

doi: 10.3978/j.issn.2095-6959.2021.11.020

View this article at: <https://dx.doi.org/10.3978/j.issn.2095-6959.2021.11.020>

血清三酰甘油、胆固醇与绝经前女性乳腺癌的相关性

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[摘要] 目的: 回顾性研究血清三酰甘油(triglyceride, TG)、胆固醇(total cholesterol, TC)水平与绝经前女性乳腺癌的相关性。方法: 比较2016年1月至2018年12月105例绝经前健康体检女性与105例绝经前乳腺癌患者的血清TG、TC差异。根据TC水平将研究对象由低到高排序, 根据四分位数分为4组, 采用logistic回归分析比较4组不同TC水平下乳腺癌发病率的风险比(odds ratio, OR), 分析血清TC水平与绝经前乳腺癌发病之间的相关性。绘制受试者工作特征(receiver operating characteristic, ROC)曲线, 计算曲线下面积(area under curve, AUC), 评价血清TC水平预测绝经前乳腺癌发生风险的敏感性和特异性。结果: 绝经前2组的TG水平相比, 差异无统计学意义($P>0.05$), 而绝经前乳腺癌组的TC水平低于健康对照组, 差异有统计学意义($P<0.05$)。血清TG、TC水平在绝经前与乳腺癌不同肿块大小、淋巴结状态、TNM分期、分子分型方面的差异均无统计学意义(均 $P>0.05$)。随着TC水平的下降, 绝经前女性乳腺癌的发病率逐渐升高($P=0.023$), 其中低胆固醇组($2.89\sim 4.09$ mmol/mL)相对于高胆固醇组($5.20\sim 7.04$ mmol/mL)乳腺癌发病率的OR值为2.087 (95%CI: 0.957~4.549, $P=0.064$)。ROC分析发现血清TC水平预测绝经前乳腺癌的敏感性为65.7%, 特异性为61.4%, AUC为0.59($P=0.033$)。结论: 血清TC水平与绝经前女性乳腺癌的发生呈负相关, 对乳腺癌的诊断价值处于中等水平。血清TC水平变化可以作为预测绝经前乳腺癌发病风险的标志物之一。

[关键词] 胆固醇; 三酰甘油; 乳腺癌; 绝经前

Correlation between serum triglyceride, cholesterol and breast cancer in premenopausal women

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Abstract **Objective:** To study the correlation between serum triglyceride (TG), total cholesterol (TC) levels and the risk of breast cancer in premenopausal women. **Methods:** A total of 105 premenopausal breast cancer patients and

收稿日期 (Date of reception): 2021-06-07

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基金项目 (Foundation item): 江苏省自然科学基金 (Bk20161120); 江苏省青年医学人才项目 (QNRC2016102); 江苏省妇幼保健研究项目 (201628)。This work was supported by the Natural Science Foundation of Jiangsu Province (Bk20161120), the Young Medical Talents Project of Jiangsu Province (QNRC2016102), and the Maternal and Child Health Research Project of Jiangsu Province (201628), China.

105 premenopausal healthy women were recruited (2016/1 to 2018/12). The differences of serum TG and TC were compared between the breast cancer patients and the healthy women. All research subjects were ranked from low to high according to TC level, and divided into 4 groups according to quartile. Logistic regression was used to compare the odds ratio (OR) of the incidence of breast cancer at different TC levels in the 4 groups, and to analyze the correlation between serum TC levels and the incidence of premenopausal breast cancer. ROC curve was drawn and the area under the curve was calculated to evaluate the sensitivity and specificity of TC levels in predicting the risk of pre-menopausal breast cancer. **Results:** There was no significant difference in TG between premenopausal breast cancer group and healthy control group, but the TC of breast cancer group was lower than that of healthy control group, the difference was statistically significant ($P < 0.05$). There was no significant difference in the serum TG and TC among different tumor size, lymph node status, TNM stage, and molecular classification of breast cancer ($P > 0.05$). The incidence of breast cancer increased with the decreasing of the serum TC levels in pre-menopausal women ($P = 0.023$). The OR of the incidence of breast cancer in the lower cholesterol group ($2.89 - < 4.09$ mmol/mL) compared to the higher cholesterol group ($5.20 - 7.04$ mmol/mL) was 2.087 (95%CI: 0.957-4.549, $P = 0.064$). ROC analysis showed that the sensitivity and specificity of serum TC level in predicting premenopausal breast cancer were 65.7% and 61.4%, and the AUC value of the area under ROC curve was 0.59 ($P = 0.033$). **Conclusion:** Serum TC level is negatively correlated with the occurrence of breast cancer in pre-menopausal women, and its diagnostic value for breast cancer is at the medium level. TC level can be used as one of the markers to predict the risk of premenopausal breast cancer.

Keywords cholesterol; triglycerides; breast cancer; pre-menopause

乳腺癌是女性发病率第1的恶性肿瘤^[1], 严重危害女性健康。我国乳腺癌发病率呈明显上升趋势, 且日渐年轻化, 绝经前乳腺癌更容易复发, 预后差^[2]。研究^[2-4]表明: 乳腺癌的发生与肥胖、饮食习惯密切相关。三酰甘油(triglyceride, TG)和总胆固醇(total cholesterol, TC)是受饮食、体重等影响较为明显的血液学指标, 与乳腺癌发生的关系目前仍不明确^[5]。本研究主要对绝经前乳腺癌患者与健康女性的三酰甘油、TC水平进行回顾性研究, 分析绝经前乳腺癌患者血脂水平的特点, 探讨血清TG、TC水平与绝经前女性乳腺癌发病风险之间的相关性。

1 对象与方法

1.1 对象

选取2016年1月至2018年12月在南京市妇幼保健院进行体检的绝经前健康女性105例和进行手术治疗的乳腺癌病例105例作为研究对象。纳入标准: 1)健康体检者及乳腺癌患者均为绝经前女性(根据询问月经史); 2)乳腺癌患者经手术后病理确诊, 且有完整病理资料; 3)乳腺癌患者确诊前1周内清晨空腹抽血检测TG、TC。排除标准: 1)有代谢性及内分泌相关疾病; 2)长期服用

降脂或降糖药物; 3)非原发初治乳腺癌患者, 或已有远处转移; 4)合并其他恶性肿瘤病史; 5)有吸烟史。

1.2 血清TG、TC检测

所有入组者空腹10 h以上于清晨采取血清标本送检, 经AU5821全自动生化分析仪(美国贝克曼库尔特公司)进行TG、TC水平检测。正常参考范围: TG 0.48~1.88 mmol/L, TC 3.15~6.25 mmol/L。

1.3 乳腺癌患者病理资料收集

收集入组的105例绝经前乳腺癌患者的病理类型、肿块大小、淋巴结转移情况及雌激素受体(estrogen receptor, ER)、孕激素受体(progesterone receptor, PR)、人表皮生长因子受体2(Her2)、增殖指数(Ki-67)表达情况。根据美国癌症联合委员会(AJCC)第八版标准进行TNM分期, 根据中国临床肿瘤协会(Chinese Society of Clinical Oncology, CSCO)在出版的《乳腺癌诊治指南标准2020》进行分子分型。

1.4 统计学处理

采用SPSS 18.0统计学软件进行数据分析, 计量数据用均数±标准差($\bar{x} \pm s$)表示, 采用成组t检验

比较两组之间TG、TC水平的差异。采用单因素方差分析和秩和检验比较乳腺癌不同临床病理特征下TG、TC水平差异。检验水准 $\alpha=0.05$ 。选取差异有统计学意义的血清TC指标, 将所有研究对象根据TC水平由低到高排序, 按四分位数分为4组, 采用logistic回归比较4组不同TC水平下乳腺癌发病率的风险比(odds ratio, OR), 使用GraphPad Prism 7.0软件绘制森林图, 使用SPSS 18.0软件绘制受试者工作特征(receiver operating characteristic, ROC)曲线。

2 结果

2.1 一般资料

本研究共纳入绝经前健康女性105例作为健康对照组, 年龄31~51(中位数39)岁, 初潮中位年龄12岁, 初产中位年龄27岁, 10例有乳癌家族史。同时纳入绝经前乳腺癌患者105例作为绝经前乳腺癌组, 年龄28~50(中位数44)岁, 初潮中位年龄13岁, 初产中位年龄28岁, 1例有乳癌家族史。两组一般资料相比, 差异无统计学意义, 具有可比性($P>0.05$)。

在所有乳腺癌病例中, 浸润性导管癌(invasive ductal carcinoma, IDC)83例(79.0%), 浸润性小叶癌(invasive lobular carcinoma, ILC)3例(2.9%), 导管原位癌(ductal carcinoma in situ, DCIS)10例(9.5%), 髓样癌5例(4.8%), 其他类型(小管癌、黏液癌、乳头状癌等)4例(3.9%)。

2.2 2组血清TG、TC水平的比较

2组TG水平无明显差异, 而绝经前乳腺癌组TC水平降低, 差异有统计学意义($P<0.05$, 表1)。由于年龄为影响血脂水平的混杂因素, 为观察其影响程度, 采用一般线性模型统计方法, 结果显示年龄也是影响TC水平的因素($P<0.05$, 表1)。

2.3 不同病理特征下乳腺癌患者的血清TG、TC比较

血清TG、TC水平在绝经前与乳腺癌不同肿块大小、淋巴结状态、TNM分期、ER、PR、Her2及Ki-67表达状态以及分子分型方面的差异均无统计学意义($P>0.05$, 表2)。

表1 2组的血清TG、TC比较($n=105$)

Table 1 Comparison of serum TG and TC between the 2 groups ($n=105$)

组别	TG/(mmol·L ⁻¹)	TC/(mmol·L ⁻¹)
健康对照组	1.10 ± 0.41	4.77 ± 0.80
绝经前乳腺癌组	1.13 ± 0.63	4.53 ± 0.68
<i>P</i>	0.683	0.022
<i>F</i> _{组别}	0.901	11.902
<i>P</i> _{组别}	0.593	0.001
<i>F</i> _{年龄}	0.022	2.407
<i>P</i> _{年龄}	0.884	0.023
<i>F</i> _{交互}	1.339	0.884
<i>P</i> _{交互}	0.165	0.603

表2 不同病理特征下绝经前乳腺癌血清TG、TC比较

Table 2 Comparison of serum TG and TC of pre-menopausal breast cancer under different pathological features

病理特征	例数(%)	TG/(mmol·L ⁻¹)	TC/(mmol·L ⁻¹)
肿块大小			
T1	68 (64.8)	1.13 ± 0.65	4.56 ± 0.69
T2	33 (31.4)	1.10 ± 0.53	4.53 ± 0.72
T3	4 (3.8)	1.39 ± 1.03	4.17 ± 0.24
<i>P</i>		0.694	0.555
淋巴结			
阴性	85 (81.0)	1.12 ± 0.59	4.51 ± 0.67
阳性	20 (19.0)	1.17 ± 0.78	4.63 ± 0.75
<i>P</i>		0.732	0.487

续表2

病理特征	例数(%)	TG/(mmol·L ⁻¹)	TC/(mmol·L ⁻¹)
TNM分期			
I	59 (56.2)	1.13 ± 0.62	4.51 ± 0.67
II	43 (41.0)	1.09 ± 0.59	4.58 ± 0.73
III	3 (2.9)	1.63 ± 1.10	4.27 ± 0.17
<i>P</i>		0.356	0.699
ER			
阳性	78 (74.3)	1.15 ± 0.62	4.56 ± 0.68
阴性	27 (25.7)	1.07 ± 0.65	4.46 ± 0.72
<i>P</i>		0.565	0.534
PR			
阳性	64 (61.0)	1.09 ± 0.57	4.54 ± 0.66
阴性	41 (39.0)	1.19 ± 0.71	4.52 ± 0.73
<i>P</i>		0.880*	0.927*
Her2			
阳性	20 (19.0)	1.14 ± 0.65	4.43 ± 0.70
阴性	85 (81.0)	1.13 ± 0.62	4.56 ± 0.69
<i>P</i>		0.935	0.450
Ki-67			
≤14%	32 (30.5)	1.24 ± 0.66	4.61 ± 0.67
>14%	73 (69.5)	1.08 ± 0.61	4.50 ± 0.69
<i>P</i>		0.227	0.443
分子分型			
Luminal A/B	64 (61.0)	1.15 ± 0.63	4.56 ± 0.68
Her2	20 (19.0)	1.13 ± 0.65	4.43 ± 0.70
TNBC	21 (20.0)	1.07 ± 0.60	4.54 ± 0.71
<i>P</i>		0.885	0.747

* 为采用秩和检验。

* used the rank sum test.

2.4 血清TC与绝经前乳腺癌的相关性分析

随着血清TC水平的下降, 乳腺癌的发病率呈现逐渐升高的趋势, 差异有统计学意义($P_{趋势}=0.023$, 表3)。第1、2、3组研究对象相对于第4组发生乳腺癌的OR分别为2.087(95% CI: 0.957~4.459, $P=0.064$), 1.357(95% CI: 0.627~2.937, $P=0.439$), 1.043(95% CI: 0.486~2.239, $P=0.913$; 图1)。

2.5 血清TC预测绝经前乳腺癌的ROC曲线图

ROC曲线(图2)示: 预测敏感性65.7%, 特异性61.4%, AUC为0.59($P=0.033$), 说明血清TC对乳腺癌的诊断价值有统计学意义, 但诊断价值中等偏低, 可能需要联合其他与脂代谢相关的指标进行研究, 以提高TC预测绝经前乳腺癌的准确性。

表3 血清TC水平与绝经前乳腺癌发病风险的相关性分析

Table 3 Analysis of the correlation between serum TC levels and the risk of pre-menopausal breast cancer

组别	第1组 (TC 2.89~<4.09 mmol/L)/ [例(%)]	第2组 (TC 4.09~<4.60 mmol/L)/ [例(%)]	第3组 (TC 4.60~<5.20 mmol/L)/ [例(%)]	第4组 (TC 5.20~7.04 mmol/L)/ [例(%)]
健康对照组	20 (19.0)	25 (23.8)	30 (28.6)	30 (28.6)
绝经前乳腺癌组	32 (30.5)	26 (24.8)	24 (22.9)	23 (21.9)
总计	52 (24.8)	51 (24.3)	54 (25.7)	53 (25.2)
<i>P</i> 趋势	0.023			

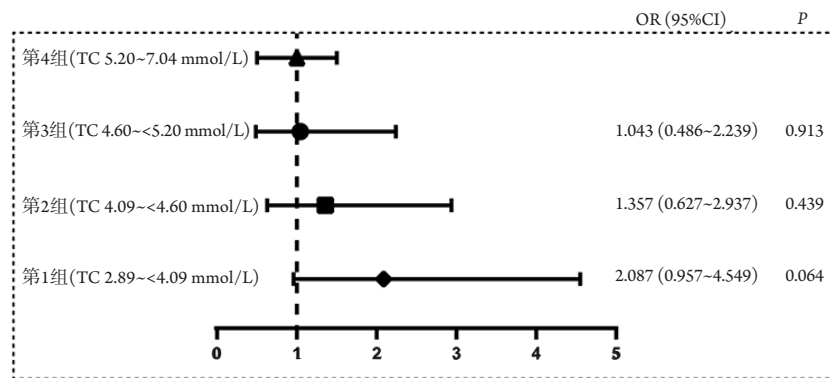


图1 根据血清TC水平分层后绝经前乳腺癌发病OR森林图

Figure 1 Forest plot of pre-menopausal breast cancer OR stratified according to serum TC levels

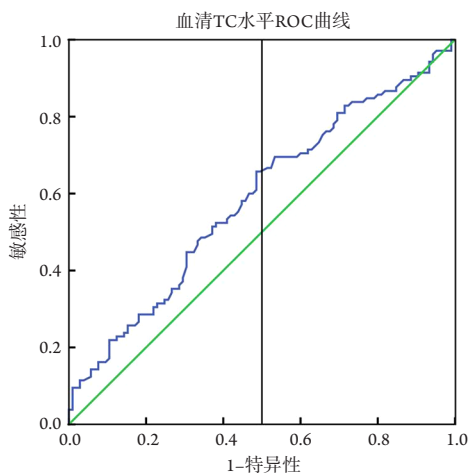


图2 血清TC预测绝经前乳腺癌发病风险的ROC曲线

Figure 2 ROC analysis of serum TC in predicting the risk of pre-menopausal breast cancer

3 讨论

目前, 已有大量研究^[6-9]表明恶性肿瘤的发生发展与人体脂质代谢异常密切相关。乳腺癌作为

全球发病率最高的女性恶性肿瘤, 学者们也对其进行了大量研究^[10-12]。有学者^[13]通过流行病学研究发现肥胖和高脂饮食是乳腺癌发生及进展的重要危险因素。研究^[14-17]表明TG与乳腺癌发生及发展之间无明显的相关性, 这也与本研究结果一致。目前有关血清TC与乳腺癌的研究主要集中在TC与乳腺癌复发风险之间的相关性, 然而TC作为乳腺癌危险因素的研究结果仍存在争议^[18-19], 这可能是由引起乳腺癌发病的多种因素造成的^[20]。Touvier等^[21]研究发现乳腺癌确诊前的血清TC与乳腺癌风险之间存在中度且有统计学意义的负相关。然而韩国一项针对17万例绝经后女性的研究^[22]却发现绝经后女性血清TC与乳腺癌发病风险无关。本研究以绝经前女性为研究对象, 结果发现血清TC与乳腺癌的发生呈负相关, 随着TC水平的下降, 乳腺癌的发病风险逐渐增加; 血清低胆固醇组女性的乳腺癌发病风险是高胆固醇组的2.087倍; 对于年龄<40岁、超重、肥胖的绝经前女性, 血清高TC患乳腺癌的发病风险较低。

目前尚不清楚TC是否会直接导致乳腺癌的发生, 考虑到细胞内TC稳态过程的复杂性, 很

难阐明血清TC水平改变对癌症发病机制的影响。两者之间的机制联系也尚未明确,有学者^[23]认为TC代谢失调可能会影响脂筏和膜流动性并促进肿瘤发展,但也有学者^[24]认为TC本身或其衍生物可以作为癌细胞中的信号分子。另有研究^[25]发现:喂食高脂肪/高TC饮食的ApoE^{-/-}小鼠会激活PI3K,磷酸化AKT/蛋白激酶B,从而促进肿瘤生长,并且当小鼠接受PI3K抑制剂BKM120治疗时,会抑制乳腺癌的生长,这强调了PI3K/AKT信号通路的重要作用。但该结果的相关性仍不确定,因为该小鼠模型血液中的TC水平超过2 000 mg/dL,远高于人类的高胆固醇血症(240 mg/dL)。目前也有学者^[26-27]经研究认为TC可能通过ERR途径参与乳腺癌的进展、转移、耐药。

尽管TC本身可能不增加乳腺癌的发病风险,但其代谢产物27-羟基TC(27-hydroxycholesterol, 27HC)作为内源性雌激素受体调节剂,可以促进乳腺癌的发生^[28],这可能与它具有刺激ER⁺乳腺癌细胞系增殖的能力相关^[29]。然而27HC在血液循环和乳腺组织局部的分布并不完全一致,在乳腺癌组织中,27HC浓度较正常乳腺组织升高,通过集中于乳腺组织局部,发挥促进肿瘤发生的作用^[30]。27HC作为TC的循环代谢产物,促进了乳腺癌的发生与发展,同时也消耗了乳腺癌患者体内的TC,这可以部分解释本研究中为何绝经前乳腺癌患者血液TC水平较健康女性偏低的原因。27-HC还具有作为肝X受体(liver X receptor, LXR)激动剂的活性。ER和LXR的共激活导致竞争性细胞内信号传导和交叉调节,促进乳腺癌细胞增殖;与TC相比,27HC可能是更好的风险生物标志物^[20]。因此在乳腺癌确诊患者中应避免摄入过多的TC,临床使用他汀类药物可以通过降低血清TC水平,减少乳腺癌复发转移的风险^[31]。

综上所述,本研究结果表明血清TC与绝经前乳腺癌发病风险之间存在负相关,血清TC水平预测绝经前乳腺癌的敏感性为65.7%,特异性为61.4%。关于TC对乳腺癌发病的预测价值,目前国内外乳腺癌风险预测模型中并未系统评价,为来还需要大规模前瞻性研究来充分控制临床前偏倚,如年龄、BMI、绝经状态、分子分型等,以证实血清TC及其组分在乳腺癌病因中的作用。

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本文引用：郭浩伟, 陆澄, 吕明明, 王凤良. 血清三酰甘油、胆固醇与绝经前女性乳腺癌的相关性[J]. *临床与病理杂志*, 2021, 41(11): 2619-2625. doi: 10.3978/j.issn.2095-6959.2021.11.020

Cite this article as: GUO Haowei, LU Cheng, LÜ Mingming, WANG Fengliang. Correlation between serum triglyceride, cholesterol and breast cancer in premenopausal women[J]. *Journal of Clinical and Pathological Research*, 2021, 41(11): 2619-2625. doi: 10.3978/j.issn.2095-6959.2021.11.020