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# 代谢综合征与绝经后乳腺癌患者及相关因素研究

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## 摘　要

**代谢综合征是一种常见的代谢性疾病，包括肥胖、高血压、高血糖和高胆固醇。与绝经后乳腺癌患者之间存在一定的关联。越来越多的证据表明代谢综合征与绝经后乳腺癌风险增加之间存在关联。其影响机制可能涉及胰岛素、胰岛素样生长因子-1、高胰岛素血症、雌激素、脂肪因子、炎症因子等多种因子。本文就代谢综合征与绝经后乳腺癌患者的相关性研究进展做一概述，为绝经后乳腺癌的预防、治疗提供新思路。**

## 关键词

**代谢综合征，绝经后乳腺癌患者，胰岛素**

# Metabolic Syndrome and Postmenopausal Breast Cancer Patients and Related Factors Study

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## Abstract

**Metabolic syndrome is a common metabolic disorder that includes obesity, high blood pressure, high blood sugar, and high cholesterol. There is an association with postmenopausal breast cancer patients. There is growing evidence of an association between metabolic syndrome and an increased**

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**risk of breast cancer after menopause. The influencing mechanism may involve a variety of factors such as insulin, insulin-like growth factor-1, hyperinsulinemia, estrogen, adiptenoid, and inflammatory factors. This article summarizes the research progress on the correlation between metabolic syndrome and postmenopausal breast cancer, and provides new ideas for the prevention and treatment of postmenopausal breast cancer.**

## Keywords

**Metabolic Syndrome, Postmenopausal Breast Cancer Patients, Insulin**



## 1. 引言

近年来，随着生活水平的日益提高，代谢综合征(MetS)也相应在全球范围内呈上升趋势，由于其与心血管疾病、2 型糖尿病和癌症的发病之间有所关联，对代谢综合征的研究具有很重要的临床意义[1]。其中代谢综合征与绝经后乳腺癌患者的发生、发展及治疗等密切相关，二者的关系是目前临床关注的热点问题之一。其中胰岛素抵抗、高胰岛素血症、脂质代谢紊乱、慢性炎症、性激素水平异常等在代谢综合征与绝经后乳腺癌患者之间的发生发展中也发挥了重要作用。

## 2. 代谢综合征与绝经后乳腺癌患者

### 2.1. 代谢综合征

代谢综合征，也称为胰岛素抵抗综合征或 X 综合征，是一种多因素代谢性疾病。代谢综合征的定义考虑了至少三个因素的存在，即腹部肥胖/高体重指数(BMI)、胰岛素抵抗、高血压、高甘油三酯血症和低高密度脂蛋白(HDL)。代谢异常不仅会增加疾病风险，加剧肿瘤进展，而且会导致不良的治疗反应和更多的治疗副作用。此外，这些代谢成分失衡引起的生化反应会影响宿主总体状态和器官特异性肿瘤微环境，导致复发率和死亡率增加[2]-[4]。越来越多的数据显示代谢综合征或其组成部分与癌症发展和癌症相关死亡率有关[5]。目前已知代谢综合征会影响生长信号传导、炎症过程、血管完整性和与癌症发展、复发和预后相关的激素信号传导[6]。

### 2.2. 绝经后乳腺癌患者

女性由于月经的永久停止，代表着有限的卵巢卵泡供应完全耗尽而失去生殖功能。由于进入老年[7]，卵巢分泌激素随之发生改变。女性更容易出现包括子宫内膜癌、卵巢癌，乳腺癌在内的多种与女性激素相关的疾病。其中乳腺癌最容易受绝经因素的影响。绝经后妇女患乳腺癌风险增加，这部分人群患乳腺癌的危险因素包括有糖尿病、动脉高血压、高脂血症、肥胖和腹围增大[8]。绝经诱导了脂肪量重新分布，导致腹部肥胖增加，并影响脂质代谢[9]，这一发生可能开始于实际绝经前几年，这可能解释了绝经后妇女代谢综合征风险增加的原因[10] [11]。

## 3. 乳腺癌与代谢综合征的流行病学研究

### 发病风险

39%的绝经后乳腺癌患者存在代谢综合征，约为最近一项人群研究报告的两倍[12]。几项最新的研究

也报告了代谢综合征的单个组分与绝经后女性乳腺癌风险之间的直接相关性[13] [14]。先前的研究发现，绝经后女性患乳腺癌的风险增加，但绝经前女性的代谢综合征风险没有增加，这表明代谢综合征与乳腺癌之间的关联可能因绝经状态而异[15]-[17]。总之，患有代谢综合征的女性在绝经后患乳腺癌的风险更高。在病理学上，代谢综合征患者的特征是慢性炎症和氧化应激，这参与了致癌作用[18] [19]。代谢综合征患者的慢性低度炎症也参与了许多恶性肿瘤的发展，包括乳腺癌[20]。先前在抗肥胖 BALB/c 雌性小鼠品系中的研究表明，高脂饮食可刺激雌激素受体(ER)阴性小鼠乳腺癌细胞系的生长。这种加速的癌症进展伴随着增强的肿瘤相关血管生成和几种促炎细胞因子(包括白细胞介素 6 和瘦素)的血清浓度增加，这表明代谢综合征、炎症和致癌作用之间存在潜在关联[21]。此外，在乳腺癌患者中，肿瘤微环境中的炎症，促炎细胞因子(如肿瘤坏死因子-$\alpha$)表达的局部升高，也与侵袭性增加和预后不良相关[22]。

## 4. 病理生理学机制

### 4.1. 胰岛素、胰岛素样生长因子-1、高胰岛素血症

胰岛素具有多种代谢功能。它是正常乳腺组织以及乳腺癌细胞中的强效促有丝分裂剂[23] [24]，通过与胰岛素受体结合而起作用，并且乳腺癌组织中的胰岛素受体浓度高于正常乳腺组织。胰岛素受体与肿瘤大小、分级[25]和死亡率[26]直接相关。胰岛素可通过其促有丝分裂活性和增加胰岛素样生长因子-I (IGF-I)的合成，促进乳腺上皮细胞和乳腺癌细胞系的细胞增殖。胰岛素受体和胰岛素样生长因子-I (IGF-1)受体在乳腺癌细胞中广泛表达，主要通过胰岛素受体底物(IRS)/磷脂酰肌醇 3-激酶(PI3K)和 Ras/促分裂原活化蛋白激酶(MAPK)途径促进细胞增殖[27] [28]。胰岛素本身促进 DNA、RNA 和 ATP 的合成，诱导有丝分裂和血管生成，并抑制细胞凋亡，导致肿瘤的发生。体外实验证明，胰岛素可诱导肿瘤细胞的 EMT、侵袭和迁移[29]。在慢性高胰岛素血症状态下，ER 被激活，通过调节细胞周期、凋亡因子和营养代谢促进肿瘤生长[30]。这一机制为二甲双胍治疗 ER (+)乳腺癌合并糖尿病患者提供了依据。此外，高胰岛素血症也介导 IGF-1 的产生，抑制肝脏中 IGFBP 的产生，增加 IGF-1 的生物利用度，并通过过度激活 PI3K-Akt-mTOR 通路和 Ras-MAPK 通路进一步刺激肿瘤生长[31]。患有代谢综合征的女性体内循环胰岛素和胰岛素样生长因子 1 (IGF-1)水平较高。后者是肿瘤细胞的有效有丝分裂原[8]。

### 4.2. 炎症因子

炎症在绝经后乳腺癌患者的发生、发展和预后中扮演着重要角色。肥胖诱导脂肪组织中的巨噬细胞积聚，其产生由脂肪组织释放的许多促炎分子，与肥胖诱导的炎症的发展有关[12]。C-反应蛋白和血清淀粉样蛋白 A 是响应炎症而释放的急性期蛋白[32]。慢性炎症则促进促炎因子如 TNF-$\alpha$、IL-6 和趋化因子的产生，抑制抗炎因子如脂联素的分泌[27] [33]。其中 TNF-$\alpha$ 参与了致癌作用，最近的研究表明，这是因为其能够激活核因子-$\kappa$B (NF-$\kappa$B)，从而促进细胞存活[34]。此外，TNF-$\alpha$ 似乎有助于肿瘤生长和转移所必需的组织结构的发展[35] [36]。它还诱导其他细胞因子、血管生成因子和基质金属蛋白酶(MMP)，从而促进肿瘤细胞的生长和存活[37]。IL-6 是免疫细胞生长和分化的重要调节剂。最近的研究表明，IL-6 调节慢性炎症，这可以创造有利于癌症生长的细胞微环境[38]。高循环 IL-6 浓度与总体癌症死亡和癌症前体病变风险增加相关。炎症与促炎细胞因子的上调相关，促炎细胞因子促进肿瘤转化和肿瘤进展。慢性炎症还通过产生诱导基因组不稳定性和 DNA 损伤的活性氧物质和活性氮物质与肿瘤发生和促进直接相关[39]。

### 4.3. 脂肪因子

脂肪因子是一组信号分子，其在食欲和能量平衡、炎症、胰岛素敏感性、血管生成、脂质代谢、细

胞增殖和动脉粥样硬化中发挥作用[40]。这些功能中的大多数被认为与代谢综合征和癌症相关，并在它们之间的关系中发挥作用。脂肪组织不仅储存脂肪细胞，它也是一个内分泌器官，产生称为脂肪因子的生物活性分子。这些脂肪因子与靶细胞表面的特异性受体结合，影响组织和器官的代谢[41]。

### 4.4. 雌激素

雌激素是一种促进乳腺肿瘤生长和肿瘤细胞存活的激素，通过血浆雄烯二酮的芳香化酶转化为雌酮而获得的。雌酮被代谢为雌二醇，在乳腺中最具生物活性[12]。雌酮和睾酮的形成增加伴随着性激素结合球蛋白水平降低的综合作用导致雌二醇的生物可利用部分增加，其可以扩散到靶细胞，并且在某些组织中，例如乳腺上皮和子宫内膜，它们促进细胞增殖并抑制细胞凋亡[42]。绝经后最重要的雌激素来源是雄激素与细胞色素 p450 酶复合物的芳构化[40]。绝经后通过增加外周组织中雄激素向雌激素的转化和减少性激素结合球蛋白(SHBG)，从而增加雌激素的水平和可用性，从而增加乳腺癌的风险[43]-[45]。但过量的雌激素会刺激乳腺组织增殖[46]。芳香酶是一种细胞色素 P450 酶，主要存在于乳房、腹部、大腿和臀部的脂肪组织中，但也可能存在于肿瘤组织中。它能催化雄烯二酮和睾酮生成雌酮和雌二醇。再者，代谢综合征和胰岛素抵抗相关的肥胖也有助于乳腺雌激素合成的增加[8]。

## 5. 小结

代谢综合征造成的机体代谢紊乱通过胰岛素抵抗和高胰岛素血症、胰岛素样生长因子 1 (IGF-a)活性升高、炎症细胞因子过度分泌、脂肪因子过量产生、循环雌激素增多等诸多因素的产生导致的失衡来支持乳腺肿瘤的生长。因此，我们有理由把重点放在这些途径上，并开发预防和治疗乳腺癌的干预措施。

## 6. 展望

代谢综合征是导致乳腺癌患者死亡的一个重要危险因素，尤其是绝经后妇女。未来的研究需要更好地阐明代谢失调与肿瘤亚型和死亡率结果之间的联系机制，特别是在年轻的乳腺癌患者中[47]。在接受乳腺癌治疗的女性中，存在代谢综合征往往会增加死亡风险，绝经后妇女乳腺癌诊断中是否存在代谢综合征可能是评估治疗预后、转移潜力和最佳辅助治疗的关键因素[8]。代谢综合征的存在被认为是预后不良的指标[48]。研究结果也表明代谢综合征与乳腺癌转移、复发和死亡率相关[49]。代谢综合征患者癌症预防的基本方法是预防危险因素，其中生活方式的改变，包括减肥和健康饮食，特别是地中海饮食，目前已知可以降低正常人群的癌症风险[50]。代谢综合征的患病率很高，并且随着世界范围内乳腺癌发病率的上升而增加。通过营养、体育锻炼和其他生活方式的改变来控制代谢综合征可能对改善癌症发病率和预后做出重大贡献[51]，这可能使每位女性都从中得到获益。

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