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Joanna Kruk

Joshua Bernstein

Basil Aboul-Enein

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OBESITY, PHYSICAL ACTIVITY AND PROSTATE CANCER: AN OVERVIEW

Joanna Kruk[A, B, C ,D]

Faculty of Physical Culture and Health, University of Szczecin, Poland
ORCID: 0000-0002-7551-1927 | e-mail: joanna.kruk@usz.edu.pl

Joshua Bernstein[B]

A.T. Still University of Health Sciences, College of Graduate Health Studies, Kirksville, Missouri, USA
ORCID: 0000-0002-4229-8867 | e-mail: jbernstein@atsu.edu

Basil H. Aboul-Enein[B, D]

Johnson & Wales University, College of Health & Wellness, Department of Health Science, Providence, Rhode Island, USA
London School of Hygiene & Tropical Medicine, Faculty of Public Health and Policy, London, United Kingdom
ORCID: 0000-0002-4957-2136 | e-mail: basil.aboulenein@jwu.edu, e-mail: basil.aboul-enein@lshtm.ac.uk

[A] Study Design; [B] Data Collection; [C] Statistical Analysis; [D] Manuscript Preparation

Abstract Obesity and a lack of sufficient physical activity (PA) are recognized as risk factors for most civilization diseases, including cancer. This study synthesized the current evidence evaluating the relationship between excess body weight and prostate cancer (PCa) in the relation to the disease risk, progression, and mortality, and identifies biological plausibility of the association. We also estimated the importance of PA in intentional body weight loss.

Several electronic major databases to identify eligible articles were searched until March 2022. A total 22 observational articles, the literature on the underlying biological mechanisms, and the crucial evidence of a role of PA in body weight maintenance and reduction were reviewed.

The available knowledge suggests that association between body mass index and PCa is conflicting. However, the most research consistently shown that overweight/obesity was associated with higher risk of high-grade PCa and dying of PCa.

Overweight/obesity can promote high-grade PCa through increased levels of secreted adipokines, increased formation of proinflammatory agents, and reduced concentration of adiponectin, among others. Being obese may by also linked with a higher risk of mortality. Exercise can decrease these health consequences related with obesity and may be effective in reduction of PCa-specific mortality, however, there are relative few studies on PA and PCa prevention among obese individuals.

Key words overweight, obesity, prostate cancer, inflammation, physical activity

Introduction

Prostate cancer (PCa) is the second most frequently diagnosed malignancy in men worldwide (7.1% of the total cancer cases) and deaths (3.8% of the total dying from cancer) (Bray, Ferlay, Soerjomataram, Siegel, Torre, Jemal, 2018). Consistent with potential PCa risk factors, age, obesity, family history of the disease, smoking status, alcohol consumption, race, physical inactivity, and high energy intake are generally considered the most influential

risk factors (Giovannucci, Liu, Platz, Stampfer, Willett, 2007, Ferro et al., 2017). Obesity is a major risk for several diseases: Cardiovascular, musculoskeletal and some cancers, including PCa. Globally more than 1.9 billion (39%) adults were overweight in 2016, of these more than 650 million (13%) were obese (WHO, 2016). Literature search on the association between excess body weight and PCa generates mixed findings: Overweight and obese men may have a greater likelihood of developing more advanced PCa and dying from the disease than those within a normal weight range. Some studies also suggested that overweight/obesity may decrease the risk of in situ cancer or they are without effect on the PCa development (MacInnis, English, 2006; Renehan, Tyson, Egger, Heller, Zwahlen, 2008; Allott, Masko, Freedland, 2013). Thus, the collective evidence is not entirely consistent. Also, there are controversial associations between body weight excess and biochemical recurrence and PCa-specific mortality (Allott et al., 2013).

Interest in the role of physical activity (PA) in the primary prevention of obesity and normal body weight maintenance and cancer is increasing as the evidence for the beneficial effects of PA on metabolic rate, increased energy expenditure, body mass and fat reduction, and attenuation of morbidity and mortality risks rapidly accumulates (Kim et al., 2017). Evidence has showed that obesity may be linked with low PA level, however to what extent exercise can decrease the risk associated with overweight/obesity remains unclear (Kim et al., 2017). In view of these conflicting facts and limited knowledge of the efficacy of PA in body weight reduction among obese individuals, the main objective of this review article is to summarize what is currently known about the association between overweight/obesity and PCa development, progression, biochemical recurrence (BH), PCa-specific death and the role of PA in the body weight reduction and maintenance. We also identify gaps of the observational studies to give general overview of current state of knowledge in this area of research and discuss the proposed biological mechanisms linking overweight/obesity with PCa, risk, emphasizing the possible preventive role of PA.

Materials and methods

Search strategy

A literature search was carried out in PubMed, Scopus, Health Source, Scientific Direct, Web of Science, and MEDLINE for studies reporting obesity or overweight – mediated changes in the PCa risk, progression, and the disease specific death until March 2022. The following combination of search terms and key words was used: *prostate cancer/prostate carcinoma and overweight/obesity/body weight excess, physical activity/exercise*, *sedentary lifestyle and overweight/obesity/body weight excess and prostate cancer/prostate carcinoma*. Only English language papers were included in the analyses. The following criteria we used to assess relevance to the study problem: Original cohort and case-control studies which investigated the relationship between overweight/obesity and the risk of PCa development progression, or the risk of BH and cancer mortality among PCa survivors.

Inclusion criteria

This overview included papers reporting observational epidemiological studies, reviews, meta-analyses, case-control studies, and cohort studies dealing with the association between overweight/obesity PA and PCa. Articles as conference abstracts, commentaries, and editorials were excluded. Inclusion criteria included physical-diagnosed cancer confirmed by histopathological examination (biopsy or radical prostatectomy), PCa grades (e.g., in situ, locally advanced, advanced, fatal), and overweight/obesity measurement tools. Case-control studies

were included when odds ratio (OR) with 95% confidence interval (CI) or P value trends (determining statistical significance), numbers of cases and controls for each specific cancer grade and adjustment at least for age were reported. Cohort studies were included with relative risk (RR), hazard ratio (HR) estimates, and number of PCa cases and controls or those reporting incident cases and person-year. Both case-control and cohort studies had to include the representative numbers of cases and controls and were adjusted for the main PCa risk or contained the matched groups with respect to age, family history of PCa, and ethnicity groups.

Data extraction

Data on the type of study, study design, authors, publication journal and year, participant characteristic, grade of cancer, number of patients (cases) and controls, variables of adjustment and the study limitations, and effect size were extracted from articles. References were also searched to identify additional articles.

Results and discussion

Body weight excess in relation to prostate carcinoma

Overweight/obesity is a significant public health problem occurring in both developed and developing countries (De Pergola, Silvestris, 2013; Renehan, Zwahlen, Egger, 2015). Overweight and obesity are assessed using Body Mass Index (BMI – body weight/height, kg/m^2), waist circumference, and waist-hip ratio (WCRFI/AICR, 2014). Overweight is defined as a BMI of 25 kg/m^2 to 29.9 kg/m^2. Obesity is a stage in obesogenesis (a disorder arising from chronic deregulation of energy balance and characterized by the inordinate accumulation of fat) and is determined by BMI of 30 kg/m^2 or greater (WHO, 1997). Excess body weight results from several risk factors, including genetic predispositions, unhealthy dietary patterns, physical inactivity, metabolic, environmental, socioeconomic, and psychological factors (Dobbins, Decorby, Choi, 2013).

According to a World Health Organization (WHO) estimation, worldwide obesity has reached approximately threefold increase since 1975, and in 2016 more than 1.9 billion adults (including over 650 million obese people) were overweight (Smith, Smith, 2016; WHO, 2018). According to the World Population Review, 2020 statistic (Obesity rates by country 2020, 2020) the number of overweight people worldwide in 2019 was estimated at 2.1 billion, what is about 30% of the total population. Obesity caused three million deaths. It is expected that 58% of adults globally will be overweight or obese by year 2030 (Smith, Smith, 2016).

For PCa classification the Gleason grading system and its modification by The International Society of Urological Pathology have been used by pathologists and clinicians as predictors of BH (Humphery, 2004; Chen, Zhang, 2016). Briefly, the Gleason scores system realized scale, ranging from 1 to 5 degrees and a sum of Gleason scores, determining two dominating cancer cell types in a sample during biopsy, ranging theoretically from 2 to 10. However, Gleason score 1 + 1 = 2 should not be diagnosed and a Gleason score 3 (grades 1 + 2, 2 + 1) or score 4 (grades 2+2) has been reported as controversial (Chen, Zhan, 2016). Gleason score 5 (comprised of grades 2 + 3 = 5 or 3 + 2 = 5) would be diagnosed if the edge of a tumor exhibits slight irregularity (Chen, Zhan, 2016). Consequently, Gleason scores range from 6 to 10, and scores of 6 and 7 determine low and intermediate grades of cancers, respectively, whereas a scores of 8 to 10 determine a high-grade tumor (Humphery, 2004). In turn, the modified Gleason grading system (the Grade Groups) is based on five grades, 1 through 5: Grade Group 1 (Gleason score ≤6) – low/very low risk group, Grade Group 2 (Gleason score 7 (3 + 4) and Grade Group 3 (Gleason score

7 (4 + 3)) – intermediate risk group, Grade Group 4 (Gleason score 8 (4 + 4)) and Grade Group 5 (Gleason score 9–10) – high/very high-risk group (Egevad et al. 2016; Cancer Foundation, 2022).

Table 1 shows the characteristics of the representative epidemiological studies presenting the effect of overweight/obesity on PCa risk (n = 22) including first author name, year of publication, participants, cases, main results, and comments from each study (Bashir, Ahmad, Malik, 2014; Vidal et al., 2014; Bai et al., 2015; De Cobelli et al., 2015; Hu et al., 2015; Lee, Chia, 2015; Heir, Falk, Robsahm, Sandvik, Erikssen, Tretli, 2016; Khan et al., 2016; Möller et al., 2016; Dickerman et al., 2017; Kelly et al., 2017; Perez-Cornago et al., 2017; Vidal et al., 2017; Wu et al., 2017; Zhao et al., 2017; Lavalette et al., 2018; Yu, Byun, Lee, Hong, 2018; Zeigler-Johnson, Hudson, Glanz, Spangler, Morales, 2018; Kelly et al., 2019; Langlais et al., 2019; Hurwitz et al., 2020; Vidal et al., 2020). In most of the studies BMI has been applied as a measure of overweight/obesity.

Table 1. Epidemiological studies looking at the effect of excess body weight on prostate cancer

Study	Study design/sample size (follow-up time)	Sample size	Control for confounding	Main results and comments cancer risk (95% CI)
1	2	3	4	5
Bashir et al., 2014 Pakistan	Hospital-based case-control study (2012–2013)	140 cases, 280 controls	Yes	*Increased risk* of total PCa BMI >25 kg/m^2 *vs* ≤25 kg/m^2 OR: 5.79 (2.66–12.60)
Vidal et al., 2014 USA	Clinical study (REDUCE) (4 years)	1,739 normal weight 3,384 overweight 1,304 obese after at least one biopsy	Yes	*Decreased risk* of low-grade PCa by 21% in men with BMI ≥30 kg/m^2 *vs* <30 kg/m^2 and no cancer *Increased risk* of high-grade PCa by 28% in men with BMI ≥30 kg/m^2 *vs* <30 kg/m^2 and no cancer
Bai et al., 2015 China	Retrospective study (February 2006 – December 2014)	211 patients treated with prostatectomy	Yes	*Increased risk* Higher BMI positively correlated with higher biopsy Gleason score (≥7) and BH OR: 1.163 (1.023–1.322) OR: 1.22 (1.06–1.41), respectively
De Cobelli et al., 2015 Italy	Retrospective study (November 2008 – May 2014)	311 patients after radical prostatectomy	No	*Increased risk* Obese men were found at higher risk of upgraded (Gleason score ≥7) disease by 21% and upstaged (pathological stage >pT2) disease by 23%, for 1 unit increase in BMI
Hu et al., 2015 China	Retrospective study (December 2004 – February 2014)	1,651 men with initial multicore ≥10 of prostate biopsy, 750 cases (419 with high grade PCa)	Yes	*Increased risk* of overall PCa BMI ≥30.0 kg/m^2 *vs* <18.5–22.9 kg/m^2 OR: 1.17 (1.10–1.20) No association for high-grade PCa OR: 1.03 (0.97–1.09)
Lee and Chia, 2015 Singapore	Retrospective study (January 2012 – April 2014)	458 men (125 men with positive PCa on biopsy)	Yes	*Increased risk* of positive initial biopsy BMI = 25–29.9 kg/m^2 *vs* <25 kg/m^2 OR: 2.6 (1.58–4.30) BMI ≥30 kg/m^2 *vs* <25.0 kg/m^2 OR: 3.26 (1.37–7.73)
Heir et al., 2016 Norway	Cohort (aged 40-59y) in 1972-1975 followed through 2012	1,997 healthy men (213 cases, 62 cases in advanced cancer stage)	Yes	*Decreased risk* of overall PCa BMI ≥25 kg/m^2 *vs* <25.0 kg/m^2 SHR: 0.69 (0.52–0.93)

1	2	3	4	5
Khan et al., 2016 USA	Population-based cross-sectional case-control study	2,049 men diagnosed with PCa	Yes	*Increased risk* of advanced PSA (Gleason sum ≥8 or PCa >20 ng/mL or Gleason sum = 7 and clinical stage cT3-cT4) BMI ≥30.0 kg/m^2 *vs* 18.5–25.0 kg/m^2 White Americans: OR: 1.98 (1.14–3.43) *No significant association* found in the overall sample and in Black subjects
Möller et al., 2016 USA	Health Professionals Follow-up Study (1986-2010)	47,491 individuals, 6183 cases	Yes	*Decreased risk* BMI ≥30.0 kg/m^2 *vs* <21.0 kg/m^2 Age 21y Total PCa RR: 0.89 (0.80–0.98), advanced (T3b/T4 stage) PCa RR: 0.69 (0.53–0.89). Gleason score 7 RR: 0.77 (0.64–0.93). Age ≤65y Total PCa RR: 0.64 (0.51–0.78) Non-advanced PCa RR: 0.57 (0.41–0.74) *No association* for men aged >65y
Kelly et al., 2017 USA	Prospective cohort follow-up study (11.5 years)	69,873 men from 10 cancer screening centers (7,822 cases, 3,078 aggressive, 4,587 nonaggressive, and 255 fatal PCa)	Yes	*Increased risk* of mortality (fatal PCa) BMI estimated in the range 18.5–≥ 30 kg/m^2 HR: 1.27 (1.03–1.58) for an increment of 5 kg/m^2 of BMI BMI ≥30 kg/m^2: HR = 1.69 (0.75–3.82), P trend = 0.004 BMI ≥30 kg/m^2: Age 20 years HR = 1.69 (0.75–3.82), P trend = 0.004, Age of 50y HR = 1.55 (1.05–2.29), P trend = 0.05 Change in BMI between age 20 years and baseline (mean 63 years) increased significantly risk of mortality: HR = 1.95 (1.21–3.12) (normal to obese) HR = 2.65 (1.35–5.18) (overweight to obese cases) *No significant association with BMI for aggressive and nonaggressive PCA*

1	2	3	4	5
Dickerman et al., 2017 USA	Prospective cohort study (1986–2012)	51,529 men 5,158 with localized PCa (T1/T2), (371 lethal cases, 804 biochemical recurrence events)	Yes	*Increased risk* of lethal PCa with long-term weight gain among never smokers (N = 2,559) HR = 1.59 (1.01–2.50), P trend 0.06 for weight gain >30 pounds. The relationship between weight change and PCa was stronger among men with BMI ≥25 kg/m^2 at age 21 comparing with those with BMI <25 kg/m^2 Obesity and weight gain were not associated with BH
Perez-Cornago et al., 2017 France	Multicenter prospective cohort study (EPIC) (13.9 years of follow-up)	7,024 PCa cases (726 with high grade PCa, 1,384 with advanced stage) 2,622 with localized cancer 931 deaths from PCa	Yes	*Increased risk* of aggressive PCa BMI >27.0 kg/m^2, Gleason score of ≥8 HR = 1.32 (1.01–1.72) WC >103 cm HR = 1.43 (1.07–1.92) *Increased risk* of PCa deaths BMI >29.2 kg/m^2 HR = 1.35(1.09-1.69) Waist circumference >103 cm HR = 1.55 (1.23–1.96)
Zhao et al., 2017 China	Retrospective cohort study (December 2004 – February 2014)	3,102 patients (974 diagnosed as PCa cases, 700 treated with prostatectomy, 1,031 had biopsy negative (reference group). 217 normal weight (BMI <25 kg/m^2), 218 overweight (BMI = 25–<30 kg/m^2), 140 middle obese (BMI = 30–<35 kg/m^2), 125 severe obese (BMI ≥35 kg/m^2)	Undefined	*Increased risk* of aggressive PCa Overweight OR = 2.304 (1.469–3.615) Middle obese OR = 3.144 (1.869–5.290) Moderately and severe obese OR = 3.300 (1.852–5.880), *vs* normal weight Increased risk of BH after radical prostatectomy among obese men vs nonobese men HR = 1.405 (1.405–1.903) Increased risk of BH with low level of the high-density lipoprotein cholesterol
Vidal et al., 2017 USA	Retrospective study (followed from 1990)	4,268 men after radical prostatectomy (at least 6.8 years)	Yes	*Increased risk* of PCa specific mortality BMI 25.0–29.9 kg/m^2 *vs* <25 kg/m^2 HR: 1.88 (0.97–3.63) (insignificant) BMI ≥30.0 kg/m^2 *vs* <25.0 kg/m^2 HR: 2.05 (1.04–4.06)
Wu et al., 2017 USA	Retrospective study (January 2001 – March 2016)	1,788 men after radical prostatectomy (37.5% overweight, 32.9% obese)	Yes	*Increased risk* Obesity positively linked with advanced PCa but not with ethnicity

1	2	3	4	5
Lavalette et al., 2018	EPICAP population-based case-control study (2012–2013)	819 cases (183 with aggressive PCa) 879 controls	Yes	*Increased risk of aggressive PCa* WC, cm: 95–102 *vs* ≤94 OR: 2.20 (1.32–3.69) >102 *vs* ≤94 OR: 3.27 (1.70–6.30), Ptrend = 0.004 WHR: 0.95–0.99 vs <0.95 OR: 1.40 (0.87–2.23) ≥1.00 OR: 1.77 (1.08–2.87) Ptrend ≤0.02 Obesity is a risk for PCa particularly for aggressive cancer; WC is a better index of abdominal obesity than WHR A lack of association between BMI and PCa risk
Zeigler-Jonson et al., 2018 USA	Study of Clinical Outcomes Risk and Ethnicity (SCORE) (1998–2010)	1,576 radical prostatectomy patients categorized on three risk recurrence groups: low, medium, high (Kattan nomogram score <10 CaPSURE/cPDR score <7.2; 10–50; 7.1–16.7; 50–100; >16.7, respectively) based on PSA value, Gleason score and tumor stage (338 obese, 820 overweight, 373 normal weight men)	Yes	*Increased risk* of BH in medium and advanced PCa groups: Medium risk group HR = 2.99 (2.29–3.88) High risk group HR = 8.84 (5.91–13.20), *vs* low risk group A lack of statistically significant association between risk of BH groups across BMI groups
Yu et al., 2018 Korea	Retrospective cohort study (January 2006 – May 2017)	2,997 radical prostatectomy patients: 867 normal weight (BMI <23 kg/m^2), 1,799 overweight (BMI ≥23–<27.5 kg/m^2), 331 obese (BMI ≥27.5 kg/m^2)	Yes	*Obesity was significantly associated* with BH BMI ≥27.5 kg/m^2 was an independent predictor of BH-free- survival: HR = 1.268 (1.095–1.899) *vs* normal weight patients For PCa specific mortality: HR = 2.334 (1.501–3.080) Positive surgical margin rates, extra prostatic invasion, advanced Gleason score (≥8), and lymph node invasion were significantly greater among obese men compared to overweight and normal patients
Langlais et al., 2019 USA	Retrospective cohort study (1995–2018)	3,230 radical prostatectomy cases: 937 normal weight 1,998 overweight 719 obese 193 very obese	Yes	*Increased prognostic risk* at time of diagnosis for obese men OR = 1.5 (1.2–1.8), and very obese OR = 1.7 (1.12–2.30)

1	2	3	4	5
Kelly et al., 2019 USA	Prospective cohort study within National Institutes of Health-American Association of Retired Persons (1995–1996)	153,730 men 630 fatal PCa cases, 16,896 incident cases (2,185 aggressive)	Yes	*Increased risk* of fatal PCa for an increment of 5 kg/m^2 of BMI increase Mid-to-late BMI (mean age 63 year) HR = 1.12 (1.01–1.24) Adulthood maximum BMI (all ages) HR = 1.2 (1.02–1.24) Increased risk of fatal PCa for substantial weight gain during adulthood among never smokers (all ages) HR = 1.27 (1.02–1.49) Increased BMI from normal (18.5–24.9kg/m^2) to obese (≥30.0 kg/m^2) (n = 18 cases) HR = 2.37 (1.38–4.09) *vs* men who maintained a stable BMI
Hurwitz et al., 2020 USA	Case-control study	566 cases, 964 controls	Yes	*Increased risk* of PCa incidence BMI ≥30 kg/m^2 *vs* BMI <25 kg/m^2 OR = 1.86 (1.11–3.13) Elevated WC: OR = 1.76 (1.24–1.51) Elevated WHR OR = 1.46 (0.99–2.16) Overal and abdominal obesity positively linked with PCa risk regardless of cancer grade
Vidal et al., 2020 USA	Retrospective cohort follow-up study (7.4 years)	5,929 patients (1983 black men: 1321 normal weight, 2605 overweight, 2003 obese. Patients identified with BH 1891, with castration-resistant PCa 181, 259 men had metastasis, and 135% had died of PCa	Yes	*Increased risk of mortality* *Obesity was significantly linked with PCa* – specific mortality (p = 0.035): HR = 1.78 (1.04–3.04), regardless of race. A lack of association between overweight/obesity and BH, castration-resistant PCa, or metastasis

Note. PCa – prostate cancer; BMI – body mass index; HR – hazard ratio; CI – convenience interval; OR – odds ratio; BH – biochemical disease recurrence; WC – waist circumference; WHR – waist-hip-ratio.

The following associations between overweight/obesity and PCa were reported: significant increased risk of total cancer associated with excess body weight (17–579%) (Bashir et al., 2014; Hu et al., 2015;Lee, Chia, 2015; Langlais et al., 2019; Hurwitz et al., 2020), aggressive cancer progression (16–330%) (Vidal et al.; 2014, Bai et al.; 2015, De Cobelli et al.; 2015, Khan et al.; 2016, Perez-Cornago et al., 2017; Wu et al., 2017;Zhao et al., 2017; Lavalette et al., 2018), PCa-specific mortality (35–205%) (Dickerman et al., 2017; Kelly et al., 2017; Perez-Cornago et al., 2017; Vidal et al., 2017; Yu et al., 2018; Kelly et al., 2019; Vidal et al., 2020), and BH (22–884%) (Bai et al., 2015; Zhao et al., 2017;Yu et al., 2018; Zeigler-Johnson et al., 2018). Several researchers reported a decreased risk of low-grade overall PCa in overweight/obese individuals (21–53%) (Vidal et al., 2014; Heir et al., 2016; Möller et al., 2016) as well as the non-advanced and advanced cancer (Möller et al., 2016). A lack of association between excess of BMI and total PCa (Khan et al., 2016; Möller et al., 2016; Lavalette et al., 2018) or BH was also observed (Dickerman et al., 2017). The incidence ratios were adjusted mostly for the important confounding factors, such as age, race, education, and PCa screening history. Unfortunately, only two studies reviewed here were adjusted for PA (Möller et al., 2016; Perez-Cornago et al., 2017), six studies for cigarette smoking (Bashir et al., 2014; Möller et al., 2016; Kelly et al., 2017; Perez-Cornago et al., 2017; Langlais et al., 2019; Hurwitz et al., 2020), and one study for alcohol

intake (Bashir et al., 2014). Also, other possible confounding factors in the study of for the obesity/overweight and PCa association, like environmental factors (radiation, infection agents, occupational exposures) were not included in the analyses. We found evidence that increased BMI and/or BMI change during a life course that resulted in obesity were linked with greater risk of advanced and fatal prostate cancers. Observational evidence confirmed also a consistent and strong correlation between obesity and PCa-specific death. Although, few observational studies also reported a protective role of obesity for the risk of local PCa. These results agree with existing literature.

Evidence from previous reviews and meta-analyses clearly demonstrate a significant relationship between overweight/obesity and PCa development, progression, and cancer specific mortality, however, results are mixed (Cao, Ma, 2011; Discacciati, Orsini, Wolk, 2012; Chen et al., 2016; Zhong et al., 2016; Jiang, Chen, 2017). Most meta-analyses included large cohort studies with modest enhancing effect of BMI on the incidence of advanced and high risk PCa (men who have a high Gleason grade, elevated PSA and high tumor stage), subjects experienced a 2-33% higher risk for every 5-kg increase in BMI (Discacciati et al., 2012; Chen et al., 2016; Jiang, Chen, 2017; Vidal et al., 2017). A few of them (Cao, Ma, 2011; Chen et al., 2016; Zhong et al., 2016; Jiang, Chen, 2017) reported an increase from 12% to 20% in PCa specific mortality for every 5-kg increase in BMI, however one study (Zhong et al., 2016) reported only prediagnostic BMI but not post-diagnostic BMI that could be linked with increased risk of death from PCa. In turn, Discacciati et al. (2012) showed an inverse relationship between BMI and localized PCa, reporting a 6% decrease in cancer risk per 5 kg/m2 increase of BMI, and Vidal and Freedland (2017) presented decreased risk of low-grade cancer by 20% among Caucasians and increased risks in obese black men for both low- and high-grade PCa by 122% and 81%, respectively. The authors underlined the importance of cancer progression duration, e.g. a lack of cancer progression for 12 months, but strongly increased progression for longer observation time. Two meta-analysis studies (Bai et al., 2015; Cao, Ma, 2011) reported an approximate 20% higher risk of BH in overweight/obese individuals after primary PCa treatment, however, in one of them (Bai et al., 2015) the association between BMI and the cancer recurrence did not reach statistical significance. Also, review by Trivedi, Samson, Orekoya (2016) reported strong evidence that obesity is associated with both PCa aggressiveness and mortality. In turn, a review of three much earlier meta-analyses, published between 2001–2008 by Allott et al. (2013), indicated a positive relationship between obesity and aggressive PCa risk. The authors found statistically significant increases in the PCa risk by 1–5% per 1 kg/m^2 increase in BMI and a dichotomous effect of obesity on PCa incidence, i.e., including a protective effect of obesity against cancer assessed in some prospective cohort studies, similarly to what we observed in several recent studies presented in Table 1.

The magnitudes of positive association of advanced PCa risk and mortality found in our study were larger than the summary relative risks reported by the reviews' authors. However, these results must be viewed with caution due to significant heterogeneity across the rated studies. In addition, these conflicting outcomes may result from large geographical differences in incidence rates of PCa and obesity and in genetic susceptibility as well as from the use of different methodologies and individual follow-up times. In addition, observational studies often did not include a full list of potential confounders in statistical models, e.g. PA or nutrition, thus often suffered from high heterogeneity.

There are several hypothesized mechanisms where overweight and obesity may influence prostate carcinogenesis and metastasis due to adipose tissue, such as elevated levels of insulin in serum, insulin-like growth factor-1 (IGF-1) and triglycerides, insulin resistance, deregulation of steroid hormones concentrations, resulting in the increased estrogen to androgen ratio, and alteration of proinflammatory adipokines level, e.g. leptin

(as summarized in Figure 1) (Calle, Kaaks, 2004; Roberts, Dive, Renehan, 2010; Rowlands et al., 2012; Williams, 2012; Hopkins, Goncalves, Cantley, 2016; Santoni et al., 2019).

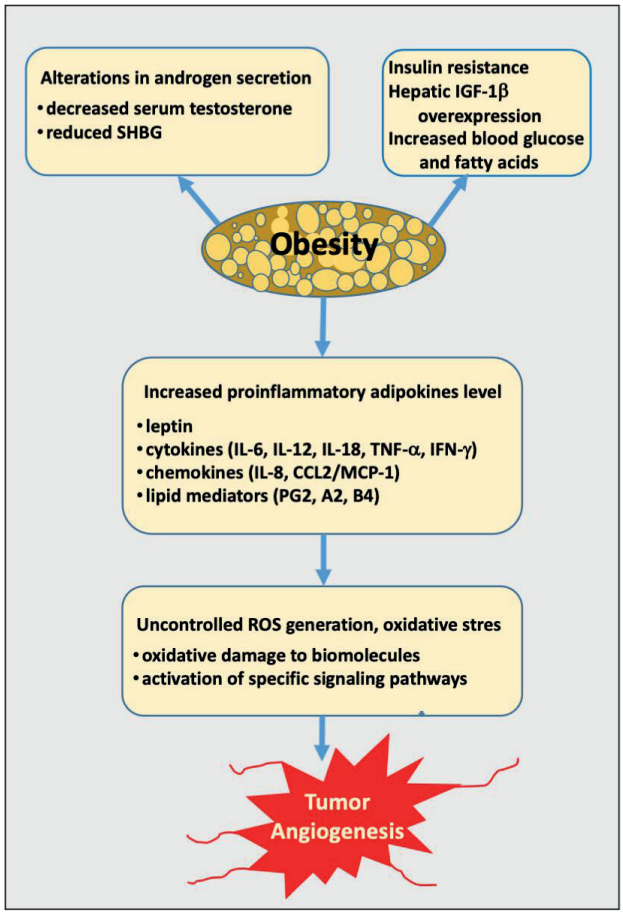

Figure 1. Schematic overview of potential effects of overweight/obesity on prostate carcinogenesis

Evidence shows that excess adipose tissue acting as an endocrine organ involves metabolic dysregulation and secretes adipokines. Obese individuals have increased levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), leptin, insulin and IGF-1, and decreased level of adiponectin (Santoni et al., 2019). Insulin resistance often accompanying obesity and high concentration of IGF-1 can activate and up-regulate IGF-1 and insulin receptors and activate several intercellular signaling pathways, e.g. P13K/AKT (phosphoinositide 3-kinase/protein kinase B), HIF-1α (hypoxia-inducible factor-1 alpha), VEGF (vascular endothelial growth factor), mTOR (mechanistic target of rapamycin), promoting the survival and proliferation of tumor cells (Santoni et al., 2019). Also, a higher blood glucose concentration is a source of energy for cancer cell growth and proliferation (Champ, Francis, Klement,

Dickerman, Smith, 2016). In addition, increased levels of blood fatty acids in obese individuals and their catabolism via β-oxidation support cancer growth and survival (Koundouros, Poulogiannis, 2020). Further, high levels of leptin in obese individuals can lead to the leptin/leptin receptor ratio dysregulation, and via JAK2/STAT (janus kinase-2/signal transducer and activator of transcription), P13K/AKT, and MAPK (mitogen-activated protein kinase) signaling pathways to the development of cancer (Dutta, Ghosh, Pandit, Mukhopadhyay, Chowdhury, 2012). In addition, leptin may directly induce the generation of the ROS intermediates in macrophages, neutrophils and endothelial cells as well as enhances expression of NO synthase, among others, and contributes to chronic inflammation in obesity (Mancuso, 2016). Epidemiological evidence maintained extremely high leptin concentrations in serum of patients with several types of cancer, including PCa.

Several recent studies concluded that adiponectin may be a very important hormone in mediation of the association between obesity and PCa (Fang, Judd, 2018). This protein hormone modulates several metabolic processes, among them glucose level and fatty acids oxidation. Adiponectin also increases activity of peroxisome proliferator – activated receptor alpha (PPARα) ligand (Fang, Judd, 2018) and inhibits VEGF A activity in PCa cells (Gao, Zheng, Yao, Peng, 2015). Unfortunately, adiponectin levels in obese individuals are low.

The latest evidence on the role of obesity in aggressive cancer development suggests that infiltration of periprostatic adipose tissue by tumor cells and secretion of proinflammatory cytokines, e.g. interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-α, are key steps in cancer progression (Fujita, Hayashi, Matsushita, Uemura, Nonomura, 2019; Santoni et al., 2019). In addition, increased levels of reactive oxygen and nitrogen species (ROS, RNS, respectively), released at inflammation sites due to deregulation of homeostasis, can drive carcinogenesis (Klaunig, Kamendulis, Hocevar, 2010; Kruk, Aboul-Enein, 2017; Aggarwal et al., 2019). A dual role of inflammation is known. The first role is protective, when the process is directed against an infection with foreign organisms, injury or the therapeutic application. The second role – harmful, when the process leads to chronic inflammation being the precursor of inflammatory diseases, including cancer. The long-term inflammation along with oxidative stress (OS) and nitrosative stress (NS) is a key factor in cancer onset and progression by forming tumor microenvironment (Aggarwal et al., 2019). Evidence shows an interconnection between OS and inflammation. Under pathological conditions due to excess of ROS/RNS production, inflammation can enhance OS, e.g. through enhancing COX-2 activity and ROS/RNS are formed in excess, increasing cell damage. Metabolic changes linked with long-term weight gain can lead to the disturbance of cellular homeostasis towards ROS/RNS overproduction and contribution to abnormal gene expression and mutations. The excessive production of ROS plays a crucial role in the stimulation of signaling pathways and angiogenic factors, oncogenes activation, apoptosis inhibition, necrosis induction, and tumor suppressors inactivation (Klaunig et al., 2010, Aggarwal et al., 2019). Indeed, an increased concentration of ROS has been detected in several cancers, including PCa. These oxygen species can stimulate carcinogenesis by participation in all its stages (Klaunig, Kamendulis, Hocevar, 2010).

The collective evidence we reviewed agrees with the judgment of the WCRF/AICR Continuous Update Project (2014). Based on the global scientific research of 9,858,000 men including 191,000 PCa cases, Expert Panel concluded that “greater body fatness (marked by BMI, waist circumference, and waist-hip ratio) is *probably* a cause of advanced PCa” (p. 36).

Effect of physical activity/exercise on body weight and body fat

Energy expenditure is the sum of the amount of energy used for basal metabolism (the basal and resting metabolic rate, BMR) to maintain vital activity of cells, respiration, and circulation, energy expenditure from spontaneous PA, activity linked with daily living, and dietary thermogenesis (the energy needed to digest, absorb, and store food). The BMR component of total energy expenditure makes up 60–70%, the component linked with PA comprises 20–30% and diet induced thermogenesis – approximately 10% (Lakka, Bouchard, 2007). Energy expenditure during PA is the most variable component of the total energy expenditure ranging from 400 to 3,000 kcal/day between individuals. Total daily energy expenditure is affected by endogenous and exogenous factors, e.g., genetics, age, metabolism, BMI, and diet or endocrine responses to a stressful agent (Melzer, 2011). The complete characteristic of PA includes domains of activity (e.g., resistance exercise, aerobic exercise), frequency, duration, and intensity. During resistance exercise the body uses glycogens as a fuel and strength of muscles, e.g. exercising with weight machines or lifting heavy load. In turn, in aerobic exercise larger groups of muscle are engaged, and the energy originates from burning of glycogens and fat stores, running, swimming and brisk walking are examples. Intensity of PA/exercise is commonly expressed using metabolic equivalents (METs) estimating the energy cost of individuals. The following intensity levels are specified: Sedentary behavior <1.6 METs, light-intensity, 1.6–2.9 METs, moderate-intensity, 3.0–5.9 METs, vigorous-intensity, ≥6 METs (WHO, 2020). One MET corresponds to a standard resting metabolic rate of 1.0 kcal · kg^{-1} · h^{-1} (the energy expenditure corresponds to individuals at rest). The MET values determine the ratio of the activity-related metabolic rate to a standard resting metabolic rate.

Previous and current epidemiological studies have provided strong evidence for PA/exercise-induced weight and body fat reductions (Thorogood et al., 2011; Kim et al., 2017; Holliday et al., 2018). For example, findings from 14 trials (1,847 obese individuals) involved in a 6-month moderate exercise intervention experienced a weight reduction of 1.6 kg (95% CI: 1.56–1.64) and higher reduction (1.7 kg (95% 1.11–2.29)) and a decrease in WC (1.95 cm (95% CI: 1.29–3.62)) during 12-month intervention (Thorogood et al., 2011). Further, Holliday and co-workers observed that 150 min moderate intensity exercise/week resulted in significant reduced body weight (–3.3 ±5.9 kg) and WC (–2.8 ±4 cm) compared with controls (2.1 ±6.6 cm) in inactive overweight/obese women during a 24-week intervention (Holliday et al., 2018).

There is now clear evidence providing a combination of diet caloric restriction and regular PA as the most effective action to achieve a negative energy balance (Petridou, Siopi, Mougios, 2019). An interesting meta-analysis by Kim et al. (2017) examined the effect of aerobic PE of moderate and high intensity and resistance training with and without caloric restriction on body weight loss. The authors found stronger significant body weight reduction induced by exercise of high intensity (>5%) compared to that of moderate intensity (2–3%). When an exercise intervention was combined with caloric restrictions, body mass reductions were above 5% and 3–5%, respectively, and were stronger than those caused by diet reduction only. Study participants also experienced reduction in WC. Resistance training without caloric restrictions produced no change in body weight. Researchers noted the combination of caloric restriction and increased energy consumption through PA, e.g. brisk walking, climbing stairs will let obese individuals maintain weight for long periods after initial weight loss, thus they recommend 200–300 min/week of moderate intensity PA. The authors noticed that aerobic exercise may be a mean for body weight and fat mass reductions, while the beneficial effect of resistance training on weight loss was not confirmed. Also, a review by Mohamad et al. (2015) of randomized controlled trials (n = 20) carried out up August 2013 reported

the exercise intervention in combination with diet was effective in weight loss (mean body weight decreases were between 0.8 kg and 6.1 kg), the exercise intervention alone did not lead to weight loss.

So far, there are limited findings regarding compensatory changes, i.e. increased energy intake and/or non-exercise activity thermogenesis, accompanying aerobic exercise of high intensity. Evidence shows that a moderate dose of exercise might cause increase non-exercised activity thermogenesis without increased energy intake, while a dose of vigorous exercise could result in increased energy intake and an elevation of level of energy balance (Rosenkilde, Auerbach, Reichkendler, Ploug, Stallknecht, Sjödin, 2012). For this reason, observed losses in body mass and fat mass were not in proportion to the energy expenditure.

Summarizing, the current evidence has generally shown that regular PE of moderate intensity along with diet plays a key role in controlling body weight and preventing obesity. Independently on a magnitude of body weight loss or even its lack, each form of exercise is beneficial for obese individuals, considering exercise ability to fight the chronic low-grade inflammation and prevent against OS which accompany obesity.

Effect of physical activity on prostate cancer in overweight/obese men

The evidence for an association between PA/exercise and PCa incidence shows changing effect (Liu et al., 2000; Littman, Kristal, White, 2006; Lynch, 2010; Liu et al., 2011; Grotta et al., 2015; Benke, Leitzmann, Behrens, Schmid, 2018; McTiernan et al., 2018; Berger et al., 2019; Deb, Emmanuel, Emara, 2019) and is classified as limited suggestive (WCRF/AICR, 2018, McTiernan et al., 2019). Physical activity has not been consistently associated with PCa incidence, some studies have suggested an association between higher PA and decreased risk of PCa incidence, whereas other studies did not find such association. For example, Deb et al. (2019) reviewed studies from 1980 to 2018 on the relationship between PA and PCa incidence risk. The authors found increased risk or no effect of occupational PA in 10 studies, positive trend decreasing cancer risk with increasing level of PA in 4 studies, and a statistically significant decreased risk in the more active men (based on 10 studies). Evidence from this study has suggested that leisure-time PA was inversely associated with the risk of PCa cancer or showed adverse trend or no clear effect (17 studies), exhibited positive trend (9 studies) and a significant decrease of the risk with higher PA (6 studies). Twenty seven of these 56 studies were adjusted for BMI. The question of whether BMI influences the association between PA and PCa risk has rarely been demonstrated (Friedenreich, Stone, Cheung, Hayes, 2020). The previous studies by Giovannucci et al. (2005) and Patel et al. (2005) reported lower risks of more advanced PCa or high stage disease with increased recreational activity, the associations were independent on BMI. Further, a prospective study by Liu et al. (2000) (6,048 men) found no overall effect of PA on PCa risk in the total group as well as among men with BMI >25 kg/m^2. Findings of a prospective cohort study (34,757 participants, 583 incident cases) by Littman et al. (2006) found that greater activity (≥10.5 MET-hours/week) was associated with a non-significantly elevated risk of PCa incidence (HR = 1.5, 95% CI: 0.94–1.52) in the total group, while men who were normal weight had a decreased risk to marginal significance (HR = 0.69, 95% CI: 0.46–1.00) for this dose activity *versus* no activity. However, the authors noted a 37% decrease in risk in inactive obese men compared to inactive normal weight men. Another observational study of Zeeger et al. (2015) evaluated the association between PA and PCa risk with specific emphasis on interaction with BMI (58,279 participants, 1386 incident cases, follow up period 9.3 years. They observed an increased risk PCa for obese men (BMI >30 kg/m^2) who reported >1 hour/day PA and those with a high baseline energy intake. In turn, Grotta et al. (2015) analyzed data from 13,109 men (904 cases, follow-up period 13 years) on self-reported recreational and occupational PA and localized or advanced PCa,

focusing on modulating effect of BMI. The authors noted that high levels of occupational activity were associated with a nonsignificant decreased risk of overall localized, and advanced PCa. A significant interaction between BMI and leisure time activity was noted.

A meta-analysis by Liu et al. (2011) of 19 cohort and 24 case-control studies (88,294 incident cases) on the association between PA and incidence of the risk for PCa showed the decreased risks of PCa incidence associated with total PA (RR = 0.90, 95%CI: 0.84–0.95), occupational activity (RR = 0.81, 95% CI: 0.73–0.91) and recreational activity (RR = 0.95, 95% CI: 0.89–1.00) in men aged <65 years, comparing the highest level versus lowest level of activity. Stratified analyses on BMI attenuated nonsignificantly the risk reductions. The results showed that BMI is not an important confounder of the association PA with PCa. For example, PA was nonsignificant associated with a reduced risk of PCa (RR = 0.98, CI: 0.81–1.20) in individuals with BMI <25 kg/m^2 as well as in the group with BMI >25kg/m^2 (RR = 0.95, CI: 0.82–1.11).

The recent systematic review and meta-analysis conducted in January 2019 of 12 prospective studies (30,810 incident cases) published by Berger et al. (2019) found a statistically significant increased risk of PCa incidence (RR = 1.80, 95% CI: 1.01–1.39) for sedentary lifestyle in analyses not adjusted for BMI. The association was attenuated to null (RR = 1.02, 95% CI: 0.94–1.11) after BMI adjustment. Moreover, the authors noticed a 21% significantly increased risk of aggressive PCa in analysis that was not adjusted for BMI, and the association equal to null after an adjustment for BMI. Another meta-analysis of observational studies (48 cohort studies and 24 case-control studies, 151,748 incident cases) by Benke et al. (2018) found non-significant risk reductions for advanced and non-advanced PCa incidence by 8 and 5%, respectively. They observed a significant inverse association between long-term occupational activity (reduction of total PCa by 17%) based on 13 studies. Evaluation of the association by cancer subtype showed a 49% risk reduction for occupational activity and a 25% reduction of advanced/aggressive PCa risk with increasing recreational activity. The authors observed no statistically significant heterogeneity of the PA-PCa relationship according to BMI.

However, there is growing evidence suggesting that PA has shown to be more effective in reduction of PCa-specific mortality and probability of a relapse of this cancer site (Kenfield, Stampfer, Giovannucci, Chan, 2011; Richman et al., 2011; Baumann, Zopf, Bloch, 2012; McTiernan et al., 2018; Newton et al., 2018; Friedenreich et al., 2020; Kenfield et al., 2021). Kenfield et al. (2011) demonstrated a 61% reduction of PCa-specific mortality, while Richman et al. (2011) found a 57% reduction in cancer progression among individuals with higher PA levels (≥3 hours/week) compared with those with lower activity. In turn, McTiernan et al. (2019) reported a 38% significant reduction in the risk for PCa-specific mortality in individuals with the highest levels of PA compared with those with the lowest levels of total (recreational, non-sedentary occupational and leisure-time activities). Friedenreich et al. (2020) reviewed 136 articles through November 1, 2018, focusing on the association between prediagnosis and postdiagnosis PA and survival for all cancer sites. Evidence showed that higher postdiagnosis levels of total, recreational, occupational and transportation activities significantly decreased cancer specific mortality, HRs: 0.47, 95% CI: 0.31–0.71, 0.69, 95% CI: 0.56–0.85, 0.64, 95% CI: 0.47–0.91, 0.64, 95% CI: 0.43–0.93, respectively. The researchers also demonstrated a subgroup meta-analysis of the relationship between PA before cancer diagnosis and postdiagnosis and cancer-specific mortality separately by BMI ≥25 kg/m^2 *vs* <25 kg/m^2. The analysis did not show that benefit due to postdiagnosis activity was greater for PCa cases with BMI <25 kg/m^2 compared with those with BMI ≥25 kg/m^2.

In summary, the literature does not provide sufficient evidence on the preventive role of PA against all types of PCa (Kruk, Aboul-Enein, 2016; WCRFI, 2016; Benke, Leitzmann, Behrens, Schmid, 2018). However, data have emerged showing that individuals more engaged in PE may have a lower risk of developing of some subtypes of PCa and the risk of aggressive PCa. Moreover, PE delays the disease progression and PCa-specific mortality (Campos et al., 2018; Newton et al., 2018). Evidence has suggested several biological pathways of PA cope with PCa, although the detailed mechanisms require further research due to the complex nature of PE interaction on individuals and complexity of the carcinogenesis process, independly on BMI (Litman et al., 2006; Lynch, 2010; Wekesa, Harrison, Watson, 2016). An important mechanism involves production, secretion, and expression of myokines by the skeletal muscles or other cytokines in response to exercise (Lee, Jun, 2019; Severinsen, Pedersen, 2020). Other mechanisms for the exercise-PCa interaction involve indirect protective effects, such as: Reduction of overweight/obesity and adiposity, change of metabolic and sex hormones levels (estradiol, testosterone), decrease of IGF-1, increase of SHBG and insulin growth factor-binding protein-3 (IGFBP-3), reduction of proinflammatory factors and OS, increase of natural killer cells and T lymphocytes, improvement of the immune system function, enhancement of DNA repair mechanisms, amplification of the antioxidant enzyme system efficiency, increasing the level of one of the most important tumor suppressor genes (p53), decrease of the IGF-1/IGFBP-1 ratio, and activation of protein kinases, among others (Wekesa et al., 2015; Hojman, Gehl, Christensen, Pedersen, 2018). Importantly, PA may also decrease mortality risk of cancer patients with advanced PCa through a change of the tumor microenvironment for the less favorable conditions for tumor progression, influencing e.g., microvascular oxygenation hypoxia and vascular action (Wekesa et al., 2015).

Regarding overweight/obesity, alternations in levels of endogenous hormones have been suggested as the most acceptable mechanism through obesity may affect tumorigenesis and cancer progression (Litmann et al., 2006). Moreover, there is common consensus and clarity on the complex association between steroid hormones level and cancer disease. Evidence has shown that exercise increases SHBG and lowers testosterone levels, while obesity increases levels of estrogens and decreases concentrations of SHBG. In addition, it is important to note that acute bouts of long-lasting and high-intensity endurance exercises generate an excess of ROS/RNS and create OS, thus, exhibit the proinflammatory action. In this case, the interactions and synergy between obesity and PA in proinflammatory actions are probable. Evidence on the positive and negative effects of PA in humans was widely discussed in our previous article (Kruk et al., 2020). More research with good evaluation of PA all domains intensity, frequency, duration, BMI and PCa types is needed to explain whether the effect of PA on PCa risk varies between lean and overweight/obese individuals.

Conclusions

Overweight/obesity and a lack of sufficient PA are recognized risk factors for most chronic diseases, including cancer. Findings of recently published observational studies, being the subject of this overview, confirm the previous data that overweight/obesity may be important risk factor for prostate carcinoma and increased PCa-specific death rate. Current evidence suggests greater baseline BMI is linked with developing a greater risk of high-grade PCa recurrence and with risk of PCa-specific mortality. We observed magnitudes of risk reduction larger than the averages previously reported in the subject literature. However, several discrepancies occurred in this area which include different study groups, study design, limited number of prospective studies, small sample sizes, and often the statistical models were not matched for confounding factors, such as PA, diet, smoking, or alcohol intake which

may interfere with the PA-overweight/obesity association. We also observed a lack of randomized controlled trials in this field of study. We noticed multiple and interrelated mechanisms can cooperatively participate in the association of excess weight and PCa risk, among them are higher estrogen to androgen ratio and chronic psychological stress with consequent increased generation of proinflammatory agents and alteration in the cellular redox homeostasis. Obese individuals are characterized by increased levels of secreted adipokines, such as TNF-α, IL-6, IGF-1, leptin and insulin, blood fatty acids, and the reduced level of adiponectin that activate various signaling cellular pathways and support cancer cell growth, proliferation, and metastasis of tumors. Current evidence suggests that excess body weight in men after radical treatment for localized PCa may increase the risk of the disease BH. Moreover, findings generated an important hypothesis: Monitoring BMI change during the adult life course may help identify men at higher risk of developing fatal stage of PCa. Limited number of studies have carried out a separate risk estimates for the BMI category, evaluating the effect of PA on PCa risk, this requires future studies. There is a suggestion that overweight/obesity may attenuate benefits from PA in cancer survivors. This study highlights the importance of PA/exercise in intentional weight loss among men with PCa and prevention of weight regain. These lifestyle components are means of weight and fat loss, though the potency of their effects in obese individuals remains unknown. Growing evidence maintains that regular exercise of moderate intensity can affect PCa progression by reducing insulin resistance, decreasing IGF-1 and IL-6 levels, increasing adiponectin levels, and enhancing cellular antioxidant homeostasis. Future studies with control groups and longer time of follow-up should examine the underlying biological mechanisms involved in the pathways between overweight/obesity and PCa risk and progression and explore better intervention of PA dose that is required to reduce obesity among advanced disease patients.

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