

# 血清睾酮与前列腺癌关系的研究进展

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## 摘要

前列腺癌(Prostate Cancer, PCa)发病率在我国呈上升趋势, 睾酮与PCa密切相关。过去认为高的血清睾酮是PCa的促进因素, 但这一观点正在被逐渐打破, 更多的研究发现治疗前低的血清睾酮水平是PCa的危险因素, 并且接受睾酮替代疗法(Testosterone Replacement Therapy, TRT)似乎不会增加PCa发生和复发风险。本文对低、高血清睾酮水平以及TRT治疗与PCa关系的研究进行了综述。

## 关键词

前列腺癌, 睾酮, 睾酮替代疗法

# Research Progress on the Relationship between Serum Testosterone and Prostate Cancer

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## Abstract

The incidence of prostate cancer (PCa) is increasing in my country, and there is a close association between PCa and testosterone. Previously, it was believed that high levels of serum testosterone promoted PCa, but this belief is gradually being challenged. Recent studies have shown that low levels of serum testosterone before treatment are actually a risk factor for PCa. Furthermore, it has been found that receiving testosterone replacement therapy (TRT) does not increase the risk of developing or recurring PCa. This article provides a comprehensive review of the research on the relationship between low and high levels of serum testosterone, TRT treatment, and PCa.

## Keywords

### Prostate Cancer, Testosterone, Testosterone Replacement Therapy

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## 1. 引言

全球癌症数据显示,前列腺癌(Prostate Cancer, PCa)新发病例数位居第四,占比达 7.3%,PCa 是威胁男性健康的首要癌症,在美国 2023 年预计将有 190 万新发癌症病例和 609,820 人死于癌症,其中 PCa 是美国男性的第一大癌症[1] [2]。睾酮和前列腺特异性抗原均是 PCa 患者的重要监测指标,治疗后血清睾酮达到去势水平是临床目标。但是治疗前血清睾酮水平与 PCa 的关系仍是一个有争论的话题,本文对血清睾酮及睾酮替代疗法(Testosterone Replacement Therapy, TRT)与 PCa 的关系进行了综述。

## 2. 睾酮的生理作用

睾酮是一种类固醇类激素,是人体内主要的雄激素,男女均有。男性 90%以上的睾酮来自睾丸的间质细胞,少部分由肾上腺产生。在人体中,性激素结合球蛋白结合睾酮(40%~50%)、白蛋白结合睾酮(Albumin Binds Testosterone, Alb-T, 30%~50%)和游离睾酮(Free Testosterone, FT, 1%~2%)是血清总睾酮的三种主要存在形式,Alb-T 与 FT 被称为生物可利用睾酮(Bioavailable Testosterone, Bio-T),具有生物活性的 Bio-T 能更好地作为生理状态或是病理状态的监测指标[3]。睾酮对人类健康有着重要的作用,包括增强性欲、力量、免疫功能、对抗骨质疏松症等功效,另一方面睾酮在社会关系参与同性竞争和异性求偶也发挥着作用[4]。随着年龄的增加,男性的体力、身体机能以及性欲也会减退,这可能与睾酮水平密切相关,因为睾酮水平低下的发生率会随着年龄的增长而增加,但睾酮与年龄的关系还不清楚,一项包含 1486 名男性的队列研究发现特定年龄睾酮的中间三分位数水平分别为 409~558 ng/dL (20~24 岁)、413~575 ng/dL (25~29 岁)、359~498 ng/dL (30~34 岁)、352~478 ng/dL (35~39 岁)和 350~473 ng/dL (40~44 岁) [5] [6]。有研究发现,睾酮有助于人类更好地适应社会压力,睾酮可以根据外部社会环境调节人体对外部压力的反应,适宜的睾酮水平可以改善焦虑和抑郁[7] [8]。在男性的泌尿生殖器官前列腺中,不论是良性的前列腺增生还是 PCa 都会受到睾酮的影响,前列腺是雄激素的主要靶器官[9]。

## 3. 低血清睾酮与 PCa 的关系

因为 Huggins 和 Hodges 发现了雄激素剥夺疗法(Androgen Deprivation Therapy, ADT)在 PCa 中的作用,认为 PCa 具有雄激素依赖特性,高雄激素水平一直被作为促进 PCa 的危险因素[10]。上世纪 Morgentaler 等首次发现性腺功能低下的男性 PCa 活检阳性率更高,后续研究中也发现了与 Morgentaler 等人一致的结果[11] [12] [13]。之后越来越多的研究表明低睾酮水平与 PCa 的不良预后有关,睾酮与 PCa 发生发展之间的关系出现了不同的声音。Gao 等在他们的一项多因素分析显示低血清睾酮是根治术后病理升级的独立预测因子( $P = 0.01$ ),同时 Martin 等发现睾酮水平大于 11 nmol/L 是降低生化复发风险的独立预测因子( $HR = 0.53$ , 95% CI 为 0.31~0.90,  $P = 0.02$ ) [14] [15]。其他研究也一致显示,在 ADT 治疗前血清总睾酮较低的 PCa 患者的疾病更具侵袭性、治疗效果和预后更差[16] [17]。

## 4. 高血清睾酮与 PCa 的关系

高血清睾酮水平与 PCa 关系的研究也呈现了不同的结果。Gann [18]等研究发现,与对照组相比,高血清睾酮男性发生 PCa 风险更高(OR = 2.6, 95% CI 为 1.34~5.02,  $P = 0.004$ )。随后的一项 Meta 分析结果支持了 Gann 的发现,但该 Meta 分析只纳入了三项研究从而限制了结果的可靠性[19]。高血清睾酮与 PCa 临床特征关系的研究结果也有所差异,有学者发现治疗前睾酮水平较高的男性病理结果 Gleason  $\geq 8$  分的风险更高,而另有学者认为高血清总睾酮水平与 Gleason  $< 7$  分呈正相关[20] [21]。一项研究认为根治术前睾酮水平是预测早期生化复发的独立因素(HR = 1.43;  $P = 0.03$ ),但是更多更大型的研究表明治疗前高血清睾酮是 PCa 的保护性因素[22] [23] [24]。

## 5. TRT 治疗与 PCa 的关系

PCa 具有雄激素依赖的特性,过去把 TRT 视为 PCa 患者的禁忌,但目前并没有充足可靠的证据表明 TRT 会增加 PCa 诊断和进展的风险[25]。Haider [26]等在他们的前瞻性队列研究中显示,接受 TRT 治疗的性腺功能低下男性中 PCa 的发病率低于长期随访的大型人群研究中的发病率。在对几十项无 PCa 的男性接受 TRT 治疗的前瞻性研究的回顾中,没有研究表明 TRT 和 PCa 风险之间存在关联[27]。Kaplan 等通过大型的流行病学调查显示 TRT 与 PCa 患者总死亡率和癌症特异性死亡率无关, Pastuszak 等也发现根治术后接受 TRT 并不会增加 PCa 患者复发风险[28] [29]。但也有研究显示 PCa 患者在接受 TRT 治疗 15 个月后,43% 的患者出现了 PSA 进展,其中 7 例患者在停药后出现了影像学进展[30]。尽管目前研究有限,但睾酮缺乏男性接受 TRT 似乎不会增加 PCa 风险或 PCa 诊断时发生更具侵袭性疾病的可能性,在局部 PCa 治疗后接受 TRT 似乎也没有更高的复发率或更差的结局,TRT 治疗的患者接受主动监测的早期报告也没发现不良进展事件[31] [32] [33]。

## 6. 总结

血清睾酮水平与 PCa 的关系目前仍有争论,虽然越来越多的证据表明低血清睾酮与 PCa 风险相关,但睾酮和 PCa 的相互作用机制十分复杂,内在机制也未被完全阐明。TRT 对 PCa 患者的安全性问题仍值得讨论。期待更大型更严谨的研究能给出答案。

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## 参考文献

- [1] Sung, H., Ferlay, J., Siegel, R.L., et al. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, **71**, 209-249. <https://doi.org/10.3322/caac.21660>
- [2] Siegel, R.L., Miller, K.D., Wagle, N.S., et al. (2023) Cancer Statistics, 2023. *CA: A Cancer Journal for Clinicians*, **73**, 17-48. <https://doi.org/10.3322/caac.21763>
- [3] Goldman, A.L., Bhasin, S., Wu, F.C.W., et al. (2017) A Reappraisal of Testosterone's Binding in Circulation: Physiological and Clinical Implications. *Endocrine Reviews*, **38**, 302-324. <https://doi.org/10.1210/er.2017-00025>
- [4] Geniole, S.N. and Carré, J.M. (2018) Human Social Neuroendocrinology: Review of the Rapid Effects of Testosterone. *Hormones and Behavior*, **104**, 192-205. <https://doi.org/10.1016/j.yhbeh.2018.06.001>
- [5] Cunningham, G.R., Stephens-Shields, A.J., Rosen, R.C., et al. (2015) Association of Sex Hormones with Sexual Function, Vitality, and Physical Function of Symptomatic Older Men with Low Testosterone Levels at Baseline in the Testosterone Trials. *The Journal of Clinical Endocrinology & Metabolism*, **100**, 1146-1155.

- <https://doi.org/10.1210/jc.2014-3818>
- [6] Zhu, A., Andino, J., Daignault-Newton, S., *et al.* (2022) What Is a Normal Testosterone Level for Young Men? Rethinking the 300 ng/dL Cutoff for Testosterone Deficiency in Men 20-44 Years Old. *Journal of Urology*, **208**, 1295-1302. <https://doi.org/10.1097/JU.0000000000002928>
- [7] Kutlikova, H.H., Durdiaková, J.B., Wagner, B., *et al.* (2020) The Effects of Testosterone on the Physiological Response to Social and Somatic Stressors. *Psychoneuroendocrinology*, **117**, Article ID: 104693. <https://doi.org/10.1016/j.psyneuen.2020.104693>
- [8] Mchenry, J., Carrier, N., Hull, E. and Kabbaj, M. (2014) Sex Differences in Anxiety and Depression: Role of Testosterone. *Frontiers in Neuroendocrinology*, **35**, 42-57. <https://doi.org/10.1016/j.yfrne.2013.09.001>
- [9] Welén, K. and Damber, J.E. (2022) Androgens, Aging, and Prostate Health. *Reviews in Endocrine and Metabolic Disorders*, **23**, 1221-1231. <https://doi.org/10.1007/s11154-022-09730-z>
- [10] Desai, K., Mcmanus, J.M. and Sharifi, N. (2021) Hormonal Therapy for Prostate Cancer. *Endocrine Reviews*, **42**, 354-373. <https://doi.org/10.1210/endrev/bnab002>
- [11] Morgentaler, A., Bruning III, C.O. and Dewolf, W.C. (1996) Occult Prostate Cancer in Men with Low Serum Testosterone Levels. *JAMA*, **276**, 1904-1906. <https://doi.org/10.1001/jama.1996.03540230054035>
- [12] Morgentaler, A. and Rhoden, E.L. (2006) Prevalence of Prostate Cancer among Hypogonadal Men with Prostate-Specific Antigen Levels of 4.0 ng/mL or Less. *Urology*, **68**, 1263-1267. <https://doi.org/10.1016/j.urology.2006.08.1058>
- [13] Shin, B.S., Hwang, E.C., Im, C.M., *et al.* (2010) Is a Decreased Serum Testosterone Level a Risk Factor for Prostate Cancer? A Cohort Study of Korean Men. *Korean Journal of Urology*, **51**, 819-823. <https://doi.org/10.4111/kju.2010.51.12.819>
- [14] Gao, Y., Jiang, C.Y., Mao, S.K., *et al.* (2016) Low Serum Testosterone Predicts Upgrading and Upstaging of Prostate Cancer after Radical Prostatectomy. *Asian Journal of Andrology*, **18**, 639-643. <https://doi.org/10.4103/1008-682X.169984>
- [15] Røder, M.A., Christensen, I.J., Berg, K.D., *et al.* (2012) Serum Testosterone Level as a Predictor of Biochemical Failure after Radical Prostatectomy for Localized Prostate Cancer. *BJU International*, **109**, 520-524. <https://doi.org/10.1111/j.1464-410X.2011.10335.x>
- [16] Dai, B., Qu, Y., Kong, Y., *et al.* (2012) Low Pretreatment Serum Total Testosterone Is Associated with a High Incidence of Gleason Score 8-10 Disease in Prostatectomy Specimens: Data from Ethnic Chinese Patients with Localized Prostate Cancer. *BJU International*, **110**, E667-E672. <https://doi.org/10.1111/j.1464-410X.2012.11465.x>
- [17] Massengill, J.C., Sun, L., Moul, J.W., *et al.* (2003) Pretreatment Total Testosterone Level Predicts Pathological Stage in Patients with Localized Prostate Cancer Treated with Radical Prostatectomy. *Journal of Urology*, **169**, 1670-1675. <https://doi.org/10.1097/01.ju.0000062674.43964.d0>
- [18] Gann, P.H., Hennekens, C.H., Ma, J., *et al.* (1996) Prospective Study of Sex Hormone Levels and Risk of Prostate Cancer. *Journal of the National Cancer Institute*, **88**, 1118-1126. <https://doi.org/10.1093/jnci/88.16.1118>
- [19] Shanefelt, T., Husein, R., Bublely, G. and Mantzoros, C.S. (2000) Hormonal Predictors of Prostate Cancer: A Meta-Analysis. *Journal of Clinical Oncology*, **18**, 847-853. <https://doi.org/10.1200/JCO.2000.18.4.847>
- [20] Platz, E.A., Leitzmann, M.F., Rifai, N., *et al.* (2005) Sex Steroid Hormones and the Androgen Receptor Gene CAG Repeat and Subsequent Risk of Prostate Cancer in the Prostate-Specific Antigen Era. *Cancer Epidemiology, Biomarkers & Prevention*, **14**, 1262-1269. <https://doi.org/10.1158/1055-9965.EPI-04-0371>
- [21] Porcaro, A.B., Petroziello, A., Brunelli, M., *et al.* (2016) High Testosterone Preoperative Plasma Levels Independently Predict Biopsy Gleason Score Upgrading in Men with Prostate Cancer Undergoing Radical Prostatectomy. *Urologia Internationalis*, **96**, 470-478. <https://doi.org/10.1159/000443742>
- [22] Salonia, A., Abdollah, F., Capitanio, U., *et al.* (2013) Preoperative Sex Steroids Are Significant Predictors of Early Biochemical Recurrence after Radical Prostatectomy. *World Journal of Urology*, **31**, 275-280. <https://doi.org/10.1007/s00345-012-0856-7>
- [23] Yamamoto, S., Yonese, J., Kawakami, S., *et al.* (2007) Preoperative Serum Testosterone Level as an Independent Predictor of Treatment Failure following Radical Prostatectomy. *European Urology*, **52**, 696-701. <https://doi.org/10.1016/j.eururo.2007.03.052>
- [24] Ahmadi, H., Allameh, F., Baradaran, N., *et al.* (2011) Circulating Sex Hormones Play No Role in the Association between Sexual Activity and the Risk of Prostate Cancer. *The Journal of Sexual Medicine*, **8**, 905-913. <https://doi.org/10.1111/j.1743-6109.2010.02115.x>
- [25] Morales, A. and Siemens, D.R. (2022) Testosterone Therapy and Prostate Cancer: Incorporating Low-Level Evidence into Practical Recommendations. *Urologic Clinics of North America*, **49**, 573-582. <https://doi.org/10.1016/j.ucl.2022.07.002>

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- [26] Haider, A., Zitzmann, M., Doros, G., *et al.* (2015) Incidence of Prostate Cancer in Hypogonadal Men Receiving Testosterone Therapy: Observations from 5-Year Median Followup of 3 Registries. *Journal of Urology*, **193**, 80-86. <https://doi.org/10.1016/j.juro.2014.06.071>
- [27] Khera, M., Crawford, D., Morales, A., *et al.* (2014) A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications. *European Urology*, **65**, 115-123. <https://doi.org/10.1016/j.eururo.2013.08.015>
- [28] Kaplan, A.L., Trinh, Q.D., Sun, M., *et al.* (2014) Testosterone Replacement Therapy following the Diagnosis of Prostate Cancer: Outcomes and Utilization Trends. *The Journal of Sexual Medicine*, **11**, 1063-1070. <https://doi.org/10.1111/jsm.12429>
- [29] Pastuszak, A.W., Pearlman, A.M., Lai, W.S., *et al.* (2013) Testosterone Replacement Therapy in Patients with Prostate Cancer after Radical Prostatectomy. *Journal of Urology*, **190**, 639-644. <https://doi.org/10.1016/j.juro.2013.02.002>
- [30] Leibowitz, R.L., Dorff, T.B., Tucker, S., *et al.* (2010) Testosterone Replacement in Prostate Cancer Survivors with Hypogonadal Symptoms. *BJU International*, **105**, 1397-1401. <https://doi.org/10.1111/j.1464-410X.2009.08980.x>
- [31] Lenfant, L., Leon, P., Cancel-Tassin, G., *et al.* (2020) Testosterone Replacement Therapy (TRT) and Prostate Cancer: An Updated Systematic Review with a Focus on Previous or Active Localized Prostate Cancer. *Urologic Oncology: Seminars and Original Investigations*, **38**, 661-670. <https://doi.org/10.1016/j.urolonc.2020.04.008>
- [32] Kaplan, A.L., Hu, J.C., Morgentaler, A., *et al.* (2016) Testosterone Therapy in Men with Prostate Cancer. *European Urology*, **69**, 894-903. <https://doi.org/10.1016/j.eururo.2015.12.005>
- [33] Kumar, R., Sena, L.A., Denmeade, S.R. and Kachhap, S. (2023) The Testosterone Paradox of Advanced Prostate Cancer: Mechanistic Insights and Clinical Implications. *Nature Reviews Urology*, **20**, 265-278. <https://doi.org/10.1038/s41585-022-00686-y>