Energy Balance and Cancer 14

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Energy Balance and Prostate Cancer

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Preface

Prostate cancer is the most common cancer in American men with an age adjusted incidence of 123.2 per 100,000 men per year and 20 deaths per 100,000 per year. In 2017, it is estimated that there will be more than 161,360 new cases diagnosed and 26,730 deaths, making prostate cancer the third leading cause of cancer deaths in American men. Overall, it is estimated that 14% of men will be diagnosed with prostate cancer at some time during their lifetime and that the total number of US men living with some stage of prostate cancer reaches about 2.8 million.

All aspects of prostate cancer including incidence, screening, diagnostic procedures, comorbid conditions, approach and response to therapeutic options including surgery, radiation therapy, chemotherapy, hormone therapy as well as quality of life may be profoundly affected by overweight and obesity which is currently at pandemic proportions, affecting 60–70% of the adult population. Overweight and obesity is particularly prevalent in the older adult population, where the peak incidence of prostate cancer is noted to be in 66-year-old men.

The confluence of obesity with prostate cancer in older men has profound implications for healthcare planning and has been the target of intense fundamental, epidemiologic, and clinical research. In addition to obesity, the course of prostate cancer and its comorbidities may be significantly affected by other aspects of energy balance including physical activity and sleep.

The overall goal of this volume will be to explore areas of research linking energy balance to prostate cancer, identify impact on understanding implications for prostate cancer prevention, clinical care, and mitigation, and manage men with prostate cancer as well as indications of future needs. The volume initially focuses on epidemiology of prostate cancer and its relation to energy balance in terms of incidence, recurrence, mortality, race, and genetics as well as mechanisms by which energy balance impacts prostate cancer and associated comorbidities. Subsequent chapters will concentrate on research trials and their clinical implications to prevent and/or enhance effects of energy balance in men with prostate cancer. This volume provides a comprehensive treatise on the latest studies concerning the interface of prostate cancer and energy balance which together constitute major challenges and

opportunities for research scientist, clinicians, and healthcare planners, especially those dealing with the expanding geriatric population.

We are pleased to have an international group of expert physicians and scientists to author these chapters on Energy Balance and Prostate Cancer. In Chap. 1, Nikos Papadimitriou, University of Ioannina, Ioannina, Greece; Elena Critselis, Academy of Athens, Athens, Greece; and Konstantinos K. Tsilidis, University of Ioannina, Ioannina, Greece, and the School of Public Health, Imperial College London, London, United Kingdom, provide an epidemiologic overview and critical appraisal of the literature indicating an association of obesity with prostate cancer, its apparent association with advanced and fatal prostate cancer, and research needed to further define this relation. Chapter 2, by David S. Lopez, University of Texas, Houston TX, reviews racial and ethnic influences on lifestyle factors affecting prostate cancer. In Chap. 3, Jeanette M. Schenk and Jonathan L. Wright, Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA, review the relationship between common obesity-related comorbidities and the impact of their therapy on prostate cancer. Cheryl L. Thompson and Mackenzie Reece, Case Western Reserve University, Cleveland OH, in Chap. 4 discuss mechanisms by which adipokines mediate the association between obesity and prostate cancer risk and aggressiveness. In Chap. 5, Mieke Van Hemelrijck, King's College London, UK, and Sabine Rohrmann, University of Zurich, Zurich, Switzerland, collaborate to discuss cross-sectional and intervention studies to evaluate how alterations in energy metabolism potentially affect mediators of prostate cancer progression. Chapter 6, written by Daniel S. Han and J. Kellogg Parsons, University of California San Diego Health, CA, discusses the complex influence of obesity on cancer screening, diagnosis, and management. In Chap. 7, Grace Huang and Shehzad Basaria, Harvard Medical School, Boston MA, discuss the important interaction and risks associated with obesity and androgen deprivation therapy in men with prostate cancer. In Chap. 8, Ciaran M. Fairman, the Ohio State University, Columbus, OH; Alexander R. Lucas, Wake Forest School of Medicine, Winston Salem, NC; Elizabeth Grainger, Steven K. Clinton, and Bryan C. Focht, the Ohio State University, Columbus, OH, provide an in-depth analysis of dietary intervention and exercise in men with prostate cancer, and in Chap. 9, Yonaira M. Rivera and Katherine Clegg Smith, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, discuss strategies and benefits of energy balance interventions in patients with prostate cancer. An important area of concern, not covered in this volume due to lack of information, is the influence of obesity on decision making and on outcomes of Active Surveillance, all of which forms an important focus for future research.

Overall, this volume provides a comprehensive treatise on the latest studies linking prostate cancer with energy balance, which together constitute a major challenge and opportunity for research scientists and clinicians especially those dealing with the expanding population of older men confronted with obesity and associated comorbidities. This volume should be a valuable resource to physicians, oncologists, urologists, endocrinologists, nurses, nutritionists, dieticians, and exercise therapists dealing with men with energy balance issues and/or questions regarding

the linkage between energy balance and cancer. Moreover, this volume should serve as an important resource for cancer researchers, especially for scientists studying lifestyle modification and prevention strategies to better understand and disrupt the linkage between obesity and cancer.

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Chapter 1
Epidemiology, Energy Balance and Prostate Cancer Incidence and Mortality

Nikos Papadimitriou, Elena Critselis, and Konstantinos K. Tsilidis

Abstract Energy balance is defined as the equilibrium between energy consumed and expended. A substantial number of prospective epidemiological studies have been conducted to investigate the association of obesity and physical activity with risk of prostate cancer. The aim of this chapter is to provide an overall review and critical appraisal of the literature on these two purported risk factors and prostate cancer incidence overall, incidence of advanced and non-advanced disease, and prostate cancer mortality. Markers of general and central obesity have been associated with an increased risk of advanced and fatal disease, and a decreased risk of localized prostate cancer, but hints of bias were identified in this literature. The literature evidence is sparse and inconsistent for other adiposity indices and physical activity. Future prospective studies and large consortia with valid and direct assessment of the time-varying nature of body fatness and physical activity and with a focus on lethal prostate cancer are needed to draw firmer conclusions.

Keywords Relation BMI to Risk Prostate Cancer Severity • Relation BMI to Risk Prostate Cancer Fatality • Relation Physical Activity to Prostate Cancer Severity

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Introduction

It is widely postulated that energy balance-related factors such as obesity and physical inactivity play an important role in the occurrence of several cancers. For prostate cancer, the literature investigating the role of obesity in prostate cancer incidence and mortality is extensive, while for physical inactivity the literature is less extensive. After reviewing the definition of energy balance, and the descriptive epidemiology of obesity, physical inactivity, and prostate cancer, in this chapter, we present the epidemiological evidence for obesity and physical activity in the etiology of prostate cancer incidence overall and by stage and grade, and mortality. We highlight the evidence for these associations with advanced disease and fatal prostate cancer, which are the most clinically important endpoints.

Definition of Energy Balance

Energy balance is defined as the equilibrium between energy consumed and expended. A sustained positive energy balance, when an individual consumes more energy than is needed for maintenance of body size, produces weight gain, which may be countered by increased energy expenditure through physical activity.

One of the most widely used anthropometric measures is body mass index (BMI). BMI is calculated as an individual's weight in kilograms divided by the square of height in meters. A higher BMI is indicative of increased body size [1]. The presence of adult obesity is defined as BMI larger than or equal to 30 kg/m^2 and is classified into the following subcategories: (a) Class 1: 30 $\leq$ BMI < 35 kg/m^2; (b) Class 2: 35 $\leq$ BMI < 40 kg/m^2; and, (c) Class 3: BMI $\geq$ 40 kg/m^2 [2]. A BMI of 25 to less than 30 kg/m^2 is classified as the overweight range. BMI less than 18.5 kg/m^2 is considered to be in the underweight range. BMI is a readily applicable and reliable surrogate measure of body size, but it does not measure body fat directly and it does not provide information about the distribution of body fat (i.e., abdominal vs. general obesity) [3, 4]. Waist circumference (WC) and waist to hip circumference ratio (WHR) are widely used as markers of abdominal (i.e., central) obesity. Abdominal obesity is linked to hyperinsulinemia and type II diabetes, and is hypothesized to be a stronger risk factor than general obesity for the development of several chronic, non-communicable diseases [5], although this hypothesis was not verified in a recent large pooled analysis [6].

Physical activity is defined as any movement that involves the use of skeletal muscles during occupational, household, and recreational activities. Based on its absolute and relative intensity, physical activity may be classified into sedentary, light, moderate (i.e., walking briskly, ballroom dancing, light gardening activities, etc.) and vigorous (i.e., jogging, intensive swimming, hiking uphill, etc.) activity [7]. Recently both the World Health Organization (WHO) and the American Cancer Society recommended that adults should engage in either at least 150 min of moderate or 75 min of vigorous aerobic physical activity each week [8, 9].

Descriptive Epidemiology of Obesity and Physical Inactivity

The worldwide prevalence of overweight and obesity is increasing and has achieved epidemic proportions particularly in developed countries [10]. In 2014, the prevalence of obesity worldwide was 11% in adult men and 15% in women [11]. During the period between 1975 and 2014, the global age-standardized mean BMI increased from 21.7 kg/m^2 to 24.2 kg/m^2 in men, an increase of 0.63 kg/m^2 per decade, and from 22.1 kg/m^2 to 24.4 kg/m^2 in women, an increase of 0.59 kg/m^2 per decade [12]. It is anticipated that by 2025, 18% of men and more than 20% of women will be obese [12]. The prevalence of obesity is more than two-fold higher in developed countries [11]. In particular, the highest prevalence was documented in the United States of American (USA), where more than 30% of the adult population is obese [12]. Since 2006, the rise in the prevalence of obesity appears to be curtailed in developed countries, but the corresponding rates are rising in developing countries [13].

Globally, 20% of men and 27% of women were unable to meet WHO recommendations for physical activity levels [11]. The prevalence of inadequate physical activity was highest in the WHO regions of America and East Mediterranean, while the lowest rates were observed in Africa and South-East Asia [11]. Physical inactivity rates were almost two-fold greater in high (33%) as compared to low-income countries (17%). Rising trends in physical inactivity are primarily attributed to urbanization and sedentary lifestyles, which have been readily adopted in high income countries [11, 14, 15]. Worldwide, approximately 1.6 million deaths in 2015 alone and 35 million lost disability adjusted life years are attributed to physical inactivity [16].

Epidemiology of Prostate Cancer

Incidence Rates

Prostate cancer is the second most commonly diagnosed cancer in men following lung cancer. It is estimated that 1.1 million men worldwide were diagnosed with prostate cancer in 2012, 70% of whom resided in economically developed countries [17]. The age-adjusted incidence rate of prostate cancer in developed countries is 69 cases per 100,000 person-years exceeding corresponding rates for lung and colorectal cancers [17]. There is large variability in the incidence rates of prostate cancer across the globe with highest rates (85–110 cases per 100,000) reported in Australia, New Zealand, North America and Europe, whereas the lowest incidence rates are observed in Asian populations (about 9 cases per 100,000) [17, 18]. The different trends in prostate cancer incidence may be partly attributed to differences in country-specific recommendations for the use of prostate-specific antigen (PSA) as a screening tool for detecting prostate cancer [19]. In countries such as the USA, Canada

and Australia, where regular PSA screening was adopted early on in clinical practice, initial dramatic spikes in incidence rates of prostate cancer were observed [20–22]. Similar, albeit deduced, increases were observed in Western Europe, where regular PSA testing was adopted later [23]. Rates have since been declining in these countries, but continued increases of smaller magnitude in the incidence rates of prostate cancer during the past two decades have been observed in several Asian and Eastern European countries, where PSA testing is not widely used, suggesting changes in prostate cancer risk factors [20, 21, 24]. In addition, geographic differences in prostate cancer incidence rates were apparent prior to the introduction of PSA screening, further highlighting a potential role of environmental and lifestyle factors in the etiology of this disease.

Mortality Rates

Prostate cancer is the fifth most common cause of cancer death worldwide, corresponding to approximately 6.6% of all deaths in men [17]. Mortality rates are generally high in populations of African descent (19–29 deaths per 100,000), intermediate in the Americas and Oceania, and very low in Asia (2.9 per 100,000). During the past one or two decades, prostate cancer mortality rates have declined in many countries in men of all race/ethnicities, the reasons of which remain controversial [25]. However, it is noteworthy that most recently rising mortality rates have been reported in Russia, Belarus, and Bulgaria [17, 19, 21, 26, 27].

Heterogeneity of Prostate Cancer

Prostate cancer is a clinically heterogeneous disease ranging from microscopic, well-differentiated indolent tumors to aggressive disease; the latter comprises 10–20 % of all tumors and can lead to considerable morbidity and mortality [28]. This clinical heterogeneity may reflect the underlying heterogeneity and inconsistency of study results on putative risk factors, and may have implications for screening, treatment and prognosis. Efforts to understand risk factors for prostate cancer with a lethal phenotype are central to contemporary prostate cancer research.

Risk Factors

Despite the large amount of epidemiological research on prostate cancer etiology, the only well-established risk factors are age, race, family history, and low-penetrance genetic variants. The probability of developing prostate cancer increases from 0.3% in men aged younger than 49 years to 11.2% in those older

than 70 years [29, 30]. Individuals of African descent are at highest risk of developing prostate cancer, followed by those of Caucasian and Asian descent. In particular, African-American men have 1.6 times higher incidence rates than Caucasian-Americans [31]. A positive family history of prostate cancer in a first degree relative puts men at an approximately two-fold increased risk of developing prostate cancer [29]. During the last decade, genome-wide association studies have identified more than 100 independent low-penetrance genetic loci associated with risk of prostate cancer, which combined explain more than one third of the disease variability [32, 33].

Epidemiological Evidence of an Association Between Obesity and Prostate Cancer

Overview

If this association is causal, it may be important for public health, because obesity and prostate cancer affect substantial proportions of men. However, reported associations could also be a product of residual confounding or several biases as shown in prior empirical research in the field of cancer epidemiology [34–38]. We recently conducted two umbrella reviews to evaluate the strength of the evidence and assess the extent of potential biases in the field of diet, nutrition, obesity, physical activity and risk of several cancers [39, 40]. We systematically identified all published systematic reviews or meta-analyses of prospective studies in this field and applied several criteria to assess evidence strength and validity. Data from 46 meta-analyses on the association between seven somatometric factors (i.e., BMI, weight, WC, WHR, weight gain, BMI at age 18–21, and birth weight) and risk of eight different prostate cancer endpoints were retrieved, a summary of which is presented in Table 1.1. The associations were categorized into five evidence judgments: strong, highly suggestive, suggestive, weak, and not significant evidence.

While none of these associations presented strong evidence (Table 1.1), statistically significant positive associations were observed for BMI and risk of advanced or fatal prostate cancer, the majority of which were graded with suggestive evidence. Similar associations in magnitude and direction were observed for weight, WC and WHR with risk of advanced or fatal disease, but the evidence judgments were in general weaker compared to associations for BMI. Statistically significant inverse associations between BMI and risk of low-grade or localized prostate cancer were observed, but these associations were graded with suggestive or weak evidence. None of the associations between the other measures of the adiposity and risk the other prostate cancer endpoints, including total prostate cancer, was statistically significant (Table 1.1). All of these associations are described in more detail in the following sections.

Table 1.1 Associations between adiposity indices and risk of prostate cancer (unless otherwise specified) in published meta-analyses[a]

Author, year	Risk factor	Contrast	Outcome	Studies	Sample size Cohort/Cases	Summary random effects			I^2	Egger's P-value[b]	Evidence grading[c]
						RR	95% CI	*P*-value			
WCRF, 2014	BMI	Per 5 kg/m^2	PrCa (inc & mort)	45	4,271,317/91,206	1.00	0.98, 1.03	0.75	67	0.59	Not significant
WCRF, 2014	BMI	per 5 kg/m^2	PrCa	39	3,798,746/88,632	1.00	0.97, 1.03	0.92	70	0.45	Not significant
Renehan, 2008	BMI	Per 5 kg/m^2	PrCa	26	3,027,773/69,740	1.03	0.99, 1.06	0.10	76	0.72	Not significant
WCRF, 2014	BMI	Per 5 kg/m^2	Low-grade PrCa	4	293,630/9928	0.93	0.89, 0.97	5.1E-04	32	0.33	Suggestive
WCRF, 2014	BMI	Per 5 kg/m^2	Non-advanced PrCa	14	1,142,902/25,887	0.95	0.92, 0.98	1.4E-03	40	0.48	Weak
Discaccati, 2012	BMI	Per 5 kg/m^2	Localised PrCa	12	1,033,009/19,130	0.94	0.91, 0.97	4.6E-4	20	0.46	Suggestive
WCRF, 2014	BMI	Per 5 kg/m^2	High-grade PrCa	6	306,596/3485	1.08	1.01, 1.15	0.02	13	0.98	Weak
WCRF, 2014	BMI	Per 5 kg/m^2	Advanced PrCa	23	1,676,220/11,204	1.08	1.04, 1.12	2.4E-04	19	0.11	Suggestive
Discaccati, 2012	BMI	Per 5 kg/m^2	Advanced PrCa	13	1,080,790/7067	1.09	1.02, 1.16	0.01	40	0.02	Weak
WCRF, 2014	BMI	Per 5 kg/m^2	PrCa mort	12	1,580,914/9826	1.11	1.06, 1.17	1.5E-05	20	0.40	Suggestive
Cao, 2011	BMI	Per 5 kg/m^2	PrCa mort	6	1,263,483/6817	1.15	1.06, 1.25	8.3E-4	59	0.30	Suggestive
WCRF, 2014	BMI	Highest—lowest	PrCa (inc & mort)	43	4,224,170/91,655	0.99	0.94, 1.04	0.64	37	0.83	Not significant

Zhang, 2015	BMI	Obese—normal	PrCa	14	2,342,066/73,851	1.00	0.95, 1.06	0.92	40	0.64	Not significant
WCRF, 2014	BMI	Highest—lowest	Advanced PrCa	21	1,591,046/10,210	1.14	1.04, 1.25	3.7E-03	13	0.46	Weak
WCRF, 2014	BMI	Highest—lowest	Fatal PrCa	21	1,591,046/8596	1.14	1.04, 1.25	3.7E-03	13	0.46	Weak
WCRF, 2014	BMI	Highest—lowest	PrCa mort	12	1,601,800/10,032	1.30	1.17, 1.44	1.8E-06	0	0.70	Suggestive
Zhang, 2015	BMI	Obese—normal	PrCa mort	10	2,339,669/14,179	1.24	1.15, 1.33	1.8E-08	0	0.03	Highly suggestive
WCRF, 2014	Weight	Per 5 kg	PrCa	14	807,552/26,176	1.01	1.00, 1.02	0.23	24	0.06	Not significant
WCRF, 2014	Weight	Per 5 kg	Non-advanced PrCa	5	433,176/15,655	0.99	0.97, 1.00	0.15	56	0.69	Not significant
WCRF, 2014	Weight	Per 5 kg	Advanced PrCa	5	433,176/3376	1.03	1.01, 1.06	2.6E-03	0	0.83	Weak
WCRF, 2014	Weight	Per 5 kg	PrCa mort	4	485,756/1180	1.09	1.04, 1.14	3.7E-04	16	0.98	Suggestive
WCRF, 2014	Weight	Highest—lowest	PrCa (inc & mort)	16	2,128,085/59,340	1.09	1.00, 1.18	0.05	76	0.23	Not significant
WCRF, 2014	Waist circum.	Per 10 cm	PrCa (inc & mort)	9	203,342/6624	1.00	0.97, 1.03	0.98	0	0.65	Not significant
MacInnis, 2006	Waist circum.	Per 10 cm	PrCA	4	56,699/1936	1.03	0.97, 1.09	0.34	0	0.44	Not significant

(continued)

Table 1.1 (continued)

Author, year	Risk factor	Contrast	Outcome	Studies	Sample size Cohort/Cases	Summary random effects			I^2	Egger's P-value[b]	Evidence grading[c]
						RR	95% CI	*P*-value			
WCRF, 2014	Waist circum.	Per 10 cm	Non-advanced PrCa	4	182,460/2906	1.01	0.90, 1.12	0.87	71	0.42	Not significant
WCRF, 2014	Waist circum.	Per 10 cm	Advanced PrCa	4	182,460/1230	1.12	1.04, 1.21	4.0E-03	14	0.95	Weak
WCRF, 2014	Waist circum.	Highest—lowest	PrCa (inc & mort)	8	230,204/7428	0.99	0.91, 1.08	0.79	0	0.83	Not significant
WCRF, 2014	Waist circum.	Highest—lowest	Advanced PrCa	3	187,541/1427	1.25	1.05, 1.50	0.01	0	0.37	Weak
WCRF, 2014	Waist-to-hip	Per 0.1 units	PrCa (inc & mort)	5	183,283/5633	1.01	0.96, 1.06	0.73	0	0.35	Not significant
WCRF, 2014	Waist-to-hip	Per 0.1 units	Non-advanced PrCa	4	182,460/2906	0.99	0.90, 1.09	0.87	20	0.82	Not significant
WCRF, 2014	Waist-to-hip	Per 0.1 units	Advanced PrCa	4	182,460/1230	1.15	1.03, 1.28	0.01	0	0.30	Weak
WCRF, 2014	Waist-to-hip	Highest—lowest	PrCa (inc & mort)	5	214,728/6494	1.01	0.92, 1.10	0.90	0	0.14	Not significant
WCRF, 2014	Waist-to-hip	Highest—lowest	Advanced PrCa	3	187,541/1427	1.22	0.99, 1.50	0.06	0	0.03	Not significant
Keum, 2015	Weight gain	Per 5 kg	PrCA	4	102,109/6882	0.98	0.94, 1.02	0.23	51	0.67	Not significant
Keum, 2015	Weight gain	Per 5 kg	Localised PrCA	4	101,742/5404	0.96	0.92, 1.00	0.08	35	0.12	Not significant
Keum, 2015	Weight gain	Per 5 kg	Advanced PrCA	4	101,692/1094	1.04	0.99, 1.09	0.12	0	<0.01	Not significant
Keum, 2015	Weight gain	Highest—lowest	PrCA	8	426,104/19,377	0.98	0.91, 1.06	0.59	31	0.67	Not significant

WCRF, 2014	BMI (age 18-21)	Per 5 kg/m^2	PrCa	7	465,132/14,815	0.99	0.93, 1.06	0.79	29	0.09	Not significant
WCRF, 2014	BMI (age 18-21)	Per 5 kg/m^2	Non-advanced PrCa	4	397,318/10,158	1.00	0.86, 1.16	0.99	71	0.09	Not significant
WCRF, 2014	BMI (age 18-21)	Per 5 kg/m^2	Advanced PrCa	5	445,099/11,388	1.04	0.86, 1.25	0.70	71	0.73	Not significant
WCRF, 2014	BMI (age 18-21)	Per 5 kg/m^2	PrCa mort	3	323,878/729	1.13	0.93, 1.37	0.21	0	0.52	Not significant
WCRF, 2014	BMI (age 18-21)	Highest—lowest	PrCa (inc & mort)	8	492,297/15,152	0.98	0.91, 1.07	0.72	36	0.06	Not significant
WCRF, 2014	Birth weight	Per 500 g	PrCa	7	177,548/2695	1.03	0.99, 1.08	0.18	0	0.13	Not significant
WCRF, 2014	Birth weight	Per 500 g	Advanced PrCa	2	40,821/246	1.09	0.97, 1.22	0.13	0	NA	Not significant
WCRF, 2014	Birth weight	Per 500 g	PrCa mort	2	3,316/902	1.09	0.96, 1.25	0.18	0	NA	Not significant
WCRF, 2014	Birth weight	Highest—lowest	PrCa (inc & mort)	5	64,843/1559	1.18	0.97, 1.44	0.09	64	0.09	Not significant

Abbreviations: *WCRF* World Cancer Research Fund, *BMI* body mass index, *CI* confidence interval, *inc* incidence, *mort* mortality, *circum* circumference, *PrCA* prostate cancer, *RR* relative risk

[a]A selection of published meta-analyses of only prospective studies are shown using data from two published relevant umbrella reviews [39, 40]

[b]*P*-value from the Egger's regression asymmetry test

[c]For more details, please see the following references [39, 40]