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Hans汉斯

甲状腺癌的危险因素研究进展

焦　丽[1*]，张生军[2]

[1]延安大学医学院，陕西　延安
[2]延安大学附属医院腺体血管外科，陕西　延安

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摘　要

目的：了解国内外甲状腺癌发生的危险因素，为进一步制定针对性甲状腺癌发生防治策略提供参考。方法：对国内外相关文献进行检索，提取主题，分别从自身状况、肥胖、性别和生活方式以及居住环境等4个方面总结归纳甲状腺癌发生的危险因素。结果：综述发现，染色体改变以及遗传性疾病、患桥本氏甲状腺炎和(或)系统性红斑狼疮疾病、肥胖、女性、不良的生活习惯以及居住环境均是其危险因素。结论：临床医师通过及时准确识别可改变危险因素，并制定针对性干预措施对其一级预防至关重要，未来可结合我国国情，构建本土化甲状腺癌发生风险预警模型，并制定针对性干预措施，从根源防治，以此降低甲状腺癌的发生率。

关键词

甲状腺癌，危险因素，研究进展

Research Progress on Risk Factors of Thyroid Cancer

Li Jiao[1*], Shengjun Zhang[2]

[1]School of Medicine, Yan'an University, Yan'an Shaanxi
[2]Glandular Vascular Surgery, Affiliated Hospital of Yan'an University, Yan'an Shaanxi

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Abstract

Objective: To investigate the risk factors of thyroid cancer at home and abroad, and to provide reference for further developing targeted prevention and treatment strategies for thyroid cancer.

*通讯作者。

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Methods: The relevant literature at home and abroad was searched, the theme was extracted, and the risk factors of thyroid cancer were summarized from four aspects: personal status, obesity, gender, lifestyle and living environment. Results: The review found that chromosome changes and genetic diseases, Hashimoto's thyroiditis and/or systemic lupus erythematosus disease, obesity, female, poor living habits and living environment were risk factors. Conclusion: Timely and accurate identification of modifiable risk factors by clinicians and the formulation of targeted intervention measures are crucial for primary prevention of thyroid cancer. In the future, based on China's national conditions, a localized thyroid cancer risk early warning model can be built, and targeted intervention measures can be formulated to prevent and treat thyroid cancer from the root cause, so as to reduce the incidence of thyroid cancer.

Keywords

Thyroid Cancer, Risk Factors, Research Progress

1. 引言

甲状腺癌(TC)是目前常见的内分泌癌[1]。TC 分为分化型甲状腺癌(DTC)、甲状腺髓样癌(MTC)和甲状腺未分化癌(ATC)，其中 DTC 占 85%以上[2]。根据几项研究，近几十年来，TC 的患病率显著增加[3]。根据患病率的上升趋势，预计到 2030 年，TC 将成为第四大常见癌症，超过结直肠癌，仅次于乳腺癌、前列腺癌和肺癌[4] [5]。TC 病例的显著增加将不可避免地导致临床和经济负担的大幅增加[6]。因此，本文将总结与甲状腺癌发生有关的一系列危险因素，进而为临床上甲状腺癌的防治策略提供理论价值。

2. 自身状况

国内外相关研究认为染色体改变以及遗传性疾病与 TC 都有关联。Bonnefond S 等人认为：丝裂原活化蛋白激酶(MAPK)和磷酸肌肽 3 激酶-akt (PI3K-AKT)信号通路的激活可能在甲状腺癌的生长中起一定作用[7]。有一项相关研究得出：易位引起的 RAS 癌基因突变和 PAX8/PPARγ 融合蛋白分别在 40%和 30%的受试者中表达，且不受细胞生长的调节，并发现其在滤泡性甲状腺癌中表达[8]。家族性非髓样甲状腺癌可能是遗传易感程度最高的癌症之一，但由于体细胞遗传改变，90%以上的癌症是散发性的[9]。约 3%至 9%的 TC 为家族性非髓样甲状腺癌(FNMTC)，其中 PTC 是最常见的组织学亚型(85%~91%) [10]，与散发性 PTC 相比，家族性 PTC 具有更强的侵袭性，转移早，复发率高，经常需要放射性碘治疗[11]。桥本氏甲状腺炎与甲状腺癌之间的关系长期以来一直是争议的话题[12]。有相关文献报道认为：桥本氏甲状腺炎与甲状腺癌的发生是有关的[13] [14]，一项荟萃分析显示，与良性甲状腺疾病患者相比，甲状腺乳头状癌(PTC)患者的 HT 发生率高 2.77 倍。此外，在甲状腺癌患者中，PTC 患者的 HT 相关性是其他病理类型甲状腺癌患者的 1.99 倍[15]。但至今，桥本氏甲状腺炎与甲状腺恶性肿瘤相关的机制尚不完全清楚。一种可能的解释是基于慢性炎症引起的 DNA 损伤，是指炎症反应可能通过形成活性氧继而引起 DNA 损伤，导致突变，最终导致甲状腺癌的发生发展[16]。有研究表明：患有系统性红斑狼疮多年的患者发生 TC 的风险更高，而羟氯喹治疗可能是一个保护因素[17]。与多结节性甲状腺肿相比，单结节甲状腺的 TC 患病率是否不同还尚不确定[18]。

3. 肥胖

既往有很多研究表明肥胖是会影响甲状腺癌的发病率。例如，Tresallet 等人发现，甲状腺乳头状瘤的直径大于 10 mm 的肥胖患者疾病复发风险是增加的(OR = 3.8, 95% CI: 1.6~8.8, P = 0.03) [19]。Dong Z 等人也同样认为：患者的 BMI 与 PTC 肿瘤大小呈正相关(r = 0.087, P < 0.001)，与正常体重的 PTC 患者相比，超重和肥胖 PTC 患者双侧患病风险更大[20]。此外，研究者还认为患者的 BMI 不仅与癌症的发病率有关，并且与癌症的侵袭性也有关，但肥胖影响甲状腺癌的过程以及机制还需要更多的研究进行阐述[21]。

4. 性别

有相关研究者们发现：甲状腺癌的发病率也存在着性别差异。如 Li CL 等人发现：在两性中，女性肥胖和侵袭性病理特征的比例显著升高。男性和女性之间的主要区别在于肥胖不会增加男性发生甲状腺外扩展(ETE)以及高 T 分期的风险[22]。这可能是由于在一些研究中已表明，外源性雌激素会增加患甲状腺癌的风险，而卵巢雌激素的早期丢失会降低患甲状腺癌的风险。迄今为止进行的许多实验研究表明，雌二醇对良性或恶性肿瘤都具有刺激作用[23]。但雌激素在甲状腺癌发展中的作用在许多流行病学研究中仍然是一个有争议的问题。

5. 生活方式和居住环境

国内外研究发现，某些生活方式以及居住环境与甲状腺癌的发生和发展有一定的关联性。提高对甲状腺癌可改变危险因素的认识将有助对甲状腺癌疾病的准确预防和控制以及治疗。这将为未来研究适合甲状腺癌高危人群的生活方式以及居住环境提供科学依据。

5.1. 吸烟

研究表明，每天吸烟超过 10 支、吸烟超过 15 年、累计吸烟剂量超过 10 支(累积剂量 = 平均每天吸烟次数 × 吸烟年数，以一包 20 支香烟计算)的人患 TC 的风险较低[24]；这与先前的看法相反，并且相当多的研究表明，烟熏实际上是预防 TC 的保护因素[25] [26]，但其潜在机制仍不确定，可能涉及多种机制。需要进一步的研究来全面、清晰地解释吸烟影响 TC 的机制。

5.2. 饮酒

多项研究采用队列研究和病例对照研究发现，饮酒与 TC 呈负相关[27]；同时发现戒除酒精会增加患 TC 的可能性，与饮酒相关的 TC 风险降低的原因可能是由于酒精对甲状腺的毒性作用以及酒精引起的 TSH 水平降低，但其研究中没有明确饮酒剂量与其具体关系[28]。

5.3. 睡眠

一些研究将睡眠质量与 TC 的发生率联系起来，表明良好的睡眠质量和规律的睡眠时间表可以作为预防 TC 的保护因素[29] [30]。当昼夜节律被打乱时，它会损害睡眠质量，这是 TC 的一个独立危险因素[31]。相反，持续的睡眠习惯和睡眠可以降低老年人发生 TC 的风险[32]。

5.4. 饮食习惯

饮食在TC中起着至关重要的作用，因为它会影响甲状腺和甲状腺的分泌[33]。有相关研究结果表明，TC 的风险与食用淀粉类食品、精制谷物、加工食品、富含硝酸盐和亚硝酸盐的脂肪产品以及糖果(尤其是女性)有关。在严重缺碘的地区，高碘摄入量对 TC 有保护作用，尤其是在滤泡 TC 的情况下。相反，在碘摄入量充足的地区，对于 TC 的发病率没有显著影响[34]。研究还发现十字花科蔬菜、豆类、牛奶和

乳制品的摄入对于发生 TC 的风险是降低的[35]。这种风险的降低也与水果消费的增加有关，尤其是柿子和橙子[36]。关于咖啡消费与 TC 风险之间的关联一直存在争议。最近的一项权威分析发现，饮用咖啡与患 TC 的风险之间没有关联[37]。过去，许多研究得出的关于鱼类对 TC 影响的结果不一致。最近一项相关研究通过对混杂因素进行调整后，进一步发现食用鱼类与 TC 之间没有很强的关联[35]。现有的研究只是阐明了饮食和饮食与 TC 之间的一些关联。然而，对于饮食的频率和数量仍然没有统一的共识。需要大量的前瞻性研究来阐明饮食频率和数量与 TC 风险之间的关系。

5.5. 手机使用情况

今天的智能手机不仅用于通话，还用于访问互联网。自 1940 年以来，人们就已经确定辐射是 TC 的独立危险因素，研究同时还发现：智能手机对人类具有潜在的致癌性[38]。这可能是由于智能手机的天线通常位于其底部，由此使用者的颈部甲状腺比大脑更容易受到射频电磁辐射的影响[39] [40]。

5.6. 锻炼

多项研究表明，定期锻炼可以作为预防各种癌症的保护因素[41]。一项回归性研究结果表明：随着运动强度的增加，人类患 TC 的概率越低[42]。Fiore M 等人的相关研究取得了类似结果，他们同时建议每天至少步行 30 m，这可以显著降低患 TC 的风险[43]。此外，现仍然缺乏各种锻炼计划与 TC 之间关联的强度性研究，为了更好地理解运动与 TC 之间的关系，需要进一步控制混杂因素后进行深入探讨两者的关联性。

5.7. 夜间工作或高压下工作

有相关研究表明：夜班工作可导致人体的 TSH、FT3 和 FT4 分泌增加，其中 TSH 已被证实作为 TC 的独立预测因子[44]。同样，高工作压力会导致人体免疫系统发生变化，从而增加患癌症的风险[45]，持续的高压力工作不仅会削弱人体的免疫系统，还会引起一系列炎症[46]，炎症进而使患 TC 的风险增加并且还会加速肿瘤的进展[41]。以前的研究明确表明，工作压力或夜班会增加患 TC 的风险，但目前的研究数量仍然不足。现有的大多数研究都是回顾性的，有一定的回忆偏倚，需要大量的前瞻性研究来确认工作压力或夜班与 TC 之间的关系。

5.8. 居住环境

Suzuki K 等的研究认为：如果人类居住在核电站附近的话，核电站的辐射是电离辐射，它能够诱导甲状腺滤泡细胞的衰老和随后的死亡，进而引起炎性细胞因子的释放，人体就建立了一个炎症环境，从而为甲状腺的初始癌变创造有利的条件，这也是人类应远离核电站居住的重要原因[47]。还有许多研究表明，居住在火山区附近 20 km 以内的人 TC 发生率显著高于居住在无火山区的人，造成这种情况的主要原因是火山地区的暴露会增加各种患癌症的风险[48]。还有可能是位于火山附近的居民地区，砷、硼、镉、汞、锰、硒、钼、钯、铀、钒和钨等浓度比普通无火山居民区的浓度高 3 至 50 倍，其中砷、镉和镉被认为是致癌物[49]，而在其相关性研究中，11 个生活在火山地区的居民身体组织中增加了致癌物质，特别是甲状腺中的砷和砷分别增加了 16.5%和 25% [50]，这也可以解释居住于火山附近的居民患 TC 风险远高于无火山地区的居民。此外，一项研究发现，居住在农药生产厂下风向的居民患 TC 的风险显著增加[51]。2022 年在加利福尼亚州进行的一项相关研究发现，在彼此相距 500 m 以内的居民区接触杀虫剂可被视为 TC 的危险因素，同时研究者认为，发生 TC 的风险随着农药暴露程度的增加而增加，其中草甘膦、羟氟菊、百草枯和苯甲酰等农药已被证实会增加患 TC 的风险[52]，但农药对 TC 的影响机制还存在争议。所以我们还需要进一步的大量前瞻性研究，特别是研究各种农药的协同效应及其可能的作用机制[53]。

6. 总结

近年来，甲状腺癌的发病率显著增加。全球这一数字不断增长的原因仍然未知，很可能是多因素的。据认为，发病率的增加在很大程度上是由于甲状腺超声检查和穿刺活检的广泛应用性，以此检测到更多的小甲状腺肿瘤。然而，根据许多作者的认为，TC 发病率的上升不仅仅是因为通过更高质量的筛查和检测发现来解释，也是和人类长期以来暴露在 TC 的危险因素中有关联。因此本文总结和回顾了许多相关文献，重点总结可能的危险因素，包括染色体和遗传基因改变、自身健康状况、性别、肥胖、生活方式以及居住环境对 TC 的影响。最后，本文对这些危险因素进行详细总结，以期为准确、科学地预防和控制 TC 提供理论依据，以此来提高医师、患者和普通民众对 TC 的认识，并减轻患者和社会的负担和压力。

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