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甲状腺疾病与乳腺癌关系的研究进展

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摘　要

近年来甲状腺疾病与乳腺癌的关系一直备受人们关注。由于甲状腺和乳腺这两个腺体都受下丘脑－垂体－腺体轴调控，所以甲状腺疾病和乳腺疾病两者存在某种共同的病因。因此研究两者的关系对于进一步了解肿瘤的生物学行为有着重要的意义，也有助于两种疾病的诊断和临床管理。该研究总结了甲状腺功能减退、自身免疫性甲状腺炎和甲状腺癌等甲状腺疾病在乳腺癌发病中的作用以及相关机制的研究进展。认为甲减可能减低乳腺癌的风险，自身免疫性甲状腺炎通过免疫系统参与乳腺癌的发生发展，甲状腺癌与乳腺癌之间存在双向联系。

关键词

甲状腺疾病，乳腺肿瘤，危险因素，因果关系

Research Progress on the Relationship between Thyroid Diseases and Breast Cancer

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Abstract

In recent years, the relationship between thyroid disease and breast cancer has attracted much attention. Because both thyroid gland and mammary gland are regulated by the hypothalamus-pituitary-ggland axis, thyroid disease and mammary gland disease have some common cause.

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Therefore, the study of the relationship between the two is of great significance for further understanding the biological behavior of tumors, as well as for the diagnosis and clinical management of the two diseases. This study summarized the role of thyroid diseases such as hypothyroidism, autoimmune thyroiditis and thyroid cancer in the pathogenesis of breast cancer and the research progress of related mechanisms. It is believed that hypothyroidism may reduce the risk of breast cancer. Autoimmune thyroiditis participates in the occurrence and development of breast cancer through the immune system. There is a two-way relationship between thyroid cancer and breast cancer.

Keywords

Thyroid Disease, Breast Neoplasms, Risk Factors, Causal Relationship

1. 引言

甲状腺癌和乳腺癌是女性中最常见的癌症。相关文献表明，甲状腺疾病和乳腺癌之间可能存在某种关系[1]。乳腺癌患者自身免疫性和非自身免疫性甲状腺疾病的患病率增加[2]。研究中，诊断出甲状腺癌后患乳腺癌的几率更高[3]。一项病例对照研究表明，原发性乳腺癌患者自身免疫性疾病的发病率更高，尤其是在绝经前诊断时[4]。由于目前，关于良性甲状腺疾病与乳腺癌之间的关系尚未达成共识[5]。因此，本研究的目的是帮助阐明甲状腺功能减退(hypothyroidism)、自身免疫性甲状腺炎(Autoimmune thyroiditis)和甲状腺癌(Thyroid carcinoma)等甲状腺疾病在乳腺癌发病中的作用以及相关机制的研究进展。

2. 甲减在 ROS 调控后参与乳腺癌的发生发展

1、乳腺癌是一种高度异质性疾病，具有与其发展相关的大量风险因素，其中就包括甲状腺功能障碍。近期流行病学研究相互矛盾，甲状腺功能减退症和甲状腺功能亢进症都与乳腺癌有关，最近在接种转移性乳腺癌细胞的甲亢小鼠中显示出较高的肿瘤生长率和免疫抑制微环境，而甲减动物的肿瘤生长较低，但肺转移的数量较高。然而其他研究并未表明乳腺癌与甲状腺功能障碍之间存在关联。

2、甲状腺功能减退会导致乳房氧化应激，即通过内源性或外源性损伤累积产生的活性氧(ROS)/活性氮(RNS)被称为氧化应激，从而对机体产生负面作用。活性氧(ROS)可以氧化脂质、蛋白质和 DNA 分子，并可能促进肿瘤发生[6]。活性氧形成的增加会压倒身体的抗氧化保护，并随后诱导 DNA 损伤、脂质过氧化、蛋白质修饰和其他效应，所有这些都是许多疾病的症状[7]。但是目前大量证据证实了 ROS 的“双面”特征，即细胞内的 ROS 在细胞内信号级联中充当二级信使，诱导和维持癌细胞的致癌表型，然而，ROS 也可以诱导细胞衰老和凋亡因此可以作为抗肿瘤物种发挥作用[8]。所以甲状腺功能减退不太可能会影响乳腺癌的临床过程或生存[9]。相反甲状腺功能减退可能会降低乳腺癌的风险[10]。由于 ROS 在乳腺癌中具有的抗肿瘤作用，所以甲状腺功能减退在一定程度上对乳腺癌的发展起到了保护作用。

3. AITD 与乳腺癌的关系

1、几十年来，人们一直在争论乳腺癌与良性甲状腺疾病，特别是甲状腺自身免疫之间的关系。甲状腺自身免疫可能与其他自身免疫性内分泌疾病或非内分泌疾病有关，并且在乳腺癌中存在先天性和适应

性免疫细胞。由于自身免疫因素是甲状腺自身免疫和乳腺癌的共同特征，因此这两种疾病可能在某些患者中同时发生[11]自身免疫性甲状腺炎患者患乳腺癌的风险增加，最近研究表明，甲状腺自身抗体阳性和阴性患者患乳腺癌的优势比(OR)均有所提高[12]。免疫系统在乳腺癌的发生发展中起着复杂的作用，自身免疫因子在乳腺癌的发展中同样发挥至关重要的作用，比如 TPO-Ab 可能与乳腺癌有相关性。

2、大量研究表明，炎症与癌症的发生有着千丝万缕的联系，炎症在癌症的发生发展中起着重要作用[13]。甲状腺自身免疫性疾病，尤其是桥本甲状腺炎，在很大程度上是甲状腺疾病患者增加乳腺癌患病率的原因[14]。目前研究表明患有桥本甲状腺炎的女性更容易患上乳腺癌[15]。一项已发表的研究改变声称自身免疫是乳腺癌的负面预后因素[16]。虽然尚未证明 TPO-Ab 与位于癌性乳腺组织上的受体相互作用。但是自身免疫性阳性患者腋窝淋巴结受累率较低可归因于该组 TPO-Ab 水平较高，诊断前低水平的 TPO-Ab 与乳腺癌风险增加相关，这种增加主要限于侵袭性较低的乳腺癌亚组的较高发病率[17]。可见高水平的 TPO-Ab 在乳腺癌发生发展方面具有一定的保护作用。TPO 在乳腺癌中的表达及其抗原活性可能对 TPO-Ab 阳性乳腺癌患者有益[18]。然而，需要进一步的研究来证实 TPO-Ab 的有益作用并更好地了解潜在的机制。TPO-Ab 作为甲状腺疾病和乳腺疾病的一项监测指标，将有助于识别具有发展甲状腺疾病和乳腺疾病潜在风险的正常受试者，因此有助于密切监测、频繁随访和早期治疗决策，以防止长期发病率和相关疾病[19]。

4. 甲状腺癌与乳腺癌的双向关系

1、乳腺癌和甲状腺癌是女性发病率最高的两种恶性肿瘤，这些癌症经常异时或同步发生。乳腺癌和甲状腺癌在患者中异时或同步发生的频率高于偶然发生的频率[20]。此外甲状腺癌是乳腺癌幸存者中最常见的继发性恶性肿瘤之一[21]。患有甲状腺癌的女性患乳腺癌的风险增加；患有乳腺癌的女性后来发展为甲状腺癌的发生率也相应增加，这种双向关系在世界范围内都有报道。一项荟萃分析表明，甲状腺癌作为乳腺癌的第二原发性恶性肿瘤的风险显着增加[22]。此外，与甲状腺癌后发生第二原发恶性肿瘤的一般风险相比，发生乳腺癌作为甲状腺癌的第二原发恶性肿瘤的风险略有增加。因此乳腺癌和甲状腺癌在发生和发展方面可能存在一些关联，例如激素、遗传易感性或碘化钠同向转运体(NIS)等方面存在某些联系。

2、作为激素反应组织，乳腺和甲状腺共享内分泌信号。乳腺细胞对甲状腺激素信号有反应，并受到甲状腺激素水平改变的影响。甲状腺细胞对性激素，特别是雌激素有反应，并在雌激素刺激下经历促瘤过程[23]。同样乳腺癌组织中雌激素受体蛋白的水平也提供了肿瘤对激素依赖的指示[24]。甲状腺激素作用的典型途径是通过核激素受体甲状腺激素受体 α (TRα)和甲状腺激素受体 β (TRβ)。在这些受体中，TRβ 在乳腺和甲状腺组织中均有表达[25]。一项回顾性病例对照研究中表明，与仅患有乳腺癌的患者相比，并存甲状腺癌的乳腺癌患者组织中雌激素和孕激素受体的表达均显着升高[26]。这一研究表明甲状腺激素在甲状腺癌和乳腺癌的发生发展以及后期的治疗和预后中起到重要作用。

3、有关报道表明甲状腺癌和乳腺癌具有遗传易感性，但是最近一项研究指出，甲状腺癌和乳腺癌家族史患者的 HABP2p.G534E 突变与遗传性无关[27]。这与来自文献和数据库的数据一致，HABP2 的表达在肝脏中最高，在其他 3 个测试组织(乳房、肾脏、脑)中低得多，但在甲状腺中未发现[28] [29]。目前涉及家族性的遗传机制仍然难以捉摸，需要进一步研究。

4、据报道基因畸变(如 BRAF、RAS 和 RET/PTC 重排)是 DTC 的发生、进展和去分化的主要责任，主要通过激活丝裂原活化蛋白激酶(MAPK)和磷酸肌醇 3-激酶(PI3K)/AKT 信号通路。最终，这些改变会导致碘化钠同向转运体(NIS)缺乏[30]。晚期、转移性分化型甲状腺癌(DTCs)预后不良，主要是由于 NIS 表达降低。NIS 的错误定位可能导致 NIS 表达异常，从而导致碘缺乏。因此 NIS 表达数量将会直接影响甲状腺的摄碘功能。除甲状腺外乳腺也存在碘化钠同向转运体(NIS)的表达。相关文献报道碘化钠同向转运体在两个腺体

中均有表达[31]。最近研究不同甲状腺疾病中的乳腺癌患病率及其对风险和结果的影响；甲状腺自身免疫的可能作用、甲状腺肿大、放射性碘治疗的作用、稳定碘的作用、可能的联合抗原碘化钠转运蛋白和甲状腺过氧化物酶与甲状腺－乳腺癌的巧合。但阐明这种关联背后的机制仍然难以捉摸。目前，几乎没有理由将甲状腺洞察力作为一种可能的乳腺癌治疗干预措施[32]。所以 NIS 不太可能是常见的甲状腺/乳腺癌共有抗原[33]。

5. 结语与展望

综上所述，我们认为甲状腺功能减退可以降低乳腺癌的风险，并且甲状腺功能减退对乳腺癌的发生发展起到一定保护作用。AITD 如何通过免疫系统参与乳腺癌的发生发展仍需要更深入的研究。甲状腺癌与乳腺癌之间存在双向联系，但因果关系和确切机制仍需要进一步探讨。近年来，甲状腺癌的发病率持续上升，乳腺癌和甲状腺癌之间的双向联系将引起更多的关注，两种癌症的治疗方法也将持续得到改善。我们建议应让乳腺癌幸存者意识到甲状腺疾病(包括甲状腺恶性肿瘤)可能增加的风险，以便他们进行筛查和随访。

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