前列腺癌相关危险因素的研究进展

孙殿钦[1],雷　林[2],蔡　颖[3],李　贺[1],曹毛毛[1],何思怡[1],于欣阳[1],彭　绩[2],陈万青[1]
(1. 国家癌症中心/国家肿瘤临床医学研究中心/中国医学科学院北京协和医学院肿瘤医院,北京 100021;2. 深圳市慢性病防治中心,广东 深圳 518020;3. 北京大学公共卫生学院,北京 100191)

摘　要:前列腺癌居全球男性最常见癌症第二位。前列腺癌目前没有明确病因,大量流行病学研究探讨了生活行为、生理、环境和遗传因素与前列腺癌的关系,但研究结果争议较多。本综述总结了前列腺癌相关危险因素的现有流行病学证据,旨在为前列腺癌筛查的人群风险分层以及一级预防提供参考。

关键词:前列腺肿瘤;危险因素;预防;筛查
中图分类号:R737.25　　**文献标识码**:A　　**文章编号**:1004-0242(2020)04-0292-07
doi:10.11735/j.issn.1004-0242.2020.04.A009

Research Advances in Risk Factors for Prostate Cancer

SUN Dian-qin[1],LEI Lin[2],CAI Ying[3],LI He[1],CAO Mao-mao[1],HE Si-yi[1],YU Xin-yang[1],PENG Ji[2],CHEN Wan-qing[1]
(1. National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital,Chinese Academy of Medical Sciences and Peking Union Medical College,Beijing 100021,China;2. Shenzhen Centre for Chronic Disease Control and Prevention,Shenzhen 518020,China;3. School of Public Health,Peking University,Beijing 100191,China)

Abstract:Prostate cancer is the second most common malignancy in men worldwide. There is no definite cause for prostate cancer. Enormous studies have investigated the association of prostate cancer with behavioral,physiological,environmental and genetic factors;however,results are conflicting. This article reviews up-to-date epidemiological evidence on various risk factors for prostate cancer aiming to benefit risk-based screening and primary prevention of prostate cancer.

Key words:prostate neoplasms;risk factor;prevention;screening

前列腺癌是全球男性第二位最常见的恶性肿瘤[1]。中国前列腺癌的发病率与西方国家相比较低，但近年一直呈上升趋势[2]。基于前列腺特异性抗原(prostate-specific antigen,PSA)的前列腺癌筛查可降低筛查人群前列腺癌死亡率[3-4],但会造成过度诊断[5],导致过度治疗及医疗资源的浪费。考虑到过度诊断和过度治疗的问题,学界对于前列腺癌筛查一直存在争议。美国预防服务工作组 2012 年指南反对 PSA 筛查前列腺癌,2018 年指南改为推荐 55 至 69 岁的男性视个体情况接受PSA 筛查。欧洲泌尿外科学会认为预期寿命大于 10~15 年的男性可基于个人风险考虑前列腺癌筛查。为了提高筛查效率并减少过度诊断,识别出可能从筛查中受益的高危个体，有效定位筛查人群是十分必要的。基于风险分层的筛查方法已经在乳腺癌和肺癌筛查中得到应用，能够提高筛查效益和效率[6-7]。一项模型研究表明基于风险分层的前列腺癌筛查可减少过度诊断并提高成本效益[8]。明确前列腺癌的危险因素是进行人群风险分层的基础。然而前列腺癌目前公认的风险因素仅包括年龄、种族和家族史,大量流行病学研究虽对生活行为、生理、环境和遗传因素与前列腺癌的关系进行了探讨,但研究结果并不一致甚至差异较大[9-10]。本综述总结了前列腺癌相关危险因素的现有流行病学证据,旨在为前列腺癌筛查的人群风险分层以及一级预防提供参考。

1　生活行为因素

1.1　吸　烟

尽管大量研究证实吸烟是多种癌症的危险因素,但吸烟与前列腺癌的关系仍存在争议。最近一项

收稿日期:2020-01-07;修回日期:2020-02-18
基金项目:深圳医疗卫生三名工程(SZSM201911015);中国医学科学院医学与健康科技创新工程(2016-I2M-2-004)
通信作者:陈万青,E-mail:chenwq@cicams.ac.cn

基于19个欧美人群队列的897 021例个体数据Meta分析表明,吸烟者较从不吸烟者前列腺癌发病风险更低 (relative risk [RR]:0.81,95% confidence interval [CI]:0.72~0.91),但吸烟与前列腺癌死亡的相关性无统计学意义(RR:1.26,95%CI:0.97~1.64)[11]。并且研究者们发现这种关联只存在于吸烟与早期前列腺癌之间,吸烟与晚期前列腺癌发病的相关性无统计学意义[12-13]。对于吸烟对早期前列腺癌的保护效应,可能的解释是从不吸烟者较吸烟者健康意识更强,倾向于接受前列腺癌筛查,因而被诊断前列腺癌的几率更高[11]。Islami等[14]人的Meta分析佐证了这一观点,他们同样发现了吸烟会降低前列腺癌发病风险(RR:0.90,95%CI:0.85~0.96),但他们对1995年之前(未开展前列腺癌筛查时期)的研究进行Meta分析发现,吸烟与前列腺癌发病呈正相关(RR:1.06,95%CI:1.00~1.12)。未来研究需将吸烟者与不吸烟者前列腺癌筛查率纳入考虑,进一步明确吸烟与前列腺癌之间是否存在因果关联。

1.2 饮 酒

关于饮酒与前列腺癌发病的关系现有证据并不一致。Vartolomei等[15]人的Meta分析发现饮白酒是前列腺癌的危险因素 (RR:1.26,95%CI:1.10~1.43),而饮红酒是前列腺癌的保护因素(RR:0.88,95%CI:0.78~0.999)。此外,Michael等[16]人的研究发现在15~19岁每周饮酒大于等于7次者成年后高级别前列腺癌发病风险更高 (OR:3.21,95%CI:1.22~8.41)。然而医疗专业人员随访研究(health professionals follow-up study,HPFS)对47 568名男性随访26年却发现,与不饮酒相比,饮酒可降低致死性前列腺癌(存在远处转移或因前列腺癌死亡)的发病风险(hazard ratio [HR]:0.84,95%CI:0.71~0.99)[17]。

1.3 膳 食

膳食营养因素在预防癌症中的作用备受关注,也因营养流行病学的复杂性和不完善而争议较多。西红柿、绿茶、硒及维生素E等含有抗氧化活性成分,被认为可能是前列腺癌的潜在保护因素。Rowles等[18]人的Meta分析发现西红柿摄入量较高组前列腺癌发病风险较低(RR:0.81,95%CI:0.71~0.92)。在高级别前列腺上皮内瘤变患者中开展的随机对照试验表明绿茶儿茶素可降低前列腺癌的发病风险[19]。硒和维生素E预防癌症试验 (selenium and vitamin e cancer prevention trial,SELECT) 因没有证据显示前列腺癌发病率下降而被提前终止,维生素E补充剂组的前列腺癌发病风险较安慰剂组显著增加(HR:1.17,99%CI:1.004~1.36),硒补充剂组的发病风险有增加但无统计学意义(HR:1.09,99%CI:0.93~1.27)[20]。黄豆含有植物雌激素,或许可通过改变男性体内激素环境以降低前列腺癌发生风险。多项病例-对照研究以及Meta分析为黄豆的潜在保护作用提供了支持[21-22]。在153例PSA升高患者中开展的随机对照试验发现服用大豆异黄酮组和对照组的前列腺癌检出率没有明显区别,但在65岁及以上研究对象中,两组差别有统计学意义 (28.0% *vs* 57.1%,P=0.031) [23]。有证据提示乳制品摄入会增加前列腺癌风险,López-Plaza等[24]人对现有Meta分析再分析后认为基于现有证据仍不能得出明确结论。此外,一项孟德尔随机化研究还发现单不饱和脂肪酸是前列腺癌的保护因素(OR:1.11,95%CI:1.02~1.20)[25]。

近年来,膳食模式对癌症的影响受到越来越多的关注。膳食炎症指数 (dietary inflammatory index,DII)是评估膳食中炎症成分多少的指标。通过衡量食物对特定炎症标志物的影响对每种食物进行评分,将食物得分乘摄入量可求得炎症指数得分。2018年以来发表的4篇Meta分析均表明高DII饮食(饱和脂肪酸和碳水化合物占比较高)会增加前列腺癌发病风险[26-29]。Zhu等[27]人的Meta分析表明DII每升高一个单位,前列腺癌发病风险增高10%(OR:1.10,95%CI:1.04~1.17)。Schwingshackl等[30]人的一项Meta分析发现,地中海饮食(蔬菜水果、全谷物、豆类和坚果占比较高)是前列腺癌的保护因素,但效应有限(RR:0.96,95%CI:0.92~1.00)。

1.4 体力活动

体力活动与前列腺癌发病的关系仍无定论。两篇最近发表的Meta分析均未发现体力活动与前列腺癌发病有相关性[31-32]。然而,2019年的一篇孟德尔随机化研究表明加速度计测量的体力活动水平是前列腺癌发病的保护因素(OR:0.49,95%CI:0.33~0.72)[25]。研究者们试图用检出偏倚来解释现有证据的不一致,有研究表明体力活动多的人更倾向于规律地进行前列腺癌筛查,因而被诊断前列腺癌的可能性更大[33]。基于HPFS队列49 160人26年的随访结果,Pernar等[33]人发现经常剧烈运动的男性患晚期前列

腺癌(HR:0.70,95%CI:0.53~0.92)或致死性前列腺癌(HR:0.75,95%CI:0.59~0.94)的风险较低,并且剧烈运动与局限性前列腺癌和所有前列腺癌发病的关联无统计学意义。但作者在仅对筛查次数高的人群进行分析后发现剧烈运动是局限性前列腺癌(HR:0.82,95% CI:0.68 ~0.98) 和所有前列腺癌(HR:0.83,95%CI:0.70~0.97)的保护性因素,提示检出偏倚或许会掩盖剧烈运动的保护效应。

1.5 性生活

现有证据表明,射精频率、性伴数量可能与前列腺癌发病有关。最近的一项剂量反应 Meta 分析表明每周射精 2~4 次患前列腺癌的风险最低(OR:0.91,95%CI:0.87~0.96)[34]。一项对 31 925 名男性随访十年的队列研究发现,在 20~29 岁时射精频率大于 21 次/月者较 4~7 次/月者的风险比为 0.81 (95% CI:0.72~0.92),在 40~49 岁时射精频率大于 21 次/月的男性相比于 4~7 次/月者发生前列腺癌的风险更低(HR:0.78,95%CI:0.69~0.89)[35]。Jian 等[34]人的 Meta 分析表明性伴数量越多的男性患前列腺癌的风险越大 (OR:1.10,95%CI:1.01~1.21)。一项纳入 1181 个病例和 875 个对照的病例对照研究发现与性伴数量小于三个的男性相比,一生中性伴数量大于七个的男性前列腺癌发病风险升高一倍(OR:2.00,95%CI:1.49~2.68)[36]。尽管有证据提示输精管结扎术与晚期前列腺癌发病有关[37],但大多数研究并不支持输精管结扎术会增大前列腺癌发病或死亡风险[38-40]。2017 年的一篇 Meta 分析发现输精管结扎术与前列腺癌发病关联微弱(RR:1.05,95%CI:1.02~1.09),与高危或致死性前列腺癌均无统计学意义相关性[41]。此外,输精管结扎术后复通对前列腺癌发病并未呈现保护作用[42]。

2 生理因素

2.1 身高和肥胖

2016 年的一篇 umbrellareview 在对 34 篇研究进行分析后,认为有较为充分的证据表明身高与前列腺癌存在相关性 (RR:1.04,95%CI:1.03~1.05)[10]。但两项孟德尔随机化研究均未发现身高与前列腺癌相关[43-44],提示之前观察到的身高与前列腺癌的关系反映的可能是与身高相关的早期环境因素与前列腺癌的相关性。一篇纳入 27 项研究的 Meta 分析表明肥胖与前列腺癌发病率之间存在微弱的相关性(RR:1.03,95%CI:1.00~1.07)。但两项孟德尔随机化研究未发现肥胖与前列腺癌相关[44-45]。有证据显示 BMI 增加与血清 PSA 下降有关[46-47],而后者可能造成前列腺癌的漏诊,因此辨明肥胖对前列腺癌的真实影响可能较为困难。

2.2 炎症和感染

慢性炎症和感染一直被视为癌症的重要危险因素。多项 Meta 分析[48-49]表明前列腺炎与前列腺癌发病有很强的关联,但前列腺炎可能带来的检出偏倚并未得到充分考虑,并且有证据表明前列腺炎患者 PSA 水平会升高[50],更加大了前列腺炎患者接受前列腺组织活检的概率。2019 年的一篇 Meta 分析发现前列腺炎与前列腺癌明显正相关(OR:2.05,95% CI:1.64~2.57),但在考虑检出偏倚仅纳入方法学足够严谨的研究后,结果显示前列腺炎与前列腺癌相关性并没有统计学意义 (OR:1.16,95%CI:0.77~1.74)[51]。炎症性肠病包括溃疡性结肠炎和克罗恩病,近年来被认为可能是前列腺癌的潜在危险因素。最近的 Meta 分析表明炎症性肠病患者 (standardized incidence ratio [SIR]:1.33,95%CI:1.03~1.71)特别是溃疡性结肠炎患者(SIR:1.58,95%CI:1.08~2.30)患前列腺癌风险升高[52]。

有证据提示患淋病的男性前列腺癌发病风险增高[53-54]。一篇纳入 6 项病例对照研究的 Meta 分析表明感染过阴道毛滴虫的男性前列腺癌发病风险增高(OR:1.17,95%CI:1.01~1.36)[55]。基于医师健康研究(physicians' health study,PHS)的巢式病例对照研究[56]报道阴道毛滴虫感染会增高晚期前列腺癌的发病风险(OR:2.69,95%CI:1.37~5.28)。但最近 Tsang 等[57]人基于 HPFS 和 PHS 队列的研究未发现阴道毛滴虫感染与前列腺癌死亡有关。

2.3 性激素

雄激素与前列腺癌的进展密切相关,Huggins 教授因发现去势治疗能缓解前列腺癌而获得诺贝尔医学和生理学奖。但雄激素是否与前列腺癌发病有关仍无定论。Klap 等[58]人总结了 45 篇文献后发现,有 18 篇文献报道了雄激素水平与前列腺癌负相关,17 篇研究报道了两者正相关,另外 10 篇文章认为两者没有关系。其中,一项纳入 3886 例前列腺癌患者和 6438 例对照的巢式病例对照研究方法学较为完善,

发现前列腺癌发病与多种性激素水平包括雄激素水平均无关[59]。

2.4 药　物

流行病学证据表明他汀类药物、二甲双胍和非甾体类消炎药可能有预防癌症的效果。他汀类药物与前列腺癌的关系尚存争议，但大多数证据支持其可降低晚期前列腺癌的发病风险[60-61]。二甲双胍预防前列腺癌的效果备受关注，最近的 Meta 分析表明二甲双胍与前列腺癌发病无关，但对前列腺癌患者预后可能会有改善作用[62-64]。一项包含 12 226 例病例和 122 260 例对照的巢式病例对照研究发现二甲双胍可以降低前列腺癌发病风险(OR：0.84，95%CI：0.74~0.96) [65]。然而该发现并未得到后续研究的支持[66-67]。非甾体类消炎药(nonsteroidal anti-inflammatory drug，NSAID)特别是阿司匹林应用广泛，价廉易得，其潜在的抗癌效果一直是热点问题，2018 年发表的两篇 Meta 分析提供了支持性证据[68-69]。Jacobs 等[70]对 70 144 名男性随访 9 年发现长期规律使用 NSAID 可降低前列腺癌风险(RR：0.82，95% CI：0.71~0.94)，一项随机对照试验表明现在规律服用阿司匹林或曾经规律服用都可以降低致死性前列腺癌的风险 (现在服用 RR：0.68，95%CI：0.52~0.89；曾经服用 RR：0.54，95%CI：0.40~0.74)[71]。

5-α 还原酶可将睾酮还原为活性更强的双氢睾酮，因此，5-α 还原酶抑制剂被寄希望于可以降低前列腺癌发病风险。非那雄胺和度他雄胺的随机对照试验证实 5-α 还原酶抑制剂虽可降低前列腺癌风险，但可能会增加晚期前列腺癌发生风险[72-73]。后续对非那雄胺的临床试验数据二次分析提示可能是因为非那雄胺缩小了前列腺体积，增大了 PSA 筛查和直肠指检的灵敏度[74]。近期 Unger 等[75]结合非那雄胺临床试验数据与美国医疗照顾保险索赔数据，发现受试者在整个随访期间 (中位随访时间 16 年)与安慰剂组相比降低了 21.1% 的发病风险(HR：0.79，95%CI：0.74~0.84)，提示服用一定期限(7 年)5-α 还原酶抑制剂在预防前列腺癌方面可能确实有长期益处。

3　环境因素

有证据提示橙剂、双酚 A、石棉等环境致癌物可能是前列腺癌的危险因素，此类研究较少并且较难开展，但对于致癌赔偿的判定会有重要意义。一项针对越南老兵的队列研究发现橙剂暴露史会增高前列腺癌发病风险(OR：2.19，95%CI：1.75~2.75)[76]，但该发现未得到后续证据支持。Chang 等[77]人总结分析了橙剂或二噁英与前列腺癌关系的文献，认为现有证据不足以说明橙剂或二噁英暴露会导致前列腺癌。双酚 A 广泛存在于日用品中，香港的一项包含 431 例病例和 402 例对照的病例对照研究显示，双酚 A 暴露与前列腺癌发病风险存在剂量反应关系(暴露量最高组 *vs* 最低组 OR：1.57，95%CI：1.01~2.44)[78]。澳大利亚的一项队列研究发现居住环境可能存在石棉暴露的男性前列腺癌发病率较高(SIR：1.29，95%CI：1.07~1.54) [79]。电离辐射被国际癌症研究署列为一类致癌物。一项纳入 431 例前列腺癌患者及 409 例对照的病例对照研究发现，五年前接受钡剂灌肠(OR：2.06，95%CI：1.01~4.20)和骨盆 X 光片(OR：2.23，95%CI：1.42~3.49)的研究参与者前列腺癌风险增高[80]。非电离辐射紫外线暴露对前列腺癌却可能会有保护作用[81-82]，这可能与维生素 D 合成有关。

4　遗传因素

种族和家族史是前列腺癌目前较为明确的危险因素。众多研究表明黑人男性较其他人种前列腺癌的发病风险明显要高。与白人男性相比，非洲裔美国人的前列腺癌发病风险升高 81% (RR：1.81，95%CI：1.27~2.58)[83]，晚期前列腺癌发病风险升高 1.16 倍(OR：2.26，95%CI：1.43~3.58)[84]。在小于 50 岁的男性中，非洲裔美国人的前列腺癌发病率也显著高于白人(8.3% *vs* 3.3%，*P*<0.0001)[85]。一项 Meta 分析报道有一个一级亲属患前列腺癌的男性前列腺癌发病风险升高 1.48 倍(RR：2.48，95%CI：2.25~2.74)，有多个一级亲属患前列腺癌的男性发病风险升高 3.39 倍(RR：4.39，95%CI：2.61~7.39)[86]。最近的北欧双生子研究估计 57%的前列腺癌风险可归因于遗传因素[87]。目前全基因组关联分析 (genome-wide association study，GWAS) 已经识别出超过 160 个易感基因位点，可以解释超过 30%的前列腺癌家族风险[88]。其中多个研究证实 BRCA1、BRCA2、MMR、HOXB13、

CHEK2 和 NBS1 基因携带者前列腺癌发病风险升高[89]。英国的一项研究表明 BRCA2 携带者 65 岁前患前列腺癌的概率甚至高达 15%[90]。英国的研究者们计划在 BRCA1/2 突变基因携带者和非携带者中开展持续 5 年的 PSA 筛查，初始结果显示携带者的前列腺癌检出率更高并且前列腺癌分期更高[91]。前列腺癌相关 GWAS 研究目前多集中在欧美国家，亚洲人群数据较少，发现的易感基因位点仍待在亚洲人群中进一步验证。

5 其他因素

经常倒夜班可能会促使激素分泌紊乱，两篇 Meta 分析表明倒夜班会增加前列腺癌风险[92-93]，但固定夜班工作与前列腺癌发病无关。一些农药有雌激素特性，长期接触农药可能是前列腺癌的潜在危险因素[94]，需要使用农药的农民与不接触农药的农民相比患前列腺癌的风险较高(HR：1.20，95%CI：1.01~1.42)[95]。此外，有研究提示矿工[96]前列腺癌发病率较普通人群更低(OR：0.35，95%CI：0.16~0.75)，但这种关联可能是健康工人效应造成的偏倚。

6 小 结

由于前列腺癌起病隐匿、发展较慢，在 PSA 筛查参与率较高的地区，无症状前列腺癌检出率较高，容易出现检出偏倚而混淆暴露因素与前列腺癌的真实关联。因此，在进行或者评价前列腺癌危险因素研究时，遇到以下三种情况应充分考虑检出偏倚带来的影响：①暴露因素与研究对象的健康意识相关，如吸烟、体育锻炼等；②暴露因素与 PSA 水平相关，如肥胖、5-α 还原酶抑制剂等；③暴露因素为泌尿系统疾病，如前列腺增生、前列腺炎等。一些研究还提示生命早期暴露是前列腺癌的潜在危险因素，如青少年时期饮酒[16]等。生命早期暴露以及生命历程累积暴露等的影响值得进一步探讨。个人风险预测模型是实施基于风险分层筛查的有效工具。本综述总结了前列腺癌相关危险因素的研究进展，可为一级预防和模型预测变量的选择提供参考。生物标志物如 PSA 等可作为前列腺癌发病风险预测变量，但不在本综述讨论范围之内。此外，危险因素在不同人群中的分布情况、前列腺癌的人群分期分布特征以及前列腺癌筛查的人群参与率等对相关研究结果可能造成影响，需审慎外推研究结论。

参考文献：

[1] Bray F，Ferlay J，Soerjomataram I，et al. Global cancer statistics 2018：globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA Cancer J Clin，2018，68(6)：394-424.

[2] Culp MB，Soerjomataram I，Efstathiou JA，et al. Recent global patterns in prostate cancer incidence and mortality rates[J]. Eur Urol，2020，77(1)：38-52.

[3] Tsodikov A，Gulati R，Heijnsdijk EAM，et al. Reconciling the effects of screening on prostate cancer mortality in the erspc and plco trials [J]. Ann Intern Med，2017，167(7)：449-455.

[4] Osses DF，Remmers S，Schröder FH，et al. Results of prostate cancer screening in a unique cohort at 19yr of follow-up[J]. Eur Urol，2019，75(3)：374-377.

[5] Fenton JJ，Weyrich MS，Durbin S，et al. Prostate-specific antigen-based screening for prostate cancer：evidence report and systematic review for the us preventive services task force[J]. JAMA，2018，319(18)：1914-1931.

[6] Katki HA，Kovalchik SA，Berg CD，et al. Development and validation of risk models to select ever-smokers for CT lung cancer screening[J]. JAMA，2016，315(21)：2300-2311.

[7] Ten Haaf K，Jeon J，Tammemagi MC，et al. Risk prediction models for selection of lung cancer screening candidates：a retrospective validation study [J]. PLoS Med，2017，14(4)：e1002277.

[8] Callender T，Emberton M，Morris S，et al. Polygenic risk-tailored screening for prostate cancer：a benefit-harm and cost-effectiveness modelling study[J]. PLoS Med，2019，16(12)：e1002998.

[9] Brookman-May SD，Campi R，Henríquez JDS，et al. Latest evidence on the impact of smoking，sports，and sexual activity as modifiable lifestyle risk factors for prostate cancer incidence，recurrence，and progression：a systematic review of the literature by the european association of urology section of oncological urology (esou) [J]. Eur Urol Foc，2019，5(5)：756-787.

[10] Markozannes G，Tzoulaki I，Karli D，et al. Diet，body size，physical activity and risk of prostate cancer：an umbrella review of the evidence[J]. Eur J Cancer，2016，69：61-69.

[11] Ordóñez-Mena JM，Schöttker B，Mons U，et al. Quantification of the smoking-associated cancer risk with rate advancement periods：Meta-analysis of individual participant data from cohorts of the chances consortium[J]. BMC Med，2016，14(1)：62.

[12] Rohrmann S，Linseisen J，Allen N，et al. Smoking and the risk of prostate cancer in the european prospective investigation into cancer and nutrition[J]. Br J Cancer，2013，108(3)：708-714.

[13] Watters JL，Park Y，Hollenbeck A，et al. Cigarette smoking and prostate cancer in a prospective us cohort study [J]. Cancer Epidemiol Biomarkers Prev，2009，18(9)：2427.

[14] Islami F，Moreira DM，Boffetta P，et al. A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies [J]. Eur Urol，2014，66(6)：1054-1064.

[15] Vartolomei MD，Kimura S，Ferro M，et al. The impact of moderate wine consumption on the risk of developing prostate cancer[J]. Clin Epidemiol，2018，10：431-444.

[16] Michael J，Howard LE，Markt SC，et al. Early-life alcohol intake and high-grade prostate cancer：results from an equal-access，racially diverse biopsy cohort[J]. Cancer Prev Res，2018，11(10)：621.

[17] Downer MK，Kenfield SA，Stampfer MJ，et al. Alcohol intake and risk of lethal prostate cancer in the health profes-

sionals follow-up study [J]. J Clin Oncol, 2019, 37(17): 1499–1511.
[18] Rowles JL 3rd, Ranard KM, Applegate CC, et al. Processed and raw tomato consumption and risk of prostate cancer: a systematic review and dose-response meta-analysis [J]. Prostate Cancer Prostatic Dis, 2018, 21(3): 319–336.
[19] Brausi M, Rizzi F, Bettuzzi S. Chemoprevention of human prostate cancer by green tea catechins: Two years later. A follow-up update[J]. Eur Urol, 2008, 54(2): 472–473.
[20] Klein EA, Thompson IM, Jr., Tangen CM, et al. Vitamin e and the risk of prostate cancer: The selenium and vitamin e cancer prevention trial (select)[J]. JAMA, 2011, 306(14): 1549–1556.
[21] Applegate CC, Rowles JL, Ranard KM, et al. Soy consumption and the risk of prostate cancer: an updated systematic review and meta-analysis[J]. Nutrients, 2018, 10(1): E40.
[22] Yan L, Spitznagel EL. Meta-analysis of soy food and risk of prostate cancer in men [J]. Int J Cancer, 2005, 117(4): 667–669.
[23] Miyanaga N, Akaza H, Hinotsu S, et al. Prostate cancer chemoprevention study: an investigative randomized control study using purified isoflavones in men with rising prostate-specific antigen[J]. Cancer Sci, 2012, 103(1): 125–130.
[24] López-Plaza B, Bermejo LM, Santurino C, et al. Milk and dairy product consumption and prostate cancer risk and mortality: an overview of systematic reviews and meta-analyses[J]. Adv Nutr, 2019, 10(suppl_2): S212–S223.
[25] Kazmi N, Haycock P, Tsilidis K, et al. Appraising causal relationships of dietary, nutritional and physical-activity exposures with overall and aggressive prostate cancer: two-sample mendelian-randomization study based on 79 148 prostate-cancer cases and 61 106 controls [J]. Int J Epidemiol, 2019.[Epub ahead of print]
[26] Mohseni R, Abbasi S, Mohseni F, et al. Association between dietary inflammatory index and the risk of prostate cancer: a meta-analysis[J]. Nutr Cancer, 2019, 71(3): 359–366.
[27] Zhu Y, Li Q, Xu X. Dietary inflammatory index and the risk of prostate cancer: a dose-response meta-analysis [J]. Eur J Clin Nutr, 2019.[Epub ahead of print]
[28] Moradi S, Issah A, Mohammadi H, et al. Associations between dietary inflammatory index and incidence of breast and prostate cancer: a systematic review and meta-analysis [J]. Nutrition, 2018, 55–56: 168–178.
[29] Jayedi A, Emadi A, Shab-Bidar S. Dietary inflammatory index and site-specific cancer risk: a systematic review and dose-response meta-analysis[J]. Adv Nutr, 2018, 9(4): 388–403.
[30] Schwingshackl L, Hoffmann G. Adherence to mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies [J]. Int J Cancer, 2014, 135(8): 1884–1897.
[31] Benke IN, Leitzmann MF, Behrens G, et al. Physical activity in relation to risk of prostate cancer: a systematic review and meta-analysis[J]. Ann Oncol, 2018, 29(5): 1154–1179.
[32] Liu F, Wang J, Wu HL, et al. Leisure time physical activity and risk of prostate cancer: a dose-response meta-analysis[J]. Minerva Urol Nefrol, 2018, 70(2): 152–161.
[33] Pernar CH, Ebot EM, Pettersson A, et al. A prospective study of the association between physical activity and risk of prostate cancer defined by clinical features and tmprss2: Erg[J]. Eur Urol, 2019, 76(1): 33–40.
[34] Jian Z, Ye D, Chen Y, et al. Sexual activity and risk of prostate cancer: a dose-response meta-analysis[J]. J Sex Med, 2018, 15(9): 1300–1309.
[35] Rider JR, Wilson KM, Sinnott JA, et al. Ejaculation frequency and risk of prostate cancer: updated results with an additional decade of follow-up [J]. Eur Urol, 2016, 70(6): 974–982.
[36] Nair-Shalliker V, Yap S, Nunez C, et al. Adult body size, sexual history and adolescent sexual development, may predict risk of developing prostate cancer: results from the new south wales lifestyle and evaluation of risk study (clear)[J]. Int J Cancer, 2017, 140(3): 565–574.
[37] Siddiqui MM, Wilson KM, Epstein MM, et al. Vasectomy and risk of aggressive prostate cancer: a 24-year follow-up study[J]. J Clin Oncol, 2014, 32(27): 3033–3038.
[38] Nayan M, Hamilton RJ, Macdonald EM, et al. Vasectomy and risk of prostate cancer: population based matched cohort study[J]. BMJ, 2016, 355: i5546.
[39] Jacobs EJ, Anderson RL, Stevens VL, et al. Vasectomy and prostate cancer incidence and mortality in a large us cohort[J]. J Clin Oncol, 2016, 34(32): 3880–3885.
[40] Shoag J, Savenkov O, Christos PJ, et al. Vasectomy and risk of prostate cancer in a screening trial[J]. Cancer Epidemiol Biomarkers Prev, 2017, 26(11): 1653.
[41] Bhindi B, Wallis CJD, Nayan M, et al. The association between vasectomy and prostate cancer: a systematic review and meta-analysis[J]. JAMA Intern Med, 2017, 177(9): 1273–1286.
[42] Randall S, Boyd J, Fuller E, et al. The effect of vasectomy reversal on prostate cancer risk: international meta-analysis of 684, 660 vasectomized men[J]. J Urol, 2018, 200(1): 121–125.
[43] Khankari NK, Shu XO, Wen W, et al. Association between adult height and risk of colorectal, lung, and prostate cancer: results from meta-analyses of prospective studies and mendelian randomization analyses[J]. PLoS Med, 2016, 13(9): e1002118.
[44] Davies NM, Gaunt TR, Lewis SJ, et al. The effects of height and bmi on prostate cancer incidence and mortality: a mendelian randomization study in 20, 848 cases and 20, 214 controls from the practical consortium [J]. Cancer Causes Control, 2015, 26(11): 1603–1616.
[45] Gao C, Patel CJ, Michailidou K, et al. Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer [J]. Int J Epidemiol, 2016, 45(3): 896–908.
[46] Bañez LL, Hamilton RJ, Partin AW, et al. Obesity-related plasma hemodilution and psa concentration among men with prostate cancer[J]. JAMA, 2007, 298(19): 2275–2280.
[47] Freedland SJ, Platz EA, Presti JC, Jr., et al. Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection[J]. J Urol, 2006, 175(2): 500–504; discussion 504.
[48] Jiang J, Li J, Yunxia Z, et al. The role of prostatitis in prostate cancer: Meta-analysis[J]. PLoS One, 2013, 8(12): e85179.
[49] Perletti G, Monti E, Magri V, et al. The association between prostatitis and prostate cancer. Systematic review and meta-analysis [J]. Archivio Italiano di Urologia e Andrologia, 2017, 89(4): 259–265.
[50] Bozeman CB, Carver BS, Eastham JA, et al. Treatment of chronic prostatitis lowers serum prostate specific antigen [J]. J Urol, 2002, 167(4): 1723–1726.
[51] Langston ME, Horn M, Khan S, et al. A systematic review and meta-analysis of associations between clinical prostatitis and prostate cancer: new estimates accounting for detection bias[J]. Cancer Epidemiol Biomarkers Prev, 2019, 28(10): 1594–1603.
[52] Ge Y, Shi Q, Yao W, et al. The association between inflammatory bowel disease and prostate cancer risk: a meta-analysis[J]. Prostate Cancer Prostatic Dis, 2019.[Epub ahead of print]
[53] Wang YC, Chung CH, Chen JH, et al. Gonorrhea infection increases the risk of prostate cancer in asian population: a nationwide population-based cohort study [J]. Eur J Clin Microbiol Infect Dis, 2017, 36(5): 813–821.
[54] Vázquez-Salas RA, Torres-Sánchez L, López-Carrillo L, et al. History of gonorrhea and prostate cancer in a population-based case-control study in mexico[J]. Cancer Epidemiol, 2016, 40: 95–101.
[55] Najafi A, Chaechi Nosrati MR, Ghasemi E, et al. Is there association between trichomonas vaginalis infection and prostate cancer risk? A systematic review and meta-analysis[J]. Microb Pathog, 2019, 137: 103752.

[56] Stark JR, Judson G, Alderete JF, et al. Prospective study of trichomonas vaginalis infection and prostate cancer incidence and mortality: Physicians' health study [J]. J Natl Cancer Inst, 2009, 101(20): 1406–1411.
[57] Tsang SH, Peisch SF, Rowan B, et al. Association between trichomonas vaginalis and prostate cancer mortality[J]. Int J Cancer, 2019, 144(10): 2377–2380.
[58] Klap J, Schmid M, Loughlin KR. The relationship between total testosterone levels and prostate cancer: a review of the continuing controversy[J]. J Urol, 2015, 193(2): 403–413.
[59] Roddam AW, Allen NE, Appleby P, et al. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies [J]. J Natl Cancer Inst, 2008, 100 (3): 170–183.
[60] Alfaqih MA, Allott EH, Hamilton RJ, et al. The current evidence on statin use and prostate cancer prevention: are we there yet?[J]. Nat Rev Urol, 2017, 14(2): 107–119.
[61] Wang K, Gerke TA, Chen X, et al. Association of statin use with risk of gleason score-specific prostate cancer: a hospital-based cohort study [J]. Cancer Med, 2019, 8(17): 7399–7407.
[62] He K, Hu H, Ye S, et al. The effect of metformin therapy on incidence and prognosis in prostate cancer: a systematic review and meta-analysis[J]. Sci Rep, 2019, 9(1): 2218.
[63] Ghiasi B, Sarokhani D, Najafi F, et al. The relationship between prostate cancer and metformin consumption: a systematic review and meta-analysis study [J]. Curr Pharm Des, 2019, 25(9): 1021–1029.
[64] Wang Y, Liu X, Yan P, et al. Effect of metformin on the risk of prostate cancer in patients with type 2 diabetes by considering different confounding factors: a meta-analysis of observational studies [J]. Eur J Cancer Prev, 2020, 29 (1): 42–52.
[65] Preston MA, Riis AH, Ehrenstein V, et al. Metformin use and prostate cancer risk[J]. Eur Urol, 2014, 66(6): 1012–1020.
[66] Haggstrom C, Van Hemelrijck M, Zethelius B, et al. Prospective study of type 2 diabetes mellitus, anti-diabetic drugs and risk of prostate cancer[J]. Int J Cancer, 2017, 140(3): 611–617.
[67] Chen CB, Eurich DT, Majumdar SR, et al. Metformin and the risk of prostate cancer across racial/ethnic groups: a population-based cohort study[J]. Prostate Cancer Prostatic Dis, 2017, 20(1): 122–126.
[68] Shang Z, Wang X, Yan H, et al. Intake of non-steroidal anti-inflammatory drugs and the risk of prostate cancer: a meta-analysis[J]. Front Oncol, 2018, 8: 437.
[69] Sauer CM, Myran DT, Costentin CE, et al. Effect of long term aspirin use on the incidence of prostate cancer: a systematic review and meta-analysis [J]. Crit Rev Oncol Hematol, 2018, 132: 66–75.
[70] Jacobs EJ, Rodriguez C, Mondul AM, et al. A large cohort study of aspirin and other nonsteroidal anti-inflammatory drugs and prostate cancer incidence[J]. J Natl Cancer Inst, 2005, 97(13): 975–980.
[71] Downer MK, Allard CB, Preston MA, et al. Regular aspirin use and the risk of lethal prostate cancer in the physicians' health study[J]. Eur Urol, 2017, 72(5): 821–827.
[72] Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer [J]. N Engl J Med, 2003, 349(3): 215–224.
[73] Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer [J]. N Engl J Med, 2010, 362(13): 1192–1202.
[74] Redman MW, Tangen CM, Goodman PJ, et al. Finasteride does not increase the risk of high-grade prostate cancer: a bias-adjusted modeling approach [J]. Cancer Prevention Research, 2008, 1(3): 174–181.
[75] Unger JM, Hershman DL, Till C, et al. Using medicare claims to examine long-term prostate cancer risk of finasteride in the prostate cancer prevention trial [J]. J Natl Cancer Inst, 2018, 110(11): 1208–1215.
[76] Chamie K, DeVere White RW, Lee D, et al. Agent orange exposure, vietnam war veterans, and the risk of prostate cancer[J]. Cancer, 2008, 113(9): 2464–2470.
[77] Chang ET, Boffetta P, Adami HO, et al. A critical review of the epidemiology of agent orange/tcdd and prostate cancer[J]. Eur J Epidemiol, 2014, 29(10): 667–723.
[78] Tse LA, Lee PMY, Ho WM, et al. Bisphenol a and other environmental risk factors for prostate cancer in Hong kong[J]. Environ Int, 2017, 107: 1–7.
[79] Korda RJ, Clements MS, Armstrong BK, et al. Risk of cancer associated with residential exposure to asbestos insulation: a whole-population cohort study [J]. The Lancet Public Health, 2017, 2(11): e522–e528.
[80] Myles P, Evans S, Lophatananon A, et al. Diagnostic radiation procedures and risk of prostate cancer [J]. Br J Cancer, 2008, 98(11): 1852–1856.
[81] Luscombe CJ, Fryer AA, French ME, et al. Exposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer [J]. Lancet, 2001, 358 (9282): 641–642.
[82] John EM, Dreon DM, Koo J, et al. Residential sunlight exposure is associated with a decreased risk of prostate cancer[J]. J Steroid Biochem Mol Biol, 2004, 89–90(1–5): 549–552.
[83] Platz EA, Rimm EB, Willett WC, et al. Racial variation in prostate cancer incidence and in hormonal system markers among male health professionals [J]. J Natl Cancer Inst, 2000, 92(24): 2009–2017.
[84] Hoffman RM, Gilliland FD, Eley JW, et al. Racial and ethnic differences in advanced-stage prostate cancer: the prostate cancer outcomes study [J]. J Natl Cancer Inst, 2001, 93(5): 388–395.
[85] Parker PM, Rice KR, Sterbis JR, et al. Prostate cancer in men less than the age of 50: a comparison of race and outcomes[J]. Urology, 2011, 78(1): 110–115.
[86] Kiciński M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis[J]. PLoS One, 2011, 6(10): e27130.
[87] Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in nordic countries [J]. JAMA, 2016, 315(1): 68–76.
[88] Benafif S, Kote-Jarai Z, Eeles RA. A review of prostate cancer genome-wide association studies (gwas)[J]. Cancer Epidemiol Biomarkers Prev, 2018, 27(8): 845.
[89] Dias A, Kote-Jarai Z, Mikropoulos C, et al. Prostate cancer germline variations and implications for screening and treatment[J]. Cold Spring Harb Perspect Med, 2018, 8(9): a030379.
[90] Kote-Jarai Z, Leongamornlert D, Saunders E, et al. Brca2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients[J]. Br J Cancer, 2011, 105(8): 1230–1234.
[91] Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in brca1 and brca2 mutation carriers: results from the initial screening round of the impact study [J]. Eur Urol, 2014, 66(3): 489–499.
[92] Gan Y, Li L, Zhang L, et al. Association between shift work and risk of prostate cancer: a systematic review and meta-analysis of observational studies [J]. Carcinogenesis, 2018, 39(2): 87–97.
[93] Mancio J, Leal C, Ferreira M, et al. Does the association of prostate cancer with night-shift work differ according to rotating vs. Fixed schedule? A systematic review and meta-analysis [J]. Prostate Cancer Prostatic Dis, 2018, 21 (3): 337–344.
[94] Lewis-Mikhael AM, Bueno-Cavanillas A, Ofir Guiron T, et al. Occupational exposure to pesticides and prostate cancer: a systematic review and meta-analysis[J]. Occup Environ Med, 2016, 73(2): 134.
[95] Lemarchand C, Tual S, Boulanger M, et al. Prostate cancer risk among french farmers in the agrican cohort [J]. Scand J Work Environ Health, 2016, 42(2): 144–152.
[96] Girschik J, Glass D, Ambrosini GL, et al. Could mining be protective against prostate cancer? A study and literature review[J]. Occup Environ Med, 2010, 67(6): 365–374.