

肿瘤防治研究

Cancer Research on Prevention and Treatment

胆固醇——乳腺癌风险和预后的预测因子

陈妮娜, 赵磊, 曹邦伟

引用本文:

陈妮娜, 赵磊, 曹邦伟. 胆固醇——乳腺癌风险和预后的预测因子[J]. 肿瘤防治研究, 2019, 46(09): 847-850.

CHEN Ni'na, ZHAO Lei, CAO Bangwei. Cholesterol: A Predictor of Risk and Prognosis of Breast Cancer[J]. *Zhong Liu Fang Zhi Yan Jiu*, 2019, 46(09): 847-850.

在线阅读 View online: <https://doi.org/10.3971/j.issn.1000-8578.2019.19.0265>

您可能感兴趣的其他文章

Articles you may be interested in

2012年湖北省乳腺癌发病与死亡情况分析

Breast Cancer Incidence and Mortality in Hubei Province, 2012

肿瘤防治研究. 2018, 45(2): 96-100 <https://doi.org/10.3971/j.issn.1000-8578.2018.17.1073>

乳腺癌组织中PDK4的表达及其与预后的关系

PDK4 mRNA Expression in Breast Cancer and Its Relationship with Prognosis

肿瘤防治研究. 2018, 45(2): 73-76 <https://doi.org/10.3971/j.issn.1000-8578.2018.17.0737>

乳腺癌基因分型与患者临床病理及预后的关系

Correlation of Genotypes with Clinicopathological and Prognostic Characteristics of Breast Cancer Patients

肿瘤防治研究. 2018, 45(10): 752-757 <https://doi.org/10.3971/j.issn.1000-8578.2018.17.1658>

Ubiquilin1蛋白在乳腺癌组织中的表达与预后意义

Expression of Ubiquilin1 Protein in Breast Cancer Tissues and Its Prognostic Significance

肿瘤防治研究. 2017, 44(8): 535-539 <https://doi.org/10.3971/j.issn.1000-8578.2017.17.0153>

BRCA突变型乳腺癌的靶向治疗研究进展

Review of Targeted Therapy for Breast Cancer with BRCA Genes Mutation

肿瘤防治研究. 2017, 44(1): 75-78 <https://doi.org/10.3971/j.issn.1000-8578.2017.01.016>



杂志官网



微信公众号

doi:10.3971/j.issn.1000-8578.2019.19.0265

• 综述 •

胆固醇——乳腺癌风险和预后的预测因子

陈妮娜¹, 赵磊², 曹邦伟²**Cholesterol: A Predictor of Risk and Prognosis of Breast Cancer**CHEN Nina¹, ZHAO Lei², CAO Bangwei²

1. Department of Oncology, Beijing Huairou Hospital, Beijing 101400, China; 2. Cancer Center, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Corresponding Author: CAO Bangwei, E-mail: oncology@ccmu.edu.cn

Abstract: Breast cancer is the most common malignant tumor in women. Some studies have shown that elevated cholesterol level is associated with poor prognosis and increased risk of breast cancer, and cholesterol plays different roles in breast cancer with different molecular types. Statin, especially lipophilic statins, has a great role in reducing the risk of breast cancer and improving prognosis. This article reviews the role of cholesterol in the pathogenesis and progression of breast cancer, as well as the effect of lipid-lowering therapy on the recurrence and prognosis of breast cancer. It can provide more evidence for the basic research and clinical work of the relation between hypercholesterolemia and breast cancer.

Key words: Cholesterol; Breast cancer; Pathogenesis; Prognosis

摘要: 乳腺癌是女性发病率最高的恶性肿瘤, 研究表明, 胆固醇水平的升高与乳腺癌的预后不良及复发风险增大有关, 而且胆固醇在不同分子分型的乳腺癌中作用也不尽相同, 他汀类降脂药物尤其是亲脂性他汀类药物对于降低乳腺癌复发风险、改良预后有重大作用。本文就胆固醇在乳腺癌发病及进展中的作用以及降脂治疗对乳腺癌复发和预后的影响进行综述, 可对高胆固醇血症与乳腺癌之间关系的基础研究及临床工作提供更多的依据。

关键词: 胆固醇; 乳腺癌; 发病; 预后

中图分类号: R737.9

文献标识码: A

开放科学(资源服务)标识码(OSID):



0 引言

近年来癌症的发病率及死亡人数逐年增高, 已成为仅次于心脏病的第二大死因, 乳腺癌是女性发病率最高的恶性肿瘤, 约占女性恶性肿瘤发病人数的30%, 根据美国癌症协会的统计, 2019年全美约有27.1万患者被诊断为乳腺癌, 4.2万患者死于乳腺癌, 而且随着年龄的增长, 乳腺癌发病率逐渐升高^[1]。既往研究表明, 乳腺癌的易患因素为遗传^[2]、初潮及绝经年龄、生育第一胎的年龄、既往癌症病史和生活方式^[3-4]。近年来, 越来越多的研究表明生活方式是影响乳腺癌发病率的首要原因, 其中肥胖^[5]、代谢综合征^[6]、II型糖尿病^[7]和高胆固醇血症都被确定为乳腺癌危险因素, 运动则是乳腺癌发病的保护因素^[4]。多年临床实践证

实, 体内胆固醇代谢紊乱是许多疾病的特征, 包括动脉粥样硬化^[8]以及多种类型的恶性肿瘤^[9-10]。其中, 胆固醇水平的升高与乳腺癌的预后有着密切的联系, 已经引起国内外专家的高度重视^[4]。本文就胆固醇在乳腺癌发病中的作用及对乳腺癌预后的影响进行综述, 以期对高胆固醇血症与乳腺癌之间关系的研究提供新的思路和方向。

1 胆固醇的代谢

胆固醇是细胞膜的重要组成部分, 在细胞完整性和细胞功能中起着关键作用^[11-12]。外源性胆固醇主要从食物中获得, 在肠腔内与磷脂和胆汁酸结合, 在肠黏膜吸收后形成胆固醇酯。内源性胆固醇在细胞胞质和内质网中合成, 不能通过血液运输, 因此它以高密度脂蛋白 (high-density lipoprotein, HDL) 或低密度脂蛋白 (low-density lipoprotein, LDL) 的形式结合在脂质和蛋白质中, 其限速酶为羟甲基戊二酰辅酶A也称HMGCoA还原酶 (HMGCoA reductase) ^[12-13]。当它到达目标组织时, 细胞吞噬低密度脂蛋白, 其中的胆固

收稿日期: 2019-03-07; 修回日期: 2019-04-02

作者单位: 1. 101400 北京, 北京怀柔医院肿瘤血液科; 2. 100050 北京, 首都医科大学附属北京友谊医院肿瘤中心

通信作者: 曹邦伟, E-mail: oncology@ccmu.edu.cn

作者简介: 陈妮娜 (1982-), 女, 硕士, 主治医师, 主要从事乳腺癌的个体化治疗工作

醇被释放出来,成为细胞膜的结构成分或用于合成类固醇及维生素D^[14]。此外,游离胆固醇还负调节甾醇调节元件结合蛋白-2 (Sterol regulatory element-binding protein 2, SREBP-2),这是细胞内胆固醇水平的主要转录因子之一^[15]。

2 胆固醇与乳腺癌的发生发展

多项基础研究表明,胆固醇水平的异常与乳腺癌细胞的增殖和迁移密切相关。动物实验研究表明,高胆固醇膳食有可能增加乳腺癌小鼠模型MMTV-pyMT中的肿瘤进展和转移^[16]。为了进一步确定高脂血症在乳腺癌生长中的作用,Alikhani等将乳腺癌细胞系Met-1和Mvt-1注射到载脂蛋白E (apolipoprotein E, ApoE)基因敲除小鼠和野生型小鼠的乳腺脂肪垫中,并给予两组小鼠高脂肪/高胆固醇饮食。与野生型小鼠相比,载脂蛋白E敲除小鼠的转移和肿瘤生长明显增加^[17]。进一步研究表明,喂食高胆固醇的载脂蛋白E基因敲除小鼠可激活磷脂酰肌醇3-激酶 (phosphatidylinositol 3-kinase, PI3K)、磷酸化蛋白激酶B (protein kinase B, PKB, 也成为AKT),从而促进肿瘤生长。此外,当用PI3K抑制剂BKM120治疗小鼠时,乳腺癌的生长速度降低^[17]。乳腺癌发病机制与几种对胆固醇稳态有重要作用的酶和蛋白质失调有关^[16]。Nelson等研究表明,高胆固醇已成为乳腺癌发病的危险因素,胆固醇升高与乳腺癌预后不良有关,服用降低胆固醇的药物可以降低乳腺癌的复发。胆固醇的代谢产物27-羟基胆固醇 (27-hydroxycholesterol, 27-OHC)可作为内源性选择性雌激素受体调节剂,促进乳腺癌细胞的增殖、分化、迁移^[18]。Zhao等研究表明,羧基末端结合蛋白 (C-terminal-binding protein, CtBP)具有转录辅助抑制因子的功能,可以通过抑制胆固醇和激活转化生长因子- β (transforming growth factor- β , TGF- β)信号转导抑制乳腺癌的转移^[19]。

3 各型乳腺癌中胆固醇水平差异的研究进展

激素受体 (hormone receptor, HR) 状态、人表皮生长因子受体2 (human epidermal growth factor receptor-2, HER-2) 过度扩增和核细胞增殖分子Ki-67的表达水平在乳腺癌中具有极大的预后价值^[20]。Luminal分子分型就是基于上述因素对乳腺癌进行分型,各型预后及治疗差别较大,研究胆固醇对各型乳腺癌的影响,可以更好对乳腺癌预后进行研究,并进一步对各型乳腺癌患者进行个体化治疗。

3.1 胆固醇对雌激素受体 (estrogen receptor, ER) 阳性乳腺癌的影响

雌激素对于乳腺的生长和发育至关重要,并可促进乳腺癌的进展,大多数人类乳腺癌最初依赖于雌激素并且雌激素水平降低时乳腺癌细胞生长减慢,雌激素通过两种核雌激素受体 (ER α 和ER β) 发挥作用^[21]。在分子水平上,乳腺癌的发生主要由雌激素和雌激素受体的异常活性驱动^[22]。Esau等研究表明,胆固醇酯转移蛋白 (Cholesteryl ester transfer protein, CETP) 的功能是将HDL转化为LDL或者超低密度脂蛋白 (very low density lipoprotein, VLDL),完成胆固醇的逆转运。在ER+乳腺癌细胞系MCF-7中敲除CETP,可使胆固醇水平下降,此时细胞对细胞毒性化合物 (他莫昔芬) 的抵抗性较小,更易发生细胞凋亡^[23]。Simigdala等表明,ER阳性乳腺癌中如有长期雌激素缺乏会引起胆固醇合成增加,在ER阴性乳腺癌中则不会出现此类情况,此外,应用小干扰RNA (siRNA) 靶向胆固醇生物合成途径的各个基因可导致ER+乳腺癌细胞增殖下降30%~50%^[24]。

3.2 胆固醇对孕激素受体 (progesterone receptor, PR) 阳性乳腺癌的影响

孕激素在雌性生殖系统中调节细胞增殖和分化。研究表明,孕激素受体表达量与病理分级、肿瘤大小和腋窝淋巴结受累呈负相关。因此,孕激素受体阳性肿瘤较阴性肿瘤预后更好^[25]。Liang等表明,胆固醇合成抑制剂RO 48-8071 (RO) 通过泛素依赖性降解途径降低PR蛋白表达最终降低醋酸甲羟孕酮 (medroxyprogesterone acetate, MPA) 诱导的CD44蛋白表达,进而抑制乳腺癌的生长及转移。因此,RO可用于临床治疗和预防激素依赖性乳腺癌^[26]。

3.3 胆固醇对HER-2阳性乳腺癌的影响

HER2是一种跨膜酪氨酸激酶受体,参与细胞生长、分化和迁移,有18%~20%的患者为HER2阳性乳腺癌。有研究表明,HER2阳性乳腺癌比HER2阴性乳腺癌预后差^[27]。Gallagher等进行了一项动物实验,研究表明HER2过表达的小鼠乳腺癌细胞低密度脂蛋白受体 (low-density lipoprotein receptor, LDLR) 高表达,并且具有高循环低密度脂蛋白胆固醇 (low-density lipoprotein cholesterol, LDL-C) 的小鼠比低LDL-C的小鼠肿瘤更大。沉默肿瘤细胞中的LDLR小鼠后,HER2过表达肿瘤的生长减少,并且含半胱氨酸的天冬氨酸蛋白水解酶-3 (cysteinyl aspartate specific proteinase-3,

Caspase-3) 裂解增加, 从而使肿瘤细胞凋亡增加。此外, 体外实验也表明, 沉默LDLR导致血清饥饿条件下细胞存活率降低, 也与Caspase-3裂解相关^[28]。

3.4 胆固醇对三阴性乳腺癌的影响

三阴性乳腺癌 (triple-negative breast cancer, TNBC) 约占乳腺癌的12%~17%, 其特点是缺乏HER-2、ER和PR。与激素受体阳性和HER-2阳性乳腺癌相比, 三阴性乳腺癌更具侵袭性, 并且预后更差^[29]。Shim等研究了苦瓜提取物抑制小鼠模型中三阴性乳腺癌的作用机制, 结果显示, 苦瓜提取物抑制乳腺癌中的胆固醇酰基转移酶1 (cholesterol acyltransferase 1, ACAT-1) 从而降低胆固醇水平, 进而抑制三阴性乳腺癌细胞生长^[30]。Torres-Adorno等研究表明, 二十碳五烯酸 (Eicosapentaenoic acid, EPA) 作用于Ephrin A型受体2 (Ephrin type-A receptor 2, EPHA2), 从而抑制乳腺癌细胞的三磷酸腺苷结合转运子 (ATP binding cassette transporter A1, ABCA1), 随后导致胆固醇体内平衡失调, 癌细胞膜极性消失, 最终造成癌细胞凋亡^[31]。

4 降脂药物对乳腺癌预后的影响

目前研究调查他汀类药物对癌症复发影响的临床试验较少, 大部分恶性肿瘤中降脂药物的作用仍然模棱两可。然而, 在乳腺癌中, 大多数临床证据支持他汀类药物可以减少乳腺癌复发^[28]。基础研究表明, 他汀类药物可以通过靶向限速酶HMG-CoA还原酶而影响癌细胞中的甲羟戊酸途径^[32]。HMG-CoA还原酶在乳腺癌和非乳腺癌中差异表达, 因此可以作为乳腺癌预后的标志物^[33]。另有研究表明, 他汀类药物可以通过降低胆固醇及胆固醇代谢物27-羟基胆固醇 (27-hydroxycholesterol, 27-HC) 水平间接影响肿瘤细胞的生长^[34]。此外, 他汀类药物应用于乳腺癌患者后, 检测细胞核中的细胞周期蛋白D1 (cyclin D1) 表达显著降低 ($P=0.008$)。肿瘤抑制因子p27的蛋白质表达显著增加^[35]。

除基础研究外, 多项临床试验也证实了他汀类药物对乳腺癌复发的抑制作用。Manthravadi及其同事证明, 服用亲脂性他汀类药物的乳腺癌患者复发风险降低了36%^[36]。Arun等研究表明, 乳腺癌患者服用阿托伐他汀可显著降低血浆中的C-反应蛋白 (C-reactive protein, CRP) 水平^[37]。Borgquist等进行了一项随机对照实验 (实验代号: Breast

International Group 1-98, BIG 1-98), 纳入了8 110例早期激素依赖性乳腺癌的绝经后妇女, 在患者内分泌治疗期间应用降胆固醇药物可预防激素受体阳性早期乳腺癌的复发^[38]。Ahern等对丹麦女性进行了一项前瞻性队列研究, 以评估他汀类药物使用与乳腺癌复发之间的关系。纳入标准为被诊断患有I~III期浸润性乳腺癌的丹麦女性, 分别给予亲脂性和亲水性他汀类药物。使用亲脂性药物辛伐他汀的乳腺癌患者复发的风险降低, 而亲水性他汀类药物对乳腺癌复发无明显影响^[39], 该结果也与Liu等^[40]进行的一项不同他汀类降脂药物在乳腺癌中作用的Meta分析相一致。

5 展望

多项研究证明, 胆固醇水平与乳腺癌的预后及复发风险密切相关, 而且降脂药物, 尤其是亲脂性他汀类药物, 对于减少乳腺癌复发有重要作用, 但是, 它们在乳腺癌中的应用还存在其他问题: 首先, 他汀类药物对具有不同分子亚型的乳腺癌细胞的功效尚不清楚, 应研究他汀类药物在许多乳腺癌细胞系, 包括激素受体阳性、HER2阳性和三阴性乳腺癌的易感性, 以确定分子亚型是否在他汀类药物敏感性中起作用。其次, 乳腺癌患者需口服他汀类药物的胆固醇标准尚未统一, 这也是科研工作者和临床医师需要关注和积累经验之处。

参考文献:

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019[J]. CA Cancer J Clin, 2019, 69(1): 7-34.
- [2] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours[J]. Nature, 2012, 490(7418): 61-70.
- [3] Singletary SE. Rating the risk factors for breast cancer[J]. Ann Surg, 2003, 237(4): 474-482.
- [4] Baek AE, Nelson ER. The Contribution of Cholesterol and Its Metabolites to the Pathophysiology of Breast Cancer[J]. Horm Cancer, 2016, 7(4): 219-228.
- [5] Gravena AAF, Romeiro Lopes TC, Demitto MO, et al. The Obesity and the Risk of Breast Cancer among Pre and Postmenopausal Women[J]. Asian Pac J Cancer Prev, 2018, 19(9): 2429-2436.
- [6] Dibaba DT, Ogunsina K, Braithwaite D, et al. Metabolic syndrome and risk of breast cancer mortality by menopause, obesity, and subtype[J]. Breast Cancer Res Treat, 2019, 174(1): 209-218.
- [7] Maskarinec G, Shvetsov YB, Conroy SM, et al. Type 2 diabetes as a predictor of survival among breast cancer patients: the multiethnic cohort[J]. Breast Cancer Res Treat, 2019, 173(3): 637-645.
- [8] Amani M, Darbin A, Pezeshkian M, et al. The role of cholesterol-enriched diet and paraoxonase 1 inhibition in atherosclerosis progression[J]. J Cardiovasc Thorac Res, 2017, 9(3): 133-139.

- [9] Tie G, Yan J, Khair L, *et al.* Hypercholesterolemia Increases Colorectal Cancer Incidence by Reducing Production of NKT and $\gamma\delta$ T Cells from Hematopoietic Stem Cells[J]. *Cancer Res*, 2017, 77(9): 2351-2362.
- [10] Jeon JC, Park J, Park S, *et al.* Hypercholesterolemia Is Associated with a Shorter Time to Castration-Resistant Prostate Cancer in Patients Who Have Undergone Androgen Deprivation Therapy[J]. *World J Mens Health*, 2016, 34(1): 28-33.
- [11] Reboldi A, Dang E. Cholesterol metabolism in innate and adaptive response[J]. *F1000Res*, 2018: 7. pii: F1000 Faculty Rev-1647.
- [12] Ribas V, García-Ruiz C, Fernández-Checa JC. Mitochondria, cholesterol and cancer cell metabolism[J]. *Clin Transl Med*, 2016, 5(1): 22.
- [13] Bietz A, Zhu H, Xue M, *et al.* Cholesterol Metabolism in T Cells[J]. *Front Immunol*, 2017, 8: 1664.
- [14] Craig M, Walik A. Biochemistry, Cholesterol[M/OL]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019-. 2019 Apr 17.
- [15] Gopoju R, Panangipalli S, Kotamraju S. Metformin treatment prevents SREBP2-mediated cholesterol uptake and improves lipid homeostasis during oxidative stress-induced atherosclerosis[J]. *Free Radic Biol Med*, 2018, 118: 85-97.
- [16] Munir MT, Ponce C, Powell CA, *et al.* The contribution of cholesterol and epigenetic changes to the pathophysiology of breast cancer[J]. *J Steroid Biochem Mol Biol*, 2018, 183: 1-9.
- [17] Alikhani N, Ferguson RD, Novosyadlyy R, *et al.* Mammary tumor growth and pulmonary metastasis are enhanced in a hyperlipidemic mouse model[J]. *Oncogene*, 2013, 32(8): 961-967.
- [18] Nelson ER. The significance of cholesterol and its metabolite, 27-hydroxycholesterol in breast cancer[J]. *Mol Cell Endocrinol*, 2018, 466: 73-80.
- [19] Zhao Z, Hao D, Wang L, *et al.* CtBP promotes metastasis of breast cancer through repressing cholesterol and activating TGF- β signaling[J]. *Oncogene*, 2019, 38(12): 2076-2091.
- [20] Nelson DJ, Clark B, Munyard K, *et al.* A review of the importance of immune responses in luminal B breast cancer[J]. *Oncoimmunology*, 2017, 6(3): e1282590.
- [21] Haldosén LA, Zhao C, Dahlman-Wright K. Dahlman-Wright, Estrogen receptor beta in breast cancer[J]. *Mol Cell Endocrinol*, 2014, 382(1): 665-672.
- [22] Yang J, Wei X, Tufan T, *et al.* Recurrent mutations at estrogen receptor binding sites alter chromatin topology and distal gene expression in breast cancer[J]. *Genome Biol*, 2018, 19(1): 190.
- [23] Esau L, Sagar S, Bangarusamy D, *et al.* Identification of CETP as a molecular target for estrogen positive breast cancer cell death by cholesterol depleting agents[J]. *Genes Cancer*, 2016, 7(9-10): 309-322.
- [24] Simigdala N, Gao Q, Pancholi S, *et al.* Cholesterol biosynthesis pathway as a novel mechanism of resistance to estrogen deprivation in estrogen receptor-positive breast cancer[J]. *Breast Cancer Res*, 2016, 18(1): 58.
- [25] Qi XL, Yao J, Zhang Y. No association between the progesterone receptor gene polymorphism (+331G/a) and the risk of breast cancer: an updated meta-analysis[J]. *BMC Med Genet*, 2017, 18(1): 123.
- [26] Liang Y, Goyette S, Hyder SM. Cholesterol biosynthesis inhibitor RO 48-8071 reduces progesterone receptor expression and inhibits progesterin-dependent stem cell-like cell growth in hormone-dependent human breast cancer cells[J]. *Breast Cancer (Dove Med Press)*, 2017, 9: 487-494.
- [27] Li S, Wei W, Jiang Y, *et al.* Comparison of the efficacy and survival analysis of neoadjuvant chemotherapy for Her-2-positive breast cancer[J]. *Drug Des Devel Ther*, 2018, 12: 3085-3093.
- [28] Gallagher EJ, Zelenko Z, Neel BA, *et al.* Elevated tumor LDLR expression accelerates LDL cholesterol-mediated breast cancer growth in mouse models of hyperlipidemia[J]. *Oncogene*, 2017, 36(46): 6462-6471.
- [29] Ye J, Xia X, Dong W, *et al.* Cellular uptake mechanism and comparative evaluation of antineoplastic effects of paclitaxel-cholesterol lipid emulsion on triple-negative and non-triple-negative breast cancer cell lines[J]. *Int J Nanomedicine*, 2016, 11: 4125-4140.
- [30] Shim SH, Sur S, Steele R, *et al.* Disrupting cholesterol esterification by bitter melon suppresses triple-negative breast cancer cell growth[J]. *Mol Carcinog*, 2018, 57(11): 1599-1607.
- [31] Torres-Adorno AM, Vitrac H, Qi Y, *et al.* Eicosapentaenoic acid in combination with EPHA2 inhibition shows efficacy in preclinical models of triple-negative breast cancer by disrupting cellular cholesterol efflux[J]. *Oncogene*, 2019, 38(12): 2135-2150.
- [32] Clendening JW, Penn LZ. Targeting tumor cell metabolism with statins[J]. *Oncogene*, 2012, 31(48): 4967-7498.
- [33] Bjarnadottir O, Romero Q, Bendahl PO, *et al.* Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial[J]. *Breast Cancer Res Treat*, 2013, 138(2): 499-508.
- [34] Nelson ER, Wardell SE, Jasper JS, *et al.* 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology[J]. *Science*, 2013, 342(6162): 1094-1098.
- [35] Feldt M, Bjarnadottir O, Kimbung S, *et al.* Statin-induced anti-proliferative effects via cyclin D1 and p27 in a window-of-opportunity breast cancer trial[J]. *J Transl Med*, 2015, 13: 133.
- [36] Manthravadi S, Shrestha A, Madhusudhana S. Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis[J]. *Int J Cancer*, 2016, 139(6): 1281-1288.
- [37] Arun BK, Gong Y, Liu D, *et al.* Phase I biomarker modulation study of atorvastatin in women at increased risk for breast cancer[J]. *Breast Cancer Res Treat*, 2016, 158(1): 67-77.
- [38] Borgquist S, Giobbie-Hurder A, Ahern TP, *et al.* Cholesterol, Cholesterol-Lowering Medication Use, and Breast Cancer Outcome in the BIG 1-98 Study[J]. *J Clin Oncol*, 2017, 35(11): 1179-1188.
- [39] Ahern TP, Pedersen L, Tarp M, *et al.* Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study[J]. *J Natl Cancer Inst*, 2011, 103(19): 1461-1468.
- [40] Liu B, Yi Z, Guan X, *et al.* The relationship between statins and breast cancer prognosis varies by statin type and exposure time: a meta-analysis[J]. *Breast Cancer Res Treat*, 2017, 164(1): 1-11.

[编辑: 安凤; 校对: 邱颖慧]

作者贡献:

陈妮娜: 查阅文献, 撰写、校正文稿

赵磊: 查阅文献

曹邦伟: 文章立意, 校正文稿