; Hcy: homocysteine.

2.3 基于月经状态分析乳腺癌相关 CVD 危险因素 结果（表 3、表 4）显示：绝经前，除糖尿病患者比例及 HDL-C 水平外，乳腺癌组和乳腺良性病变组其他指标差异均有统计学意义（*P*＜0.05）；绝经后，除 HDL-C 水平外，乳腺癌组和乳腺良性病变组其他指标差异均有统计学意义（*P*＜0.05）。将组间差异有统计学意义及有临床意义的指标纳入 logistic 回归分析，结果（表 5、表 6）显示：绝经前，年龄、TG、CRP、D-二聚体和 Hcy 为乳腺癌独立相关因素（*P*＜0.05）；绝经后，除高血压患者比例、HDL-C 水平外，其他指标均为乳腺癌独立相关因素（*P*＜0.05）。

表 3 两组绝经前患者临床、实验室指标比较

Table 3 Comparison of clinical and laboratorial indices in premenopausal patients between the two groups

Index	Breast cancer group (*n*=65)	Benign breast disease group (*n*=204)	*P*
Age/year	42.4±5.8	37.6±7.4	＜0.001
Diabetes *n*(%)	1(1.5)	1(0.5)	0.978
Hypertension *n*(%)	8(12.3)	9(4.4)	0.047
BMI/(kg•m^{-2})	23.5±3.2	21.5±2.7	＜0.001
FPG/(mmol•L^{-1})	5.0±1.3	4.7±0.5	0.011

Continued table 3

Index	Breast cancer group (*n*=65)	Benign breast disease group (*n*=204)	*P*
TG/(mmol•L^{-1})	1.6±1.5	1.1±0.5	0.001
TC/(mmol•L^{-1})	4.9±1.3	4.5±0.7	0.004
LDL-C/(mmol•L^{-1})	2.8±0.8	2.4±0.7	＜0.001
HDL-C/(mmol•L^{-1})	1.4±0.4	1.4±0.4	0.327
CRP/(mg•L^{-1})	1.7±2.0	0.5±0.6	＜0.001
D-dimer/(mg•L^{-1})	0.6±0.7	0.2±0.1	＜0.001
Hcy/(μmol•L^{-1})	9.3±3.5	5.6±2.0	＜0.001

BMI: body mass index; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; Hcy: homocysteine.

表 4 两组绝经后患者临床、实验室指标比较

Table 4 Comparison of clinical and laboratorial indices in postmenopausal patients between the two groups

Index	Breast cancer group (*n*=235)	Benign breast disease group (*n*=96)	*P*
Age/year	64.2±8.0	59.1±7.4	＜0.001
Diabetes *n*(%)	36(15.3)	6(6.2)	0.039
hypertension *n*(%)	127(54.0)	30(31.2)	＜0.001
BMI/(kg•m^{-2})	24.2±3.9	22.9±2.6	0.001
FPG/(mmol•L^{-1})	5.7±1.5	5.0±0.8	＜0.001
TG/(mmol•L^{-1})	1.8±1.3	1.2±0.5	＜0.001
TC/(mmol•L^{-1})	5.2±1.0	4.7±0.9	＜0.001
LDL-C/(mmol•L^{-1})	3.0±0.9	2.6±0.8	＜0.001
HDL-C/(mmol•L^{-1})	1.3±0.4	1.3±0.3	0.525
CRP/(mg•L^{-1})	3.8±8.1	0.6±0.6	＜0.001
D-dimer/(mg•L^{-1})	0.8 ±1.1	0.3±0.2	＜0.001
Hcy/(μmol•L^{-1})	9.7±3.1	6.3±2.0	＜0.001

BMI: body mass index; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; Hcy: homocysteine.

表 5 Logistic 回归分析绝经前心血管疾病危险因素与乳腺癌的相关性

Table 5 Logistic regression analysis of associations between risk factors for cardiovascular disease and breast cancer in premenopausal patients

Variable	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P*	OR(95%CI)	*P*
Age	1.12(1.06-1.17)	＜0.001	1.09(1.01-1.18)	0.024
Diabetes	3.04(1.12-8.24)	0.029	0.85(0.10-7.42)	0.884
Hypertension	3.17(0.20-51.44)	0.417		
BMI	1.26(1.14-1.39)	＜0.001	1.19(0.81-1.76)	0.373
FPG	1.90(1.15-3.14)	0.012	1.14(0.60-2.14)	0.689
TG	2.20(1.37-3.54)	0.001	2.15(1.02-4.53)	0.044
TC	1.69(1.20-2.39)	0.003	0.90(0.33-2.41)	0.828
LDL-C	2.14(1.44-3.18)	＜0.001	1.73(0.56-5.31)	0.340
HDL-C	0.72(0.34-1.53)	0.395		
CRP	2.84(1.92-4.20)	＜0.001	3.48(1.71-7.07)	＜0.001
D-dimer	299.82(51.23-1 754.73)	＜0.001	51.52(4.94-537.64)	0.001
Hcy	1.98(1.66-2.37)	＜0.001	2.45(1.75-3.43)	＜0.001

BMI: body mass index; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; Hcy: homocysteine.

表 6 Logistic 回归分析绝经后心血管疾病危险因素与乳腺癌的相关性

Table 6 Logistic regression analysis of associations between risk factors for cardiovascular disease and breast cancer in postmenopausal patients

Variable	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P*	OR(95%CI)	*P*
Age	1.09(1.06-1.13)	＜0.001	1.12(1.06-1.17)	＜0.001
Diabetes	2.59(1.57-4.27)	＜0.001	3.04(1.12-8.24)	0.029
Hypertension	2.71(1.10-6.67)	0.03	3.17(0.20-51.44)	0.417
BMI	1.12(1.04-1.21)	0.004	1.26(1.14-1.39)	＜0.001
FPG	2.08(1.49-2.91)	＜0.001	1.90(1.15-3.14)	0.012
TG	2.35(1.56-3.54)	＜0.001	2.20(1.37-3.54)	0.001
TC	1.91(1.45-2.52)	＜0.001	1.69(1.20-2.39)	0.003
LDL-C	1.77(1.32-2.37)	＜0.001	2.14(1.44-3.18)	＜0.001
HDL-C	0.82(0.43-1.57)	0.556	0.72(0.34-1.53)	0.395
CRP	3.59(2.10-6.15)	＜0.001	2.84(1.92-4.20)	＜0.001
D-dimer	182.73(35.30-945.98)	＜0.001	202.28(21.08-1 940.80)	＜0.001
Hcy	2.23(1.77-2.81)	＜0.001	2.01(1.58-2.56)	＜0.001

HT: hypertension; BMI: body mass index; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; Hcy: homocysteine.

3 讨 论

我国女性乳腺癌发病率有明显的年龄和地域分布特点：在城市地区，2013 至 2017 年，年龄标准化发病率在 45～49 岁年龄组开始升高，在 60～64 岁年龄组达峰值；在农村地区，乳腺癌发病年龄集中于 45～49 岁和 60～64 岁[10]。CVD 年龄分布特点：女性总体患病率随年龄增加而升高，在 45 岁后发生率升高明显，65 岁后升高加快，在 95 岁及以上年龄组达峰值[11]。两种疾病流行病学特征显示，45～65 岁年龄段人群同时发生两种疾病的可能性更高，是实施两种疾病“共病筛查”须重点关注的高危人群。本研究显示，乳腺癌组与乳腺良性病变组年龄差异有统计学意义（*P*＜0.001），年龄与乳腺癌独立相关（*P*＜0.05）。

炎症是动脉粥样硬化发病机制的核心[12]，而 CRP 是反映全身性炎症负担的重要生物标志物之一。已有大量研究[5, 13-14]证实，CRP 对心血管事件有很强的预测价值。CRP 对恶性肿瘤也有预测价值[15]。有临床研究[16-17]显示，血清 CRP 水平升高与乳腺癌易感性增强有关。本研究显示，两组 CRP 差异有统计学意义（*P*＜0.001），CRP 与乳腺癌独立相关（*P*＜0.001）。目前尚缺乏 CRP 导致 CVD 与乳腺癌的直接证据，可能与以下机制有关：肿瘤遗传学改变（如癌基因的激活和抑癌基因的失活）既诱导肿瘤形成，又促进各种细胞因子和趋化因子产生，从而产生炎症微环境[18]；肿瘤细胞将炎症细胞招募到肿瘤微环境中，刺激肿瘤生长并导致更差的预后[19-20]；体外实验[21]表明，CRP 可以激活整合素 α2 信号通路，促进乳腺癌和三阴性乳腺癌细胞的生长、黏附和侵袭。

D-二聚体为评估血栓形成和纤维蛋白溶解程度的标志物，升高提示机体处于高凝状态，而高凝状态与 CVD 的发生密切相关[22]。肿瘤细胞可以直接激活凝血反应，导致血栓形成，并促进血管内皮细胞、血小板、单核细胞和白细胞噬菌体的促凝特性，抑制其抗凝特性[23]。D-二聚体增加在肿瘤患者中常见。Lu 等[22]对 15 项 D-二聚体与乳腺癌发病关系的研究进行了荟萃分析，共纳入 1 244 例乳腺癌患者，结果显示，与良性对照组和健康对照组相比，乳腺癌组的 D-二聚体水平较高，且升高与乳腺癌的孕激素受体（PR）表达、TNM 分期和转移有关。本研究结果与荟萃分析相似。

Hcy 是一种含巯基的非必需氨基酸，产生于甲硫氨酸和半胱氨酸相互转化过程。Hcy 代谢需要叶酸参与，乳腺癌细胞扩增情况下需要消耗大量的叶酸，导致 Hcy 代谢减慢而在血液中蓄积[24]。Hcy 通过炎症、脂质过氧化和血小板活化等多种机制在内皮功能障碍、动脉粥样硬化和血栓形成中发挥关键作用[25-26]。另有研究[27]显示，Hcy 代谢相关基因突变和多态性与乳腺癌的发生有关。本

研究中，Hcy 是乳腺癌发生的独立相关因素（$P<0.001$）。Hcy 影响肿瘤细胞生长和增殖的机制，以及乳腺癌和 CVD 之间 Hcy 代谢存在的共同分子途径和内在联系有待进一步研究。

本研究中，绝经前、后人群中，年龄、TG、CRP、D-二聚体及 Hcy 均与乳腺癌独立相关。本研究中，BMI 仅与绝经后乳腺癌独立相关，可能与以下因素有关：（1）超重和肥胖的绝经后女性脂肪中雄烯二酮和睾酮向雌激素的转化增加，导致雌激素水平升高[28-29]；（2）肥胖妇女体内脂肪组织较多导致内源性雌激素合成增加[30]；（3）与正常体质量人群相比，超重和肥胖人群的瘦素水平更高[31]，而瘦素会增加雌激素水平[32]。

综上所述，本研究显示，乳腺癌与 CVD 存在交叉因素，其中年龄增加，TG、CRP、D-二聚体和 Hcy 水平升高是乳腺癌发生独立危险因素，提示这两种疾病在激素代谢、脂质代谢、炎症、凝血、Hcy 代谢等方面存在共同的分子途径。这些共同分子途径介导乳腺癌与 CVD 之间相互影响。通过联合多中心进行更大样本量的前瞻性队列研究等可验证本研究结论。在目前全球女性乳腺癌与 CVD 发病率持续上升的趋势下，针对 CVD 危险因素进行乳腺癌的易感性分析有重要意义。

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