

膀胱癌与代谢综合征的相关性研究

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摘要

代谢综合征(Metabolic syndrome, MS)是一组与胰岛素抵抗相关的因素, 包括肥胖、糖耐量受损、血脂异常和高血压, 并且一直与心血管疾病和2型糖尿病的风险增加有关, 最近还与某些部位的癌症风险增加有关。最近关于代谢综合征(MetS)与癌症关系的最新研究认为代谢综合征(MetS)在癌变过程中扮演着重要作用。越来越多的证据显示, 代谢综合征(MetS)与膀胱癌的风险增加有关。本文着重阐述代谢综合征(MetS)与膀胱癌的关系。

关键词

代谢综合征, 膀胱癌

Study on the Correlation between Bladder Cancer and Metabolic Syndrome

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Abstract

Metabolic syndrome is a group of factors associated with insulin resistance, including obesity, impaired glucose tolerance, dyslipidemia and high blood pressure, and has been associated with an increased risk of cardiovascular disease and type 2 diabetes, and more recently with an increased risk of cancer in certain sites. Recent studies on the relationship between MS and cancer

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suggest that MS plays an important role in the development of cancer. There is growing evidence that MS is associated with an increased risk of bladder cancer. This article focuses on the relationship between MS and bladder cancer.

Keywords

Metabolic Syndrome (MS), Bladder Cancer

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1. 引言

代谢综合征(Metabolic syndrome)在世界范围内的发病率越来越高,一些恶性肿瘤的发病率也越来越高,特别是结直肠癌和乳腺癌,这意味着每年都有许多癌症病例是由代谢综合征(Metabolic syndrome)引起的。随着我国饮食结构与生活方式的改变,近几十年,中国人代谢综合征的发病率也逐年升高。根据2005年的数据分析显示,高达20%的中国成人患有代谢综合征(Metabolic syndrome)。本文着重阐述代谢综合征与膀胱癌的关系及可能的机制,为后续的治疗及干预的研究提供理论依据。

2. 代谢综合征的定义

代谢综合征(Metabolic syndrome)最早是由 Reaven 在 1988 年提出的以胰岛素抵抗作为基础条件的“综合征 X”。代谢综合征包括了一系列代谢异常因素,其中每一项都是动脉粥样硬化的重要危险因素。随着对代谢综合征概念的不断加深和研究,目前认为,胰岛素抵抗是最重要的因素之一。目前公认的诊断标准都采取腹型肥胖、血脂异常、高血压、和糖代谢异常来定义。根据 2004 年中华医学会制定的标准进行代谢综合征(Metabolic syndrome)的诊断,具备以下 4 项中的任意 3 项及以上即诊断为 MS: 1) 超重或肥胖: 体质指数(body mass index, BMI) ≥ 25 ; 2) 高血压: 血压 $\geq 140/90$ mmHg (1 mmHg = 0.133 kPa), 或已确诊为高血压并治疗者; 3) 高血糖: 空腹血糖(fast-ing plasma glucose FBG) ≥ 6.1 mmol/L 和(或)餐后 2 h 血糖 ≥ 7.8 mmol/L, 或者已确诊为 DM 并接受治疗者; 4) 血脂异常, 空腹血甘油三酯(TG) ≥ 1.7 mmol/L 和(或)空腹血高密度脂蛋白胆固醇(high-density lipoprotein cholesterol HDL-C)男性 < 0.9 mmol/L, 女性 < 1.0 mmol/L。

3. 代谢综合征和肿瘤

代谢综合征已经成为世界范围内的一个主要公共健康问题,并且在肥胖发病率高和西方饮食模式的国家中是一种常见的临床疾病。代谢综合征与许多部位的常见癌症有关,最近的荟萃分析表明,代谢综合征与常见癌症有关,包括男性的肝癌、结直肠癌和膀胱癌,以及女性的子宫内膜癌、胰腺癌、绝经后乳腺癌和结直肠癌[1]。在不同人种中,代谢综合征与肿瘤的关系也不完全相同:在亚洲人群中,代谢综合征与肝癌更强;在欧洲与女性结肠癌、美国男性前列腺癌相关性更大。患有代谢综合征的肿瘤患者一般预后较差,在前列腺癌患者中,肥胖患者更容易患上高级别和侵袭性的前列腺癌[2] [3] [4]。

4. 代谢综合征与膀胱癌

世界范围内,膀胱癌发病率居恶性肿瘤的第 9 位,在男性排第 7 位,女性排在第 10 位之后,死亡率

居恶性肿瘤的第 13 位。在欧美, 膀胱癌发病率居男性恶性肿瘤的第 4 位, 位于前列腺癌、肺癌和结肠癌之后, 在女性恶性肿瘤亦排在 10 位之后。根据 2019 年发布的数据显示, 2015 年我国膀胱癌发病率为 5.80/10 万, 位居全身恶性肿瘤的第 13 位, 其中膀胱癌男性发病率 8.83/10 万, 位居第 7 位, 女性发病率 2.61/10 万, 位居第 17 位; 2015 年我国膀胱癌死亡率为 2.37/10 万, 位居全身恶性肿瘤的第 13 位, 其中膀胱癌男性死亡率 3.56/10 万, 位居第 11 位, 女性死亡率 1.11/10 万, 位居第 16 位[5]。膀胱癌最常见的亚型是尿路上皮癌, 占膀胱癌的 90% 以上。膀胱癌的病因及发病机制尚未完全阐明目前认为与遗传、吸烟、长期接触工业化学产品与慢性感染等因素有关。中华人民共和国经年龄调整的代谢综合征患病率男性为 9.8%, 女性为 17.8%。它一直与心血管疾病和二型糖尿病病的风险增加有关, 也与尿路疾病的风险有关。近年来, 大量流行病学研究表明, 代谢综合征与多种恶性肿瘤的发生和发展密切相关。此外, 一些研究表明, 代谢综合征(Metabolic syndrome)通过许多炎症分子促进肿瘤的发生, 包括白细胞介素-6 和肿瘤坏死因子- α 。然而, 对于单独的成分和合并的代谢综合征因素对膀胱癌的影响至今未有大量研究数据[6] [7] [8]。

5. 高血压与膀胱癌

高血压或抗高血压药物是否影响癌症发病率和癌症死亡率一直是许多科学争论的话题。几项前瞻性研究观察到高血压导致癌症的风险增加。最常与原有高血压相关的癌症部位是肾脏。在 Grossman 等人进行的汇总分析中, 高血压与全因癌症死亡率的年龄和吸烟调整汇总优势比为 1.23 [95% 置信区间(CI) 1.11~1.36]和肾细胞癌死亡率的 1.75 (95% CI: 1.61~1.90)相关[9]。对于除肾细胞癌之外的癌症, 没有发现与高血压有明显的联系。在被建议增加癌症风险的抗高血压药物中, 最有力的证据是与肾细胞癌相关的利尿剂[10] [11] [12] [13]。据推测, 高血压和癌症可能与共同的风险因素有关, 如代谢综合征或共同的病理生理途径, 包括胰岛素抵抗和氧化应激介导的细胞凋亡。谷胱甘肽硫转移酶(GSTs)的多态性在多种活性氧(ROS)和外源性物质的代谢中发挥重要作用, 也与高血压和包括膀胱癌在内的癌症的发病机制有关。[14] [15] [16] [17]临床前实验研究表明, 抗高血压药物, 如血管紧张素转换酶抑制剂(ACEI)、血管紧张素 II 受体阻滞剂(ARB)、钙通道阻滞剂(CCB)和 β 受体阻滞剂, 可促进或干扰肿瘤细胞增殖、迁移和凋亡以及血管生成。此外, 血管紧张素转换酶抑制剂和血管紧张素受体拮抗剂显示出抗血管生成作用, 降低了膀胱恶性肿瘤中血管内皮生长因子的表达[18] [19] [20] [21]。

6. 肥胖与膀胱癌

超重, 无论是超重还是肥胖, 越来越被认为是许多常见癌症的重要危险因素[22] [23]。在过去的几年里, 身体质量指数和膀胱癌风险之间的联系受到了很多关注, 但是这些发现仍然存在争议。到目前为止, 还没有任何研究基于前瞻性队列研究来检验身体质量指数和膀胱癌风险之间的剂量 - 反应关系的确切形式[24] [25] [26] [27] [28]。尽管先前的研究报告了几种癌症部位与不同肥胖标志物的关联, 但这些研究大多是在亚洲人群中进行的[29] [30] [31], Lee 等人报告了 2290 万韩国成年人中 18 种癌症与腰围(WC)的关联。类似地, 王等人在中国生物库报告了包括 BMI、WC、腰臀比(WHR)和体脂百分比(BF%)在内的四种肥胖症标记物与 15 种癌症的关联[31]-[36]。2014 年, 巴斯卡兰等人报告称, 身体质量指数与 520 万英国成年人中的 17 种癌症有关。这项研究还强调了对其他肥胖标记物进一步研究的需要, 因为身体脂肪分布的测量, 如中心性肥胖和身体脂肪可能是比身体质量指数更强的特定癌症部位的决定因素, 正如对其他健康结果, 如心血管疾病所观察到的那样[37] [38] [39] [40] [41]。身体质量指数和膀胱癌风险之间关联的潜在机制尚不确定。一个可能的原因是超重和膀胱癌风险之间的生物学机制。众所周知, 过量的体脂与胰岛素的产生有关, 胰岛素是一种促有丝分裂刺激因子, 可以通过增加游离胰岛素样生长因子-1 (IGF-1)

来促进肿瘤生长。也已经证明, IGF-1 可以刺激细胞增殖和抑制凋亡, 这可能与膀胱癌有关[42] [43]。此外, 炎症介质如 C-反应蛋白和白细胞介素-6 可能有助于肥胖相关的膀胱癌风险。需要进一步研究体重和膀胱癌之间的致癌机制[44] [45] [46] [47]。

7. 糖尿病与膀胱癌

糖尿病和癌症都是严重而普遍的疾病, 在世界范围内迅速增加。糖尿病是一种代谢性疾病, 患者的血糖水平很高。在全球范围内, 2014 年糖尿病患者人数为 4.22 亿, 一项新的研究预测, 到 2035 年, 病例数量将增加到至少 5.92 亿[48]。与此同时, 癌症已经被大多数医学研究人员认为是一种代谢性疾病, 世界卫生组织估计, 全球癌症患者人数将从 2012 年的 1400 万增加到 2032 年的 2200 万[49]。

近年来, 糖尿病和癌症的发病率显著增加。此外, 糖尿病和癌症都有许多常见的风险因素, 如肥胖、久坐不动的生活方式、吸烟和衰老。大量流行病学证据表明, 糖尿病被认为是不同类型癌症发生率和死亡率增加的独立危险因素。各种类型癌症的发病率和死亡率, 如胰腺癌、肝癌、结直肠癌、乳腺癌、子宫内膜癌和膀胱癌, 在糖尿病患者中略有增长[50]。尽管潜在的生物学机制尚未完全了解, 但研究证实, 胰岛素/胰岛素样生长因子(IGF)轴(包括胰岛素抵抗、高胰岛素血症和 IGF)、高血糖症、炎症细胞因子和性激素为癌细胞增殖和转移提供了良好的环境。胰岛素/IGF 轴激活几种代谢和有丝分裂信号通路; 高血糖为癌细胞生长提供能量; 炎症细胞因子影响癌细胞凋亡。因此, 这三个因素影响所有类型的癌症, 而性激素只在乳腺癌、子宫内膜癌和前列腺癌中起重要作用[51] [52]。

8. 血脂异常与膀胱癌

有许多研究证实血脂异常对癌症的发生、发展起着重要作用。肿瘤或癌症生长和转移的主要标准之一是合成新细胞的能力, 这需要增加脂质合成。众所周知, 脂质和磷脂代谢在细胞运动、细胞侵袭和肿瘤转移中起着关键作用, 这些都是癌细胞的标志。有人认为磷脂代谢的紊乱与许多癌症有关[53] [54] [55]。几乎所有的癌症都有六个共同的特征或标志: 1) 刺激自身的生长(即生长信号的自我可持续性); 2) 对抑制信号的抗性发展(对抗生长信号不敏感); 3) 逃避凋亡信号; 4) 无限增殖能力; 5) 刺激血管以持续向肿瘤提供营养(血管生成可持续性); 6) 侵入局部组织并扩散到各种器官(转移能力) [56] [57]。Piyarathna 等人对病理证实的 BLCA 组织进行了首次脂质组学研究, 并确定了良性和 BLCA 之间不同类别脂质的变化, 如磷胆碱(PCs)、磷脂酰乙醇胺、血浆蛋白和甘油三酯(TGs)。将这些改变的脂质定位到相应的基因, 并与来自 TCGA 的转录组学整合, 产生了与 BLCA 患者存活率显著相关的基因信号[58]。许多研究已经检查了胆固醇水平和特定部位癌症之间的相关性。Strohmaier 等人最近检查了一项前瞻性队列研究的结果, 包括来自 Me-Can 项目的数据; 总的来说, 总胆固醇水平与女性及男性相关癌症风险的降低相关, 如(胆囊、肝脏、皮肤与淋巴等) [59]。关于 BCa 的发病率, 在两性中都没有发现显著的相关性。就 BCa 而言, 一项基于人群的大型病例对照研究表明, 长期(超过 4 年)使用他汀类药物与增加的 BCa 风险相关(OR 1.29)。在接受 RC 治疗的 MIBCa 患者中, 他汀类药物使用者没有更高的疾病复发和癌症特异性死亡率的风险[60] [61]。

9. 代谢综合征与膀胱癌的相关机制

代谢综合征与膀胱癌之间的相互作用是复杂的, 涉及胰岛素抵抗(IR), 炎症, 血管生成, 细胞基质相互作用及许多其他重要方面。包括由这些相互关联的组成部分的各种因素与信号通路的复杂网络, 用于调节代谢综合征与膀胱癌之间的串扰。

9.1. 胰岛素抵抗

高胰岛素血症与胰岛素抵抗被认为是与代谢综合征相关的代谢障碍的主要基础。胰岛素是能够刺激

细胞增殖的最重要的合成代谢激素之一。许多研究表明, 肥胖与许多恶性肿瘤有关[62] [63]。众所周知, 肥胖与糖尿病, 尤其是二型糖尿病病之间的关系是明确的。肥胖和糖尿病是代谢综合征的两个重要组成部分; 流行病学研究表明, 肥胖和二型糖尿病病与几种癌症的风险增加有关, 如肾脏、结肠和肝脏[64] [65]。肥胖和癌症之间的联系似乎与胰岛素抵抗和高血清胰岛素样生长因子(IGF)-1 有关。IGF-1 可能刺激增殖和抑制凋亡有关, 最终可能导致癌症。先前的报告显示, IGF-1 在前列腺癌、肺癌和肝癌的发展中起着重要作用。与膀胱癌的关联也已被提出[66] [67]。到目前为止, 有许多研究探索肥胖和膀胱癌风险之间的联系。几项流行病学研究也证实了肥胖与膀胱癌风险正相关[62] [63]。可以用两个原因来解释这些结果。从生物化学角度来说, 宿主体内过多的能量会增加致癌风险[68]。过多的脂肪还与全身炎症反应有关, 这可能在癌症中起重要作用。詹等人进行了第一项研究, 以调查中国人群中不同类型癌症的糖代谢特征; 结果显示, 高水平的空腹血糖与膀胱癌有一定关系, 在同一种或不同种类的癌症中, 高血糖的发生率高于低血糖的发生率。根据相关的研究, 发现糖尿病与膀胱癌的病理分级和分期有关。可能的原因可能是 1) 胰岛素敏感性降低和 IGF-1 水平升高, 这反过来可能刺激细胞增殖, 并在癌症发展和转移的过程中发挥重要作用。2) 此外, 高血糖导致由蛋白激酶 C 家族调节的重要细胞信号系统功能障碍, 这在癌症发生中诱导肿瘤生长和转移的过程[69] [70]。

9.2. 炎症

100 多年前, 鲁道夫·维尔周首次注意到慢性炎症和癌症发展之间的联系, 当时他在肿瘤组织中观察到大量白细胞[71]。此后, 在多种癌症类型中观察到了慢性炎症作为癌症发展前体的作用, 包括胃炎和胃癌、炎症性肠病(IBD)和结肠癌, 以及胰腺炎和胰腺癌[72] [73]。在人类癌症的各种小鼠模型中, 炎症也显示对肿瘤的促进和进展。像脂肪组织一样, 肿瘤微环境由多种类型细胞组成, 包括上皮细胞、成纤维细胞、肥大细胞以及先天和适应性免疫系统的细胞, 这些细胞有利于促炎、原生环境[74] [75]。此外, 肿瘤细胞和基质细胞增加肿瘤组织中 COX-2 的表达。COX-2 被认为是多种癌症类型预后不良的指标[76]。肿瘤相关巨噬细胞(TAMs)的存在有助于促炎肿瘤环境。肿瘤微环境中 TAMs 的募集很大程度上依赖于单核细胞趋化蛋白-1。肿瘤组织中单核细胞趋化蛋白-1 的水平与卵巢癌、乳腺癌、膀胱癌和胰腺癌中的积累高度相关。此外, TAMs 还产生生长因子, 促进增殖、血管生成, 并有助于相关组织的沉积和溶解[77]。

总之, 关于代谢综合征与膀胱癌的联系已有充分的证据, 并且代谢综合征的每个组成部分可能与膀胱癌有紧密的因果关系。最新关于代谢综合征与膀胱癌的相关机制已有重大发现, 日后可制定相关分子机制的治疗干预措施。此外, 代谢综合征至少部分源于不健康的生活方式, 保持健康的生活方式可能对预防很多癌症很重要(包括膀胱癌)。

参考文献

- [1] Esposito, K., Capuano, A. and Giugliano, D. (2014) Metabolic Syndrome and Cancer: Holistic or Reductionist? *Endocrine*, **45**, 362-364. <https://doi.org/10.1007/s12020-013-0056-2>
- [2] Brooks, N.A., Kokorovic, A., Xiao, L., Matulay, J.T., Li, R., Ranasinghe, W.K., *et al.* (2020) The Obesity Paradox: Defining the Impact of Body Mass Index and Diabetes Mellitus for Patients with Non-Muscle-Invasive Bladder Cancer Treated with Bacillus Calmette-Guerin. *BJU International*, **128**, 65-71. <https://doi.org/10.1111/bju.15296>
- [3] Turner, R.M., Kwok, C.S., Chen-Turner, C., Maduakor, C.A., Singh, S. and Loke, Y.K. (2014) Thiazolidinediones and Associated Risk of Bladder Cancer: A Systematic Review and Meta-Analysis. *British Journal of Clinical Pharmacology*, **78**, 258-273. <https://doi.org/10.1111/bcp.12306>
- [4] Newton, C.C., Gapstur, S.M., Campbell, P.T. and Jacobs, E.J. (2013) Type 2 Diabetes Mellitus, Insulin-Use and Risk of Bladder Cancer in a Large Cohort Study. *International Journal of Cancer*, **132**, 2186-2191. <https://doi.org/10.1002/ijc.27878>
- [5] Malats, N. and Real, F.X. (2015) Epidemiology of Bladder Cancer. *Hematology/Oncology Clinics of North America*,

- 29, 177-189. <https://doi.org/10.1016/j.hoc.2014.10.001>
- [6] Tseng, C.H. (2012) Pioglitazone and Bladder Cancer in Human Studies: Is It Diabetes Itself, Diabetes Drugs, Flawed Analyses or Different Ethnicities? *Journal of the Formosan Medical Association*, **111**, 123-131. <https://doi.org/10.1016/j.jfma.2011.10.003>
- [7] Tang, H., Shi, W., Fu, S., Wang, T., Zhai, S., Song, Y., *et al.* (2018) Pioglitazone and Bladder Cancer Risk: A Systematic Review and Meta-Analysis. *Cancer Medicine*, **7**, 1070-1080. <https://doi.org/10.1002/cam4.1354>
- [8] Tai, Y.S., Chen, C.H., Huang, C.Y., Tai, H.-C., Wang, S.-M., and Pu, Y.-S. (2015) Diabetes Mellitus with Poor Glycemic Control Increases Bladder Cancer Recurrence Risk in Patients with Upper Urinary Tract Urothelial Carcinoma. *Diabetes/Metabolism Research and Reviews*, **31**, 307-314. <https://doi.org/10.1002/dmrr.2614>
- [9] Grossman, E., Messerli, F.H., Boyko, V. and Goldbourt, U. (2002) Is There an Association between Hypertension and Cancer Mortality? *American Journal of Medicine*, **112**, 479-486. [https://doi.org/10.1016/S0002-9343\(02\)01049-5](https://doi.org/10.1016/S0002-9343(02)01049-5)
- [10] Larsson, S.C., Andersson, S.O., Ohansson, J.E. and Wolk, A. (2008) Diabetes Mellitus, Body Size and Bladder Cancer Risk in a Prospective Study of Swedish Men. *European Journal of Cancer*, **44**, 2655-2660. <https://doi.org/10.1016/j.ejca.2008.07.012>
- [11] Huang, W.L., Huang, K.H., Huang, C.Y., Pu, Y.-S., Chang, H.-C. and Chow, P.-M. (2020) Effect of Diabetes Mellitus and Glycemic Control on the Prognosis of Non-Muscle Invasive Bladder Cancer: A Retrospective Study. *BMC Urology*, **20**, Article No. 117. <https://doi.org/10.1186/s12894-020-00684-5>
- [12] Chestnut, C., Smelser, W., Dum, T., Bechtel, M., Hand, L., Michel, C., *et al.* (2020) Glycemic Impact of a Diet and Lifestyle Intervention on Diabetics and Prediabetics during Treatment for Non-Muscle Invasive Bladder Cancer. *Nutrition and Cancer*, **72**, 1219-1224. <https://doi.org/10.1080/01635581.2019.1672761>
- [13] Jiang, X., Castela, J.E., Yuan, J.M., Groshen, S., Stern, M.C., Conti, D.V., *et al.* (2010) Hypertension, Diuretics and Antihypertensives in Relation to Bladder Cancer. *Carcinogenesis*, **31**, 1964-1971. <https://doi.org/10.1093/carcin/bgq173>
- [14] Yu, H., Hemminki, O., Försti, A., Sundquist, K. and Hemminki, K. (2018) Familial Urinary Bladder Cancer with Other Cancers. *European Urology Oncology*, **1**, 461-466. <https://doi.org/10.1016/j.euo.2018.06.002>
- [15] Friedenreich, C.M., Ryder-Burbidge, C. and Mcneil, J. (2021) Physical Activity, Obesity and Sedentary Behavior in Cancer Etiology: Epidemiologic Evidence and Biologic Mechanisms. *Molecular Oncology*, **15**, 790-800. <https://doi.org/10.1002/1878-0261.12772>
- [16] Amara, C.S., Vantaku, V., Lotan, Y. and Putluri, N. (2019) Recent Advances in the Metabolomic Study of Bladder Cancer. *Expert Review of Proteomics*, **16**, 315-324. <https://doi.org/10.1080/14789450.2019.1583105>
- [17] Wigner, P., Grębowski, R., Bijak, M., Saluk-Bijak, J. and Szmraj, J. (2021) The Interplay between Oxidative Stress, Inflammation and Angiogenesis in Bladder Cancer Development. *International Journal of Molecular Sciences*, **22**, Article No. 4483. <https://doi.org/10.3390/ijms22094483>
- [18] Xie, Y., Xu, P., Wang, M., Zheng, Y., Tian, T., Yang, S., *et al.* (2020) Antihypertensive Medications Are Associated with the Risk of Kidney and Bladder Cancer: A Systematic Review and Meta-Analysis. *Aging*, **12**, 1545-1562. <https://doi.org/10.18632/aging.102699>
- [19] Tuccori, M., Filion, K.B., Yin, H., Yu, O.H., Platt, R.W. and Azoulay, L. (2016) Pioglitazone Use and Risk of Bladder Cancer: Population Based Cohort Study. *BMJ*, **352**, Article No. i1541. <https://doi.org/10.1136/bmj.i1541>
- [20] Wang, Q., Zhang, T., Wu, J., Wen, J., Tao, D., Wan, T., *et al.* (2019) Prognosis and Risk Factors of Patients with Upper Urinary Tract Urothelial Carcinoma and Postoperative Recurrence of Bladder Cancer in Central China. *BMC Urology*, **19**, Article No. 24. <https://doi.org/10.1186/s12894-019-0457-5>
- [21] Lewis, J.D., Habel, L., Quesenberry, C., Mamtani, R., Peng, T., Bilker, W.B., *et al.* (2014) Proteinuria Testing among Patients with Diabetes Mellitus Is Associated with Bladder Cancer Diagnosis: Potential for Unmeasured Confounding in Studies of Pioglitazone and Bladder Cancer. *Pharmacoepidemiology and Drug Safety*, **23**, 636-645. <https://doi.org/10.1002/pds.3619>
- [22] Zhao, L., Tian, X., Duan, X., Ye, Y., Sun, M. and Huang, J. (2017) Association of Body Mass Index with Bladder Cancer Risk: A Dose-Response Meta-Analysis of Prospective Cohort Studies. *Oncotarget*, **8**, 33990-34000. <https://doi.org/10.18632/oncotarget.16722>
- [23] Xu, X., Zhou, L., Miao, R., Chen, W., Zhou, Y., Pang, Q., *et al.* (2016) Association of Cancer Mortality with Post-diagnosis Overweight and Obesity Using Body Mass Index. *Oncotarget*, **7**, 5023-5029. <https://doi.org/10.18632/oncotarget.6517>
- [24] Choi, J.B., Kim, J.H., Hong, S., Han, K.-D. and Ha, U.-S. (2019) Association of Body Mass Index with Bladder Cancer Risk in Men Depends on Abdominal Obesity. *World Journal of Urology*, **37**, 2393-2400. <https://doi.org/10.1007/s00345-019-02690-1>
- [25] Choi, J.B., Lee, E.J., Han, K., Hong, S.-H. and Ha, U.-S. (2018) Estimating the Impact of Body Mass Index on Bladder

- Cancer Risk: Stratification by Smoking Status. *Scientific Reports*, **8**, Article No. 947. <https://doi.org/10.1038/s41598-018-19531-7>
- [26] Lin, Y., Wang, Y., Wu, Q., Jin, H., Ma, G., Liu, H., *et al.* (2018) Association between Obesity and Bladder Cancer Recurrence: A Meta-Analysis. *Clinica Chimica Acta*, **480**, 41-46. <https://doi.org/10.1016/j.cca.2018.01.039>
- [27] Noguchi, J.L., Liss, M.A. and Parsons, J.K. (2015) Obesity, Physical Activity and Bladder Cancer. *Current Urology Reports*, **16**, Article No. 74. <https://doi.org/10.1007/s11934-015-0546-2>
- [28] Shi, J., Zhao, L., Gao, Y., Niu, M., Yan, M., Chen, Y., *et al.* (2021) Associating the Risk of Three Urinary Cancers with Obesity and Overweight: An Overview with Evidence Mapping of Systematic Reviews. *Systematic Reviews*, **10**, Article No. 58. <https://doi.org/10.1186/s13643-021-01606-8>
- [29] Chu, K.F., Rotker, K. and Ellsworth, P. (2013) The Impact of Obesity on Benign and Malignant Urologic Conditions. *Postgraduate Medicine*, **125**, 53-69. <https://doi.org/10.3810/pgm.2013.07.2679>
- [30] Dabi, Y., Rouscoff, Y., Anract, J., Delongchamps, N.B., Sibony, M., Saighi, D., *et al.* (2017) Impact of Body Mass Index on the Oncological Outcomes of Patients Treated with Radical Cystectomy for Muscle-Invasive Bladder Cancer. *World Journal of Urology*, **35**, 229-235. <https://doi.org/10.1007/s00345-016-1852-0>
- [31] Jee, S.H., Yun, J.E., Park, E.J., Cho, E.R., Park, I.S., Sull, J.W., Ohrr, H. and Samet, J.M. (2008) Body Mass Index and Cancer Risk in Korean Men and Women. *The International Journal of Cancer*, **123**, 1892-1896. <https://doi.org/10.1002/ijc.23719>
- [32] Ahn, J.H., Jung, S.I., Yim, S.U., Kim, S.W., Hwang, E.C. and Kwon, D.D. (2016) Impact of Glycemic Control and Metformin Use on the Recurrence and Progression of Non-Muscle Invasive Bladder Cancer in Patients with Diabetes Mellitus. *Journal of Korean Medical Science*, **31**, 1464-1471. <https://doi.org/10.3346/jkms.2016.31.9.1464>
- [33] Cantiello, F., Cicione, A., Salonia, A., Autorino, R., De Nunzio, C., Briganti, A., *et al.* (2015) Association between Metabolic Syndrome, Obesity, Diabetes Mellitus and Oncological Outcomes of Bladder Cancer: A Systematic Review. *International Journal of Urology*, **22**, 22-32. <https://doi.org/10.1111/iju.12644>
- [34] Cresswell, J. (2013) Diabetes Mellitus and Non-Muscle-Invasive Bladder Cancer: Not Just a Coincidence? *BJU International*, **112**, 1055-1056. <https://doi.org/10.1111/bju.12491>
- [35] Parra-Soto, S., Cowley, E.S., Rezende, L.F.M., Ferreccio, C., Mathers, J.C., Pell, J.P., *et al.* (2021) Associations of Six Adiposity-Related Markers with Incidence and Mortality from 24 Cancers—Findings from the UK Biobank Prospective Cohort Study. *BMC Medicine*, **19**, Article No. 7. <https://doi.org/10.1186/s12916-020-01848-8>
- [36] Batty, G.D., Shipley, M.J., Jarrett, R.J., Breeze, E., Marmot, M.G. and Smith, G.D. (2005) Obesity and Overweight in Relation to Organ-Specific Cancer Mortality in London (UK): Findings from the Original Whitehall Study. *International Journal of Obesity*, **29**, 1267-1274. <https://doi.org/10.1038/sj.ijo.0803020>
- [37] Sørensen, K.K., Jensen, B.W., Thomas, P.E., Madsen, K., Eriksson, F., Aarestrup, J., *et al.* (2020) Early Life Body Size and Its Associations with Adult Bladder Cancer. *Annals of Human Biology*, **47**, 166-172. <https://doi.org/10.1080/03014460.2019.1707873>
- [38] Huynh, M.J., Wang, Y., Chang, S.L., Tully, K.H., Chung, B.I., Wright, J.L., *et al.* (2020) The Cost of Obesity in Radical Cystectomy. *Urologic Oncology: Seminars and Original Investigations*, **38**, 932-939. <https://doi.org/10.1016/j.urolonc.2020.05.014>
- [39] Rezaei, F., Tabatabaee, H., Rahmani, V., Mirahmadizadeh, A. and Hassanipour, S. (2019) The Correlation between Bladder Cancer and Obesity, Overweight, Physical Inactivity, and Tobacco Use: An Ecological Study in Asian Countries. *Annals of Global Health*, **85**, Article No. 102. <http://doi.org/10.5334/aogh.2545>
- [40] Sanchez, A., Kissel, S., Coletta, A., Scott, J. and Furberg, H. (2020) Impact of Body Size and Body Composition on Bladder Cancer Outcomes: Risk Stratification and Opportunity for Novel Interventions. *Urologic Oncology: Seminars and Original Investigations*, **38**, 713-718. <https://doi.org/10.1016/j.urolonc.2020.03.017>
- [41] Wade, K.H., Carslake, D., Sattar, N., Smith, Davey, G. and Timpson, N.J. (2018) BMI and Mortality in UK Biobank: Revised Estimates Using Mendelian Randomization. *Obesity*, **26**, 1796-1806. <https://doi.org/10.1002/oby.22313>
- [42] Aarestrup, J., Bjerregaard, L.G., Meyle, K.D., Pedersen, D.C., Gjarde, L.K., Jensen, B.W., *et al.* (2020) Birthweight, Childhood Overweight, Height and Growth and Adult Cancer Risks: A Review of Studies Using the Copenhagen School Health Records Register. *International Journal of Obesity*, **44**, 1546-1560. <https://doi.org/10.1038/s41366-020-0523-9>
- [43] 肖荣, 于佳, 徐建华, 杨元强. 膀胱癌分期分级与代谢综合征及组分的相关性研究[J]. 临床医药文献电子杂志, 2019, 6(39): 17-18.
- [44] De Ridder, J., Julián-Almárcegui, C., Mullee, A., Rinaldi, S., Van Herck, K., Vicente-Rodríguez, G., *et al.* (2016) Comparison of Anthropometric Measurements of Adiposity in Relation to Cancer Risk: A Systematic Review of Prospective Studies. *Cancer Causes & Control*, **27**, 291-300. <https://doi.org/10.1007/s10552-015-0709-y>
- [45] Fang, H., Yao, B., Yan, Y., Xu, H., Liu, Y., Tang, H., *et al.* (2013) Diabetes Mellitus Increases the Risk of Bladder

- Cancer: An Updated Meta-Analysis of Observational Studies. *Diabetes Technology & Therapeutics*, **15**, 914-922. <https://doi.org/10.1089/dia.2013.0131>
- [46] Gild, P., Ehdai, B. and Kluth, L.A. (2017) Effect of Obesity on Bladder Cancer and Renal Cell Carcinoma Incidence and Survival. *Current Opinion in Urology*, **27**, 409-414. <https://doi.org/10.1097/MOU.0000000000000425>
- [47] Teleka, S., Jochems, S.H.J., Häggström, C., Wood, A.M., Järholm, B., Orho-Melander, M., *et al.* (2021) Association between Blood Pressure and BMI with Bladder Cancer Risk and Mortality in 340,000 Men in Three Swedish Cohorts. *Cancer Medicine*, **10**, 1431-1438. <https://doi.org/10.1002/cam4.3721>
- [48] Davidson, M.B. (2016) Pioglitazone (Actos) and Bladder Cancer: Legal System Triumphs over the Evidence. *J Diabetes Complications*, **30**, 981-985. <https://doi.org/10.1016/j.jdiacomp.2016.04.004>
- [49] Zhu, Z., Zhang, X., Shen, Z., Zhong, S., Wang, X., Lu, Y., *et al.* (2013) Diabetes Mellitus and Risk of Bladder Cancer: A Meta-Analysis of Cohort Studies. *PLoS ONE*, **8**, e56662. <https://doi.org/10.1371/journal.pone.0056662>
- [50] Wang, M., Yang, Y. and Liao, Z. (2020) Diabetes and Cancer: Epidemiological and Biological Links. *World Journal of Diabetes*, **11**, 227-238. <https://doi.org/10.4239/wjcd.v11.i6.227>
- [51] Dąbrowski, M. (2021) Diabetes, Antidiabetic Medications and Cancer Risk in Type 2 Diabetes: Focus on SGLT-2 Inhibitors. *International Journal of Molecular Sciences*, **22**, Article No. 1680. <https://doi.org/10.3390/ijms22041680>
- [52] Lundberg, E., Hagberg, O., Jahnson, S. and Ljungberg, B. (2019) Association between Occurrence of Urinary Bladder Cancer and Treatment with Statin Medication. *Turkish Journal of Urology*, **45**, 97-102. <https://doi.org/10.5152/tud.2019.94495>
- [53] Goossens, M.E., Zeegers, M.P., Bazelier, M.T., De Bruin, M.L., Buntinx, F. and de Vries, F. (2015) Risk of Bladder Cancer in Patients with Diabetes: A Retrospective Cohort Study. *BMJ Open*, **5**, Article No. e7470. <https://doi.org/10.1136/bmjopen-2014-007470>
- [54] Gupta, S., Gupta, K., Ravi, R., Mehta, V., Banerjee, S., Joshi, S., *et al.* (2015) Pioglitazone and the Risk of Bladder Cancer: An Indian Retrospective Cohort Study. *Indian Journal of Endocrinology and Metabolism*, **19**, 639-643. <https://doi.org/10.4103/2230-8210.163187>
- [55] Han, E., Jang, S.Y., Kim, G., Lee, Y.-H., Choe, E.Y., Nam, C., *et al.* (2016) Rosiglitazone Use and the Risk of Bladder Cancer in Patients with Type 2 Diabetes. *Medicine*, **95**, Article No. e2786. <https://doi.org/10.1097/MD.0000000000002786>
- [56] Xu, Y., Huo, R., Chen, X. and Yu, X. (2017) Diabetes Mellitus and the Risk of Bladder Cancer: A PRISMA-Compliant Meta-Analysis of Cohort Studies. *Medicine*, **96**, Article No. e8588. <https://doi.org/10.1097/MD.0000000000008588>
- [57] Yang, S.L., Wang, J.J., Chen, M., Xu, L., Li, N., Luo, Y.-L., *et al.* (2018) Pioglitazone Use and Risk of Bladder Cancer: An *in Vitro* Study. *International Journal of Medical Sciences*, **15**, 228-237. <https://doi.org/10.7150/ijms.22408>
- [58] Lin, C., Travis, R.C., Appleby, P.N., Tipper, S., Weiderpass, E., Chang-Claude, J., *et al.* (2018) Pre-Diagnostic Circulating Insulin-Like Growth Factor-I and Bladder Cancer Risk in the European Prospective Investigation into Cancer and Nutrition. *International Journal of Cancer*, **143**, 2351-2358. <https://doi.org/10.1002/ijc.31650>
- [59] Turati, F., Polesel, J., Di Maso, M., Montella, M., Libra, M., Grimaldi, M., *et al.* (2015) Diabetes Mellitus and the Risk of Bladder Cancer: An Italian Case-Control Study. *British Journal of Cancer*, **113**, 127-130. <https://doi.org/10.1038/bjc.2015.178>
- [60] Gislefoss, R.E., Stenehjem, J.S., Hektoen, H.H., Andreassen, B.K., Langseth, H., Axcrone K., *et al.* (2018) Vitamin D, Obesity and Leptin in Relation to Bladder Cancer Incidence and Survival: Prospective Protocol Study. *BMJ Open*, **8**, Article No. e019309. <https://doi.org/10.1136/bmjopen-2017-019309>
- [61] Nagano, T., Otsoshi, T., Hazama, D., Kiri, T., Umezawa, K., Katsurada, N., *et al.* (2019) Novel Cancer Therapy Targeting Microbiome. *OncoTargets and Therapy*, **12**, 3619-3624. <https://doi.org/10.2147/OTT.S207546>
- [62] Ferwana, M., Firwana, B., Hasan, R., Al-Mallah, M.H., Kim, S., Montori, V.M., *et al.* (2013) Pioglitazone and Risk of Bladder Cancer: A Meta-Analysis of Controlled Studies. *Diabetic Medicine*, **30**, 1026-1032. <https://doi.org/10.1111/dme.12144>
- [63] Evers, J., Grotenhuis, A.J., Aben, K., Kiemeny, L.A. and Vrieling, A. (2020) No Clear Associations of Adult BMI and Diabetes Mellitus with Non-Muscle Invasive Bladder Cancer Recurrence and Progression. *PLoS ONE*, **15**, e229384. <https://doi.org/10.1371/journal.pone.0229384>
- [64] Larsson, S.C., Orsini, N., Brisman, K. and Wolk, A. (2006) Diabetes Mellitus and Risk of Bladder Cancer: A Meta-Analysis. *Diabetologia*, **49**, 2819-2823. <https://doi.org/10.1007/s00125-006-0468-0>
- [65] Hu, J., Chen, J.B., Cui, Y., Zhu, Y.-W., Ren, W.-B., Zhou, X., *et al.* (2018) Association of Metformin Intake with Bladder Cancer Risk and Oncologic Outcomes in Type 2 Diabetes Mellitus Patients: A Systematic Review and Meta-Analysis. *Medicine*, **97**, Article No. e11596. <https://doi.org/10.1097/MD.00000000000011596>

- [66] Lewis, J.D., Habel, L.A., Quesenberry, C.P., Strom, B.L., Peng, T., Hedderson, M.M., *et al.* (2015) Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons with Diabetes. *JAMA*, **314**, 265-277. <https://doi.org/10.1001/jama.2015.7996>
- [67] Levin, D., Bell, S., Sund, R., Hartikainen, S.A., Tuomilehto, J., Pukkala, E., *et al.* (2015) Pioglitazone and Bladder Cancer Risk: A Multipopulation Pooled, Cumulative Exposure Analysis. *Diabetologia*, **58**, 493-504. <https://doi.org/10.1007/s00125-014-3456-9>
- [68] Li, Z., Sun, M., Wang, F., Shi, J. and Wang, K. (2017) Association between Pioglitazone Use and the Risk of Bladder Cancer among Subjects with Diabetes Mellitus: A Dose-Response Meta-Analysis. *International Journal of Clinical Pharmacology and Therapeutics*, **55**, 210-219. <https://doi.org/10.5414/CP202670>
- [69] Mackenzie, T., Zens, M.S., Ferrara, A., Schned, A. and Karagas, M.R. (2011) Diabetes and Risk of Bladder Cancer: Evidence from a Case-Control Study in New England. *Cancer*, **117**, 1552-1556. <https://doi.org/10.1002/cncr.25641>
- [70] Liu, Y., Wu, X., Wang, G., Hu, S., Zhang, Y. and Zhao, S. (2019) *CALDI*, *CNN1*, and *TAGLN* Identified as Potential Prognostic Molecular Markers of Bladder Cancer by Bioinformatics Analysis. *Medicine*, **98**, e13847. <https://doi.org/10.1097/MD.00000000000013847>
- [71] Ng, Y., Husain, I. and Waterfall, N. (2003) Diabetes Mellitus and Bladder Cancer—An Epidemiological Relationship? *Pathology Oncology Research*, **9**, Article No. 30. <https://doi.org/10.1007/BF03033711>
- [72] Zhu, Z., Wang, X., Shen, Z., Lu, Y., Zhong, S. and Chen, X. (2013) Risk of Bladder Cancer in Patients with Diabetes Mellitus: An Updated Meta-Analysis of 36 Observational Studies. *BMC Cancer*, **13**, Article No. 310. <https://doi.org/10.1186/1471-2407-13-310>
- [73] Yang, X.Q., Xu, C., Sun, Y. and Han, R.-F. (2013) Diabetes Mellitus Increases the Risk of Bladder Cancer: An Updated Meta-Analysis. *Asian Pacific Journal of Cancer Prevention*, **14**, 2583-2589. <https://doi.org/10.7314/APJCP.2013.14.4.2583>
- [74] Xu, X., Wu, J., Mao, Y., Zhu, Y., Hu, Z., Xu, X., *et al.* (2013) Diabetes Mellitus and Risk of Bladder Cancer: A Meta-Analysis of Cohort Studies. *PLoS ONE*, **8**, e58079. <https://doi.org/10.1371/journal.pone.0058079>
- [75] Wei, L., Macdonald, T.M. and Mackenzie, I.S. (2013) Pioglitazone and Bladder Cancer: A Propensity Score Matched Cohort Study. *British Journal of Clinical Pharmacology*, **75**, 254-259. <https://doi.org/10.1111/j.1365-2125.2012.04325.x>
- [76] Warren, H., Raison, N. and Dasgupta, P. (2016) Pioglitazone and Bladder Cancer. *BJU International*, **118**, 16-17. <https://doi.org/10.1111/bju.13352>
- [77] Wang, Z., Ong, W., Tong, S., Sng, J.-H., Mani Lata, R., Mahendran, R., *et al.* (2020) Beyond Diabetes Mellitus: Role of Metformin in Non-Muscle Invasive Bladder Cancer. *Singapore Medical Journal*. <https://doi.org/10.11622/smedj.2020121>