

UCSF

UC San Francisco Electronic Theses and Dissertations

Title

Impact of Modifiable Diet and Lifestyle Factors on Prostate Cancer Progression and Mortality

Permalink

<https://escholarship.org/uc/item/4fc451d5>

Author

Langlais, Crystal

Publication Date

2022

Peer reviewed|Thesis/dissertation

Impact of Modifiable Diet and Lifestyle Factors on Prostate Cancer Progression and Mortality

by
Crystal Langlais

DISSERTATION

Submitted in partial satisfaction of the requirements for degree of
DOCTOR OF PHILOSOPHY

in

Epidemiology and Translational Science

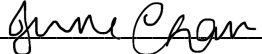
in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Approved:

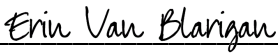
DocuSigned by:

E00433DE984A43E... June Chan
Chair

DocuSigned by:

Stacey Kenfield

DocuSigned by:

John Neuhaus

DocuSigned by:

9AB88B0A6CD942B... Erin Van Blarigan

Committee Members

Copyright 2022

by

Crystal Silva Lenglais

Dedication

My sincerest gratitude goes to my mentor and dissertation chair, June Chan. Thank you for the opportunity to work with you on meaningful and impactful work. My PhD training would not have been as rewarding without your support, mentorship, and endeavors to ensure my access to numerous opportunities. I am eternally grateful for the time you selflessly invested in me and your genuine interest in my personal growth and wellness. Thank you.

To Stacey Kenfield and Erin Van Blarigan, members of my dissertation committee: Thank you both for engaging me in research outside of my dissertation work. These opportunities expanded my network and the breadth of my research and undoubtedly made me a better scientist. Stacey, the opportunity to engage directly with prostate cancer survivors as a member of your 2019 NCI SPRINT team enhanced the importance of the work detailed in my dissertation, for which I am truly grateful. Erin, your consistently thoughtful and thorough feedback was so appreciated and has made me a stronger writer.

To John Neuhaus, a member of my dissertation committee: Thank you for challenging my thinking and pushing me to utilize multiple methods to ensure the robustness of findings. Your mentorship has undoubtedly strengthen my methodological skillset. Thank you.

To our PhD Program Director, Maria Glymour: I am so grateful for your reassuring words and advice, and particularly your intuition to know when I needed it, often before I did.

A special thank you to Rebecca Graff, with whom I co-authored several papers, including all three of my dissertation papers. I could always count on you for thoughtful feedback and usually a laugh, for which I am very grateful.

Thank you to Peter Carroll and the CaPSURE team, especially Janet Cowan and Jenny Broering, for welcoming me to CaPSURE and working so closely with me on numerous projects during my time as a PhD student. Findings from CaPSURE have contributed to improving the care of men with prostate cancer, including making the work, herein, possible.

I am also grateful to my fellow PhD students, who made this program both feasible and enjoyable. I relied on many of you for laughs, commiserations, exposure to other avenues of research, and to challenge my understanding of course material and my own research.

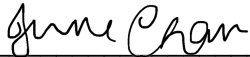
To my parents Tony and Kenda, and my sister Brandy: Thank you for always believing in me and supporting me. Your pride in me and unconditional love made this journey possible. I am very lucky you are my family.

Finally, to my husband, Blake: Thank you for supporting and encouraging my ambitions. Your love, support, and understanding throughout this program was invaluable and allowed me to succeed in this program and beyond. Thank you for always believing in me and taking pride in my accomplishments. I look forward to our future adventures.

Contributions

A version of Chapter 1 in this dissertation was published in *Current Oncology Reports*.¹ The Dissertation Committee members supervised the research that forms the basis of this dissertation chapter and the published material is substantially the product of Crystal Langlais' period of study at UCSF and was primarily conducted and written by her. The work she completed for this published manuscript is comparable to a standard dissertation chapter.

Approved:

DocuSigned by:

E00433DE984A43E...

June Chan, ScD, Dissertation Chair

¹Langlais CS, Graff RE, Van Blarigan EL, Palmer NR, Washington SL 3rd, Chan JM, Kenfield SA. Post-Diagnostic Dietary and Lifestyle Factors and Prostate Cancer Recurrence, Progression, and Mortality. *Curr Oncol Rep.* 2021;23(3):37.

Impact of Modifiable Diet & Lifestyle Factors on Prostate Cancer Progression

Crystal Silva Langlais

Abstract

With over 3.6 million men living with prostate cancer nationally, identifying ways these men can minimize their risk of disease progression is an important public health need. Intervening on modifiable behavioral factors may prevent disease progression and improve quality of life following prostate cancer diagnosis. Several studies have examined the associations of various modifiable factors with prostate cancer progression. These studies have sometimes yielded apparently conflicting results, in particular for dietary factors, potentially confusing clinicians and patients regarding which behaviors to modify. This may be due in part to the limitations of studying a single dietary or other behavioral factor in isolation. Specifically, this approach does not accurately reflect the complex interplay between multiple factors and their ability to act synergistically or antagonistically to impact health. A better understanding of the biological processes relating lifestyle patterns to disease progression is also warranted, as it may aid our understanding of progression risk.

The first chapter of my dissertation is a comprehensive summary of the existing evidence relating various diet and other modifiable behaviors with prostate cancer recurrence and progression, prostate cancer-specific mortality, and overall mortality. Across these outcomes, results from this study identified consistently positive associations with body mass index, smoking, and intake of whole milk, saturated fats, and red and processed meats, as well as consistently inverse associations with physical activity and moderate wine intake. These results provided the evidence for the prostate cancer-specific composite risk score evaluated in Chapter 2. In addition to this disease-specific composite risk score, Chapter 2 also explores the association of cancer prevention and survivorship guidelines published by the World Cancer Research Fund / American Institute for Cancer Research and the American Cancer Society, as well as an evidence-based composite risk score created for the risk of developing lethal prostate

cancer among disease-free men. Chapter 3 utilizes dietary and lifestyle indices developed to predict biomarkers of inflammation and insulin secretion, to examine the biological mechanisms driving prostate cancer progression and prostate cancer-specific mortality.

As a body of work, my dissertation provides insights into the modifiable risk factors driving prostate cancer progression and prostate cancer-specific mortality and improves our understanding of the underlying mechanisms, providing a foundation for future research. Clinically, these findings can inform patient recommendations and aid behavioral change in the survivorship care setting.

Table of Contents

Chapter 1: Post-Diagnostic Dietary and Lifestyle Factors and Prostate Cancer

Recurrence, Progression, and Mortality.....	1
Abstract	2
Introduction	3
Methods	3
Results	4
Discussion	17

Chapter 2: Post-Diagnostic Health Behavior Scores and the Risk of Prostate

Cancer Progression and Mortality.....	27
Abstract	28
Introduction	30
Methods	31
Results	39
Discussion	41

Chapter 3: Post-Diagnostic Inflammatory, Hyperinsulinemic, and Insulin

Resistant Diets and Lifestyles and the Risk of Prostate Cancer Progression and Mortality.....	56
Abstract	57
Introduction	58
Methods	59
Results	65

Discussion.....	66
References	79
Funding.....	100

List of Tables

Table 1.1. Characteristics of studies by diet and lifestyle factor	18
Table 1.2. Summary of associations between diet and lifestyle components and prostate cancer progression, prostate cancer-specific mortality, and all-cause mortality.....	24
Table 2.1. Operationalization of the 2021 Score, 2015 Score, ACS Score, and WCRF/AICR Score	44
Table 2.2. Individuals Items Included in Each Component of the 2021 Score, 2021 Score + Diet, 2015 Score, ACS Score, ACS Score + Alcohol, and WCRF/AICR Score	47
Table 2.3. Patient and clinical characteristics of men diagnosed with non-metastatic prostate cancer by tertile of health behavior scores	49
Table 2.4. Post-diagnostic health behavior scores and the risk of prostate cancer progression among men with non-metastatic prostate cancer, estimated via parametric (Weibull) survival models to account for interval censoring.....	50
Table 2.5. Post-diagnostic health behaviors scores and the risk of prostate cancer mortality among men with non-metastatic prostate cancer, estimated via Cox proportional hazards models.....	51
Table 2.6. Post-diagnostic health behavior scores and the risk of prostate cancer progression among men with non-metastatic prostate cancer, estimated via parametric (Weibull) survival models to account for interval censoring with time zero set to date of diagnosis	52

Table 2.7. Post-diagnostic health behavior scores and the risk of prostate cancer progression among men with non-metastatic prostate cancer, estimated using both Cox Proportional Hazards and Fine-Gray methods	53
Table 2.8. Characteristics of men with and without complete data to assess the missing-at-random assumption of multiple imputation.....	54
Table 2.9. Post-diagnostic health behavior scores and the risk of prostate cancer progression among 2,056 men with non-metastatic prostate cancer after multiple imputation to preserve observations with missingness in covariates	55
Table 3.1. Items included in the calculations of each component of the dietary and lifestyle indices.....	70
Table 3.2. Participant and clinical characteristics of men diagnosed with non-metastatic prostate cancer by quintile of inflammatory, hyperinsulinemia, and insulin resistance dietary indices	72
Table 3.3. Participant and clinical characteristics of men diagnosed with non-metastatic prostate cancer by quintile of hyperinsulinemia and insulin resistance lifestyle indices	73
Table 3.4. Correlations between post-diagnostic inflammatory, hyperinsulinemia, and insulin resistance diet and lifestyle indices	74
Table 3.5. Multivariable models estimating associations of post-diagnostic inflammatory, hyperinsulinemia, and insulin resistance diets and lifestyles with the risk of prostate cancer progression and prostate	

cancer-specific mortality among men diagnosed with non-metastatic prostate cancer	75
Table 3.6. Associations of inflammatory and insulinemia diets and lifestyles with the risk of prostate cancer progression among men with non- metastatic prostate cancer, estimated via Cox proportional hazards and Fine-Gray models to assess competing risks	76
Table 3.7. Associations of inflammatory and insulinemia diets and lifestyles with the risk of prostate cancer progression among men with non- metastatic prostate cancer, estimated via parametric (Weibull) survival models after multiple imputation to preserve observations with missingness in covariates	77
Table 3.8. Minimally-adjusted models estimating the associations between post- diagnostic inflammatory, hyperinsulinemia, and insulin resistance diets and lifestyles with the risk of prostate cancer progression and prostate cancer-specific mortality among men diagnosed with non- metastatic prostate cancer.....	78

List of Abbreviations

- ACM – all-cause mortality
- AA/B – African-American/Black
- ACS – American Cancer Society
- AICR – American Institute for Cancer Research
- AS – active surveillance
- BMI – body mass index
- CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor
- CDL – CaPSURE Diet & Lifestyle sub-study
- CI – confidence interval
- CPS – Cancer Prevention Study
- CRP – C-reactive protein
- EDIH – empirical dietary index for hyperinsulinemia
- EDIP – empirical dietary inflammatory pattern
- EDIR – empirical dietary index for insulin resistance
- ELIH – empirical lifestyle index for hyperinsulinemia
- ELIR – empirical lifestyle index for insulin resistance
- FFQ – food frequency questionnaire
- HCaP-NC – Health Care Access and Prostate Cancer Treatment in North Carolina
- HPFS – Health Professionals Follow-up Study
- HR – hazard ratio
- IL-6 – interleukin-6
- MEAL – Men’s Eating and Living trial
- METs – metabolic equivalent of task
- PA – physical activity
- PC – prostate cancer

PCSM – prostate cancer-specific mortality

PHS – Physicians' Health Study

PROCAP – Progression in Cancer of the Prostate

PROSCARE – Prostate Cancer Risk Evaluation

PSA – prostate-specific antigen

RERI – relative excess risk due to interaction

RP – radical prostatectomy

RT – radiotherapy

SEARCH – Shared Equal Access Regional Cancer Hospital

SD – standard deviation

TAG:HDL – triacylglycerol to high density lipoprotein cholesterol

TNF α R2 – tumor necrosis factor alpha receptor 2

WW – watchful waiting

WCRF – World Cancer Research Fund

Chapter 1: Post-Diagnostic Dietary and Lifestyle Factors and Prostate Cancer

Recurrence, Progression, and Mortality

Crystal S. Langlais, Rebecca E. Graff, Erin L. Van Blarigan, Nynikka R. Palmer, Samuel L.

Washington 3rd, June M. Chan, Stacey A. Kenfield

Abstract

Purpose of review: To summarize evidence published between 1999 and June 2020 examining diet and lifestyle after prostate cancer diagnosis in relation to risk of biochemical recurrence, prostate cancer progression, and prostate cancer -specific mortality.

Recent Findings: Secondary prevention is an important research area in cancer survivorship. A growing number of studies have reported associations between post-diagnostic modifiable behaviors and risk of prostate cancer outcomes.

Summary: Evidence on modifiable lifestyle factors and prostate cancer remains limited. Where multiple studies exist, findings are often mixed. However, studies consistently suggest that smoking and consumption of whole milk/high-fat dairy are associated with higher risk of prostate cancer recurrence and mortality. In addition, physical activity and ½ to 1 glass of red wine/day have been associated with lower risk of recurrence and prostate cancer -specific mortality. Greater inclusion of racially/ethnically diverse groups in future research is necessary to understand these relationships in populations most impacted by adverse prostate cancer outcomes.

Introduction

Prostate cancer is the second most common malignancy diagnosed among men worldwide, with an estimated 1.3 million diagnoses worldwide in 2018 [1]. Despite its relatively high survival rate, it remains the fifth most common cause of cancer-related death among men worldwide, with 358,989 deaths reported in 2018. Moreover, it is the leading cancer-related cause of death in men in 46 countries [1]. The varying disease courses prostate cancer can take underscore its heterogeneity in presentation and prognosis and highlight the importance of secondary prevention. Over the past two decades, there has been a growing interest in identifying modifiable factors, such as diet and lifestyle factors, associated with overall health, disease progression, and mortality among men with prostate cancer.

Methods

In this review, we summarize findings from studies evaluating associations of *post-diagnostic* dietary and lifestyle (e.g., physical activity, body size, smoking) behaviors with prostate cancer recurrence, progression, and mortality; highlight important new research; and discuss where additional research is needed. We focused on observational studies to complement a recent review of randomized trials on this topic [2]. Although focused on literature from the last five years, additional studies from the past two decades provide further context. We used the search terms “prostate cancer”, “progression”, and “mortality” in combination with each dietary or lifestyle factor (see sub-section headers below) to search PubMed for articles published through June 22, 2020. Papers that examined all-cause mortality (ACM) were included if a prostate cancer -specific outcome [recurrence/progression, prostate cancer -specific mortality (PCSM)] was also evaluated. A single author (CSL) reviewed titles and abstracts of 1,894 returns and identified 168 unique articles for further review. Eighty-three were deemed relevant, 33 of which were published between 2015-2020. Most common reasons for

exclusion included exposure assessment prior to diagnosis and lacking assessment of any of the outcomes of interest.

Given known racial/ethnic disparities in prostate cancer, including a greater mortality burden among African American/Black (AA/B) men, we assessed the race/ethnicity distributions of the populations studied. **Table 1.1** summarizes characteristics of the studies reviewed, stratified by exposure. **Table 1.2** summarizes the findings of all included observational studies. Where relevant, we supplement our discussion with findings from randomized trials [2].

Results

Fish. Five studies published between 2006-2020 examined post-diagnostic fish intake in relation to prostate cancer outcomes, three of which considered recurrence or progression.[3-5] One of these, a study of 1,202 men with non-metastatic prostate cancer from the Health Professionals Follow-up Study (HPFS), observed evidence of an inverse association in models adjusted for pre-diagnostic fish intake [hazard ratio (HR) for 1 serving/day increase: 0.52, $p=0.006$; 95% confidence interval (CI) unavailable] [5]. The other two – a study of 940 men with stage $\leq T3$ prostate cancer from Washington University and a study of 1,294 men with localized/regional disease from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE™) – observed no association [3, 4]. However, the Washington University study reported a statistically significant inverse association for recurrence when modeling the substitution of fish/poultry for red meat [3]. The remaining two studies examined PCSM and ACM and observed no statistically significant associations for fish intake, though one of these reported a borderline statistically significant inverse trend per 1 standard deviation (SD) of greater fish intake and ACM (HR: 0.90; CI: 0.80 to 1.01; $p=0.08$) [6, 7]. No study reported an elevated risk of adverse prostate cancer outcomes with fish intake. In summary, evidence that

fish intake following prostate cancer diagnosis is associated with prostate cancer outcomes is very limited.

Meat, Poultry, and Eggs. Three studies conducted between 2006-2016 considered post-diagnostic consumption of meat, poultry, and eggs in relation to recurrence/progression and observed no associations with total poultry or total, processed, or unprocessed red meat (**Table 1.2**) [3-5]. A study of 1,294 men with localized/regional prostate cancer in CaPSURE observed a positive association between poultry with skin and risk of prostate cancer progression ($HR_{\text{tertile3 vs 1}}: 2.26$; CI: 1.36, 3.76; $p\text{-trend}=0.003$) [4]. This study also observed a borderline statistically significant association with egg intake ($HR_{\text{quartile 4 vs 1}}: 2.02$; CI: 1.10, 3.72; $p\text{-trend}=0.05$), which was not replicated by a later study of 940 men from Washington University [3].

Three studies examined post-diagnostic intake of meat, poultry, and eggs with respect to PCSM, with mostly null results [6-8]. However, a study of 4,882 men with non-metastatic prostate cancer from the Cancer Prevention Study-II Nutritional Cohort (CPS-II) reported an inverse relationship with unprocessed red meat ($HR_{\text{quartile 4 vs 1}}: 0.64$; CI: 0.46, 0.91; $p\text{-trend}=0.01$) [7]. While a study of 926 men with non-metastatic prostate cancer from the Physicians' Health Study (PHS) observed a higher risk per 1 SD increase in processed meats ($HR: 1.32$; CI: 1.06, 1.64; $p=0.01$) [6].

Two studies examining PCSM also examined ACM, with mixed findings (**Table 1.2**) [6, 7]. In the PHS, there was a higher risk per 1 SD increase in intake of processed meats ($HR: 1.17$; CI: 1.06, 1.30; $p=0.003$) and eggs ($HR: 1.12$; CI: 1.02, 1.24; $p=0.02$), but no association with total red meat [6]. Conversely, the CPS-II study observed an association with total red meat ($HR_{\text{quartile 4 vs 1}}: 1.22$; CI: 1.07, 1.39; $p\text{-trend}=0.03$), but not with eggs [7]. Further, despite not demonstrating a statistically significant trend, each upper quartile (Q) of processed red meat intake in CPS-II had a higher risk of ACM compared to Q1 ($HR_{Q4}: 1.17$; CI: 1.04, 1.33. $HR_{Q3}: 1.15$; CI: 1.02, 1.30. $HR_{Q2}: 1.14$; CI: 1.01, 1.28; $p\text{-trend}=0.07$) [7]. This study also reported an

inverse association with total poultry and ACM (HR_{Q4}: 0.84; CI: 0.75, 0.95; p-trend=0.01), which was not examined in the PHS.

In summary, recommendations on post-diagnostic meat, poultry, or egg intake specifically for prostate cancer outcomes cannot be made due to lack of concordance across a limited number of studies. However, based on national guidelines for general and cardiovascular health, it is prudent to limit consumption of processed meat and select lean choices of meat or skinless poultry [9, 10].

Dairy. Three studies conducted between 2006-2018 considered post-diagnostic dairy intake in relation to prostate cancer recurrence or progression [5, 11, 12]. Where there was overlap in exposures examined, studies agreed. Studies in CaPSURE and HPFS both found no association with total, high fat, or low-fat dairy, but reported positive associations between >4 servings/week versus 0-3 servings/month of whole milk and risk of progression (HR: 1.73; CI: 1.00, 2.98; p-trend=0.04. HR: 1.51; CI: 1.03, 2.20; p-trend=0.03) [11, 12]. Two studies from the HPFS found no association between total milk and risk of prostate cancer progression [5, 12]. Although, one of these noted a positive association in models adjusting for pre-diagnostic intake (HR_{continuous}: 1.12, p=0.04, CI unavailable) [5]. **Table 1.2** shows various other dairy items that were examined by a single study [11].

Three studies examined post-diagnostic dairy intake and PCSM (**Table 1.2**) [6, 12, 13]. While results for most sub-categories of dairy were null, there were consistent positive associations for whole milk. One of these, a study of 3,918 men with localized/locally-advanced prostate cancer from the HPFS, observed a relationship with >4 serving/week versus 0-3 servings/month of whole milk (HR: 2.15; CI: 1.28, 3.60; p-trend<0.01) [12]. A population-based study of 525 Swedish men did not observed this association in the full cohort but replicated this finding for ≥3 versus <1 serving/day of high-fat milk among 230 men diagnosed with localized disease (HR: 4.86; CI: 1.52, 15.57; p-trend=0.003) [13].

Two studies examining PCSM also examined ACM; both observed an association with high-fat dairy intake (HR_{1 SD increase}: 1.18; CI: 1.07, 1.30; p=0.001. HR_{≥4.5 serv/day}: 1.04; CI: 0.73, 1.49; HR_{3-<4.5 serv/day}: 0.82; CI: 0.58, 1.17; HR_{1-<3 serv/day}: 0.75; CI: 0.53 to 1.04 versus < 1 serv/day; p-trend=0.05) [6, 13]. Effect modification was observed in the Swedish cohort based on stage at diagnosis and milk type. There was a positive association for servings/day of high-fat milk (HR_{≥3 vs <1}: 3.32; CI: 1.85, 5.97; p-trend=0.001) among men diagnosed with localized prostate cancer, while low-fat milk was positively associated with ACM among 295 men diagnosed with advanced prostate cancer (HR_{≥2 vs <1}: 1.72; CI: 1.14, 2.57; p-trend=0.02) [13].

In summary, men should limit whole milk to <4 servings/week following a prostate cancer diagnosis to minimize risk of progression and PCSM. Limiting high-fat dairy is also advised, and consistent with heart-healthy diet recommendations, to decrease risk of ACM following prostate cancer diagnosis.

Dietary Fats. Five studies examined post-diagnostic dietary fats in relation to prostate cancer outcomes, with only one published in the last 5 years [14-18]. Only one, a study of 390 men who underwent radical prostatectomy (RP), examined risk of recurrence and reported a higher risk associated with saturated fat (HR_{Q4 vs Q1-3}: 1.90; CI: 1.16, 3.11; p-value unavailable) [14].

Four studies examined specific types of dietary fat (**Table 1.2**) with respect to PCSM [15-18]. Studies agreed that there was no association with monounsaturated, polyunsaturated, *trans*, or animal fat intake. Two studies also examined total dietary fat and found no association, although one – a Swedish study of 525 men – reported a positive trend between total dietary fat and risk of PCSM among the sub-group of men diagnosed with localized prostate cancer (HR_{Q4 vs. Q1}: 2.07; CI: 0.93, 4.59; p-trend=0.03) [15, 16]. There was mixed evidence regarding saturated and vegetable fat intake. Two studies – a Canadian study of 384 men and a study of 926 men with non-metastatic prostate cancer in the PHS – observed a relationship with saturated fat intake (HR_{tertile 3 vs 1}: 3.1; CI: 1.3, 7.7; p-trend=0.008; HR for 5% caloric exchange of saturated fat

for carbohydrates: 2.78; CI: 1.01, 7.64; p=0.05) [16, 17]. Two other studies reported no statistically significant relationships between post-diagnostic saturated fat and risk of PCSM [15, 18]. Regarding vegetable fat, a study of 4,577 men with non-metastatic prostate cancer from the HPFS observed an inverse relationship with PCSM (HR for 10% caloric exchange of vegetable fat for carbohydrate: 0.71; CI: 0.51, 0.98; p=0.04), whereas the PHS analysis did not observe a statistically significant association [17, 18].

Two studies considered ACM with mixed results [17, 18]. Both observed no association with monounsaturated or animal fat, but an inverse association with vegetable fat (PHS HR_{Q4 v Q1}: 0.65; CI: 0.45, 0.93; p-trend=0.03; HPFS HR_{quintile5 vs 1}: 0.65; CI: 0.52, 0.83; p-trend<0.001) and a positive association with saturated fat (PHS HR for 5% caloric exchange of saturated fat for carbohydrate: 1.81; CI: 1.20, 2.74; p=0.005; HPFS HR for 5% caloric exchange of saturated fat for carbohydrate: 1.30; CI: 1.05, 1.60; p=0.02) [17, 18]. The HPFS also observed an inverse relationship between polyunsaturated fat and ACM (HR_{quintile 5 vs 1}: 0.73; CI: 0.57, 0.94; p-trend=0.004) and a positive association with *trans* fat (HR_{quintile 5 vs 1}: 1.51; CI: 1.14, 2.01; p-trend=0.002) [18]. The PHS observed no associations with polyunsaturated or *trans* fats [17].

Overall, diets with higher saturated fat may increase risk of prostate cancer recurrence and mortality. Replication of findings for vegetable, polyunsaturated and *trans* fats with mortality outcomes is needed, though findings are consistent with recommendations for overall health [9, 10].

Vegetables: Tomato (Lycopene), Cruciferous. We identified three studies that considered post-diagnostic tomato intake in relation to prostate cancer outcomes [5, 6, 19]. Two of these evaluated tomatoes in relation to risk of prostate cancer progression with inconsistent findings. The first, a study of 1,560 men with non-metastatic prostate cancer from CaPSURE found no statistically significant association with either fresh tomatoes or tomato sauce [19]. In contrast, a study of 1,202 men with non-metastatic prostate cancer from the HPFS reported an inverse association with tomato sauce (HR_{1 serving/day}: 0.46, p=0.04, CI unavailable) and a positive

association with fresh tomato intake ($HR_{1 \text{ serving/day}}: 1.27, p=0.02, CI \text{ unavailable}$) [5]. However, associations were attenuated and neither was statistically significant when pre-diagnostic intake was excluded from the models [5]. Clinical trials have reported that supplemental lycopene is associated with return to normal PSA and normal bone scans in men with metastatic prostate cancer treated with orchiectomy [2]. Lycopene concentrations are higher in cooked than raw tomatoes, which may explain why a protective association is only observed for cooked tomatoes. A single study of 926 men with non-metastatic disease in the PHS examined PCSM and ACM and found no association between tomato intake as part of a Prudent diet and risk of PCSM or ACM [6].

Two observational studies examined cruciferous vegetables [6, 19]. CaPSURE reported an inverse association between cruciferous vegetable intake and risk of prostate cancer progression ($HR_{Q4 \text{ vs } Q1}: 0.41; CI: 0.22, 0.76; p\text{-trend}=0.003$) [19]. The PHS found no association with either PCSM or ACM [6].

Recent findings from the Men's Eating and Living (MEAL) trial warrant discussion. MEAL randomized 443 men with low-risk prostate cancer on active surveillance to receive counseling promoting consumption of ≥ 7 vegetable-fruit servings/day, including at least two servings each of cruciferous vegetables and tomatoes [20]. During the two-year intervention, 245 events of progression were observed. Though the intervention modestly increased daily servings of cruciferous vegetables (between group difference at 24 months: 0.49; CI: 0.33 to 0.64; $p<0.01$) and tomatoes (between group differences at 24-months: 0.14; CI: 0.03, 0.26; $p=0.02$), it did not affect risk of disease progression.

Overall, results for post-diagnostic intake of tomatoes/lycopene and cruciferous vegetables and prostate cancer outcomes are inconsistent. Nonetheless, it is prudent to encourage prostate cancer survivors to include a wide variety of vegetables in their diet for weight management and risk reduction for many chronic diseases, including diabetes and cardiovascular disease [9, 10].

Alcohol. Two studies examined post-diagnostic alcohol consumption and prostate cancer outcomes [21, 22]. Only one, a Canadian study of 829 men with $\geq T2$ disease, considered recurrence, and observed no association with total alcohol [21].

When examining PCSM, the two studies agreed there was no association for overall trend of total alcohol or liquor intake. However, the Canadian study observed a positive association with moderate intake of liquor in analyses excluding non-drinkers ($HR_{\geq 3.7 \text{ vs. } >0 < 0.9 \text{ drinks/week}}$: 2.41; CI: 1.20, 4.84; p-trend=0.01) [21]. Conflicting findings were reported for other types of alcohol. A study of 5,182 men with non-metastatic prostate cancer from the HPFS observed a borderline statistically significant positive association with beer intake ($HR_{\geq 7 \text{ vs. } 0 \text{ serving/week}}$: 2.64; CI: 0.58, 12.06; p-trend=0.05) and an inverse association with moderate total wine intake ($HR_{3 < 7 \text{ vs. } 0 \text{ serving/week}}$: 0.53; CI: 0.26, 1.07; p-trend=0.03), which appeared to be driven by red wine ($HR_{3 < 7 \text{ vs. } 0}$: 0.49; CI: 0.25, 0.97; p-trend=0.05) [22]. Notably, the inverse association was not observed among men with higher levels of wine intake. The Canadian study found no evidence that total wine or beer were associated with PCSM [21].

Both studies also examined ACM and found no association with post-diagnostic total alcohol or liquor intake [21, 22]. However, the Canadian study observed an association with total alcohol ($HR_{\geq 2 \text{ vs. } >0 < 2 \text{ drinks/day}}$: 1.45; CI: 1.06, 2.00; p=0.02) and liquor ($HR_{\geq 3.7 \text{ vs. } >0 < 0.9 \text{ drinks/week}}$: 1.82; CI: 1.20, 2.79; p-trend=0.01) in analyses excluding non-drinkers [21]. The HPFS found an inverse association with 3-<7 versus 0 servings/week of red wine (HR: 0.64; CI: 0.45, 0.90; p-trend=0.007) and total wine (HR: 0.57; CI: 0.40, 0.81; p-trend=0.08), though overall trend for the latter did not reach statistical significance [22]. The Canadian study also observed an inverse association with moderate total wine intake ($HR_{0.2 < 0.9 \text{ vs } 0 \text{ drinks/week}}$: 0.60; CI: 0.46, 0.79; p-trend=0.01) that was not observed at higher levels of wine consumption [21].

The limited data among prostate cancer survivors suggests a potential benefit of red wine at modest intake levels (1/2-1 serving/day). Men should limit total alcohol consumption to ≤ 2 drinks/day, as excess alcohol damages the heart, liver, and pancreas; increases risk of other

cancers (including head and neck, esophageal, liver, and colorectal); and weakens the immune system [23]. This aligns with recommendations from many cancer control agencies [1, 24, 25].

Selenium Supplements. A single study within the HPFS examined selenium supplements (mg/day) and prostate cancer outcomes and found an increased risk of PCSM (HR_{≥140}: 2.60; CI: 1.44, 4.70. HR₂₅₋₁₃₉: 1.33; CI: 0.77, 2.30. HR₁₋₂₄: 1.18; CI: 0.73, 1.91 versus 0; p-trend=0.001), but no association with recurrence or ACM [26].

Vitamin D Supplements or Nutrient Intake from Diet. Three studies examined vitamin D (dietary intake or serum level) and prostate cancer outcomes [13, 27, 28]. Only one, a study of 1,476 men from Seattle, examined recurrence/progression and found no association with serum 1,25(OH)₂D [27]. All three studies examined PCSM and reported no association with serum level or dietary vitamin D intake [13, 27, 28]. Two of the studies examined ACM outcomes [13, 28]. One, a study of 1,119 men from New South Wales, reported an increased risk of ACM among men with higher levels of 1,25(OH)₂D (HR_{Q4 vs Q1}: 0.45; CI: 0.29, 0.69; p-trend=0.005) [28]. The other, a study of 525 Swedish men, observed no association between dietary intake of vitamin D and ACM [13].

Calcium & Phosphorous Nutrient Intake from Diet. A single study from Sweden considered both dietary calcium and phosphorous intake and observed no association with either PCSM or ACM [13].

Overall, evidence on dietary supplement use or single nutrient intake and risk of prostate cancer recurrence or mortality is limited. Additional studies are needed to confirm the finding that selenium supplementation is associated with an increased risk of PCSM. Men with prostate cancer should follow the recommendations of the American Institute for Cancer Research and the World Cancer Research Fund and aim to meet nutritional needs through diet alone [24, 25].

Obesity. Obesity is among the most extensively studied potential risk factor among men with prostate cancer, and the evidence is inconsistent. Regarding recurrence/progression outcomes reported between 2015-2020, six studies observed no association with body mass

index (BMI), while three reported a positive association [29-37]. A report by our team attempted to clarify the discrepancies in past studies by examining adjustment for clinical and, separately, pathological characteristics in a population of men undergoing RP from CaPSURE [31]. We hypothesized that residual confounding by disease stage may partially explain positive associations reported between BMI at the time of diagnosis and risk of recurrence. We observed that with adjustment for disease severity using metrics from diagnosis (biopsy) only, there was evidence of a positive relationship between very obese men ($\text{BMI} \geq 35 \text{ kg/m}^2$) and risk of recurrence [31]. However, when we controlled for surgical pathology characteristics, the observed association was no longer statistically significant. Consistent with our finding, two of the three studies that found an association between BMI and risk of recurrence did not adjust for pathologic features [36, 37]. Four of the six studies that reported no association adjusted for pathologic features [29-31, 33]. Such data suggest that obesity influences tumor aggressiveness earlier in the natural history of prostate cancer and are consistent with a larger body of evidence implicating pre-diagnosis BMI in healthy populations and risk of fatal prostate cancer [38].

Seven studies published between 2015-2020 examined BMI and PCSM [30, 32, 36, 37, 39-41]. Only one – a study of 1,442 men treated with intensity modulated radiation therapy for localized disease, and therefore lacking pathologic measures of disease severity – observed an association ($\text{HR}_{\text{continuous}}: 1.15$; CI: 1.07, 1.23; $p < 0.001$) [37]. Three additional studies published before 2015 also reported a positive association, only one of which controlled for pathologic metrics [42-44]. The two studies that considered waist circumference and waist-to-hip ratio found no association [39, 41].

Five studies published between 2015-2020 examined BMI and ACM with mixed results [31, 37, 39-41]. Three of these reported a higher risk associated with higher BMI ($\text{HR}_{\geq 35 \text{ vs } 18.5-25}: 1.70$ (1.12, 2.60), $p\text{-trend}=0.001$. $\text{HR}_{\text{continuous}}: 1.05$; CI: 1.02, 1.08; $p=0.004$. $\text{HR}_{\text{per } 5\text{-unit}}: 1.07$; CI: 1.02, 1.12; $p=0.01$) [31, 37, 40]. The two others observed no associations with BMI, waist

circumference, or waist-to-hip ratio [39, 41]. There were numerous older studies that reported similarly null findings between BMI and ACM among men with prostate cancer (**Table 1.2**).

Evidence is mixed regarding if obesity measured *following* a prostate cancer diagnosis is associated with worse prostate cancer outcomes, and further research is warranted regarding whether weight loss among prostate cancer survivors who are obese offers prostate cancer - specific benefits. Nonetheless, given the relationship of obesity with other chronic diseases, including other malignancies and heart disease, men should be counseled to reach and maintain a healthy weight.

Physical Activity. Multiple studies have examined various forms of post-diagnostic physical activity in relation to prostate cancer outcomes (**Table 1.2**). Only three of these considered recurrence/progression outcomes with mixed results [45-47]. Two examined different types of physical activity in the same cohort of 237 Canadian men on active surveillance [45, 46]. These studies demonstrated a lower odds of disease reclassification ($OR_{>92.27 \text{ vs } <46.62}: 0.43; CI: 0.21, 0.88; p\text{-trend}=0.027$) but not risk of progression, with higher MET-hour/week of total physical activity, as well as lower odds associated with vigorous physical activity ($OR_{>0 \text{ vs } 0}: 0.42; CI: 0.20, 0.85; p=0.016$) [45, 46]. In contrast, a CaPSURE analysis of 1,455 men with localized disease found no association between vigorous physical activity and risk of prostate cancer progression. However, few men engaged in vigorous activity in this population, and brisk walking pace was associated with a statistically significant 57% lower risk of progression [47].

Six studies examined physical activity and PCSM with generally consistent findings of benefits for physical activity (**Table 1.2**) [48-53]. A HPFS study of 2,705 men with non-metastatic prostate cancer and a US-based study of 1,354 men with localized disease reported an inverse association with vigorous physical activity ($HR_{\geq 3 \text{ vs } <1 \text{ hours/week}}: 0.39; CI: 0.18, 0.84; p\text{-trend}=0.03$. $HR_{\geq 1 \text{ vs } <1 \text{ time/week}}: 0.63; CI: 0.42, 0.95; p=0.029$) [48, 49]. A Canadian study of 830 men with stage $\geq T2$ prostate cancer reported a 44% decreased risk for recreational physical

activity and PCSM (>26 vs. ≤4 MET-hours/week, CI:10%-65%) [50]. An additional study in the CPS-II cohort similarly reported a statistically significant 31% decreased risk of PCSM associated with recreational physical activity [52]. A 2015 study of 4,623 Swedish men with localized prostate cancer reported a 32% reduction in risk of PCSM for ≥1 vs. < 1 hour/week of exercise after diagnosis (CI 6%-52%); a similar benefit was reported for walking/biking ≥20 versus <20 minutes/day, but not for total recreational physical activity or household work [51]. While there has been variability in the type, duration, or intensity of physical activity associated with PCSM benefits, these reports suggest that physical activity offers benefit for reducing risk of PCSM.

Five studies examining PCSM also examined ACM and overwhelmingly reported an inverse relationship with physical activity [48, 50-53]. The risk reduction comparing the highest to lowest physical activity categories were as follows: 42-62% for total physical activity, 35-49% for vigorous physical activity, 14-37% recreational physical activity, and 7-30% for walking/biking [48, 50-52].

In summary, there is strong evidence that increased physical activity following prostate cancer diagnosis is associated with lower risk of PCSM and ACM. The 2018 National physical activity Guidelines in the United States recommend that adults do ≥150 minutes/week of moderate-intensity or ≥75 minutes/week of vigorous-intensity aerobic physical activity. These guidelines report lower risk of prostate cancer mortality as a health benefit associated with regular physical activity for prostate cancer survivors [54]. In addition, clinical trials have shown that physical activity improves bone mineral density and quality-of-life among men undergoing androgen deprivation therapy for prostate cancer [2]. Considering the totality of evidence, we recommend that prostate cancer survivors engage in regular physical activity. Trials are underway to develop interventions to help men with prostate cancer meet physical activity goals, while considering a man's current capabilities and health-related concerns (see Table 2 in ref [2]).

Smoking. Multiple studies have examined the relationship between smoking and prostate cancer recurrence/progression and PCSM (**Table 1.2**). There is overall agreement that men reporting smoking following diagnosis are at higher risk of recurrence/progression and PCSM compared to never-smokers [55-61].

Some evidence exists that the duration of smoking cessation may affect the risk of prostate cancer outcomes among former smokers. Specifically, an Austrian study of 6,538 men with localized prostate cancer reported that former smokers who had quit ≥ 10 years prior had a similar risk of recurrence as never smokers, but those who had quit < 10 years prior were at increased risk of recurrence [56]. Results from a US-based study of 752 men for the outcome of PCSM support this conclusion, though results did not reach statistical significance [60]. Limited data on former smoking duration and dose may account for the mixed evidence regarding whether former smokers are at an increased risk for poor prostate cancer outcomes [55-57, 59-62].

Fewer studies examined ACM outcomes [59, 61, 63, 64]. A Canadian study of 434 men with localized disease found no association between former or current smokers and ACM, though it was limited by a short follow-up period (median 70 months) [61]. As expected, all other studies found a statistically significant increased risk of death associated with smoking [59, 63, 64].

In summary, current smokers are at an increased risk of disease recurrence and progression, PCSM, and ACM. Men who smoke should be provided with resources to help them quit to improve their PC-specific prognosis and overall health.

Diversity of Study Population – Race/Ethnicity. AA/B men experience higher rates of prostate cancer incidence and mortality than men of any other race/ethnicity. In the United States, the rate of PCSM is more than two-fold higher in AA/B vs White men (40.8 versus 18.2 per 100,000 in AA/B and White men, respectively) [65]. Despite this fact, existing evidence on post-diagnostic modifiable risk factors has been collected almost exclusively in White

populations. Characteristics of 33 recently published (2015-2020) studies are shown in **Table 1.1**; 13 did not report the racial/ethnic distribution of their study sample [13, 21, 26, 33, 37, 41, 45, 51-53, 55, 56, 66]. An additional seven dichotomized race as White/Caucasian versus other (all $\geq 92\%$ White) [3, 6, 17, 22, 32, 40, 50]. Only six included $\geq 10\%$ AA/B/African-Caribbean men [30, 34-36, 39, 59].

Few studies have examined whether the associations between lifestyle factors and risk of prostate cancer outcomes vary by race/ethnicity. The two that provided results stratified by race (AA/B vs. White) both examined BMI as the primary exposure [30, 34]. The first was a study of 5,929 (33% AA/B) men treated via RP that observed no association between BMI and PCSM or recurrence, overall or in either race/ethnicity stratum [30]. The other was a study of 647 men that reported a positive association between BMI ≥ 30 versus BMI < 30 with prostate cancer recurrence among the 363 White men (HR: 1.80; CI: 1.09, 2.96) but not among the 284 AA/B men (HR: 1.10; CI: 0.69, 1.76) [34].

Although limited, a few studies have identified mortality disparities among other underrepresented racial/ethnic minority populations. For example, Puerto Rican and Mexican American men may have an increased risk of PCSM compared to White men [67, 68]. Future studies should report race/ethnicity for their study population and test for effect modification by race/ethnicity when numbers allow. Deliberate and targeted recruitment of AA/B men and other high-risk populations into prostate cancer-related studies is crucial. In the interim, it should be a priority to identify existing data sources with a sufficient proportion of AA/B men and other underrepresented racial/ethnic minorities to begin to address these questions.

Diversity of Study Population – Education. We intended to examine educational attainment as a measure of socioeconomic status, however only 10 of the 33 recent studies (2015-2020) reported education levels of their study populations [7, 11, 21, 34, 39, 40, 49-51, 53].

Diversity of Study Population – Cohorts. Most of what we know regarding diet and lifestyle following a prostate cancer diagnosis comes from a limited number of cohorts. **Table 1.1** displays literature by exposure, consisting of 64 (non-unique) studies. The HPFS, CaPSURE, and PHS-II account for one-third (n=22) of these. An additional 15% (n=10) are from CPS-II, the Shared Equal Access Regional Cancer Hospital (SEARCH) database, and Royal Marsden Hospital. Finally, many of the exposures were examined by only a single study (**Table 1.2**), highlighting areas where replication and confirmation is needed.

Discussion

Future Direction. In summary, research to date on post-diagnostic lifestyle factors and risk of prostate cancer recurrence and mortality has been limited to a few cohorts of predominately White men. Large cohorts that are racially/ethnically, geographically, and socio-demographically diverse are necessary to advance this field of research.

Conclusion. In this review, we focused on observational evidence of post-diagnostic modifiable diet and lifestyle factors in relation to prostate cancer outcomes. Though randomized trials are the gold standard for determining causation, many diet and lifestyle behaviors are not suitable/ethical (e.g. smoking) to randomization. Further, long-term and slow-acting exposures may require extended follow-up periods to observe outcomes of interest, which may preclude study in a randomized setting. Overall, the evidence reviewed suggests that following a prostate cancer diagnosis, men should be counseled to increase physical activity and quit smoking, consistent with general health recommendations. Additionally, it may be prudent for men with prostate cancer to minimize whole milk/high-fat dairy intake; for those who consume alcohol, consider moderate consumption of red wine (e.g., ½ to 1 glass/day) over other types of alcohol; and aim to meet nutritional needs through food rather than supplements. Future research that includes more diverse populations, particularly AA/B men, is needed.

Table 1.1. Characteristics of studies by diet and lifestyle factor

Author, Year	Country	Population	Disease Status	N	Race/ Ethnicity	Age Range & Mean/Median	Specific exposure(s) examined	Outcome(s) ^a
Fish								
Wang, 2020 [7]	USA	CPS-II Nutrition Cohort	non-metastatic	4,882	White = 98% ^b AAVB = 1% ^b Other = 1% ^b	NR ^c	Fish	PCSM, ACM
Wilson, 2016 [3]	USA	Washington University Genetics Study	≤T3 and RP as primary TX	940	White: 96% Other NR	mean: 61 range: NR	Fish, fried fish, not-fried fish	Recurrence
Yang, 2015 [6]	USA	PHS I & II	non-metastatic	926	White: 96% Other NR	mean: 69 range: NR	Fish	PCSM, ACM
Richman, 2010 [4]	USA	CaPSURE	localized or regional	1,294	White: 96% ^b AAVB: 3% ^b Other: 1% ^b	NR ^c	Fish	Progression
Chan, 2006 [5]	USA	HPFS	localized or regional	1,202	White: >95% ^d AAVB: 1% Other: NR	mean: 68 range: NR	Fish	Progression
Meat, Poultry, Eggs								
Wang, 2020 [7]	USA	CPS-II Nutrition Cohort	non-metastatic	4,882	White = 98% ^b AAVB = 1% ^b Other = 1% ^b	NR ^c	Total red and processed meat, unprocessed red meat, processed meat, poultry, unprocessed poultry, eggs	PCSM, ACM
Wilson, 2016 [3]	USA	Washington University Genetics Study	≤T3 and RP TX	940	White: 96% Other NR	mean: 61 range: NR	Total red meat, unprocessed red meat, processed meat, rare/medium rare red meat, well/very well-done red meat, poultry, fried poultry, not fried poultry, eggs	Recurrence
Yang, 2015 [6]	USA	PHS I & II	non-metastatic	926	White: 96% Other NR	mean: 69 range: NR	Processed meat, red meat, eggs	PCSM, ACM
Richman, 2011 [8]	USA	HPFS	localized or regional	3,127	White: 92% ^b Other NR	NR ^c	Total red meat, unprocessed red meat, processed red meat, total poultry, eggs, hamburger, beef/lamb/pork sandwich or mixed dish, beef/lamb/pork main dish, sausage/salami/bologna, bacon, hot dogs, chicken/ turkey with and without skin, chicken/turkey sandwiches, chicken/turkey hot dogs	Lethal PC
Richman, 2010 [4]	USA	CaPSURE	localized or regional	1,294	White: 96% ^b AAVB: 3% ^b Other: 1% ^b	NR ^c	Processed red meat, unprocessed red meat, poultry, poultry with skin, skinless poultry, eggs	Progression

Author, Year	Country	Population	Disease Status	N	Race/ Ethnicity	Age Range & Mean/Median	Specific exposure(s) examined	Outcome(s) ^a
Chan, 2006 [5]	USA	HPFS	localized or regional	1,202	White: >95% ^d AAVB: 1% Other: NR	mean: 68 range: NR	Red meat	Progression
Dairy								
Tat, 2018 [11]	USA	CaPSURE	non-metastatic	1,334	White: 96% ^e AAVB: 2% ^e Other: 2% ^e	NR ^c	Whole milk, skim/low-fat milk, total dairy, high-fat dairy, low-fat dairy, ice cream, yogurt, butter, cream, sherbet, cottage cheese, cream cheese, other cheese	Progression
Downer, 2017 [13]	Sweden	Population-based	any	525	NR	mean: 71 range: NR	Total dairy, high-fat dairy, low-fat dairy, total milk, sour milk, high-fat milk, low-fat milk, butter, cheese	PCSM, ACM
Yang, 2015 [6]	USA	PHS I & II	non-metastatic	926	White: 96% Other: NR	mean: 69 range: NR	High-fat dairy, butter	PCSM, ACM
Pettersson, 2012 [12]	USA	HPFS	localized/locally-advanced	3,918	White: 96% ^b Other: NR	NR ^c	Total milk, skim-2% milk, whole milk, total dairy, low-fat dairy, full-fat dairy	Progression, Lethal PC
Chan, 2006 [5]	USA	HPFS	localized or regional	1,202	White: >95% ^d AAVB: 1% Other: NR	mean: 68 range: NR	Milk	Progression
Dietary Fats								
Van Blarigan, 2015 [17]	USA	PHS I & II	non-metastatic	926	White: 96% ^b Other: NR	NR ^c	Saturated fat, monounsaturated fat, polyunsaturated n-6 and n-3 fatty acids, <i>trans</i> fat, animal fat, vegetable fat	PCSM, ACM
Richman, 2013 [18]	USA	HPFS	non-metastatic	4,577	White: 93% ^b Other: NR	NR ^c	Saturated fat, monounsaturated fat, polyunsaturated fat, <i>trans</i> fat, animal fat, vegetable fat	Lethal PC, ACM
Epstein, 2012 [15]	Sweden	Population-based	any	525	NR	NR ^c	Total Fat, saturated fat, monounsaturated fat, polyunsaturated omega-6 and omega-3 fatty acids ^f	PCSM
Sirom, 2008 [14]	USA	MD Anderson Cancer Center	RP TX	390	White: 100%	mean: 61 ^e range: NR	Saturated fat	Recurrence
Meyer, 1999 [16]	Canada	Population-Based	any	384	NR	mean: 67 range: NR	Total fat, saturated fat, monounsaturated fat, polyunsaturated fat	PCSM
Vegetables: Tomato (Lycopene), Cruciferous								
Yang, 2015 [6]	USA	PHS I & II	non-metastatic	926	White: 96% Other: NR	mean: 69 range: NR	Cruciferous vegetables, tomato	PCSM, ACM

Author, Year	Country	Population	Disease Status	N	Race/ Ethnicity	Age Range & Mean/Median	Specific exposure(s) examined	Outcome(s) ^a
Richman, 2012 [19]	USA	CaPSURE	non-metastatic (<T3b)	1,560	White: 95% ^e AA/B: 3% ^e Other: 2% ^e	<60: 26% ^e 60-69: 45% ^e ≥70: 29% ^e	Cruciferous vegetables, broccoli, cabbage, cauliflower, Brussels sprout, kale, tomato sauce, tomato	Progression
Chan, 2006 [5]	USA	HPFS	localized or regional	1,202	White: >95% ^d AA/B: 1% Other: NR	mean: 68 range: NR	Tomato sauce, tomato	Progression
Alcohol								
Downer, 2019 [22]	USA	HPFS	non-metastatic	5,182	White: 92% ^e Other: NR	mean: 70 ^e range: NR	Total alcohol, total wine, beer, liquor, red wine, white wine	Lethal PC, ACM
Farris, 2018 [21]	Canada	Population-based	≥T2	829	NR	mean: 67 range: NR	Total alcohol, beer, liquor, wine	Recurrence, PCSM, ACM
Supplements								
Nair-Shaliker, 2020 [28]	Australia	New South Wales PC Care Outcomes Study		1,119	Australian: 78% ^g Other: 22% ^g	65-85: 34% 60-64: 29% 55-59: 24% 49-54: 14%	serum 25 OHD, serum 1,25(OH) ₂ D	PCSM, ACM
Downer, 2017 [13]	Sweden	Population-based	newly diagnosed	525	NR	mean: 71 range: NR	Calcium, phosphorous, vitamin D	PCSM, ACM
Kenfield, 2015 [26]	USA	HPFS	non-metastatic	4,459 ^h	White: >95% ^d Other: NR	mean: 69 ^e range: NR	Selenium supplement use	Recurrence, PCSM, ACM
Holt, 2013 [27]	USA	Seattle-Puget Sound Tumor Registry	newly diagnosed	1,476	White: 90% ^e AA/B: 10% ^e	mean: 60 ^e range: NR	serum 25(OH) D	Recurrence/ Progression, PCSM
Obesityⁱ								
Jackson, 2020 [39]	Jamaica	PROSCARE Study	any	242	African-Caribbean: 100%	mean: 68 median: 69 range: NR	BMI, waist circumference, waist-to-hip ratio	PCSM, ACM
Troeschel, 2020 [40]	USA	CPS-II Nutrition Cohort	non-metastatic	8,330	White: 97% Other: 3%	≥80: 6% 75 to <80: 20% 70 to <75: 32% 65 to <70: 28% <65: 13%	BMI	PCSM, ACM
Leal-Garcia, 2020 [29]	Mexico	Multi-institution	RP TX	180	Mexican: 100%	median: NR ^c range: 45-79 median:	BMI	BCR
Vidal, 2020 [30]	USA	SEARCH	RP TX	5,929	White: 67% AA/B: 33%	63 (White) 60 (AA/B) range: NR	BMI	BCR, PCSM
Langlais, 2019 [31]	USA	CaPSURE	non-metastatic and RP TX	5,200	White: 88% ^e AA/B: 9% ^e Other: 3% ^e	mean: 61 ^e range: NR	BMI	Recurrence, ACM

Author, Year	Country	Population	Disease Status	N	Race/ Ethnicity	Age Range & Mean/Median	Specific exposure(s) examined	Outcome(s) ^a
Freedland, 2019 [35]	USA	SEARCH	RP TX	4,123	White: 59% ^e AA/B: 38% ^e Other: 3% ^e	NR ^c	BMI	BCR
Farris, 2018 [41]	Canada	Population-based cohort	≥T2	987	NR	NR	BMI, waist circumference, waist-to-hip ratio	PCSM, ACM
Vidal, 2017 [36]	USA	SEARCH	RP TX	4,268	White: 59% ^e AA/B: 37% ^e Other: 3% ^e	mean: 62° range: NR	BMI	BCR, PCSM
Dickerman, 2017 [32]	USA	HPFS	localized (T1-T2)	5,158	White: 97% ^e Other: NR	mean: 70° range: NR	BMI	Recurrence, Lethal PC
Schiffmann, 2017 [33]	Germany	Martini-Klinik Prostate Cancer Center	RP TX	16,014	NR	median: 65 range: NR	BMI	Recurrence
Khan, 2017 [34]	USA	HCaP-NC	any	647	White: 56% ^e AA/B: 44% ^e	mean: 62° 63° (White) 60° (AA/B) range: NR	BMI	Progression
Wang, 2015 [37]	USA	Fox Chase Cancer Center, Philadelphia, PA	localized (T1b-T4N0M0) and IMRT TX	1,442	NR	≥80: 5% 70-79: 37% 60-69: 41% 36-59: 17%	BMI	Recurrence, Distant Mets, PCSM, ACM
Physical Activity								
Bonn, 2019 [53]	Sweden	PROCAP study	localized	4,595	NR	mean: 63 range NR	Time spent sitting during leisure time	PCSM, ACM
Dai, 2019 [49]	USA	Population-based	localized	1,354	White: 92% ^e AA/B: 8% ^e Other: NR	NR ^c	Vigorous PA	Lethal PC
Guy, 2018 [45]	Canada	Sunnybrook Cohort & Royal Marsden Hospital AS Cohort	low-intermediate risk and AS	237	White: 86% ^k AA/B: 7% ^k Other: 6% ^k Unknown: 1% ^k	mean: 65° range: NR	Total PA, recreational PA, vigorous PA	Reclassification
Wang, 2017 [52]	USA	CPS-II Nutrition Cohort	non-metastatic	5,319	NR ^l	NR ^l	Total recreational PA, other recreational PA, walkin	PCSM, ACM

Author, Year	Country	Population	Disease Status	N	Race/ Ethnicity	Age Range & Mean/Median	Specific exposure(s) examined	Outcome ^a
Friedenreich, 2016 [50]	Canada	Alberta Cancer Registry	T 2-4	830	White: 95% Other: 5%	median: 68 range: NR	Total PA, recreational PA, non-sedentary occupational PA, household PA, vigorous PA, occupational sedentary behavior	PCSM, ACM
Vandersluis, 2016 [46]	Canada	Sunnybrook Cohort and Royal Marsden Hospital AS Cohort ^m	low-intermediate risk and AS	237	White: 86% ^e AAVB: 7% ^e Other: 6% ^e Unknown: 1% ^e	mean: 65 ^e range: NR	Total PA	Progression
Bonn, 2015 [51]	Sweden	PROCAP study	localized	4,623	NR	mean: 63 range: NR	Total recreational PA, walking or biking, household work, exercising	PCSM, ACM
Richman, 2011 [47]	USA	CaPSURE	localized	1,455	NR	mean: 65 range NR	Vigorous PA, non-vigorous PA, walking duration, walking pace	Progression
Kenfield, 2011 [48]	USA	HPFS	non-metastatic	2,705	NR	mean: 69 ^e range: NR	Total PA, vigorous PA, non-vigorous PA	PCSM, ACM
Smoking								
Riviere, 2020 [59]	USA	Veteran Affairs Health Systems	any	73,668	White: 66% ^e AAVB: 28% ^e Other: 6% ^e	NR ^c	Smoking status (current, former, never)	PCSM, ACM
Sato, 2017 [66]	Japan	Harasanshin Hospital, Kyushu University Hospital	RP without neoadjuvant or adjuvant therapy	1,165	NR	NR ^c	Smoking status (current, never/former)	Recurrence
Steinberger, 2015 [55]	USA	MSKCC	EBRT TX	2,095	NR	<65: 25% ^e >65: 72% ^e range: NR	Smoking status (current, former, never)	Recurrence, Distant Mets, PCSM
Rieken, 2015 [56]	Austria, USA	Multi-institution	localized, RP TX	6,538	NR	median: 61 range: NR	Smoking status (current, former, never), smoking cessation prior to TX	Recurrence
Moreira, 2014 [63]	USA	SEARCH	RP TX	1,670	White: 54% ^e AAVB: 40% ^e Other: 5% ^e	NR ^c	Smoking status (current, never/former)	Progression, Lethal PC, PCSM, ACM
Ngo, 2013 [69]	USA	Stanford RP Database	RP TX	630	NR	median 63 range: NR	Heavy smokers (≥20 pack-yr), light smoker (<20 pack-yr)	Recurrence
Oh, 2012 [70]	South Korea	Seoul National University	RP TX	1,165	NR	mean: 65 ^e range: NR	Smoking status (current, never/former)	Recurrence
Joshu, 2011 [57]	USA	Johns Hopkins University	RP TX	1,416	White: 95% ^e AAVB: 2% ^e Other: 3% ^e	mean: 57 ^e range: NR	Smoking status (ever, current, former, never)	Recurrence
Gong, 2008 [60]	USA	Population-Based	any	752	White: 94% AAVB: 6%	60-64: 40% 55-59: 34% 40-54: 26%	Smoking status (current, quit <10 yrs, quit >10 yrs, never)	PCSM

Author, Year	Country	Population	Disease Status	N	Race/ Ethnicity	Age Range & Mean/Median	Specific exposure(s) examined	Outcome ^a
Pantarotto, 2007 [61]	Canada	Ottawa Hospital Regional Cancer Centre	localized, EBRT TX	434	NR	median: 69 range: 46-83	Smoking status (current, former, never)	Recurrence, Lethal PC, PCSM, ACM
Merrick, 2004 [62]	USA	Schiffler Cancer Center	T1b-T3a, Brachytherapy TX	582	NR	mean: 67 median: 68 range: NR	Smoking status (current, former, never)	Recurrence
Pickles, 2004 [58]	Canada	Multi-institution	localized, EBRT TX	601	NR	NR ^c	Smoking status (current, never)	Recurrence
Oefelein, 2004 [64]	USA	Case Western Reserve University	advanced	222	NR	mean: 73 ^e range: NR	Pack-years	Progression, ACM

Abbreviations: AA/B: African American/Black; ACM: all-cause mortality; AS: active surveillance; BMI: body mass index; CaPSURE: Cancer of the Prostate Strategic Urologic Research Endeavor; CPS: Cancer Prevention Study; DX-diagnosis; HCaP-NC: Health Care Access and Prostate Cancer Treatment in North Carolina; EBRT: external beam radiation therapy; HPFS: Health Professionals Follow-up Study; IMRT: intensity modulated radiation therapy; MSKCC: Memorial Sloan Kettering Cancer Center; NR: not reported; PA: physical activity; PC: prostate cancer; PCSM: prostate cancer specific mortality; PHS: Physicians' Health Study; PROCAP: Progression in Cancer of the Prostate; RP: radical prostatectomy; PC – prostate cancer; PROSCARE: Prostate Cancer Risk Evaluation; TX: Treatment; SEARCH = Shared Equal Access Regional Cancer Hospital database; UK = United Kingdom; USA = United States of America

^aLethal disease typically defined as PC metastases or death

^bData for full cohort not provided. Estimated from demographics data provided on half (upper and lower quartile), two-fifths (upper and lower quintile) or three-fifths (upper, middle, and lower quintile) of study sample

^cOverall age of study sample not reported and not enough data available to calculate

^dAssumed from other HPFS analyses

^eData for full cohort not provided; estimated from stratified data reported.

^fStudy also considered subtypes of saturated fatty acids (lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, shorter chain), monounsaturated fatty acids (palmitoleic acid, oleic acid), omega-3 polyunsaturated fatty acids (alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, combined marine fatty acids), and omega-6 polyunsaturated fatty acids (linoleic acid, arachidonic acid)

^gRace/ethnicity reported in study as region of birth

^hAnalyses for recurrence outcome only included 3,718 men

ⁱWe reviewed an additional 29 studies published between 2004 and 2014: [42-44, 71-96]. Results are summarized in Table 1.2, but study characteristics are not reported here due to space.

^jTwo samples reported in single paper

^kAs reported in Vandersluis, 2016 [46], which used the same study population

^lStudy looked at both pre- and post-diagnostic physical activity. Demographics only provided for the pre-diagnostic physical activity cohort.

^mExamined association separately in the Sunnybrook cohort (n=131) and Royal Marsden Hospital cohort (n=106)

Table 1.2. Summary of associations between diet and lifestyle components and prostate cancer progression, prostate cancer-specific mortality, and all-cause mortality

Dietary Factors	Recurrence/Progression Association			Lethal Disease/PCSM Association			ACM Association		
	Inverse	Null	Positive	Inverse	Null	Positive	Inverse	Null	Positive
<i>Fish, Total</i>	[5] ^{a,b}	[3-5] ^a			[6, 7]			[6, 7]	
<i>Fried</i>		[3]							
<i>Non-fried</i>		[3]							
<i>Meat, Poultry, Eggs</i>									
<i>Total red meat</i>		[3, 5]			[6-8]			[6]	[7]
<i>Unprocessed red meat</i>		[3, 4]		[7]	[8]			[7]	
<i>Rare/medium-rare meat</i>		[3]							
<i>Well-done red meat</i>		[3]							
<i>Hamburger</i>					[8]				
<i>Beef/Lamb/Pork</i>					[8]				
<i>Processed red meat</i>		[3, 4]			[7, 8]			[7]	[6]
<i>Sausage/Salami/Bologna</i>					[8]				
<i>Bacon</i>					[8]				
<i>Hot dogs</i>					[8]				
<i>Total poultry</i>		[3, 4]			[7, 8]		[7]		
<i>Chicken/Turkey hot dogs</i>					[8]				
<i>Unprocessed poultry^c</i>		[4]			[7]				[7] ^d
<i>Chicken or Turkey, no skin</i>			[4]		[8]				
<i>Chicken or Turkey, with skin</i>					[8]				
<i>Chicken or Turkey</i>					[8]				
<i>Sandwiches</i>									
<i>Fried poultry</i>		[3]							
<i>Non-fried poultry</i>		[3]							
<i>Eggs</i>		[3]	[4] ^d		[6-8]			[7]	[6]
<i>Dairy</i>									
<i>Total dairy</i>		[11, 12]			[12, 13]			[13]	[6, 13] ^d
<i>High-fat/Full-fat dairy</i>		[11, 12]			[6, 12, 13]				
<i>Low-fat dairy</i>		[11, 12]			[12, 13]			[13]	
<i>Total milk</i>		[5, 12] ^a	[5] ^{a,b}		[12, 13]			[13]	
<i>Sour milk</i>					[13]			[13]	
<i>Whole/High-fat milk</i>			[11, 12]		[13] ^e			[13] ^e	[13] ^e
<i>Skim/Low-fat milk</i>					[13]			[13] ^f	[13] ^f
<i>Skim – 2% Milk</i>					[12]				
<i>Cream</i>		[11]			[6, 13]			[6, 13]	
<i>Butter</i>		[12]							
<i>Ice cream</i>		[11]							
<i>Yogurt</i>		[11]							
<i>Sherbet</i>		[11]							
<i>Cheese</i>			[11] ^d						
<i>Other Cheese</i>		[11]			[13]			[13]	

	Recurrence/Progression Association			Lethal Disease/PCSM Association			ACM Association		
	Inverse	Null	Positive	Inverse	Null	Positive	Inverse	Null	Positive
Dietary Factors									
<i>Dietary Fats, Total</i>									
Saturated			[14]		[15, 16] ^e	[15] ^e		[17, 18]	[17, 18] ^b
Monounsaturated					[15, 18]	[16, 17] ^{b,d}			
Polyunsaturated ^g					[15-18]				
Trans					[15-18]				[18]
Animal					[17, 18]				
Vegetable				[18] ^b	[17, 18]				
<i>Vegetables: Tomato, Cruciferous</i>									
(Fresh) Tomato		[5, 19] ^a	[5] ^a		[6]			[6]	
Tomato sauce		[5, 19] ^a							
<i>Cruciferous Vegetable, Total</i>		[5] ^a			[6]			[6]	
Broccoli		[19]							
Cabbage		[19]							
Cauliflower		[19]							
Brussel Sprouts		[19]							
Kale		[19]							
Lifestyle Factors									
<i>Alcohol, Total</i>									
Beer		[21]			[21, 22]			[21, 22]	
Liquor					[21]	[22] ^{b,d}		[21, 22]	
Total wine					[21, 22]			[21, 22]	
Red wine				[22] ^b	[21]		[21]	[22]	
White wine				[22]	[22]			[22]	
<i>Supplement Use</i>									
Selenium		[26]				[26]		[26]	
Vitamin D		[27] ^h			[13, 27, 28] ^{h,i}		[28] ^j	[13, 28] ^j	
Calcium					[13]			[13]	
Phosphorous					[13]			[13]	
Obesity									
Body Mass Index		[29-34, 42, 71, 73, 76, 79-81, 88, 90, 94, 96] ^{h,k,l}	[35-37, 72, 74, 75, 77, 78, 82-87, 89, 91-93, 95] ^d		[30, 32, 36, 39-42, 71, 76, 79, 90] ^{h,k,m}	[37, 42-44] ^{h,m}	[88] ^j	[39, 41, 44, 71, 76, 79, 88, 90] ^{h,i}	[31, 37, 40]
Waist Circumference									
Waist-to-Hip Ratio					[39, 41] ^h			[39, 41] ^h	

Lifestyle Factors	Recurrence/Progression Association			Lethal Disease/PCSM Association			ACM Association		
	Inverse	Null	Positive	Inverse	Null	Positive	Inverse	Null	Positive
Physical Activity, Total Vigorous	[45] [45]	[46] [47] [47]		[48] [48, 49]	[50] [50] [48]		[48, 50] [48, 50]		
Non-Vigorous Exercising ⁿ				[51] [50, 52] ^p	[51] [52]		[51] [50-52] ^p [52]		
Recreational Other (non-walking) recreational		[45]							
Household Non-sedentary occupational					[50, 51] [50] [50]		[51] [50]	[50]	
Occupational sedentary behavior					[53] ^h			[50]	
Time sitting during leisure time					[53] ^h			[53] ^h	
Walking/Walking or Biking ^[51]	[47] ^o	[47] ^o		[51]	[52]		[51, 52] ^p		
Smoking									
Current (vs never)		[61] [62]	[55-58]		[61] ^m	[55, 59-61] ^m		[61]	[59]
Current (vs never/former)		[63, 66, 70] ^r	[70] ^r			[63]			[63]
Former (vs never)		[55, 57, 61, 62]	[56]		[55, 59-61] ^m	[61] ^m		[61]	[59]
Smoking cessation Heavy ^a vs Light Smoker		[56] ^s	[56] ^s						
Per pack-year		[56] ^s	[64]						[64]

Abbreviations: AAB: African American/Black; ACM: all-cause mortality; BMI: body mass index; METs: metabolic equivalents; PCSM: Prostate cancer-specific mortality

^aStudy [5] observed no association with progression without adjustment for, and a statistically significant association with adjustment for, pre-diagnostic intake

^bStudies [5, 17, 18, 22] evaluated exposure as categorical and continuous variables; only reached statistical significance in one of these models.

^cStudy [7] only examined unprocessed poultry among sub-group of 3,344 men without known history of cardiovascular disease

^dborderline statistical significance (p=0.05) observed in the following studies: [4, 7, 11, 13, 17, 22, 95]

^eResults were provided overall and stratified by localized versus advanced disease at time of diagnosis. Association was observed in men diagnosed with localized disease but not advanced disease or in the study population as a whole: [13, 15]

^fResults were provided overall and stratified by localized versus advanced disease at time of diagnosis. Association was observed in men diagnosed with localized disease but not advanced disease or in the study population as a whole: [13]

^gStudies [15, 17] examined polysaturated n-3 and n-6 independently

^hStatistical evidence is limited; studies only presented categorized exposure and did not provide p-trend: [27, 33, 41, 44, 53, 76, 79, 80, 94]

ⁱStudy [28] examined 25 OHD and 1,25(OH)₂D; no evidence that either was associated with PCSM

^jStudy examined 25 OHD and 1,25(OH)₂D; 25 OHD was not associated with ACM, while 1,25(OH)₂D was associated

^kResults were stratified by race (AAB, White); statistically non-significant for both strata: [30]

^lResults were stratified by androgen dependence (independent, dependent); BMI was inversely associated with ACM among men with androgen-dependent disease but not androgen-independent disease. There was no association observed between BMI and progression in either strata: [88]

^mStatistically significant association with bone metastases but not PCSM: [42, 61]

ⁿExercising is defined as METs calculated from total of walking/bicycling, household work, or exercising: [51]

^oNo association observed for walking duration (hours/week) but inverse association for walking pace: [47]

^pResults were provided overall and stratified by localized versus advanced disease at time of diagnosis. Association was observed in men diagnosed with localized PC and overall, but not advanced disease: [52]

^qHeavy smoker defined as having a ≥20 pack-year history of smoking

^rResults provide overall and stratified by BMI (<25 vs ≥25 kg/m²). Association only observed among men with BMI ≥25kg/m²: [70]

^sSmoking cessation of ≥10 years was not associated with recurrence/progression compared to never smokers. Smoking cessation of 1 to 4.9 years and 5 to 9.9 years were both associated with increased risk of recurrence/progression compared to never smokers: [56]

Chapter 2: Post-Diagnostic Health Behavior Scores and the Risk of Prostate Cancer

Progression and Mortality

Crystal S. Langlais, Rebecca E. Graff, Erin L. Van Blarigan, John M. Neuhaus, Janet E. Cowan, Jeanette M. Broering, Peter Carroll, Stacey A. Kenfield*, June M. Chan*

*Contributed equality to the work

Abstract

Importance: Individual health behaviors are associated with prostate cancer (PC) progression and mortality. Their combined associations with PC outcomes after diagnosis are unknown.

Objective: To assess associations between six health behavioral scores and risk of PC progression and mortality.

Design: Cohort study including 2,056-2,447 (varied by analysis) men from the Cancer of the Prostate Strategic Urologic Research Endeavor Diet and Lifestyle Sub-study, diagnosed between 1999-2018 and followed until death or January 2019.

Setting: Multi-center; United States.

Participants: Men diagnosed with non-metastatic PC.

Exposures: 1) 3- and 4-factor scores developed based on the PC survivorship literature ('2021 Score [+ Diet]'); 2) 6-factor score developed in 2015 based on pre-diagnostic PC literature ('2015 Score'); 3) a score based on the World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations ('WCRF/AICR Score'); 4) a score based on the American Cancer Society's Cancer Survivor Guidelines ('ACS Score [+ Alcohol]'). All scores included body mass index and physical activity; some included smoking and dietary components.

Main Outcomes and Measures: Due to interval censoring, parametric (Weibull) survival models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for progression. Associations with PC mortality were estimated via Cox proportional hazards models.

Results: Mean (SD) age at diagnosis was 64.4 (7.9) years. Over a median (IQR) of 6.4 (1.3, 13.7) years, there were 192 progression and 73 PC mortality events observed. Higher (i.e., healthier) 2021 Score + Diet and WCRF/AICR Scores were inversely associated with risk of PC progression (2021 + Diet: $HR_{\text{continuous}}=0.76$, 95% CI: 0.63-0.90. WCRF/AICR: $HR_{\text{continuous}}=0.83$,

95% CI: 0.67-1.02) and mortality (2021 + Diet: $HR_{\text{continuous}}=0.65$, 95% CI: 0.45-0.93.

WCRF/AICR: $HR_{\text{continuous}}=0.71$; 95% CI: 0.57-0.89). The ACS Score + Alcohol was only associated with progression ($HR_{\text{continuous}}=0.89$, 95% CI: 0.81-0.98) while the 2021 Score was only associated with PC mortality ($HR_{\text{continuous}}=0.62$, 95% CI: 0.45-0.85). The 2015 was not associated with PC progression or mortality.

Conclusion: Scores that incorporate physical activity, healthy body weight, non-smoking, and dietary recommendations were associated with lower risk of prostate cancer progression and death, strengthening the evidence that behavioral modifications following a prostate cancer diagnosis may improve clinical outcomes.

Introduction

Prostate cancer is the most commonly diagnosed cancer among men in the United States (US), with 248,530 new cases expected to have occurred in 2021 [97, 98]. Currently, there are over 3.6 million prostate cancer survivors in the US [99]. Though the 5-year survival rate for prostate cancer approaches 100%, there remains uncertainty regarding which cancers will eventually progress, and prostate cancer remains the second leading cause of cancer death among US men [98, 100, 101]. To inform interventions and mitigate risk of progression and prostate cancer specific mortality (PCSM) for the large population of men living with the disease, there is a need to better understand how behavioral factors *after* diagnosis influence disease progression.

Several studies have linked modifiable risk factors with prostate cancer progression and PCSM [102]. However, prior reports have predominantly focused on individual exposures, which do not fully reflect the complex relationships among multiple diet and other behavioral factors [103, 104]. For example, physical activity may offset some of the negative effects of unhealthy dietary choices [11]. Therefore, scores that reflect multiple behavioral factors may be more strongly associated with outcomes among men with prostate cancer than individual health habits.

Our team previously conducted an extensive review summarizing the literature on post-diagnostic behaviors and prostate cancer progression and PCSM [102]. Using that report, we developed prostate cancer-specific behavioral scores (“2021 Score [+ Diet]”). Here, we examine the association of these scores in relation to risk of progression and PCSM among men with non-metastatic prostate cancer in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) cohort. Further, for completeness and comparability with other studies, we evaluated associations of four other scores developed to inform the risk of cancer onset or progression to understand if adherence to general cancer prevention or survivorship guidelines may improve outcomes following a prostate cancer diagnosis. One of these scores was

developed by members of our team to predict the risk of developing incident lethal prostate cancer based on pre-diagnostic behaviors (“2015 Score”) [105]. It is distinct from the 2021 Scores focused on post-diagnostic behaviors as the known behavioral risk factors for prostate cancer risk and progression differ. The other three are operationalized versions of the American Cancer Society (ACS) cancer survivorship recommendations [106, 107] and the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) cancer prevention recommendations [108, 109]. We hypothesized that men with healthier lifestyles (i.e., higher scores) would have lower risk of disease progression and mortality.

Methods

Study Sample. CaPSURE is a longitudinal observational cohort of 15,310 men with biopsy-proven prostate cancer. Men diagnosed between 1999-2018 at any of 43 participating urology practices across the US were eligible. Participating urologists provided data on clinical and pathological features, treatments, and clinical follow-up. Additional details on CaPSURE are reported elsewhere [110]. The study was conducted in accordance with the Belmont Report and U.S. Common Rule under local Institutional Review Board approval, with all participants providing written informed consent.

The CaPSURE Diet and Lifestyle (CDL) sub-study – consisting of a comprehensive lifestyle questionnaire and full-length food frequency questionnaire (FFQ) – was administered at three time points between 2004-2016; a total of 2,891 men participated in at least one administration. For the subset of men who completed more than one questionnaire (n=443), only the first administration (closest to diagnosis date) was used. We excluded men with last clinical follow-up or documented progression prior to completing their first CDL questionnaire (n= 551). Consistent with the recommended approach to address implausible energy intakes [111], we excluded men with extreme (<800 kcal/day or >4200 kcal/day) or unknown caloric intake (n=153) and/or missing ≥ 70 FFQ items (n=20). Finally, we excluded men without a

discernable clinical T-stage (n=100) or with a clinical T-stage >T3a (n=8) and those with death from unknown cause (n=3). This left us with a sample size of 2,056 men for our primary analyses of prostate cancer progression. Following the exclusion of men with documented progression prior to completing the first questionnaire, the subsequent exclusions resulted in the loss of 23 events, 2 of which were PCSM. For PCSM analyses, men who were excluded due to documented progression prior to completion of the CDL questionnaire were included – death could not occur prior to completing the questionnaire – resulting in a sample size of 2,447 men.

Diet and Lifestyle Questionnaire. Dietary intake was self-reported on a validated semiquantitative FFQ [112-114], wherein men reported how frequently they consumed a standard unit or portion size of approximately 140 different items. The nine frequency options ranged from never or less than once per month to six or more times per day. FFQ data were sent to the Nutrition Department at the Harvard T.H. Chan School of Public Health, which calculated total intake of nutrients, including total caloric intake and grams of whole grains, fiber, and alcohol. Nutrient intake was calculated by multiplying the nutrient value in the specified portion size of each item on the FFQ by its frequency of intake and then summing across all items. Nutrient values were obtained from the US Department of Agriculture databases [115] supplemented with other sources.

The survey asked men if they had smoked 20 packs of cigarettes or more in their lifetime. If they responded “yes”, they were asked to report additional details regarding their smoking history. Men who responded “no” were considered never smokers.

Men completed a validated physical activity questionnaire which asked them to report their average weekly time spent doing nine types of aerobic and resistance training activities over the prior year [116]. Ten frequency options could be selected, ranging from 0 minutes to 11 or more hours per week. Participants were also asked about their regular walking pace and ability/frequency of climbing stairs.

Other information collected on the survey included height and weight [used to calculate body mass index (BMI; kg/m²)]; education level; a brief medical history, including family history of prostate cancer; and a detailed history of the use of vitamins and supplements.

Behavioral Scores. Six scores were evaluated, as described below. All scores were oriented such that increasing values reflected healthier behaviors. Please see **Tables 2.1-2.2** for additional details.

2021 Score

The 2021 (post-diagnostic) Score was based on an extensive literature review, summarizing behaviors following a prostate cancer diagnosis associated with risk of recurrence, progression, and/or PCSM [102]. To determine the factors for inclusion in the score, we searched PubMed using the terms “prostate cancer” and “progression or mortality” in combination with terms describing individual lifestyle factors. Factors considered for the score included those that 1) exhibited a statistically significant association with metastases or PCSM in at least one study and 2) were corroborated by at least one additional study with an association in the same direction, whether or not statistically significant. In total, we identified seven such factors – smoking status [55, 57, 60, 61, 63, 64, 69, 70, 117, 118], BMI [31, 37, 42, 72, 74, 82-87, 89, 92-94, 119, 120], physical activity [47, 48, 50, 52, 121], and intake of saturated fat [16, 17, 122], whole milk [12, 123], wine [21, 22], and processed meat [6, 8]. The three non-dietary factors demonstrated the strongest evidence in the literature review. We examined two versions of the 2021 Score, one without (“2021 Score”) and one with (“2021 Score + Diet”) the dietary components. The points per behavior component ranged from 0 to 1, with the four dietary components averaged to create a single dietary sub-score ranging from 0 to 1. This was consistent with the operationalization of the ACS recommendations into the ACS Score [108]. The point values were based on where the risk associated with prostate cancer outcomes appeared to change in the literature. The points for each component were summed to create the total 2021 Score (range: 0-3) and 2021 Score + Diet (range: 0-4) for each participant.

2015 Score

Our team previously developed the 2015 (pre-diagnostic) Score to identify the risk of developing lethal prostate cancer among healthy men, based on the evidence available circa 2014 [105]. The six components – smoking status, BMI, physical activity, fatty fish intake, tomato intake, and processed red meat intake – were scored as 0 or 1 based on cut-points associated with risk as reported in the literature at the time of score creation. The sub-scores were then summed to create the total 2015 Score (range: 0-6).

ACS Score

To create a primary and an alternative ACS Score, we expanded on the operationalization of the ACS Nutrition and Physical Activity Guidelines for Cancer Survivors developed by McCullough, et al [108]. Each of the three components – BMI, physical activity, and dietary – were scored from 0 to 2 and then summed to create the primary ACS Score (range: 0-6). The dietary component included total servings and variety of fruits and vegetables, red and processed meat intake, and whole grain intake. We expanded to include strength training when assigning physical activity points, consistent with the guidelines. The “ACS Score + Alcohol” additionally included alcohol intake, scored from 0 to 2 (with the highest score for moderate alcohol intake: >0 to 2 servings/day), reflecting the inclusion of alcohol in the ACS recommendations for cancer prevention but not cancer survival (alternative score range: 0-8).

WCRF/AICR Score

The WCRF/AICR Cancer Prevention Recommendations were operationalized based on published scoring guidelines [106, 107]. The seven components – BMI, physical activity, alcohol intake, sugar-sweetened beverage intake, fruit/vegetable and fiber intake, red and processed meat intake, and percentage of total calories obtained from adapted ultra-processed foods – were scored from 0 to 1 and summed to create the WCRF/AICR Score (range: 0-7).

Outcome. The primary outcome was time to prostate cancer progression, defined as biochemical recurrence, secondary treatment, bone metastases, or PCSM, as applied

previously [11, 47, 124]. Given the small number of PCSM events (n=73) in this cohort, PCSM was evaluated as a secondary outcome.

Biochemical recurrence was defined as two consecutive prostate-specific antigen (PSA) readings ≥ 0.2 ng/mL following radical prostatectomy or a rise of 2.0 ng/mL above post-radiation nadir on two consecutive PSA readings; the date of recurrence was recorded as the date of the second elevated PSA. *Secondary treatment* was defined as any treatment started at least 6 months following primary treatment. *Bone metastases* included prostate cancer progression to bone, advancement to TNM stage M1b, a positive bone scan, and radiation to treat bone metastases. Cause of death was determined by the registry data coordinating center and through confirmation by either the vital statistics official death certificate from the state in which the death occurred or by the National Center for Health Statistics National Death Index [125]. Deaths were attributed to prostate cancer if the death certificate included ICD-9 code 185 [(metastatic) malignant neoplasm of prostate] as the primary or secondary cause of death.

Time to progression was measured from completion date of the CDL questionnaire to the date of progression (first event of biochemical recurrence, secondary treatment, bone metastases, or PCSM). For men with documented non-PCSM progression (i.e., recurrence, secondary treatment, or bone metastasis failure events), the censoring interval (i.e., window in which the event occurred) was bound by the last normal clinical visit (left limit) and the clinical visit documenting evidence of progression (right limit). For men who died from prostate cancer, the left and right limit were both date of death. Men without documented progression or PCSM were censored at their last date of follow-up or death (other cause); thus, the left limit of their censoring interval was defined by the last clinical follow-up date or date of death (non-PCSM), respectively, and the right limit was undefined (i.e., censored). Clinical follow-up was last consistently assessed across all CaPSURE sites on January 31, 2019; 26 men had a last known clinical follow-up date beyond this date and were administratively censored on that date.

Statistical Analysis

Parametric survival models with a Weibull distribution were used to accommodate interval censoring associated with uncertainty in actual date of prostate cancer progression [126]. Because the date of death is known for PCSM (i.e., interval censoring was not an issue), we utilized Cox proportional hazards models rather than parametric survival methods when assessing the PCSM outcome. Proportional hazards assumptions were assessed visually by plotting the scaled Schoenfeld residuals against follow-up time.

We fit survival models using both continuous scores (per 1-unit change) and tertiles of scores. All models were clustered by CaPSURE clinical site with robust standard errors used to calculate confidence intervals (CI). Simple models were adjusted for time between diagnosis and participants' first CDL questionnaire (continuous) and age at diagnosis. Fully adjusted models were additionally adjusted for clinical T-stage (T1, T2, T3a), Gleason score (<7, 7, >7), diagnostic PSA level (≤ 6 ng/mL, >6 to 10 ng/mL, >10 ng/mL), primary treatment (radical prostatectomy, radiation, hormonal therapy, watchful waiting/active surveillance, other), family history of prostate cancer in a brother or father (yes, no), self-identified and physician-reported race (white, non-white), selenium supplement use (non-user; <140ug/day; ≥ 140 ug/day; user with unknown daily dosage), total caloric intake (continuous, kcal/d), and the following variables if not part of the score of interest: whole milk intake (≤ 4 servings/week, >4 servings/week), wine intake (3-14 servings/week, <3 or ≥ 14 servings/week), alcohol intake (non-drinker, >0-2 servings/day, >2 servings/day), red and processed meat intake (quartiles), tomato intake (continuous, servings/day), dark fish intake (continuous, servings/day), and smoking (never, quit ≥ 10 years prior, quit <10 years prior, current). We further considered adjustment for comorbidities (diabetes, stroke, prior myocardial infarction, or other heart disease; yes/no) but the magnitudes of the estimates changed very little with adjustment, so these variables were not included in the final models.

We assessed potential interaction between each of the scores and age at diagnosis (<65 years, ≥65 years) and, separately, stage at diagnosis (T1, T2-T3a) by adding interaction terms with the scores in the models and using Wald tests. Given statistically non-significant Wald tests and small magnitudes of estimated interaction regression coefficients, interaction terms were not included in the final models. We examined goodness-of-fit of the survival models using Cox-Snell residual plots. Across all scores, goodness-of-fit was best in the fully adjusted models, with decreasing fit in the tails. Fully adjusted models for progression were also run using exponential distributions, which produced Cox-Snell residual plots that demonstrated poorer fit than Weibull models and thus were not reported.

Sensitivity Analyses. First, we were concerned about confounding due to PSA surveillance after diagnosis (i.e., men with healthier behaviors may be more likely to be monitored via PSA tests, potentially creating a positive correlation between healthy lifestyle habits and risk of progression). To address this, Poisson regression was utilized to compare the number of PSA visits to tertile of each of the six scores, with the lowest tertile (i.e., the least healthy group) as the reference. Total follow-up time was used as an offset in these models.

Second, whereas our primary analyses used time of the CDL questionnaire completion as time zero – which necessitates excluding men who experienced an event prior to the survey – sensitivity analyses re-assigned time zero as time of diagnosis. These analyses assumed that the responses on the CDL questionnaire were consistent with what would have been measured at the date of diagnosis. Men excluded from our primary analyses due to documented progression prior to CDL questionnaire were included in these sensitivity analyses, resulting in an analytic sample of 2,447 men. For this approach, we first assessed whether there was an interaction between year of diagnosis and each of the behavioral scores by adding an interaction term with the scores in the models and using Wald tests; no evidence of interaction was found.

Third, we were interested in understanding how competing events (i.e., deaths due to causes other than prostate cancer) impacted our primary results. Methods to address competing events in the presence of interval censoring are not readily available or accessible. Thus, we ran Cox proportional hazards models for progression and compared these results to Fine-Gray analyses accounting for other deaths as a competing risk. Proportional hazards assumptions were assessed visually by plotting the scaled Schoenfeld residuals against follow-up time.

Lastly, missingness in the covariates resulted in a loss of events in our fully adjusted models. Specifically, men with missing data for any of the score components were excluded from the primary analysis for that score: n=60 for 2021 Score, n=60 for the 2021 Score with Diet, n=83 for 2015 Score, n=40 for ACS Score, n=70 for the ACS Score with Alcohol, and n=43 for WCRF/AICR Score. To understand the impact of this missingness on our primary results, we performed sensitivity analyses utilizing multiple imputation to handle missing data [127], which assumes that data are missing at random. We assessed the plausibility of this assumption by summarizing participant characteristics by missingness status for each of the six scores. We performed multiple imputation via chained equations using the *chained* command in Stata to first generate 25 imputed datasets. We then fit survival models across all 25 imputed datasets and pooled the results using Rubin's Rules [128]. Our imputed models included fully observed variables (CaPSURE clinical site, age at diagnosis, BMI, days of follow-up, total energy intake, tomato intake, days from CDL return to the left interval of follow-up time, race, diagnostic T stage, and family history of prostate cancer) and variables with incomplete values (diagnostic PSA and Gleason score; total alcohol, whole milk, dark fish, total wine, and red and processed meat intake; each of the scores; smoking status; and primary treatment).

All statistical analyses were performed using Stata version 17 (StataCorp, College Station, TX) using a two-sided alpha level of 0.05 to assess statistical significance.

Results

In our main analyses, the 2,056 men who met inclusion criteria were followed for a median of 6.4 years (IQR: 1.3, 12.7) after completing the CDL questionnaire, for a total of 13,102 person-years. During the follow-up period, 192 had documented progression, including 168 (88%) with biochemical recurrence, 7 (4%) with bone metastases, and 17 (9%) deaths related to prostate cancer as the first recorded event (there were 73 PCSM events in total). Baseline characteristics by tertile of each of the four primary scores are shown in **Table 2.3**. Most participants identified as white race with a diagnostic T-stage ≤ 1 and Gleason grade < 7 and underwent radical prostatectomy as their primary treatment. Characteristics were balanced across tertiles of the scores.

Progression

Those with higher 2021 Scores had a non-statistically significant lower risk of progression (HR_{cont} : 0.84, 95% CI: 0.65-1.08); however, in models assessing score tertiles, there was no clear association with progression ($HR_{2 vs 1}$: 0.90, 95% CI: 0.62-1.32; $HR_{3 vs 1}$: 0.79, 95% CI: 0.50-1.24; $p_{trend}=0.30$). Including dietary factors in the 2021 Score (2021 Score + Diet) strengthened the associations: HR_{cont} : 0.76, 95% CI: 0.63-0.90; $HR_{2 vs 1}$: 0.82, 95% CI: 0.62-1.08 and $HR_{3 vs 1}$: 0.67; 95% CI: 0.44-1.02 ($p_{trend}=0.06$) [**Table 2.4**].

Neither the 2015 Score (HR_{cont} : 0.89, 95% CI: 0.80-1.00; $HR_{2 vs 1}$: 0.90, 95% CI: 0.60-1.35; $HR_{3 vs 1}$: 0.57, 95% CI: 0.30-1.09; $p_{trend}=0.091$) nor the ACS Score were associated with risk of prostate cancer progression (HR_{cont} : 0.93; 95% CI: 0.82-1.05; $HR_{2 vs 1}$: 1.19, 95% CI: 0.82-1.71; $HR_{3 vs 1}$: 0.83; 95% CI: 0.58-1.18; $p_{trend}=0.30$). The ACS Score + Alcohol, however, demonstrated evidence of an inverse association with risk of progression (HR_{cont} : 0.89, 95% CI: 0.81-0.98; $HR_{2 vs 1}$: 0.97, 95% CI: 0.71-1.32; $HR_{3 vs 1}$: 0.48, 95% CI: 0.28-0.82; $p_{trend}=0.007$). The WCRF/AICR Score was also inversely associated with risk of prostate cancer progression

(HR_{cont}: 0.83, 95% CI: 0.67-1.02; HR_{2 vs 1}: 0.89, 95% CI: 0.51-1.55; HR_{3 vs 1}: 0.60, 95% CI: 0.36-1.01; p_{trend}=0.05) [Table 2.4].

Prostate Cancer-Specific Mortality

The 2021 Score was statistically significantly associated with a lower risk of PCSM (HR_{cont}: 0.62, 95% CI: 0.45-0.85). However, in models assessing score tertiles, there was no clear association with PCSM (HR_{2 vs 1}: 0.50, 95% CI: 0.23-1.06; HR_{3 vs 1}: 0.71, 95% CI: 0.38-1.33; p_{trend}=0.28). When dietary factors were included (2021 Score + Diet), associations with PCSM were statistically significant in continuous (HR: 0.65; 95% CI: 0.45, 0.93) and tertile models, showing a 59% reduced risk of PCSM among those with the highest versus the lowest tertile of score (HR_{3 vs 1}: 0.41, 95% CI: 0.20, 0.85; p_{trend}=0.02) [Table 2.5].

There was no association with PCSM for the 2015 (HR_{cont}: 0.81, 95% CI: 0.63-1.04), ACS (HR_{cont}: 0.82, 95% CI: 0.65-1.04) or ACS + Alcohol (HR_{cont}: 0.92, 95% CI: 0.74-1.15) Scores (Table 2.5). The WCRF/AICR Score was inversely associated with risk of PCSM (HR_{cont}: 0.71, 95% CI: 0.57-0.89), amounting to a 48% (HR: 0.52, 95% CI: 0.33-0.81; p_{trend}=0.004) lower risk among those with the highest versus lowest tertile of score (Table 2.5).

Sensitivity Analyses

Across all scores, there was no evidence that men with higher behavioral scores presented more frequently for PSA monitoring following a diagnosis (data not shown). In models that imposed date of diagnosis as time zero, the trends were similar across all scores (Table 2.6). The results from Cox proportional hazards models for progression were similar to those from the parametric (Weibull) survival and there was no evidence that competing events impacted the results (Table 2.7). Multiple imputation resulted in 2,056 complete records and retainment of all 192 events in multivariable models. Across all scores, with the exception of age, characteristics were similar between men with and without missingness, providing some evidence that data were missing at random (Table 2.8). The results following imputation were similar to those obtained from the complete-case analysis. With the larger sample sizes,

however, the confidence intervals tightened, resulting in statistically significant estimates across all scores (**Table 2.9**).

Discussion

In this prospective study, we examined associations of behavioral risk scores with prostate cancer progression and PCSM among men diagnosed with non-metastatic prostate cancer. For each 1-unit increase (i.e., healthier) in the 2021 Score + Diet and the ACS Score + Alcohol, men had a statistically significant 24% and 11% lower risk of progression, respectively. The WCRF/AICR Score was also associated with a (statistically non-significant) reduced risk of progression, demonstrating a 17% lower risk of progression per point increase. Men in the highest tertile of the 2021 Score + Diet and WCRF/AICR Score had a 59% and 48%, respectively, lower risk of dying from prostate cancer compared to those in the lowest tertile.

The difference in associations observed between the two outcomes may reflect different mechanisms driving recurrence versus PCSM. Indeed, 94% of men with biochemical recurrence in this cohort did not die from prostate cancer during study follow-up. Another explanation is confounding: healthier men may present more often for PSA monitoring and thus be more likely to have biochemical recurrence detected. This may spuriously attenuate associations. We attempted to evaluate whether this bias impacted our results and did not observe different screening behaviors based on score levels. Nevertheless, we cannot rule this out.

Importantly, components varied across behavioral scores and were used differently within scores. For example, the ACS Score + Alcohol assigned the highest (i.e., healthiest) points for moderate alcohol intake, whereas WCRF/AICR Score preserved highest points for no alcohol intake. The 2021 Score + Diet only included moderate consumption of wine in its highest point. Aligned with ACS recommendations, the decision to consume alcohol should be made on an individual basis with a patient's provider [129].

The 2015 Score was developed based on the literature describing the risk of developing lethal prostate cancer among disease-free men [105]; our team previously reported that this score was associated with a 68% lower risk (5-6 points vs. 0-1 points) of developing lethal prostate cancer among disease-free men [105]. However, our results, in combination with existing evidence, suggest that behavioral factors associated with *developing* prostate cancer may differ from those associated with *progression and mortality following a diagnosis* [130, 131].

There are several limitations of our analyses to consider. Men in our study predominately identified as white race (95%), were well educated (77% with at least some college), and were insured (97%), meaning these results may not be generalizable to all men with prostate cancer. Social determinants of health and their impacts on health and disease status cannot be addressed in this cohort. While we observed some statistically significant inverse associations for PCSM, this was a secondary outcome given the limited number of events. Though we made efforts to address potential biases in this study (e.g., multiple imputation to address missingness, modeling PSA surveillance behavior as a function of behavioral scores to address confounding issues), these approaches are not without their own assumptions, and thus we cannot rule out bias entirely. Finally, the post-diagnostic literature that drove the creation of the 2021 Score (with and without diet) came from a limited number of study populations, which included CaPSURE [102]. This underscores the importance of confirming these findings in other populations.

In conclusion, among men diagnosed with non-metastatic prostate cancer, a behavioral score developed based on the current post-diagnostic literature (2021 Score Including Diet) was associated with a 24% lower risk of progression and 35% lower risk of PCSM per one-unit increase in the score. Men diagnosed with non-metastatic prostate cancer may improve survivorship by adhering to post-diagnostic prostate cancer-specific dietary recommendations – avoiding/limiting the consumption of whole milk, red and processed meats, and saturated fat,

while allowing moderate consumption of wine – in addition to the general recommendations to avoid smoking, maintain a healthy body size, and engage in regular physical activity.

Table 2.1. Operationalization of the 2021 Score, 2015 Score, ACS Score, and WCRF/AICR Score

Point Range:	2021 Score ^b 0-3 (with Diet: 0-4)	2015 Score 0-6	ACS ^c 0-6 (with Alcohol: 0-8)	WCRF/AICR 0-7
Smoking Status ^d	<p>1: never or quit ≥ 10 years prior</p> <p>0.5: quit <10 years prior</p> <p>0: current</p>	<p>1: never or quit ≥10 years prior</p> <p>0: quit <10 years prior or current</p>	N/A	N/A
Body Mass Index ^e	<p>1: 18.5 to <25 kg/m²</p> <p>0.5: 25 to <30 kg/m²</p> <p>0: ≥30 kg/m²</p>	<p>1: <30 kg/m²</p> <p>0: ≥30 kg/m²</p>	<p>2: 18.5 to <25 kg/m²</p> <p>1: 25 to <30 kg/m²</p> <p>0: ≥30 kg/m²</p>	<p>1: 18.5 to <25 kg/m²</p> <p>0.5: 25 to <30 kg/m²</p> <p>0: <18.5 kg/m² or ≥30 kg/m²</p>
Physical Activity	<p>1: ≥18 MET-hr/wk total PA</p> <p>0.5: 9 to <18 MET-hr/wk total PA</p> <p>0: <9 MET-hr/wk total PA</p>	<p>1: ≥3 hr/wk vigorous PA or ≥7 hr/wk brisk walking</p> <p>0: <3 hr/wk vigorous PA and <7 hr/wk brisk walking</p>	<p>1: ≥17.5 MET-hr/wk moderate or vigorous aerobic PA</p> <p>0.5: 8.75 to <17.5 MET-hr/wk moderate or vigorous aerobic PA</p> <p>0: <8.75 MET-hr/wk moderate or vigorous aerobic PA</p> <p>1: ≥40 min/wk strength training</p> <p>0.5: >0-<40 min/wk strength training</p> <p>0: 0 min/wk strength training</p>	<p>1: ≥2.5 hr/wk moderate or vigorous PA</p> <p>0.5: 1.25 to <2.5 hr/wk moderate or vigorous PA</p> <p>0: <1.25 hr/wk moderate or vigorous PA</p>
Fatty Fish	N/A	<p>1: ≥1 serv/wk</p> <p>0: <1 serv/wk</p>	N/A	N/A
Whole Milk ^f	<p>0.25: ≤4 serv/wk</p> <p>0: >4 serv/wk</p>	N/A	N/A	N/A
Alcohol ^g	<p>0.25: 3 to 14 serv/wk of wine</p> <p>0: <3 or >14 serv/wk wine</p>	N/A	<p>2: >0 to 2 serv/day</p> <p>1: 0 serv/day</p> <p>0: >2 serv/day</p>	<p>1: 0 gm/day</p> <p>0.5: >0 to 28 gm/day</p> <p>0: >28 gm/day</p>

Point Range: Score ^a :	2021 Score ^b 0-3 (with Diet: 0-4)	2015 Score 0-6	ACS ^c 0-6 (with Alcohol: 0-8)	WCRF/AICR 0-7
Sugar-Sweetened Beverages	N/A	N/A	N/A	1: 0 gm/day 0.5: >0 to 250 gm/day 0: >250 gm/day
Percentage of Calories from aUPFs	N/A	N/A	N/A	1: 1 st tertile 0.5: 2 nd tertile 0: 3 rd tertile
Fiber	N/A	N/A	N/A	0.5: ≥30 gm/day 0.25: 15 to <30 gm/day 0: <15 gm/day
Whole Fruits and Vegetables ^h	N/A	1: ≥7 serv/wk tomatoes 0: <7 serv/wk tomatoes	1: ≥5 serv/day 0: <5 serv/day 2: 3 rd tertile of unique fruits and vegetables consumed 1: 2 nd tertile of unique fruits and vegetables consumed 0: 1 st tertile of unique fruits and vegetables consumed	0.5: ≥400 gm/day 0.25: 200 to <400 gm/day 0: <200 gm/day
Red and Processed Meat ^h	1: <2 serv/wk 0: ≥2 serv/wk	1: <3 serv/wk processed red meat 0: ≥3 serv/wk processed red meat	3: 1 st quartile 2: 2 nd quartile 1: 3 rd quartile 0: 4 th quartile	1: <500 gm/wk red meat and <21 gm/wk processed meat 0.5: <500 gm/wk red meat and 21 to <100 gm/wk processed meat 0: ≥500 gm/wk red meat or ≥100 gm/wk processed meat

Point Range: ^a	2021 Score ^b 0-3 (with Diet: 0-4)	2015 Score 0-6	ACS ^c 0-6 (with Alcohol: 0-8) 3: 4 th quartile 2: 3 rd quartile 1: 2 nd quartile 0: 1 st quartile	WCRF/AICR 0-7
Whole Grains ^h	N/A	N/A		N/A
Saturated Fat ^f	1: <10% of total energy intake 0: ≥10% of total energy intake	N/A	N/A	N/A

Abbreviations: ACS – American Cancer Society; AICR – American Institute for Cancer Research; aUPFs – adapted ultra-processed foods; gm/day – grams per day; hr – hours;

MET – metabolic equivalent of task; PA – physical activity; serv – servings; WCRF – World Cancer Research Fund; wk – week

^a Higher scores implied higher compliance with the recommendations within each score.

^b The 2021 Score did not include dietary components and ranged from 0-3. The 2021 Score + Diet included dietary components and ranged from 0-4.

^c The ACS Score did not include alcohol consumption and ranged from 0-6. The ACS Score + Alcohol included alcohol and ranged from 0-8.

^d Former smokers with unknown time since quitting were excluded.

^e The 2021 Score and ACS Score excluded men with BMI <18.5kg/m².

^f Whole milk, wine, red/processed meat, and saturated fat were only included in the 2021 Score + Diet.

^g Alcohol was only included in the ACS Score + Alcohol.

^h The points from fruit and vegetable variety, unique fruits and vegetables consumed, red and processed meat, and whole grains were summed and points toward the ACS score were awarded as follows: 0 points awarded for a sum of 0 to 2, 1 point awarded for a sum of 3 to 6, 2 points awarded for a sum of 7 to 9.

Table 2.2. Individuals Items Included in Each Component of the 2021 Score + Diet, 2015 Score, ACS Score, ACS Score + Alcohol, and WCRF/AICR Score

Sub-Component	Items	2021	2021 + Diet	2015	ACS	ACS + Alcohol	AICR
Physical Activity							
Total	Walking, jogging, running, bicycling, swimming, tennis, squash or racquetball, calisthenics or rowing, other aerobic exercise, weight training	X	X				
Vigorous / Vigorous Aerobic	Walking at a very brisk/striding pace, jogging, running, bicycling, swimming, tennis, squash or racquetball, calisthenics or rowing, other aerobic exercise			X			X
Moderate or Vigorous	Walking at a normal, brisk, or very brisk/striding pace; bicycling, swimming, tennis, weight training				X		X
Moderate or Vigorous Aerobic	Walking at a normal, brisk, or very brisk/striding pace; bicycling, swimming, tennis				X	X	
Brisk Walking	Walking at a brisk or very brisk / striding pace			X			
Strength Training	any reported weight training				X	X	
Foods and Beverages							
Fatty Fish	Dark meat fish, e.g., tuna steak, mackerel, salmon, sardines, bluefish, swordfish			X			
Alcohol	Red wine, white wine, regular beer, lite beer, liquor					X	X
Wine	Red wine, white wine		X				
Sugar-Sweetened Beverages	Prune juice, apple juice or cider, orange juice, other fruit juices, Coke or Pepsi or other cola with sugar, other carbonated beverages with sugar, other sugared beverages (punch, lemonade, sports drinks)						X
Tomatoes	Tomatoes, tomato juice, tomato sauce, tomato soup, salsa, pizza			X			
Whole Fruits and Vegetables (WCRF/AICR)	Raisins or grapes, prunes, bananas, cantaloupe, watermelon, avocado, apples or pears, oranges, grapefruit, strawberries, blueberries, peaches or plums or apricots, tomatoes, tomato juice or V-8, tomato sauce, salsa, celery, string beans, broccoli, cauliflower, cabbage or coleslaw, Brussels sprouts, raw carrots, cooked carrots, mixed or stir fry vegetables or soup, yellow (winter) squash, eggplant or zucchini or other summer squash, kale or mustard greens or chard, raw spinach, cooked spinach, iceberg or head lettuce, romaine or leaf lettuce, alfalfa sprouts, green or yellow or red pepper, onion as a vegetable or rings or soup, onion as a garnish, garlic, beets						X

Sub-Component	Items	2021	2021 + Diet	2015	ACS	ACS + Alcohol	AICR
aUPFs	Non-dairy coffee whitener; sour cream or whipped cream; sherbet or ice milk; ice cream; margarine cottage or ricotta cheese; cream cheese; breaded fish cakes, pieces, or fish sticks; chicken or turkey sandwich or frozen meal; refined cold breakfast cereal; white bread (including pita); English muffins, bagels, or rolls; crackers, triskets, or wheat thins; muffins or biscuits; pancakes or waffles; pancakes or waffles; French fried potatoes; potato chips or corn chips; pizza; tortilla; lo-calorie cola, e.g., tab with caffeine; diet soda without caffeine; dairy coffee drink (cappuccino); pure chocolate candy bar or packet, e.g., Hershey's, M&M's; Mixed candy bars, e.g., Snickers, Milky Way, Reese's; Candy with no chocolate; doughnuts; cake; pie; cookies; sweet rolls, coffee cake, pastry; brownies; breakfast bars, e.g., NutriGrain, granola, kasha; Energy bars, e.g., Clif, Luna, Glucerna, Powerbar; low carb bars; e.g., Atkins, Zone, South Beach; pretzels; popcorn; chowder or cream soup; red chili sauce; Mayonnaise or other creamy salad dressing; salad dressing; regular mayonnaise; low-fat or fat-free mayonnaise; Splenda; other artificial sweetener; dark bread; mustard.				X	X	X
Whole Fruits and Vegetables (ACS) ^a	Raisins or grapes, prunes or dried plums, bananas, cantaloupe, watermelon, avocado, apples or pears, oranges, grapefruit, strawberries, blueberries, peaches or plums or apricots, tomatoes, tomato sauce, salsa, celery, string beans, broccoli, cauliflower, cabbage or coleslaw or sauerkraut, Brussels sprouts, raw carrots, cooked carrots, mixed or stir fry vegetables or soup, yellow or orange (winter) squash, eggplant or zucchini or other summer squash, kale or mustard greens or chard, raw spinach, cooked spinach, iceberg or head lettuce, romaine or leaf lettuce, alfalfa sprouts, green or yellow or red pepper, onion as a vegetable or rings or soup, onion as a garnish, beets, yams or sweet potatoes, corn, peas or lima beans fresh or frozen or canned or soup, beans or lentils baked or dried or soup, tofu or soy burger or soybeans or miso or other soy protein						
Processed Red Meat	Bacon, beef or pork hot dogs, salami or bologna or other processed meat sandwiches, other processed meats (e.g., sausage, kielbasa, etc.)		X				
Processed Meat	Bacon, beef or pork hot dogs, salami or bologna or other processed meat sandwiches, other processed meats (e.g., sausage, kielbasa, etc.), chicken or turkey hot dogs or sausage			X	X	X	X
Red Meat	Hamburgers (regular, lean, or extra lean), beef or lamb as a main dish, pork as a main dish, beef or lamb or pork as a sandwich or mixed dish		X		X	X	X

Abbreviations: ACS – American Cancer Society; AICR – American Institute for Cancer Research; aUPF – adapted ultra-processed food; WCRF – World Cancer Research Fund

^a When considering variety of whole fruits and vegetables consumed, each of the following sets contributed only one point to variety, as appropriate: tomatoes and tomato sauce and salsa; raw carrots and cooked carrots; raw spinach and cooked spinach; onions as a vegetable and onions as a garnish

Table 2.3. Patient and clinical characteristics of men diagnosed with non-metastatic prostate cancer by tertile of health behavior scores

	N ^b :	2021 Score ^a			2015 Score ^a			ACS Score ^a			WCRF/AICR Score ^a		
		1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
n		1,033	640	323	1259	475	239	710	610	696	805	560	648
Age^c (yrs), mean (SD)		64.5 (7.9)	64.0 (7.9)	64.7 (8.3)	64.6 (7.9)	64.2 (7.9)	63.3 (8.1)	64.0 (7.8)	64.8 (8.0)	64.3 (8.1)	64.4 (7.8)	64.4 (7.9)	64.3 (8.2)
White, n (%)		979 (95)	609 (95)	310 (96)	1202 (95)	455 (96)	220 (92)	672 (95)	585 (96)	660 (95)	764 (95)	531 (95)	620 (96)
T-Stage^c, n (%)													
≤T1		598 (58)	367 (57)	184 (57)	697 (55)	284 (60)	156 (65)	407 (57)	336 (55)	416 (60)	483 (60)	324 (58)	350 (54)
T2		426 (41)	268 (42)	134 (41)	550 (44)	186 (39)	81 (34)	297 (42)	270 (44)	271 (39)	315 (39)	230 (41)	292 (45)
T3a		9 (1)	5 (1)	5 (2)	12 (1)	5 (1)	2 (1)	6 (1)	4 (1)	9 (1)	7 (1)	6 (1)	6 (1)
Gleason^c, n (%)													
<7		680 (66)	435 (69)	223 (69)	816 (65)	332 (70)	174 (73)	472 (67)	404 (67)	470 (68)	518 (65)	388 (70)	440 (68)
7		278 (27)	164 (26)	75 (23)	343 (28)	115 (24)	51 (21)	178 (25)	168 (28)	182 (26)	219 (28)	138 (25)	167 (26)
>7		67 (7)	35 (6)	23 (7)	87 (7)	25 (5)	13 (5)	55 (8)	31 (5)	40 (6)	59 (7)	30 (5)	37 (6)
PSA^c (ng/ml), median (IQR)		5.6 (4.4, 8.0)	5.5 (4.3, 7.6)	5.3 (4.3, 7.5)	5.6 (4.4, 8.0)	5.5 (4.5, 7.6)	5.2 (4.1, 7.6)	5.6 (4.4, 8.0)	5.6 (4.4, 7.7)	5.4 (4.3, 7.8)	5.7 (4.4, 8.0)	5.5 (4.3, 7.7)	5.4 (4.3, 7.7)
Primary Treatment, n (%)													
Radical Prostatectomy		604 (60)	402 (65)	210 (67)	769 (62)	282 (61)	153 (67)	407 (59)	376 (63)	448 (66)	473 (60)	340 (62)	413 (66)
AS/WW		56 (6)	39 (6)	23 (7)	64 (5)	33 (7)	19 (8)	32 (5)	37 (6)	49 (7)	40 (5)	36 (7)	42 (7)
RT/Brachytherapy		245 (24)	129 (21)	58 (19)	281 (23)	101 (22)	43 (19)	175 (25)	129 (22)	131 (19)	189 (24)	123 (22)	124 (20)
Hormone Therapy		61 (6)	26 (4)	11 (4)	61 (5)	25 (5)	9 (4)	40 (6)	40 (7)	21 (3)	46 (6)	30 (5)	25 (4)
Other		47 (5)	21 (3)	11 (4)	57 (5)	19 (4)	4 (2)	37 (5)	14 (2)	27 (4)	35 (4)	22 (4)	22 (4)
Family History of PC, n (%)		186 (18)	141 (22)	79 (24)	246 (20)	105 (22)	51 (21)	143 (20)	115 (19)	151 (22)	171 (21)	121 (22)	116 (18)

Abbreviations: ACS – American Cancer Society; AICR – American Institute for Cancer Research; AS/WW – active surveillance/watchful waiting; aUPFs – adapted ultra-processed foods; BMI – body mass index; IQR – interquartile range; PC – prostate cancer; RT – radiation therapy; SD – standard deviation; WCRF – World Cancer Research Fund

^a **2021 Score** included smoking, BMI, and physical activity. **2015 Score** included smoking, BMI, physical activity, fatty fish intake, tomato intake, and processed red meat intake. **ACS Score** included BMI, physical activity, whole fruit and vegetables intake, red and processed meat intake, and whole grain intake. **WCRF/AICR Score** included BMI, physical activity, alcohol intake, sugar-sweetened beverage intake, percentage of calories from aUPFs, fiber intake, whole fruit and vegetable intake, and red and processed meat intake.

^b Missingness on score components resulted in missing scores: n=60 for 2021 Score, n=83 for 2015 Score, and n=43 for AICR Score

^c At prostate cancer diagnosis.

Table 2.4. Post-diagnostic health behavior scores and the risk of prostate cancer progression among men with non-metastatic prostate cancer, estimated via parametric (Weibull) survival models to account for interval censoring

		2021 Score – HR (95% CI)					P_{trend}
events	N	Continuous	1 st Tertile (0-2 pts)	2 nd Tertile (2.5 pts)	3 rd Tertile (3 pts)		
Simple ^a	1,996	0.79	Ref	0.77 (0.57, 1.04)	0.69 (0.46, 1.04)	0.07	
Fully Adjusted ^b	1,615	0.84	Ref	0.90 (0.62, 1.32)	0.79 (0.50, 1.24)	0.30	
2021 Score + Diet – HR (95% CI)							
events	N	Continuous	1 st Tertile (0.25-2.25 pts)	2 nd Tertile (2.5-3 pts)	3 rd Tertile (3.25-4 pts)	P_{trend}	
Simple ^a	1,996	0.78	Ref	0.83 (0.67, 1.04)	0.67 (0.46, 0.97)	0.03	
Fully Adjusted ^b	1,673	0.76	Ref	0.82 (0.62, 1.08)	0.67 (0.44, 1.02)	0.06	
2015 Score – HR (95% CI)							
events	N	Continuous	1 st Tertile (0-3 pts)	2 nd Tertile (4 pts)	3 rd Tertile (5-6 pts)	P_{trend}	
Simple ^a	1,973	0.85	Ref	0.82 (0.59, 1.14)	0.56 (0.33, 0.94)	0.03	
Fully Adjusted ^b	1,611	0.89	Ref	0.90 (0.60, 1.35)	0.57 (0.30, 1.09)	0.09	
ACS Score – HR (95% CI)							
events	N	Continuous	1 st Tertile (0-2 pts)	2 nd Tertile (2.5-3 pts)	3 rd Tertile (3.5-6 pts)	P_{trend}	
Simple ^a	2,016	0.89	Ref	0.93 (0.68, 1.28)	0.71 (0.53, 0.94)	0.02	
Fully Adjusted ^b	1,614	0.93	Ref	1.19 (0.82, 1.71)	0.83 (0.58, 1.18)	0.30	
ACS Score + Alcohol – HR (95% CI)							
events	N	Continuous	1 st Tertile (0-3.5 pts)	2 nd Tertile (4-5 pts)	3 rd Tertile (5.5-8 pts)	P_{trend}	
Simple ^a	1,986	0.88	Ref	0.77 (0.56, 1.05)	0.49 (0.29, 0.83)	0.008	
Fully Adjusted ^b	1,614	0.89	Ref	0.97 (0.71, 1.32)	0.48 (0.28, 0.82)	0.007	
WCRF/AICR Score – HR (95% CI)							
events	N	Continuous	1 st Tertile (0.75-3.25 pts)	2 nd Tertile (3.5-4 pts)	3 rd Tertile (4.25-7 pts)	P_{trend}	
Simple ^a	2,013	0.85	Ref	0.79 (0.52, 1.20)	0.63 (0.43, 0.91)	0.01	
Fully Adjusted ^b	1,618	0.83	Ref	0.89 (0.51, 1.55)	0.60 (0.36, 1.01)	0.05	

Abbreviations: ACS – American Cancer Society; Adj – adjusted; AICR – American Institute for Cancer Research; CI – confidence interval; HR – hazard ratio; pts – points; WCRF – World Cancer Research Fund; wk – week
^a Simple models were adjusted for time between diagnosis and date of first CDL questionnaire (continuous), age at diagnosis (continuous) and CaPSURE clinical site.
^b Fully-adjusted models were additionally adjusted for clinical T stage (T1, T2, T3), Gleason score (<7, 7, >7), diagnostic PSA value (≤6, >6-10, >10-20), primary treatment (radical prostatectomy, active surveillance/watchful waiting, radiotherapy/brachytherapy, hormone therapy, other), family history of prostate cancer in brother of father (yes, no), race (white, non-white), total caloric intake (continuous), plus the following variables (if not part of the score): whole milk intake (≤4 servings/wk, >4 servings/wk), wine intake (3-14 servings/wk, <3 or >14 servings/wk), total alcohol intake (non-drinker, >0-2 serving/day, >2 servings/day), red and processed meat intake (quartiles), tomato intake (continuous), dark meat fish intake (continuous), selenium supplement use (non-user, <140ug/day, ≥140ug/day, user with unknown daily dosage), smoking (never, quit ≥10 years prior, quit <10 years prior, current)

Table 2.5. Post-diagnostic health behaviors scores and the risk of prostate cancer mortality among men with non-metastatic prostate cancer, estimated via Cox proportional hazards models

2021 Score – HR (95% CI)						
events	N ^a	Continuous	1 st Tertile (0-2 pts)	2 nd Tertile (2.5 pts)	3 rd Tertile (3 pts)	P _{trend}
Simple ^b	69	2,369	0.73 (0.52, 1.03)	0.64 (0.39, 1.04)	0.73 (0.40, 1.35)	0.32
Fully Adjusted ^c	51	1,877	0.62 (0.45, 0.85)	0.50 (0.23, 1.06)	0.71 (0.38, 1.33)	0.28
2021 Score with Diet – HR (95% CI)						
events	N ^a	Continuous	1 st Tertile (0.25-2.25 pts)	2 nd Tertile (2.5-3 pts)	3 rd Tertile (3.25-4 pts)	P _{trend}
Simple ^b	69	2,369	0.76 (0.55, 1.04)	0.64 (0.37, 1.09)	0.59 (0.33, 1.06)	0.078
Fully Adjusted ^c	52	1,947	0.65 (0.45, 0.93)	0.55 (0.30, 1.02)	0.41 (0.20, 0.85)	0.02
2015 Score – HR (95% CI)						
events	N ^a	Continuous	1 st Tertile (0-3 pts)	2 nd Tertile (4 pts)	3 rd Tertile (5-6 pts)	P _{trend}
Simple ^b	65	2,336	0.86 (0.71, 1.04)	0.96 (0.64, 1.43)	0.72 (0.33, 1.57)	0.41
Fully Adjusted ^c	49	1,874	0.81 (0.63, 1.04)	0.94 (0.65, 1.37)	0.61 (0.18, 2.03)	0.42
ACS Score – HR (95% CI)						
events	N ^a	Continuous	1 st Tertile (0-2 pts)	2 nd Tertile (2.5-3 pts)	3 rd Tertile (3.5-6 pts)	P _{trend}
Simple ^b	69	2,396	0.84 (0.69, 1.02)	0.74 (0.42, 1.32)	0.64 (0.35, 1.15)	0.13
Fully Adjusted ^c	50	1,875	0.82 (0.65, 1.04)	0.65 (0.36, 1.17)	0.58 (0.29, 1.15)	0.12
ACS Score with Alcohol – HR (95% CI)						
events	N ^a	Continuous	1 st Tertile (0-3.5 pts)	2 nd Tertile (4-5 pts)	3 rd Tertile (5.5-8 pts)	P _{trend}
Simple ^b	68	2,359	0.87 (0.74, 1.03)	0.74 (0.41, 1.33)	0.73 (0.37, 1.42)	0.35
Fully Adjusted ^c	50	1,875	0.92 (0.74, 1.15)	1.07 (0.49, 2.37)	0.82 (0.35, 1.93)	0.64
WCRF/AICR Score – HR (95% CI)						
events	N ^a	Continuous	1 st Tertile (0.75-3.25 pts)	2 nd Tertile (3.5-4 pts)	3 rd Tertile (4.25-7 pts)	P _{trend}
Simple ^b	69	2,395	0.80 (0.69, 0.94)	0.66 (0.37, 1.17)	0.57 (0.38, 0.84)	0.004
Fully Adjusted ^c	50	1,883	0.71 (0.57, 0.89)	0.51 (0.25, 1.03)	0.52 (0.33, 0.81)	0.004

Abbreviations: ACS – American Cancer Society; Adj – adjusted; AICR – American Institute for Cancer Research; CI – confidence interval; HR – hazard ratio; pts – points; WCRF – World Cancer Research Fund; wk – week

^a A total of 2,447 men met inclusion for PCSM analyses, as men who were excluded from progression analysis due to having a documented progression event prior to questionnaire were included in this analysis.

^b Simple models were adjusted for time between diagnosis and date of first CDL questionnaire (continuous) and age at diagnosis (continuous)
^c Fully-adjusted models were additionally adjusted for clinical T stage (T1, T2, T3), Gleason score (<7, 7, >7), diagnostic PSA value (<6, >6-10, >10-20), primary treatment (radical prostatectomy, active surveillance/watchful waiting, radiotherapy/brachytherapy, hormone therapy, other), family history of prostate cancer in brother of father (yes, no), race (white, non-white), total caloric intake (continuous), plus the following variables (if not part of the score): whole milk intake (<4 servings/wk, >4 servings/wk), wine intake (3-14 servings/wk, <3 or >14 servings/wk), total alcohol intake (non-drinker, >2 serving/day, >2 servings/day), red and processed meat intake (quartiles), tomato intake (continuous), dark meat fish intake (continuous), selenium supplement use (non-user, <140ug/day, ≥140ug/day, user with unknown daily dosage), smoking (never, quit ≥10 years prior, quit <10 years prior, current)

Table 2.6. Post-diagnostic health behavior scores and the risk of prostate cancer progression among men with non-metastatic prostate cancer, estimated via parametric (Weibull) survival models to account for interval censoring with time zero set to date of diagnosis

		2021 Score – HR (95% CI)					P_{trend}
events	N	Continuous	1 st Tertile (0-2 pts)	2 nd Tertile (2.5 pts)	3 rd Tertile (3 pts)		
Simple ^a	2,354	0.80 (0.70, 0.92)	Ref	0.85 (0.69, 1.03)	0.76 (0.61, 0.95)	0.02	
Fully Adjusted ^b	1,870	0.82 (0.69, 0.97)	Ref	0.93 (0.72, 1.21)	0.81 (0.61, 1.08)	0.16	
2021 Score + Diet – HR (95% CI)							
events	N	Continuous	1 st Tertile (0.25-2.25 pts)	2 nd Tertile (2.5-3 pts)	3 rd Tertile (3.25-4 pts)	P_{trend}	
Simple ^a	2,354	0.82 (0.72, 0.93)	Ref	0.80 (0.67, 0.96)	0.76 (0.62, 0.93)	0.008	
Fully Adjusted ^b	1,940	0.85 (0.73, 0.99)	Ref	0.85 (0.68, 1.06)	0.82 (0.63, 1.07)	0.15	
2015 Score – HR (95% CI)							
events	N	Continuous	1 st Tertile (0-3 pts)	2 nd Tertile (4 pts)	3 rd Tertile (5-6 pts)	P_{trend}	
Simple ^a	2,322	0.91 (0.85, 0.97)	Ref	0.86 (0.66, 1.11)	0.79 (0.64, 0.99)	0.04	
Fully Adjusted ^b	1,867	0.92 (0.85, 1.00)	Ref	0.86 (0.66, 1.11)	0.81 (0.61, 1.07)	0.13	
ACS Score – HR (95% CI)							
events	N	Continuous	1 st Tertile (0-2 pts)	2 nd Tertile (2.5-3 pts)	3 rd Tertile (3.5-6 pts)	P_{trend}	
Simple ^a	2,381	0.91 (0.84, 0.97)	Ref	0.88 (0.71, 1.10)	0.76 (0.63, 0.92)	0.005	
Fully Adjusted ^b	1,868	0.93 (0.87, 1.00)	Ref	1.01 (0.78, 1.32)	0.82 (0.68, 0.99)	0.04	
ACS Score + Diet – HR (95% CI)							
events	N	Continuous	1 st Tertile (0-3.5 pts)	2 nd Tertile (4-5 pts)	3 rd Tertile (5.5-8 pts)	P_{trend}	
Simple ^a	2,345	0.90 (0.85, 0.97)	Ref	0.69 (0.54, 0.88)	0.64 (0.49, 0.84)	0.002	
Fully Adjusted ^b	1,868	0.91 (0.85, 0.96)	Ref	0.79 (0.64, 0.98)	0.63 (0.47, 0.84)	0.001	
WCRF/AICR Score – HR (95% CI)							
events	N	Continuous	1 st Tertile (0.75-3.25 pts)	2 nd Tertile (3.5-4 pts)	3 rd Tertile (4.25-7 pts)	P_{trend}	
Simple ^a	2,380	0.91 (0.81, 1.02)	Ref	0.90 (0.74, 1.09)	0.81 (0.64, 1.02)	0.07	
Fully Adjusted ^b	1,876	0.90 (0.79, 1.02)	Ref	1.00 (0.78, 1.28)	0.83 (0.64, 1.09)	0.19	

Abbreviations: ACS – American Cancer Society; Adj – adjusted; AICR – American Institute for Cancer Research; CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor; CDL – CaPSURE Diet and Lifestyle study; CI – confidence interval; HR – hazard ratio; pts – points; WCRF – World Cancer Research Fund; wk – week

^aSimple models were adjusted for time between diagnosis and date of first CDL questionnaire (continuous) and age at diagnosis (continuous)
^bFully-adjusted models were additionally adjusted for clinical T stage (T1, T2, T3), Gleason score (<7, 7, >7), diagnostic PSA value (≤6, >6-10, >10-20), primary treatment (radical prostatectomy, active surveillance/watchful waiting, radiotherapy/brachytherapy, hormone therapy, other), family history of prostate cancer in brother of father (yes, no), race (white, non-white), total caloric intake (continuous), plus the following variables (if not part of the score): whole milk intake (≤4 servings/wk, >4 servings/wk), wine intake (3-14 servings/wk, <3 or >14 servings/wk), total alcohol intake (non-drinker, >0-2 serving/day, >2 servings/day), red and processed meat intake (quartiles), tomato intake (continuous), dark meat fish intake (continuous), selenium supplement use (non-user, <140ug/day, ≥140ug/day, user with unknown daily dosage), smoking (never, quit ≥10 years prior, quit <10 years prior, current)

Table 2.7. Post-diagnostic health behavior scores and the risk of prostate cancer progression among men with non-metastatic prostate cancer, estimated using both Cox Proportional Hazards and Fine-Gray methods

		2021 Score – HR (95% CI)					
events	N	Continuous	1 st Tertile (0-2 pts)	2 nd Tertile (2.5 pts)	3 rd Tertile (3 pts)	P _{trend}	
Cox ^a	1,615	0.84 (0.65, 1.09)	Ref	0.91 (0.63, 1.32)	0.79 (0.50, 1.24)	0.30	
Fine-Gray ^a	1,615	0.87 (0.68, 1.12)	Ref	0.94 (0.65, 1.36)	0.81 (0.51, 1.28)	0.37	
		2021 Score + Diet – HR (95% CI)					
events	N	Continuous	1 st Tertile (0.25-2.25 pts)	2 nd Tertile (2.5-3 pts)	3 rd Tertile (3.25-4 pts)	P _{trend}	
Cox ^a	1,673	0.76 (0.64, 0.91)	Ref	0.83 (0.63, 1.09)	0.67 (0.44, 1.03)	0.07	
Fine-Gray ^a	1,673	0.79 (0.66, 0.94)	Ref	0.84 (0.64, 1.10)	0.70 (0.46, 1.06)	0.09	
		2015 Score – HR (95% CI)					
events	N	Continuous	1 st Tertile (0-3 pts)	2 nd Tertile (4 pts)	3 rd Tertile (5-6 pts)	P _{trend}	
Cox ^a	1,611	0.90 (0.80, 1.00)	1.00	0.90 (0.61, 1.34)	0.58 (0.31, 1.08)	0.09	
Fine-Gray ^a	1,611	0.91 (0.82, 1.02)	1.00	0.92 (0.62, 1.37)	0.60 (0.32, 1.11)	0.10	
		ACS Score – HR (95% CI)					
events	N	Continuous	1 st Tertile (0-2 pts)	2 nd Tertile (2.5-3 pts)	3 rd Tertile (3.5-6 pts)	P _{trend}	
Cox ^a	1,614	0.93 (0.82, 1.06)	Ref	1.20 (0.83, 1.74)	0.83 (0.58, 1.20)	0.32	
Fine-Gray ^a	1,614	0.94 (0.83, 1.07)	Ref	1.23 (0.85, 1.80)	0.86 (0.59, 1.24)	0.41	
		ACS Score + Alcohol – HR (95% CI)					
events	N	Continuous	1 st Tertile (0-3.5 pts)	2 nd Tertile (4-5 pts)	3 rd Tertile (5.5-8 pts)	P _{trend}	
Cox ^a	1,614	0.89 (0.81, 0.99)	Ref	0.97 (0.72, 1.33)	0.49 (0.28, 0.83)	0.009	
Fine-Gray ^a	1,614	0.90 (0.81, 1.00)	Ref	1.00 (0.73, 1.36)	0.50 (0.29, 0.86)	0.01	
		WCRF/AICR Score – HR (95% CI)					
events	N	Continuous	1 st Tertile (0.75-3.25 pts)	2 nd Tertile (3.5-4 pts)	3 rd Tertile (4.25-7 pts)	P _{trend}	
Cox ^a	1,618	0.83 (0.68, 1.03)	Ref	0.90 (0.51, 1.56)	0.61 (0.37, 1.02)	0.06	
Fine-Gray ^a	1,618	0.84 (0.69, 1.04)	Ref	0.90 (0.52, 1.56)	0.62 (0.37, 1.03)	0.06	

Abbreviations: ACS – American Cancer Society; Adj – adjusted; AICR – American Institute for Cancer Research; CI – confidence interval; HR – hazard ratio; pts – points; WCRF – World Cancer Research Fund; wk – week

^a Models were adjusted for time between diagnosis and date of first CDL questionnaire (continuous), age at diagnosis (continuous), clinical T stage (T1, T2, T3), Gleason score (<7, 7, >7), diagnostic PSA value (≤6, >6-10, >10-20), primary treatment (radical prostatectomy, active surveillance/watchful waiting, radiotherapy/brachytherapy, hormone therapy, other), family history of prostate cancer in brother of father (yes, no), race (white, non-white), total caloric intake (continuous), plus the following variables (if not part of the score): whole milk intake (≤4 servings/wk, >4 servings/wk), wine intake (3-14 servings/wk, <3 or >14 servings/wk), total alcohol intake (non-drinker, >0-2 serving/day, >2 servings/day), red and processed meat intake (quartiles), tomato intake (continuous), dark meat fish intake (continuous), selenium supplement use (non-user, <140ug/day, ≥140ug/day, user with unknown daily dosage), smoking (never, quit ≥10 years prior, quit <10 years prior, current)

Table 2.8. Characteristics of men with and without complete data to assess the missing-at-random assumption of multiple imputation

Factor ^b	2021 Score ^a		2015 Score		ACS Score		ACS Score with Alcohol		WCRF/AICR Score	
	Complete	Missing	Complete	Missing	Complete	Missing	Complete	Missing	Complete	Missing
N	1996	60	1973	83	2016	40	1986	70	2013	43
Age (yrs)	64.4 (8.0)	67.3 (7.2)	64.3 (7.9)	67.5 (8.0)	64.4 (8.0)	68.7 (6.1)	64.3 (7.9)	68.3 (7.7)	64.4 (7.9)	67.9 (7.6)
T-Stage										
≤T1	58	55	58	54	57	57	58	53	57	58
T2	41	45	41	46	42	42	41	47	42	42
T3a	1	0	1	0	1	0	1	0	1	0
Gleason										
<7	68	58	68	60	67	67	67	71	67	60
7	26	36	26	35	26	26	27	22	26	33
>7	6	7	6	5	6	8	6	7	6	7
PSA	5.6 [4.4, 7.8]	6.3 [4.4, 8.3]	5.6 [4.4, 7.8]	6.1 [4.2, 9.6]	5.6 [4.4, 7.8]	6.7 [4.9, 8.6]	5.6 [4.4, 7.8]	6.3 [4.6, 8.7]	5.6 [4.4, 7.8]	6.0 [4.5, 9.3]
Primary Treatment										
Radical Prostatectomy	63	51	63	51	63	38	63	51	63	48
AS/WW	6	10	6	10	6	15	6	12	6	14
RT/Brachytherapy	22	25	22	27	22	31	22	22	22	26
Hormone Therapy	5	8	5	10	5	5	5	10	5	5
Other	4	5	4	2	4	10	4	6	4	7
White race	95	92	95	92	95	90	95	89	95	88
Family History of PC	20	10	20	12	20	8	20	14	20	9

Abbreviations: ACS – American Cancer Society; AICR – American Institute for Cancer Research; AS/WW – active surveillance/watchful waiting; IQR – interquartile range; PC – prostate cancer; RT – radiation therapy; SD – standard deviation; WCRF – World Cancer Research Fund

^a The same men were missing the 2021 Score and the 2015 Score with Diet.

^b To ease visual comparisons, summaries are shown as mean (SD), median [IQR], or a percent

Table 2.9. Post-diagnostic health behavior scores and the risk of prostate cancer progression among 2,056 men with non-metastatic prostate cancer after multiple imputation to preserve observations with missingness in covariates

Continuous^a			
	HR	95% CI	p-value
2021 Score	0.78	(0.64, 0.95)	0.012
2021 Score with Diet	0.76	(0.66, 0.89)	<0.001
2015 Score	0.88	(0.78, 0.98)	0.021
ACS Score	0.88	(0.80, 0.98)	0.017
ACS Score with Alcohol	0.87	(0.80, 0.96)	0.004
WCRF/AICR Score	0.83	(0.71, 0.98)	0.025

Abbreviations: ACS – American Cancer Society; Adj – adjusted; AICR – American Institute for Cancer Research; CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor; CI – confidence interval; HR – hazard ratio; pts – points; PCSM – prostate cancer specific mortality; WCRF – World Cancer Research Fund; wk – week

^a Multiple imputation resulted in 2,056 complete records and retention of all 192 progression events.

^b Models were adjusted for clinical CaPSURE site, time between diagnosis and date of first CDL questionnaire (continuous) and age at diagnosis (continuous), clinical T stage (T1, T2, T3), Gleason score (<7, 7, >7), diagnostic PSA value (≤6, >6-10, >10-20), primary treatment (radical prostatectomy, active surveillance/watchful waiting, radiotherapy/brachytherapy, hormone therapy, other), family history of prostate cancer in brother of father (yes, no), race (white, non-white), total caloric intake (continuous), plus the following variables (if not part of the score): whole milk intake (≤4 servings/wk, >4 servings/wk), wine intake (3-14 servings/wk, <3 or >14 servings/wk), total alcohol intake (non-drinker, >0-2 serving/day, >2 servings/day), red and processed meat intake (quartiles), tomato intake (continuous), dark meat fish intake (continuous), selenium supplement use (non-user, <140ug/day, ≥140ug/day, user with unknown daily dosage), smoking (never, quit ≥10 years prior, quit <10 years prior, current).

Chapter 3: Post-Diagnostic Inflammatory, Hyperinsulinemic, and Insulin Resistant Diets and Lifestyles and the Risk of Prostate Cancer Progression and Mortality

Crystal S. Langlais, Rebecca E. Graff, Erin L. Van Blarigan, Stacey A. Kenfield, John M.

Neuhaus, Fred K. Tabung, Janet E. Cowan, Jeanette M. Broering, Peter Carroll, June M. Chan

Abstract

Background: Inflammatory and insulin pathways have been linked to prostate cancer; post-diagnostic behaviors activating these pathways may lead to poor outcomes. The empirical dietary inflammation pattern (EDIP), indices for hyperinsulinemia (EDIH) and insulin resistance (EDIR), and associated lifestyle indices (ELIH, ELIR) predict biomarkers of inflammation (EDIP: IL-6, TNFaR2, CRP) and insulin secretion (EDIH/ELIH: c-peptide; EDIR/ELIR: TAG:HDL) from whole foods and behaviors. **Methods:** Associations of these indices with time to prostate cancer progression (primary, n=2,056) and prostate cancer -specific mortality (PCSM; secondary, n=2,447) were estimated among men diagnosed with non-metastatic prostate cancer in the CaPSURE cohort diet and lifestyle sub-study. Because the true (versus clinically-documented) date of progression is unobserved, we used parametric (Weibull) survival models to accommodate interval-censoring and estimated adjusted hazard ratios (HR) and 95% confidence intervals (CI) for prostate cancer progression per 1-standard deviation increase in index. Cox proportional hazards models were used to estimate PCSM associations. **Results:** During a median (IQR) 6.4 years (IQR: 1.3, 12.7), 192 progression and 73 PCSM events were observed. Inflammatory (EDIP: HR=1.27, CI: 1.17-1.37), hyperinsulinemic (EDIH: HR=1.24, CI: 1.05-1.46. ELIH: HR=1.34, CI:1.17-1.54), and insulin resistant (EDIR: HR=1.22, CI: 1.00-1.48. ELIR: HR=1.36, CI:1.12-1.64) indices were positively associated with risk of prostate cancer progression. There was no evidence of associations between the indices and PCSM. **Conclusions:** Both inflammatory and insulinemic dietary and lifestyle patterns are associated with risk of prostate cancer progression. For men with prostate cancer, consuming dietary patterns that limit chronic systemic inflammation and insulin hypersecretion may improve survivorship, especially when coupled with active lifestyle and healthy body weight.

Introduction

Prostate cancer is the most commonly diagnosed cancer among men in the United States [97]. Over the past decade, research has identified various dietary and lifestyle factors associated with survival following prostate cancer diagnosis [102]. However, much of the evidence remains mixed, particularly regarding diet, leading to uncertainty about the role these factors play in improving outcomes following a diagnosis. Many past studies have examined single dietary factors in isolation, which does not adequately represent the combined impact of dietary intake on biological responses or the complex interactions in whole diets [104, 132]. Therefore, it is important to examine dietary patterns to try to understand diet-prostate cancer relationships.

Inflammation and insulin pathways have been linked to cancer development and progression [133], including in the setting of prostate cancer [134-140]. Post-diagnostic behaviors that over-activate these pathways may therefore lead to poorer prostate cancer outcomes. The empirically-derived inflammatory, hyperinsulinemic, and insulin resistance dietary indices – calculated from food frequency questionnaire (FFQ) data – and the associated lifestyle indices provide an opportunity to study the role of diet- and lifestyle-related inflammation- and insulin- promoting behaviors in prostate cancer outcomes [141, 142]. These novel indices have not been examined in men diagnosed with prostate cancer. Because they predict plasma concentrations of circulating markers of inflammation (interleukin-6, C-reactive protein, and tumor necrosis factor α receptor 2) [141], hyperinsulinemia (C-peptide) [142], and insulin resistance (triacylglycerol to high density lipoprotein cholesterol; TAG:HDL) [142], the indices allow for the measurement of the inflammatory and insulinemic potential of whole diets and associated lifestyles without the necessity for biomarker data.

Here, we used these indices to examine associations between the inflammatory and insulinemic potentials of dietary patterns and lifestyle habits after a prostate cancer diagnosis

and the risk of disease progression (primary outcome) and disease-specific mortality (secondary outcome) among men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) cohort. Given the role that increased adiposity may play in activating these pathways [133, 143], we also examined whether obesity modified associations with the dietary indices.

Methods

Study Sample. CaPSURE is a longitudinal observational cohort of 15,310 men with biopsy-proven prostate cancer. Participants were enrolled at 43 urology practices across the United States starting in 1999. Data were collected on diagnostic and other clinical features, treatments, and clinical follow-up. Additional details of the CaPSURE cohort have been previously reported [110]. All participants provided written informed consent, and the study was conducted in accordance with the Belmont Report and the U.S. Common Rule under local Institutional Review Board approval.

The CaPSURE Diet and Lifestyle (CDL) sub-study – consisting of a comprehensive lifestyle questionnaire and full-length food frequency questionnaire (FFQ) – was administered at three time points between 2004-2016; a total of 2,891 men participated in at least one administration. For the subset of men who participated in more than one administration (n=443), only the first administration (closest to diagnosis date) was used. Men with a last clinical follow-up (n=160) or documented progression (n=391) prior to completion of their first CDL questionnaire were excluded. Those with unknown or extreme caloric intake (<800 kcal/day or >4200 kcal/day; n=153) and/or missing ≥ 70 FFQ items (n=20) were also excluded, consistent with the recommended approach to address implausible energy intakes [113, 144, 145]. Finally, men with undocumented or unknown clinical T-stage (n=100) or T-stage >T3a (n=8) and those with death from an unknown cause (n=3) were excluded, resulting in a sample size of 2,056 men with non-metastatic disease.

Diet and Lifestyle Questionnaire. We collected data on education, family history of prostate cancer, smoking history, medical history, supplement use, and height and weight (used to calculate body mass index [BMI]) via questionnaire. Self-reported dietary intake was collected via a validated [112-114, 146] semiquantitative FFQ that asked about average consumption of approximately 140 foods/beverages over the past year. Participants reported how often over the prior year they had consumed a specified portion size of each of the items. They could choose from 9 frequency options ranging from never or less than one serving per month to six or more servings per day. Metabolic equivalent of task (MET) hours per week of physical activity were derived based on self-report of average weekly time spent doing various aerobic and resistance exercises. Participants could choose from 11 frequency options ranging from 0 minutes to 11 hours per week.

Inflammatory and Insulinemic Potential of Whole Diets. Development and validation of the empirical dietary inflammatory pattern (EDIP), empirical dietary index for hyperinsulinemia (EDIH), and empirical dietary index for insulin resistance (EDIR) have been detailed previously [141, 142]. Briefly, each index was derived from FFQs (similar to the FFQ administered in CaPSURE) based on 39 pre-defined food groups. The EDIP was created using reduced-rank regression and stepwise linear regression to identify a dietary pattern that was predictive of three plasma inflammatory markers (interleukin-6, C-reactive protein, and tumor necrosis factor α receptor 2), resulting in the inclusion of 9 pro-inflammatory (red meat, processed meat, organ meat, other fish, tomatoes, other vegetables, refined grains, low-energy beverages, and high-energy beverages) and 9 anti-inflammatory (coffee, tea, fruit juice, wine, beer, leafy green vegetables, dark yellow vegetables, snacks, and pizza) food groups.

Using a similar method, the EDIH and EDIR were created by identifying dietary patterns that were most predictive of plasma C-peptide and TAG:HDL, respectively. Although similar metrics, hyperinsulinemia is a consequence of prolonged insulin resistance [133] due to diminished cellular response to insulin, resulting in additional insulin secretion and subsequently

high levels of insulin relative to glucose. The EDIH included 13 pro-insulin secretion (red meat, processed meat, other fish, poultry, eggs, margarine, butter, cream soups, low-fat dairy, french fries, tomatoes, high-energy beverages, low-energy beverages) and 5 anti-insulin secretion (coffee, wine, high fat dairy, leafy green vegetables, whole fruit) food groups. The EDIR included 10 pro-insulin resistance (red meat, processed meat, other fish, tomatoes, cream soups, other vegetables, refined grains, margarine, fruit juice, and low-energy beverages) and 8 anti-insulin resistance (coffee, wine, liquor, beer, high fat dairy, nuts, leafy green vegetables, and dark yellow vegetables) food groups.

The resulting EDIP, EDIH, and EDIR are weighted sums of 18 index-specific food groups (some overlapping), with higher indices reflecting diets with greater inflammatory (EDIP) or insulineric (EDIH, EDIR) potential. A detailed list of the specific food items included in each food group for each of these indices can be found in **Table 3.1**. Weights are available in the original publications describing the creation of the indices [141, 142].

We also considered how two related indices – the empirical lifestyle index for hyperinsulinemia (ELIH) and the empirical lifestyle index for insulin resistance (ELIR), developed using the same methodology as the EDIH and the EDIR – related to prostate cancer outcomes. A lifestyle index for inflammation has not yet been created. Both lifestyle indices included BMI and physical activity in addition to dietary factors (**Table 3.1**). Details of their development and validation, as well as the weights needed to calculate the indices, are available in the original publication describing the creation and validation of these indices [142].

Primary Outcome. In this cohort of men with non-metastatic prostate cancer at diagnosis, the primary outcome was time to prostate cancer progression. Progression was defined as biochemical recurrence, secondary treatment, bone metastases, or death attributed to prostate cancer (prostate cancer-specific mortality; PCSM). Biochemical recurrence was defined as two consecutive prostate-specific antigen (PSA) readings ≥ 0.2 ng/mL after radical prostatectomy or two consecutive PSA levels at least 2.0 ng/mL greater than the post-radiation

nadir following radiation therapy [147]. The date of recurrence was recorded as the date of the second elevated PSA. Secondary treatment was defined as any treatment started ≥ 6 months following completion of primary treatment. Bone metastases were attributed to prostate cancer if a urologist reported prostate cancer progression to bone or advancement to TNM stage M1b, the patient had a positive bone scan, or the patient underwent radiation to treat bone metastases. Cause of death was determined by the registry data coordinating center and through confirmation by either the vital statistics official death certificate from the state in which the death occurred or by the National Center for Health Statistics National Death Index. Deaths were attributed to prostate cancer if the death certificate included ICD-9 code 185 [(metastatic) malignant neoplasm of prostate] as the primary or secondary cause of death. For men with multiple progression events, the earliest event date was recorded as the date of progression.

Time to progression was measured from the date of completion of the first questionnaire to the date of progression. However, the exact date of progression is unlikely to have occurred on the date of the clinic visit at which it was recorded. To account for this uncertainty, we used an interval rather than a precise date of progression. For men with documented biochemical recurrence, secondary treatment, or bone metastases, the censoring interval was bound by the last normal clinical visit (left limit) and the first clinic visit documenting evidence of progression (right limit). For men with only a progression event of PCSM, the left and right limit were both date of death. Men without documented progression were censored at their last date of follow-up or death (other cause); thus, the right limit was undefined (i.e., censored). Clinical follow-up was last consistently assessed across all CaPSURE sites on January 31, 2019. The 26 men who had a last known clinical follow-up date beyond this date were administratively censored on January 31, 2019.

Statistical Analysis. Pearson's r was used to report correlations between each of the 5 indices. Parametric survival models with a Weibull distribution were used to accommodate interval censoring. We fit survival models using both continuous indices [per 1-standard

deviation (SD) increase in index] and cohort-specific quintiles. All models were clustered by CaPSURE clinical site, with robust standard errors used to calculate confidence intervals (CI). Simple models were adjusted for age at diagnosis (continuous) and time between diagnosis and first questionnaire (continuous). Fully adjusted models additionally adjusted for T-stage (T1, T2, T3a), Gleason score (<7, 7, >7), and PSA (≤ 6 ng/mL, >6 to 10ng/mL, >10ng/mL) at diagnosis; primary treatment (radical prostatectomy, radiation, hormonal therapy, watchful waiting/active surveillance, other); self-reported race (white, other); total energy intake (continuous, kcal/day); smoking status (current, former, never); family history of prostate cancer in a brother or father (yes/no); total alcohol intake (continuous, servings/day); use of supplements (multivitamins, calcium, vitamin E, or selenium; yes, no); BMI (continuous; models for dietary indices only); and physical activity (continuous, MET-hours/week; models for dietary indices only). We further considered adjustment for height, household income, education, intake of fatty fish and cruciferous vegetables, walking pace, and history of diabetes or heart disease, but estimates were qualitatively unchanged, so these variables were not included in the final models. We examined the goodness of fit of survival models using plots of Cox-Snell residuals. Fully adjusted models were also run using exponential distributions, which produced Cox-Snell residual plots that demonstrated poorer fit than Weibull models; thus, Weibull models were used.

Interaction. We assessed interactions between each of the dietary indices (EDIP, EDIH, EDIR) and obesity in two ways. First, we created a cross product between each of the indices (continuous) and BMI (<30 vs ≥ 30 kg/m²). We then used likelihood ratio tests based on models with and without the interaction terms to look for statistically significant multiplicative interactions. To assess additive interaction, we used the BMI thresholds (<30 vs ≥ 30 kg/m²) and a dichotomized version of each index (above and below median) to create a 4-level variable (high index-high BMI, high index-low BMI, low index-high BMI, low index-low BMI) and added it to the fully adjusted model. Low index/low BMI was used as the referent and HR estimates were

used to calculate the relative excess risk due to interaction (RERI) [148, 149]. The delta method was used to calculate CI that indicated whether RERI results were different from zero (RERI \neq 0 is evidence of additive interaction) [150].

We evaluated PCSM as our secondary outcome given the small number of PCSM events (n=73) in this cohort of men initially diagnosed with non-metastatic disease. For these analyses, we utilized Cox proportional hazards models rather than parametric survival models because date of death was known. Men who were originally excluded due to documented progression prior to completion of the questionnaire were included in these secondary analyses (as death could not occur prior to completing the questionnaire), resulting in a sample size of 2,447 men. Proportional hazards assumptions were assessed graphically by plotting the scaled Schoenfeld residuals against follow-up time.

Additional Analyses. We were interested in understanding how deaths due to causes other than prostate cancer (i.e., competing risks) may have impacted our primary results. Methods to address competing risks in the presence of interval censoring are not readily available or accessible. Thus, we ran Cox proportional hazards analyses on our fully adjusted models of progression and compared these results to Fine-Gray analyses accounting for other deaths as a competing risk [151].

Although there was no missingness for any of the indices, missingness in covariates resulted in a loss of events in our fully adjusted models (n=17). To understand the impact of this missingness on our primary results, we performed a sensitivity analysis utilizing multiple imputation to handle missing data [127]. We performed multiple imputation via chained equations using the *chained* command in Stata to first generate 25 imputed datasets. We then fit survival models across all 25 imputed datasets and pooled the results using Rubin's Rules [128]. Our imputed model included all variables without missingness (EDIP, EDIH, ELIH, EDIR, ELIR, BMI, physical activity, CaPSURE clinical site, age at diagnosis, vital status, total energy intake, days in follow-up, race, clinical T stage, and family history of prostate cancer) and

variables with incomplete values (diagnostic PSA and Gleason score, smoking status, supplement use, total alcohol intake, and primary treatment).

All statistical analyses were performed using Stata version 17 (StataCorp, College Station, TX). A two-sided alpha level of 0.05 was used to assess statistical significance.

Results

Participant characteristics by quintile of the inflammatory and insulinemic dietary and lifestyle indices are shown in **Tables 3.2-3.3**. The participants had a mean (SD) age of 64.4 (7.9) years at diagnosis, and most (n=1,953; 95%) identified as white race. Characteristics were fairly balanced across quintiles of each index, although men consuming more inflammatory and insulinemic diets tended to have higher BMI and lower levels of physical activity. This was also true for men with more insulinemic lifestyles, with a more pronounced increase in BMI and decrease in physical activity, as expected (both are components of these indices). Correlations between the indices are shown in **Table 3.4**.

During a median follow-up of 6.4 years (IQR: 1.3, 12.7) after completion of the questionnaire, 192 progression events were documented, including 168 (88%) biochemical recurrences, 7 (4%) bone metastases, and 17 (9%) deaths related to prostate cancer as the first recorded event (a total of 73 men had documented PCSM, most with another progression event prior to PCSM). Secondary treatment did not account for any of the progression events.

Participants with higher inflammatory diet indices (EDIP) had an increased risk of prostate cancer progression ($HR_{\text{per } 1\text{-SD}} = 1.27$, 95% CI: 1.17-1.37), amounting to a 2.61-fold (95% CI: 1.75-3.90; $p_{\text{trend}} < 0.01$) higher risk in those in the highest versus the lowest quintile of EDIP (**Table 3.5**). Those with more insulinemic diets (EDIH) also had a higher risk of progression ($HR_{\text{per } 1\text{-SD}} = 1.24$, 95% CI: 1.05-1.46), amounting to a 1.63-fold (95% CI: 0.93-2.86; $p_{\text{trend}} = 0.05$) higher risk among those in the highest versus lowest quintile. The hyperinsulinemic lifestyle index (ELIH) was similarly associated with progression ($HR_{\text{per } 1\text{-SD}} = 1.34$, 95% CI: 1.17-

1.54), with a 2.81-fold (95% CI: 1.78-4.43; $p_{\text{trend}} < 0.01$) higher risk of progression among those in the highest versus lowest quintile of the index. There was suggestive evidence that the insulin resistance dietary index (EDIR) was associated with prostate cancer progression ($HR_{\text{per 1-SD}} = 1.22$, 95% CI: 1.00-1.48), though results from the models with EDIR modeled as quintiles were not statistically significant ($HR_{Q5 \text{ vs } Q1} = 1.38$, 95% CI: 0.62-3.11; $p_{\text{trend}} = 0.45$). The insulin resistance lifestyle index (ELIR) was statistically significantly associated with a higher risk of prostate cancer progression ($HR_{\text{per 1-SD}} = 1.36$, 95% CI: 1.12-1.64), reflecting a 2.43-fold (95% CI: 1.45-4.07; $p_{\text{trend}} < 0.01$) higher risk of progression for those with the highest versus lowest quintile of the index (**Table 3.5**).

There was no convincing evidence of associations with PCSM (**Table 3.5**), though power for these analyses was limited. There was also no evidence of interaction between any of the dietary indices and BMI (data not shown).

Results from the Cox proportional hazards models for progression were very similar to those from the Parametric (Weibull) survival models, and there was no evidence that competing events impacted the results (**Table 3.6**). Multiple imputation resulted in 2,053 complete cases across all covariates and retainment of all 192 events in the multivariable models (**Table 3.7**). The results were qualitatively unchanged from the primary analysis. The supplemental material also includes results from the simple (i.e., not fully adjusted) models (**Table 3.8**).

Discussion

In these analyses, we evaluated associations of three dietary (EDIP, EDIH, EDIR) and two lifestyle (ELIH, ELIR) indices – previously developed to estimate concentrations of biomarkers for the underlying inflammatory and insulin pathways – with prostate cancer progression and PCSM. Findings from this study suggest that diets with high inflammatory or insulinemic potential following a prostate cancer diagnosis are associated with a 2.61-fold and 1.63-fold higher risk of prostate cancer progression, respectively, for those in the highest versus

lowest quintiles. The evidence was weaker, but still consistent with a positive association, for diets promoting insulin resistance.

The hyperinsulinemic and insulin resistance *lifestyle* indices also demonstrated strong associations with prostate cancer progression. Individuals in the highest versus lowest quintile of the ELIH and ELIR had a 2.8-fold and 2.4-fold higher risk of progression, respectively. These results are consistent with prior work demonstrating that the correlation between the lifestyle indices and circulating biomarkers was more than twice the correlation observed with the diet-only indices [142]. These findings are also consistent with the World Cancer Research Fund/American Institute for Cancer Research report, which found adiposity to be the single most consistent factor predisposing men to higher risk of fatal prostate cancer [152]. Therefore, lifestyle changes that include more physical activity and achieving a healthy weight, in addition to low insulinemic and inflammatory diets, may lower risk of progression.

Although, to our knowledge, no study has examined these dietary and lifestyle indices in men with prostate cancer, these findings are consistent with our current understanding of the role of the inflammation and insulin pathways in promoting cancer growth and development. This report adds to our understanding of how these pathways may promote prostate cancer progression. Specifically, insulin is a potent growth factor that promotes cell metabolism and mitogenic processes, and cancer cells have been shown to have a disproportionately higher expression of insulin receptors than normal cells [153, 154]. The EDIH has also been associated with a higher risk of prostate cancer development among previously disease-free men [155, 156]. Thus, it is plausible that higher levels of circulating insulin would promote prostate cancer progression [133]. Inflammation can also act to promote insulin production [133], and has been independently linked to prostate cancer risk [157]. For example, IL-6, a prominent inflammatory biomarker, has been shown to promote proliferation of prostate cells and inhibit cell death, and may be involved in the transition to metastatic disease [135]. The EDIP has also been associated with increased risk of incident lethal prostate cancer among

men under 65 years of age [156]. Thus, it is also plausible that diets promoting inflammatory processes would promote cancer progression.

We observed a correlation between all three dietary indices, which is not surprising given the inflammatory and insulin pathways are interrelated [133, 158]. Indeed, prior research found that the EDIP was associated with biomarkers of hyperinsulinemia and that the EDIH was associated with biomarkers of inflammation [155, 159]. Similarly, although the insulin resistance and hyperinsulinemic indices were developed to predict different biomarkers [142], hyperinsulinemia is a consequence of prolonged insulin resistance [133]. Recent work found that the EDIH is predictive of both insulin secretion *and* insulin resistance [160], which may explain why the EDIR was not as strongly associated with prostate cancer progression as the EDIH in these analyses.

We did not find statistically significant evidence of associations between any of the indices and PCSM. While other mechanisms for the lack of associations cannot be ruled out, our results may reflect the relatively small number of cause-specific deaths in this cohort of men diagnosed with non-metastatic prostate cancer. Further research is needed to understand whether the relevant biological mechanisms are associated with PCSM among men with prostate cancer.

The inflammatory, hyperinsulinemic, and insulin resistance dietary indices were developed to predict inflammatory and insulinemic biomarkers associated with whole diet, and were not developed specific to any type of cancer. Recently, these indices have been associated with colorectal cancer incidence and mortality [161, 162], highlighting the role of inflammatory and insulin pathways across cancers [133]. Readers should focus on the importance of tailoring whole diets following a prostate cancer diagnosis to collectively minimize consumption of inflammatory foods and those known to over-stimulate insulin secretion, and avoid focusing on the role of any given component of these indices.

There are several limitations of our study. Measurement error is a known limitation of self-reported diet data. Men who self-select to participate in diet and lifestyle studies may also be relatively healthy compared to prostate cancer survivors who opt out. Men in our study predominately identified as white race, and 77% reported having at least some college-level education. While the generalizability of our results may thus be limited, the dietary indices have been applied in multiethnic samples and found to predict risk of developing type 2 diabetes with heightened risk among African- American and Hispanic women compared to European- American women [163]. Additionally, although multiple imputation was utilized to address missingness in covariates, these methods rely on the assumption that data are missing at random, which cannot readily be assessed.

In conclusion, in this cohort of men diagnosed with non-metastatic prostate cancer, diets with higher inflammatory and insulinemic potential were associated with higher risk of prostate cancer progression. Insulinemic lifestyle indices that included diet, physical activity, and BMI, were also associated with risk of disease progression. These findings add to the evidence that inflammation and insulin pathways influence prostate cancer progression and suggest that modifiable health habits may improve prostate cancer clinical outcomes.

Table 3.1. Items included in the calculations of each component of the dietary and lifestyle indices

Component	Items	EDIP ^a	EDIH ^a	EDIR ^a	ELIH ^a	ELIR ^a
Coffee	Regular coffee, decaf coffee	-	-	-	-	-
Red meat	Beef, pork, or lamb main or mixed dish, hamburger (regular and lean)	+	+	+	+	+
Wine	Red and white wine	-	-	-	-	-
Fruit juice	Apple juice or cider, orange juice, other fruit juice	-	-	+	+	+
High fat dairy	Whole milk, cream, sour cream, whipped cream, ice cream, cream cheese, other cheese	-	-	-	-	-
Leafy green vegetables	Raw or cooked spinach, iceberg or head lettuce, romaine or leaf lettuce	-	-	-	-	-
Low-energy beverages	Caffeinated and decaffeinated low-energy cola; other low-energy carbonated beverages	+	+	+	+	+
Margarine	Margarine		+	+	+	+
Processed meat	Processed meats, hotdogs (beef, pork, turkey, or chicken) sausage, salami, bologna, or other processed meats	+	+	+	+	+
Tomatoes	Fresh tomato, tomato juice, tomato sauce	+	+	+	+	+
Cream soups	Chowder or cream soup		+	+	+	+
Liquor	Liquor			-	+	-
Other fish	Canned tuna, shrimp, lobster, scallops, fish (other than dark-meat fish), other seafood, breaded fish	+	+	+		
Other vegetables	Celery, green/red/yellow pepper, corn, mixed vegetables, eggplant, zucchini, alfalfa sprouts	+		+		+
Refined grains	White bread; English muffin, bagel, or roll; muffin or biscuit, white rice, pasta, pancakes or waffles, tortillas	+		+		+
Beer	Regular and lite beer	-		-		
BMI	Body mass index (kg/m ²)				+	+
Butter	Butter		+		+	
Dark yellow vegetables	Raw or cooked carrots, yellow (winter) squash, and yams or sweet potatoes	-		-		
High-energy beverages	Caffeinated or decaffeinated cola with sugar; other carbonated beverages with sugar; fruit punch drinks	+	+			
Physical activity	MET-hours/week for the following activities: tennis/squash/racquetball, rowing, calisthenics, walking, jogging, running, bicycling, and swimming				-	-
Snacks	Potato or corn chips, popcorn, crackers	-			-	
Tea	Non-herbal tea	-				+
Whole Fruit	Raisin or grapes, prunes, avocados, bananas, melons/cantaloupe, watermelon, apples, pears, orange, grapefruit, strawberries, blueberries, apricots, plums			-		
Eggs	Eggs		+			

Component	Items	EDIP ^a	EDIH ^a	EDIR ^a	ELIH ^a	ELIR ^a
French fries	French fries		+			
Low-fat dairy	Skim, 1%, or 2% milk; sherbet or ice milk; yogurt		+			
Nuts	Peanuts, walnuts, other nuts			-		
Organ meat	Beef liver, calf or pork liver, chicken or turkey liver, other liver	+				
Pizza	Pizza	-				
Poultry	Chicken or turkey with or without skin		+			
Potatoes	Baked, boiled, mashed					+
Salad dressing	Oil and vinegar salad dressing					-

Abbreviations: EDIH – Empirical Dietary Index for Hyperinsulinemia; EDIP – Empirical Dietary Inflammatory Pattern; EDIR – Empirical Dietary Index for Insulin Resistance; ELIH – Empirical Lifestyle Index for Hyperinsulinemia; ELIR – Empirical Lifestyle Index for Insulin Resistance; MET – metabolic equivalent of task

^a “+” indicates components positively associated with score; “-” indicates components inversely associated with score

Table 3.2. Participant and clinical characteristics of men diagnosed with non-metastatic prostate cancer by quintile of inflammatory, hyperinsulinemia, and insulin resistance dietary indices

N	Empirical Dietary Inflammatory Pattern (EDIP)					Empirical Dietary Index for Hyperinsulinemia (EDIH)					Empirical Dietary Index for Insulin Resistance (EDIR)				
	1 st Point Range: -2.6 to -0.3 412	2 nd >-0.3 to -0.1 411	3 rd >-0.1 to 0.0 411	4 th >0.0 to 0.2 411	5 th >0.2 to 2.3 411	1 st >0.3 to 0.4 411	2 nd >0.1 to 0.3 411	3 rd >0.3 to 0.4 411	4 th >0.4 to 0.6 411	5 th >0.6 to 2.2 411	1 st >0.1 to 0.3 412	2 nd >0.2 to 0.1 411	3 rd >0.1 to 0.3 411	4 th >0.3 to 0.5 411	5 th >0.5 to 2.6 411
Age (years), mean (SD)	63.5 (7.9)	64.5 (8.0)	64.7 (8.0)	64.8 (8.0)	64.7 (7.9)	64.5 (7.7)	64.9 (7.8)	64.7 (8.2)	64.1 (7.8)	64.0 (8.3)	63.6 (7.6)	64.5 (7.5)	64.8 (8.4)	64.6 (7.8)	64.6 (8.4)
White, n (%)	394 (96)	390 (95)	396 (96)	396 (96)	377 (92)	392 (95)	389 (95)	392 (95)	394 (96)	386 (94)	398 (97)	394 (96)	385 (94)	396 (96)	380 (92)
BMI (kg/m²), mean (SD)	27.1 (3.7)	27.3 (4.0)	27.3 (4.1)	27.6 (4.5)	28.3 (4.9)	26.3 (3.4)	27.2 (4.2)	27.4 (4.0)	28.3 (4.4)	28.5 (4.9)	26.9 (3.5)	27.3 (4.3)	27.2 (4.1)	27.7 (4.3)	28.5 (4.9)
<18.5, n (%)	0 (0)	1 (<1)	2 (<1)	4 (1)	3 (1)	1 (<1)	3 (1)	1 (<1)	2 (<1)	3 (1)	1 (<1)	0 (0)	4 (1)	2 (<1)	3 (1)
18.5 to <25, n (%)	121 (29)	113 (27)	123 (30)	104 (25)	93 (23)	141 (34)	131 (32)	114 (28)	82 (20)	86 (21)	126 (31)	127 (31)	112 (27)	107 (26)	82 (20)
25 to <30, n (%)	225 (55)	220 (54)	203 (49)	205 (50)	186 (45)	222 (54)	200 (49)	207 (52)	213 (52)	197 (48)	220 (53)	205 (50)	212 (52)	201 (49)	201 (49)
≥30, n (%)	66 (16)	77 (19)	83 (20)	98 (24)	129 (31)	48 (12)	77 (19)	89 (22)	114 (28)	125 (30)	65 (16)	79 (19)	83 (20)	101 (25)	125 (30)
Physical Activity (MET-hours/week), mean (SD)	24.3 (26.2)	23.0 (31.5)	21.3 (29.5)	17.9 (23.8)	18.8 (25.3)	26.2 (33.8)	21.4 (26.5)	19.4 (22.2)	18.4 (25.6)	19.9 (27.4)	22.9 (28.4)	24.3 (31.0)	21.0 (27.9)	18.6 (23.2)	18.6 (26.1)
Smoking Status, n (%)	158 (39)	182 (45)	191 (47)	196 (48)	187 (47)	186 (45)	174 (43)	197 (48)	184 (45)	173 (43)	142 (35)	195 (48)	195 (48)	190 (47)	192 (48)
Never	232 (57)	205 (50)	188 (46)	196 (48)	189 (47)	206 (50)	212 (53)	196 (48)	200 (49)	196 (49)	250 (61)	188 (46)	192 (48)	193 (47)	187 (46)
Current	17 (4)	19 (5)	26 (6)	18 (4)	25 (6)	17 (4)	17 (4)	16 (4)	22 (5)	33 (8)	17 (4)	22 (5)	17 (4)	25 (6)	24 (6)
Family History of PC, n (%)	81 (20)	77 (19)	94 (23)	87 (21)	73 (18)	85 (21)	77 (19)	85 (21)	77 (19)	88 (21)	75 (18)	78 (19)	89 (22)	80 (19)	90 (22)
Clinical T-Stage, n (%)	235 (57)	237 (58)	232 (56)	236 (57)	242 (59)	247 (60)	239 (58)	227 (55)	239 (58)	230 (56)	247 (60)	232 (56)	242 (59)	225 (55)	236 (57)
T1	175 (42)	169 (41)	174 (42)	173 (42)	164 (40)	164 (40)	170 (41)	177 (43)	169 (41)	175 (43)	162 (39)	173 (42)	168 (41)	163 (45)	169 (41)
T2	2 (<1)	5 (1)	5 (1)	2 (<1)	5 (1)	1 (<1)	2 (<1)	7 (2)	3 (1)	6 (1)	3 (1)	6 (1)	1 (<1)	3 (1)	6 (1)
T3a															
Diagnostic Gleason, n (%)	276 (68)	291 (71)	271 (67)	274 (67)	260 (64)	275 (67)	298 (74)	264 (65)	283 (69)	252 (62)	281 (69)	274 (67)	279 (69)	272 (67)	266 (65)
<7	106 (26)	98 (24)	106 (26)	106 (26)	122 (30)	117 (29)	84 (21)	115 (28)	101 (25)	121 (30)	110 (27)	115 (28)	97 (24)	108 (26)	108 (26)
7	25 (6)	18 (4)	30 (7)	29 (7)	27 (7)	18 (4)	23 (6)	29 (7)	25 (6)	34 (8)	18 (4)	18 (4)	30 (7)	29 (7)	34 (8)
>7															
Diagnostic PSA (ng/mL), median (IQR)	5.3 (4.3, 7.0)	5.4 (4.3, 8.1)	5.5 (4.4, 7.7)	5.7 (4.4, 8.2)	5.8 (4.5, 7.9)	5.4 (4.3, 7.3)	5.5 (4.4, 7.7)	5.6 (4.3, 7.7)	5.5 (4.2, 7.6)	5.8 (4.5, 8.7)	5.3 (4.3, 7.0)	5.5 (4.3, 8.2)	5.7 (4.5, 7.9)	5.7 (4.3, 8.4)	5.6 (4.4, 7.9)
Primary Treatment, n (%)	272 (67)	254 (63)	248 (62)	237 (59)	235 (59)	262 (65)	247 (62)	246 (62)	255 (63)	236 (59)	289 (66)	255 (64)	226 (58)	256 (64)	240 (60)
Radical Prostatectomy	23 (6)	27 (7)	29 (7)	29 (7)	16 (4)	27 (7)	33 (8)	25 (6)	20 (5)	19 (5)	26 (6)	22 (5)	39 (10)	15 (4)	22 (6)
AS/WW	83 (21)	83 (21)	88 (22)	89 (22)	104 (26)	84 (21)	91 (23)	83 (21)	95 (24)	94 (23)	91 (22)	85 (21)	90 (23)	98 (24)	83 (21)
RT/Brachytherapy	19 (5)	16 (4)	21 (5)	23 (6)	24 (6)	14 (3)	17 (4)	27 (7)	21 (5)	24 (6)	13 (3)	16 (4)	23 (6)	33 (8)	33 (8)
Hormone Therapy	6 (1)	21 (5)	12 (3)	23 (6)	20 (5)	15 (4)	12 (3)	16 (4)	11 (3)	28 (7)	7 (2)	23 (6)	15 (4)	15 (4)	22 (6)
Other															

Abbreviations: AS/WW – Active Surveillance/Watchful Waiting; BMI – body mass index; IQR – interquartile range; MET – metabolic equivalent of task; PC – prostate cancer; PSA – prostate-specific antigen (ng/mL); RT – radiotherapy; SD – standard deviation

Table 3.3. Participant and clinical characteristics of men diagnosed with non-metastatic prostate cancer by quintile of hyperinsulinemia and insulin resistance lifestyle indices

	Empirical Lifestyle Index for Hyperinsulinemia (ELIH)					Empirical Lifestyle Index for Insulin Resistance (ELIR)				
	1 st	2 nd	3 rd	4 th	5 th	1 st	2 nd	3 rd	4 th	5 th
	0.2 to 1.1	>1.1 to 1.2	>1.2 to 1.4	>1.4 to 1.5	>1.5 to 2.7	0.2 to 1.2	>1.2 to 1.4	>1.4 to 1.5	>1.5 to 1.7	>1.7 to 3.4
N	412	411	411	411	411	412	411	411	411	411
Age (years), mean (SD)	65.3 (8.4)	65.3 (8.1)	63.9 (7.9)	64.1 (7.9)	63.6 (7.4)	64.7 (7.9)	64.2 (8.3)	65.1 (7.6)	64.5 (8.1)	63.7 (7.7)
White, n (%)	389 (94)	395 (96)	387 (94)	389 (95)	393 (96)	396 (96)	390 (95)	393 (96)	391 (95)	383 (93)
BMI (kg/m²), mean (SD)	23.6 (2.3)	25.3 (2.0)	27.0 (2.1)	28.6 (2.3)	33.1 (4.4)	24.6 (2.8)	25.8 (2.7)	27.1 (3.0)	28.2 (3.1)	31.9 (5.1)
<18.5, n (%)	10 (2)	0 (0)	0 (0)	0 (0)	0 (0)	7 (2)	1 (<1)	2 (<1)	0 (0)	0 (0)
18.5 to <25, n (%)	285 (69)	180 (44)	62 (15)	21 (5)	6 (1)	224 (54)	157 (38)	92 (22)	57 (14)	24 (6)
25 to <30, n (%)	117 (28)	225 (55)	316 (77)	287 (70)	94 (23)	170 (41)	228 (55)	254 (62)	248 (60)	139 (34)
≥30, n (%)	0 (0)	6 (1)	33 (8)	103 (25)	311 (76)	11 (3)	25 (6)	63 (15)	106 (26)	248 (60)
Physical Activity (MET-hours/week), mean (SD)	33.1 (40.4)	20.9 (22.2)	20.8 (26.0)	16.1 (19.5)	14.4 (19.6)	30.8 (37.5)	22.0 (26.1)	19.3 (23.1)	17.3 (24.3)	15.9 (20.7)
Smoking Status, n (%)										
Never	192 (47)	180 (44)	192 (48)	163 (40)	187 (46)	171 (42)	192 (47)	180 (44)	183 (46)	188 (46)
Former	192 (47)	197 (49)	194 (49)	223 (54)	204 (50)	215 (53)	190 (47)	216 (53)	190 (47)	199 (49)
Current	24 (6)	29 (7)	13 (3)	24 (6)	15 (4)	21 (5)	24 (6)	13 (3)	28 (7)	19 (5)
Family History of PC, n (%)	89 (22)	73 (18)	81 (20)	80 (19)	89 (22)	75 (18)	89 (22)	74 (18)	80 (19)	94 (23)
Clinical T-Stage, n (%)										
≤T1	248 (60)	227 (55)	246 (60)	238 (58)	223 (54)	246 (60)	224 (55)	240 (58)	231 (56)	241 (59)
T2	158 (38)	180 (44)	163 (40)	170 (41)	184 (45)	161 (39)	185 (45)	166 (40)	178 (43)	165 (40)
T3a	6 (1)	4 (1)	2 (<1)	3 (1)	4 (1)	5 (1)	2 (<1)	5 (1)	2 (<1)	5 (1)
Diagnostic Gleason, n (%)										
<7	296 (73)	267 (65)	287 (70)	271 (66)	251 (62)	283 (69)	283 (70)	281 (68)	267 (65)	258 (64)
7	93 (23)	116 (28)	93 (23)	114 (28)	122 (30)	109 (27)	101 (25)	103 (25)	118 (29)	107 (26)
>7	18 (4)	25 (6)	28 (7)	23 (6)	35 (9)	16 (4)	21 (5)	27 (7)	24 (6)	41 (10)
Diagnostic PSA (ng/mL), median (IQR)	5.5 (4.3, 7.4)	5.8 (4.5, 7.7)	5.4 (4.3, 7.6)	5.5 (4.2, 7.9)	5.7 (4.4, 8.2)	5.6 (4.4, 7.4)	5.4 (4.2, 7.7)	5.6 (4.5, 7.8)	5.7 (4.3, 8.1)	5.6 (4.4, 8.1)
Primary Treatment, n (%)										
Radical Prostatectomy	251 (63)	247 (62)	258 (64)	252 (62)	238 (60)	270 (67)	245 (62)	239 (60)	253 (63)	239 (60)
AS/WW	26 (7)	23 (6)	24 (6)	24 (6)	27 (7)	25 (6)	26 (7)	30 (8)	24 (6)	19 (5)
RT/Brachytherapy	87 (22)	94 (23)	88 (22)	90 (22)	88 (22)	83 (20)	89 (22)	98 (24)	83 (21)	94 (24)
Hormone Therapy	20 (5)	20 (5)	16 (4)	22 (5)	25 (6)	13 (3)	20 (5)	19 (5)	22 (6)	29 (7)
Other	14 (4)	17 (4)	15 (4)	16 (4)	20 (5)	14 (3)	17 (4)	14 (4)	18 (4)	19 (5)

Abbreviations: AS/WW – Active Surveillance/Watchful Waiting; BMI – body mass index (kg/m²); IQR – interquartile range; MET – metabolic equivalent of task; PC – prostate cancer; PSA – prostate-specific antigen (ng/mL); RT – radiotherapy, SD – standard deviation

Table 3.4. Correlations between post-diagnostic inflammatory, hyperinsulinemia, and insulin resistance diet and lifestyle indices

	Correlations ^a				
	EDIP	EDIH	EDIR	ELIH	ELIR
EDIP	1.000				
EDIH	0.628	1.000			
EDIR	0.736	0.738	1.000		
ELIH	0.250	0.470	0.326	1.000	
ELIR	0.513	0.660	0.769	0.736	1.000

Abbreviations: EDIH – empirical dietary index for hyperinsulinemia; EDIP – empirical dietary inflammatory pattern; EDIR – empirical dietary index for insulin resistance; ELIH – empirical lifestyle index for hyperinsulinemia; ELIR – empirical lifestyle index for insulin resistance

^aPearson's correlation coefficients

Table 3.5. Multivariable models estimating associations of post-diagnostic inflammatory, hyperinsulinemia, and insulin resistance diets and lifestyles with the risk of prostate cancer progression and prostate cancer-specific mortality among men diagnosed with non-metastatic prostate cancer

Prostate Cancer Progression ^{a,b}						
	EDIP	EDIH	EDIR	ELIH	ELIR	
Events	175	175	175	175	175	
N	1,875	1,875	1,875	1,875	1,875	
Continuous						
Per 1-SD unit	1.27 (1.17, 1.37)	1.24 (1.05, 1.46)	1.22 (1.00, 1.48)	1.34 (1.17, 1.54)	1.36 (1.12, 1.64)	
Quintile						
1 st	Ref	Ref	Ref	Ref	Ref	
2 nd	2.21 (1.25, 3.89)	1.27 (0.83, 1.95)	1.28 (0.63, 2.60)	1.66 (1.08, 2.54)	1.62 (1.03, 2.56)	
3 rd	2.60 (1.54, 4.39)	1.29 (0.79, 2.12)	1.51 (0.74, 3.10)	1.69 (0.86, 3.35)	1.27 (0.74, 2.19)	
4 th	1.91 (1.14, 3.20)	1.61 (1.03, 2.51)	1.32 (0.61, 2.85)	2.82 (1.93, 4.11)	1.95 (1.12, 3.37)	
5 th	2.61 (1.75, 3.90)	1.63 (0.93, 2.86)	1.38 (0.62, 3.11)	2.81 (1.78, 4.43)	2.43 (1.45, 4.07)	
p-trend	<0.01	0.05	0.45	<0.01	<0.01	
Prostate Cancer-Specific Mortality ^{a,c}						
	EDIP	EDIH	EDIR	ELIH	ELIR	
Events	60	60	60	60	60	
N	2,198	2,198	2,198	2,198	2,198	
Continuous						
Per 1-SD unit	1.15 (0.92, 1.44)	1.22 (0.97, 1.55)	1.14 (0.84, 1.55)	1.22 (0.90, 1.66)	1.16 (0.83, 1.62)	
Quintile						
1 st	Ref	Ref	Ref	Ref	Ref	
2 nd	1.00 (0.34, 2.91)	1.66 (0.76, 3.62)	2.28 (0.76, 6.87)	1.85 (0.78, 4.43)	1.04 (0.43, 2.47)	
3 rd	1.03 (0.39, 2.74)	1.09 (0.35, 3.40)	1.92 (0.55, 6.71)	0.87 (0.29, 2.54)	0.75 (0.25, 2.23)	
4 th	1.77 (0.68, 4.58)	1.69 (0.65, 4.42)	2.02 (0.58, 7.06)	1.95 (0.82, 4.63)	0.74 (0.24, 2.26)	
5 th	1.31 (0.47, 3.67)	1.58 (0.65, 3.86)	2.50 (0.83, 7.53)	2.20 (0.76, 6.34)	1.37 (0.44, 4.29)	
p-trend	0.30	0.39	0.24	0.17	0.83	

Abbreviations: BMI – body mass index; CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor; EDIH – empirical dietary index for hyperinsulinemia; EDIP – empirical dietary inflammatory pattern; EDIR – empirical dietary index for insulin resistance; ELIH – empirical lifestyle index for hyperinsulinemia; ELIR – empirical lifestyle index for insulin resistance; MET – metabolic equivalent of task; PCSM – prostate cancer specific mortality; PSA – prostate specific antigen; SD – standard deviation
^a Models were adjusted for age at diagnosis (continuous), time between diagnosis and questionnaire completion date (continuous), and CaPSURE clinical site, race (white, other), T stage at diagnosis (≤T1, T2, T3a), Gleason at diagnosis (<7, 7, >7), PSA at diagnosis (≤6, >6 to 10, >10), primary treatment (radical prostatectomy, radiation, hormonal therapy, watchful waiting/active surveillance, other), family history of prostate cancer in either or father (yes/no), BMI (continuous), physical activity (total MET-hours/week; continuous), smoking (never, former, current), alcohol (continuous), supplement use (yes/no), and total energy intake
^b Estimated via parametric (Weibull) survival models to account for interval censoring. A total of 2,056 met inclusion for progression analyses.
^c Estimated via Cox proportional hazards models. A total of 2,447 men met inclusion for PCSM analyses, as men who were excluded from progression analysis due to having a documented progression event prior to questionnaire were included in this analysis.

Table 3.6. Associations of inflammatory and insulinemia diets and lifestyles with the risk of prostate cancer progression among men with non-metastatic prostate cancer, estimated via Cox proportional hazards and Fine-Gray models to assess competing risks

	Empirical Dietary Inflammatory Pattern ^a (EDIP)		Empirical Dietary Index for Hyperinsulinemia ^a (EDIH)		Empirical Dietary Index for Insulin Resistance ^a (EDIR)		Empirical Lifestyle Index for Hyperinsulinemia ^b (ELIH)		Empirical Lifestyle Index for Insulin Resistance ^b (ELIR)	
	175	1,875	175	1,875	175	1,875	175	1,875	175	1,875
Events	175	1,875	175	1,875	175	1,875	175	1,875	175	1,875
N	1,875	175	1,875	175	1,875	175	1,875	1,875	1,875	175
	Cox Proportional Hazard									
Continuous^c	1.26	(1.16, 1.36)	1.23	(1.04, 1.44)	1.21	(1.00, 1.46)	1.35	(1.17, 1.55)	1.35	(1.12, 1.63)
Quintile										
1 st	Ref		Ref		Ref		Ref		Ref	
2 nd	2.20	(1.25, 3.86)	1.28	(0.83, 1.96)	1.27	(0.63, 2.57)	1.66	(1.08, 2.55)	1.58	(1.00, 2.49)
3 rd	2.53	(1.50, 4.27)	1.29	(0.78, 2.13)	1.50	(0.74, 3.03)	1.69	(0.85, 3.34)	1.24	(0.72, 2.14)
4 th	1.86	(1.12, 3.09)	1.58	(1.01, 2.46)	1.30	(0.61, 2.78)	2.77	(1.90, 4.04)	1.90	(1.10, 3.27)
5 th	2.55	(1.71, 3.80)	1.61	(0.92, 2.82)	1.36	(0.61, 3.01)	2.81	(1.78, 4.44)	2.37	(1.42, 3.95)
p-trend		<0.01		0.06		0.47		<0.01		<0.01
	Fine-Gray									
Continuous^c	1.27	(1.18, 1.37)	1.23	(1.04, 1.45)	1.21	(1.00, 1.47)	1.31	(1.15, 1.51)	1.32	(1.09, 1.60)
Quintile										
1 st	Ref		Ref		Ref		Ref		Ref	
2 nd	2.11	(1.20, 3.69)	1.29	(0.85, 1.96)	1.29	(0.64, 2.61)	1.68	(1.10, 2.56)	1.58	(0.99, 2.52)
3 rd	2.58	(1.53, 4.33)	1.31	(0.80, 2.15)	1.51	(0.76, 3.02)	1.73	(0.87, 3.43)	1.24	(0.72, 2.12)
4 th	1.87	(1.13, 3.07)	1.58	(1.02, 2.43)	1.32	(0.61, 2.83)	2.83	(1.96, 4.07)	1.89	(1.11, 3.23)
5 th	2.59	(1.74, 3.85)	1.60	(0.91, 2.83)	1.34	(0.61, 2.97)	2.73	(1.73, 4.29)	2.30	(1.38, 3.81)
p-trend		<0.01		0.06		0.48		<0.01		<0.01

Abbreviations: BMI – body mass index; CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor; MET – metabolic equivalent of task; PSA – prostate specific antigen

^a Models were adjusted for time between diagnosis and questionnaire completion date (continuous), age at diagnosis (continuous), CaPSURE clinical site, race (white, other), T stage at diagnosis (≤T1, T2, T3a), Gleason at diagnosis (≤7, 7, >7), PSA at diagnosis (≤6, >6 to 10, >10), family history of prostate cancer in either or father (yes/no), BMI (continuous), physical activity (total MET-hours/week; continuous), smoking (never, former, current), alcohol (continuous), supplement use (yes/no), and total energy intake

^b Models were adjusted for all covariates included in the models for dietary indices, except BMI and physical activity

^c Per 1-standard deviation unit increase

Table 3.7. Associations of inflammatory and insulinemia diets and lifestyles with the risk of prostate cancer progression among men with non-metastatic prostate cancer, estimated via parametric (Weibull) survival models after multiple imputation to preserve observations with missingness in covariates

	Empirical Dietary Inflammatory Pattern ^b (EDIP)	Empirical Dietary Index for Hyperinsulinemia ^b (EDIH)	Empirical Dietary Index for Insulin Resistance ^b (EDIR)	Empirical Lifestyle Hyperinsulinemia ^c (ELIH)	Empirical Lifestyle Index for Insulin Resistance ^c (ELIR)
Events	192	192	192	192	192
N^a	2,053	2,053	2,053	2,053	2,053
Continuous^d	1.26 (1.16, 1.38)	1.19 (1.02, 1.39)	1.22 (1.01, 1.47)	1.33 (1.16, 1.53)	1.36 (1.13, 1.62)
Quintile					
1 st	Ref	Ref	Ref	Ref	Ref
2 nd	2.13 (1.25, 3.60)	1.18 (0.78, 1.78)	1.25 (0.66, 2.37)	1.54 (1.06, 2.25)	1.50 (0.95, 2.38)
3 rd	2.45 (1.44, 4.18)	1.12 (0.66, 1.89)	1.39 (0.76, 2.54)	1.72 (0.94, 3.13)	1.27 (0.74, 2.18)
4 th	1.97 (1.19, 3.28)	1.51 (0.97, 2.35)	1.23 (0.64, 2.36)	2.86 (2.00, 4.09)	1.89 (1.15, 3.10)
5 th	2.52 (1.72, 3.68)	1.41 (0.85, 2.34)	1.41 (0.71, 2.78)	2.74 (1.74, 4.30)	2.40 (1.44, 4.02)

Abbreviations: BMI – body mass index; CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor; MET – metabolic equivalent of task; PSA – prostate specific antigen

^a Multiple imputation resulted 2,053 complete records across all covariates

^b Models were adjusted for time between diagnosis and questionnaire completion date (continuous), age at diagnosis (continuous), CaPSURE clinical site, race (white, other), T stage at diagnosis (<T1, T2, T3a), Gleason at diagnosis (<7, 7, >7), PSA at diagnosis (<6, >6 to <10, >10), family history of prostate cancer in brother or father (yes/no), BMI (continuous), physical activity (total MET-hours/week; continuous), smoking (never, former, current), alcohol (continuous), supplemental use (yes/no), and total energy intake

^c Models were adjusted for all covariates included in the models for dietary indices, except BMI and physical activity

^d Per 1-standard deviation unit increase

Table 3.8. Minimally-adjusted models estimating the associations between post-diagnostic inflammatory, hyperinsulinemia, and insulin resistance diets and lifestyles with the risk of prostate cancer progression and prostate cancer-specific mortality among men diagnosed with non-metastatic prostate cancer

		Prostate Cancer Progression ^{a,b}				
		EDIP	EDIH	EDIR	ELIH	ELIR
Events		192	192	192	192	192
N		2,056	2,056	2,056	2,056	2,056
Continuous						
Per 1-SD unit	1.17 (1.05, 1.31)	1.22 (1.08, 1.39)	1.10 (0.93, 1.30)	1.39 (1.20, 1.61)	1.27 (1.07, 1.51)	
Quintile						
1 st	Ref	Ref	Ref	Ref	Ref	
2 nd	1.53 (0.92, 2.55)	1.24 (0.82, 1.87)	1.11 (0.60, 2.05)	1.64 (1.10, 2.43)	1.45 (0.96, 2.19)	
3 rd	1.91 (1.16, 3.14)	1.22 (0.78, 1.92)	1.14 (0.73, 1.76)	1.68 (0.88, 3.22)	1.14 (0.74, 1.74)	
4 th	1.45 (1.02, 2.07)	1.57 (1.06, 2.34)	1.01 (0.56, 1.84)	2.84 (1.95, 4.15)	1.63 (1.00, 2.65)	
5 th	1.76 (1.08, 2.87)	1.65 (1.05, 2.60)	1.25 (0.70, 2.24)	3.04 (1.92, 4.82)	2.06 (1.29, 3.31)	
p-trend	0.02	0.01	0.58	<0.01	0.01	
		Prostate Cancer-Specific Mortality ^{a,c}				
		EDIP	EDIH	EDIR	ELIH	ELIR
Events		73	73	73	73	73
N		2,447	2,447	2,447	2,447	2,447
Continuous						
Per 1-SD unit	1.14 (0.88, 1.49)	1.17 (0.97, 1.40)	0.97 (0.77, 1.24)	1.25 (0.94, 1.67)	1.04 (0.79, 1.37)	
Quintile						
1 st	Ref	Ref	Ref	Ref	Ref	
2 nd	0.84 (0.32, 2.20)	1.31 (0.65, 2.61)	1.21 (0.63, 2.33)	1.81 (0.91, 3.57)	1.15 (0.64, 2.04)	
3 rd	1.13 (0.54, 2.33)	1.10 (0.47, 2.57)	0.93 (0.39, 2.20)	1.15 (0.48, 2.76)	0.66 (0.27, 1.57)	
4 th	1.54 (0.71, 3.31)	1.81 (0.78, 4.20)	0.85 (0.40, 1.80)	2.27 (0.99, 5.19)	0.81 (0.38, 1.76)	
5 th	1.39 (0.52, 3.74)	1.26 (0.61, 2.63)	1.12 (0.54, 2.33)	2.51 (0.94, 6.69)	1.33 (0.60, 2.97)	
p-trend	0.22	0.40	0.89	0.07	0.82	

Abbreviations: BMI – body mass index; CaPSURE – Cancer of the Prostate Strategic Urologic Research Endeavor; EDIH – empirical dietary index for hyperinsulinemia; EDIP – empirical dietary inflammatory pattern; EDIR – empirical dietary index for insulin resistance; ELIH – empirical lifestyle index for hyperinsulinemia; ELIR – empirical lifestyle index for insulin resistance.

^a Models were adjusted for age at diagnosis (continuous), time between diagnosis and questionnaire completion date (continuous), and CaPSURE clinical site.

^b Estimated via parametric (Weibull) survival models to account for interval censoring. A total of 192 progression events occurred among the 2,056 men included in progression analyses.

^c Estimated via Cox proportional hazards models. A total of 73 PCSM events occurred among 2,447 men included in PCSM analyses. The overall sample size was larger for PCSM analyses as men who were excluded from progression analysis due to having a documented progression event prior to questionnaire were included.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi: 10.3322/caac.21492.
2. • Zuniga KB, Chan JM, Ryan CJ, Kenfield SA. Diet and lifestyle considerations for patients with prostate cancer. *Urol Oncol*. 2020;38(3):105-17. doi: 10.1016/j.urolonc.2019.06.018. This is a recent review of randomized controlled trials to provide recommendations on diet and lifestyle considerations for patients diagnosed with prostate cancer.
3. Wilson KM, Mucci LA, Drake BF, Preston MA, Stampfer MJ, Giovannucci E, et al. Meat, Fish, Poultry, and Egg Intake at Diagnosis and Risk of Prostate Cancer Progression. *Cancer Prev Res (Phila)*. 2016;9(12):933-41. doi: 10.1158/1940-6207.CAPR-16-0070.
4. Richman EL, Stampfer MJ, Paciorek A, Broering JM, Carroll PR, Chan JM. Intakes of meat, fish, poultry, and eggs and risk of prostate cancer progression. *Am J Clin Nutr*. 2010;91(3):712-21. doi: 10.3945/ajcn.2009.28474.
5. Chan JM, Holick CN, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, et al. Diet after diagnosis and the risk of prostate cancer progression, recurrence, and death (United States). *Cancer Causes Control*. 2006;17(2):199-208. doi: 10.1007/s10552-005-0413-4.
6. Yang M, Kenfield SA, Van Blarigan EL, Batista JL, Sesso HD, Ma J, et al. Dietary patterns after prostate cancer diagnosis in relation to disease-specific and total mortality. *Cancer Prev Res (Phila)*. 2015;8(6):545-51. doi: 10.1158/1940-6207.CAPR-14-0442.
7. Wang Y, Jacobs EJ, Shah RA, Stevens VL, Gansler T, McCullough ML. Red and Processed Meat, Poultry, Fish, and Egg Intakes and Cause-Specific and All-Cause Mortality among Men with Nonmetastatic Prostate Cancer in a U.S. Cohort. *Cancer Epidemiol Biomarkers Prev*. 2020;29(5):1029-38. doi: 10.1158/1055-9965.EPI-19-1426.

8. Richman EL, Kenfield SA, Stampfer MJ, Giovannucci EL, Chan JM. Egg, red meat, and poultry intake and risk of lethal prostate cancer in the prostate-specific antigen-era: incidence and survival. *Cancer Prev Res (Phila)*. 2011;4(12):2110-21. doi: 10.1158/1940-6207.Capr-11-0354.
9. American Heart Association. The American Heart Association Diet and Lifestyle Recommendations. American Heart Association.: <https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/aha-diet-and-lifestyle-recommendations> (2020). Accessed September 1, 2020.
10. American Diabetes Association. What Can I Eat? American Diabetes Association.: <https://www.diabetes.org/blog/what-can-i-eat> (2019). Accessed September 1, 2020.
11. Tat D, Kenfield SA, Cowan JE, Broering JM, Carroll PR, Van Blarigan EL, et al. Milk and other dairy foods in relation to prostate cancer recurrence: Data from the cancer of the prostate strategic urologic research endeavor (CaPSURE). *Prostate*. 2018;78(1):32-9. doi: 10.1002/pros.23441.
12. Pettersson A, Kasperzyk JL, Kenfield SA, Richman EL, Chan JM, Willett WC, et al. Milk and dairy consumption among men with prostate cancer and risk of metastases and prostate cancer death. *Cancer Epidemiol Biomarkers Prev*. 2012;21(3):428-36. doi: 10.1158/1055-9965.EPI-11-1004.
13. Downer MK, Batista JL, Mucci LA, Stampfer MJ, Epstein MM, Hakansson N, et al. Dairy intake in relation to prostate cancer survival. *Int J Cancer*. 2017;140(9):2060-9. doi: 10.1002/ijc.30642.
14. Strom SS, Yamamura Y, Forman MR, Pettaway CA, Barrera SL, DiGiovanni J. Saturated fat intake predicts biochemical failure after prostatectomy. *Int J Cancer*. 2008;122(11):2581-5. doi: 10.1002/ijc.23414.

15. Epstein MM, Kasperzyk JL, Mucci LA, Giovannucci E, Price A, Wolk A, et al. Dietary fatty acid intake and prostate cancer survival in Orebro County, Sweden. *Am J Epidemiol*. 2012;176(3):240-52. doi: 10.1093/aje/kwr520.
16. Meyer F, Bairati I, Shadmani R, Fradet Y, Moore L. Dietary fat and prostate cancer survival. *Cancer Causes Control*. 1999;10(4):245-51. doi: 10.1023/a:1008913307947.
17. Van Blarigan EL, Kenfield SA, Yang M, Sesso HD, Ma J, Stampfer MJ, et al. Fat intake after prostate cancer diagnosis and mortality in the Physicians' Health Study. *Cancer Causes Control*. 2015;26(8):1117-26. doi: 10.1007/s10552-015-0606-4.
18. Richman EL, Kenfield SA, Chavarro JE, Stampfer MJ, Giovannucci EL, Willett WC, et al. Fat intake after diagnosis and risk of lethal prostate cancer and all-cause mortality. *JAMA Intern Med*. 2013;173(14):1318-26. doi: 10.1001/jamainternmed.2013.6536.
19. Richman EL, Carroll PR, Chan JM. Vegetable and fruit intake after diagnosis and risk of prostate cancer progression. *Int J Cancer*. 2012;131(1):201-10. doi: 10.1002/ijc.26348.
20. Parsons JK, Zahrieh D, Mohler JL, Paskett E, Hansel DE, Kibel AS, et al. Effect of a Behavioral Intervention to Increase Vegetable Consumption on Cancer Progression Among Men With Early-Stage Prostate Cancer: The MEAL Randomized Clinical Trial. *JAMA*. 2020;323(2):140-8. doi: 10.1001/jama.2019.20207.
21. Farris MS, Courneya KS, Kopciuk KA, McGregor SE, Friedenreich CM. Post-diagnosis alcohol intake and prostate cancer survival: A population-based cohort study. *Int J Cancer*. 2018;143(2):253-62. doi: 10.1002/ijc.31307.
22. Downer MK, Kenfield SA, Stampfer MJ, Wilson KM, Dickerman BA, Giovannucci EL, et al. Alcohol Intake and Risk of Lethal Prostate Cancer in the Health Professionals Follow-Up Study. *J Clin Oncol*. 2019;37(17):1499-511. doi: 10.1200/JCO.18.02462.
23. National Institute on Alcohol Abuse and Alcoholism. Alcohol's Effects on the Body. <https://www.niaaa.nih.gov/alcohols-effects-health/alcohols-effects-body> Accessed Aug 2020.

24. AICR: Cancer Prevention Recommendations. <https://www.aicr.org/reduce-your-cancer-risk/recommendations-for-cancer-prevention/> (2019). Accessed Oct 2019.
25. • World Cancer Research Fund. Cancer Prevention Recommendations. <https://www.wcrf.org/dietandcancer/cancer-prevention-recommendations> Accessed July 2020. These are the latest recommendations for cancer prevention from the World Cancer Research Fund, an international organization and authority on cancer prevention research, dedicated to providing practical tools and information to people to help them prevent and survive cancer.
26. Kenfield SA, Van Blarigan EL, DuPre N, Stampfer MJ, E LG, Chan JM. Selenium supplementation and prostate cancer mortality. *J Natl Cancer Inst.* 2015;107(1):360. doi: 10.1093/jnci/dju360.
27. Holt SK, Kolb S, Fu R, Horst R, Feng Z, Stanford JL. Circulating levels of 25-hydroxyvitamin D and prostate cancer prognosis. *Cancer Epidemiol.* 2013;37(5):666-70. doi: 10.1016/j.canep.2013.07.005.
28. Nair-Shalliker V, Bang A, Egger S, Clements M, Gardiner RA, Kricker A, et al. Post-treatment levels of plasma 25- and 1,25-dihydroxy vitamin D and mortality in men with aggressive prostate cancer. *Sci Rep.* 2020;10(1):7736. doi: 10.1038/s41598-020-62182-w.
29. Leal-Garcia M, Canto P, Cardenas-Cardenas E, Feria-Bernal G, Garcia-Garcia E, Mendez JP. Overweight and obesity in men with prostate cancer do not constitute risk factors for biochemical recurrence. *Aging Male.* 2020:1-6. doi: 10.1080/13685538.2020.1764523.
30. Vidal AC, Oyekunle T, Howard LE, De Hoedt AM, Kane CJ, Terris MK, et al. Obesity, race, and long-term prostate cancer outcomes. *Cancer.* 2020. doi: 10.1002/cncr.32906.
31. Langlais CS, Cowan JE, Neuhaus J, Kenfield SA, Van Blarigan EL, Broering JM, et al. Obesity at Diagnosis and Prostate Cancer Prognosis and Recurrence Risk Following Primary Treatment by Radical Prostatectomy. *Cancer Epidemiol Biomarkers Prev.* 2019;28(11):1917-25. doi: 10.1158/1055-9965.EPI-19-0488.

32. Dickerman BA, Ahearn TU, Giovannucci E, Stampfer MJ, Nguyen PL, Mucci LA, et al. Weight change, obesity and risk of prostate cancer progression among men with clinically localized prostate cancer. *Int J Cancer*. 2017;141(5):933-44. doi: 10.1002/ijc.30803.
33. Schiffmann J, Salomon G, Tilki D, Budaus L, Karakiewicz PI, Leyh-Bannurah SR, et al. Radical prostatectomy neutralizes obesity-driven risk of prostate cancer progression. *Urol Oncol*. 2017;35(5):243-9. doi: 10.1016/j.urolonc.2016.12.014.
34. Khan S, Cai J, Nielsen ME, Troester MA, Mohler JL, Fontham ETH, et al. The Association of Diabetes and Obesity With Prostate Cancer Progression: HCaP-NC. *Prostate*. 2017;77(8):878-87. doi: 10.1002/pros.23342.
35. Freedland SJ, Branche BL, Howard LE, Hamilton RJ, Aronson WJ, Terris MK, et al. Obesity, risk of biochemical recurrence, and prostate-specific antigen doubling time after radical prostatectomy: results from the SEARCH database. *BJU Int*. 2019;124(1):69-75. doi: 10.1111/bju.14594.
36. Vidal AC, Howard LE, Sun SX, Cooperberg MR, Kane CJ, Aronson WJ, et al. Obesity and prostate cancer-specific mortality after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. *Prostate Cancer Prostatic Dis*. 2017;20(1):72-8. doi: 10.1038/pcan.2016.47.
37. Wang LS, Murphy CT, Ruth K, Zaorsky NG, Smaldone MC, Sobczak ML, et al. Impact of obesity on outcomes after definitive dose-escalated intensity-modulated radiotherapy for localized prostate cancer. *Cancer*. 2015;121(17):3010-7. doi: 10.1002/cncr.29472.
38. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. *Cancer Prev Res (Phila)*. 2011;4(4):486-501. doi: 10.1158/1940-6207.CAPR-10-0229.
39. Jackson MD, Tulloch-Reid MK, McCaw-Binns AM, Aiken W, Ferguson TS, Bennett NR, et al. Central adiposity at diagnosis may reduce prostate cancer-specific mortality in African-

- Caribbean men with prostate cancer: 10-year follow-up of participants in a case-control study. *Cancer Causes Control*. 2020;31(7):651-62. doi: 10.1007/s10552-020-01306-z.
40. Troeschel AN, Hartman TJ, Jacobs EJ, Stevens VL, Gansler T, Flanders WD, et al. Postdiagnosis Body Mass Index, Weight Change, and Mortality From Prostate Cancer, Cardiovascular Disease, and All Causes Among Survivors of Nonmetastatic Prostate Cancer. *J Clin Oncol*. 2020;38(18):2018-27. doi: 10.1200/JCO.19.02185.
41. Farris MS, Courneya KS, Kopciuk KA, McGregor SE, Friedenreich CM. Anthropometric measurements and survival after a prostate cancer diagnosis. *Br J Cancer*. 2018;118(4):607-10. doi: 10.1038/bjc.2017.440.
42. Keto CJ, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL, et al. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. *BJU Int*. 2012;110(4):492-8. doi: 10.1111/j.1464-410X.2011.10754.x.
43. Negron R, Vasquez A, Nieves M, Guerrios L, Irizarry-Ramirez M. Body mass index affects the diagnosis and progression of prostate cancer in Hispanics. *Ethn Dis*. 2010;20(1 Suppl 1):S1-168-72.
44. Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, et al. Obesity and mortality in men with locally advanced prostate cancer: analysis of RTOG 85-31. *Cancer*. 2007;110(12):2691-9. doi: 10.1002/cncr.23093.
45. Guy DE, Vandersluis A, Klotz LH, Fleshner N, Kiss A, Parker C, et al. Total energy expenditure and vigorous-intensity physical activity are associated with reduced odds of reclassification among men on active surveillance. *Prostate Cancer Prostatic Dis*. 2018;21(2):187-95. doi: 10.1038/s41391-017-0010-0.
46. Vandersluis AD, Guy DE, Klotz LH, Fleshner NE, Kiss A, Parker C, et al. The role of lifestyle characteristics on prostate cancer progression in two active surveillance cohorts. *Prostate Cancer Prostatic Dis*. 2016;19(3):305-10. doi: 10.1038/pcan.2016.22.

47. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer Res.* 2011;71(11):3889-95. doi: 10.1158/0008-5472.CAN-10-3932.
48. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol.* 2011;29(6):726-32. doi: 10.1200/JCO.2010.31.5226.
49. Dai JY, Wang B, Wang X, Cheng A, Kolb S, Stanford JL, et al. Vigorous Physical Activity Is Associated with Lower Risk of Metastatic-Lethal Progression in Prostate Cancer and Hypomethylation in the CRACR2A Gene. *Cancer Epidemiol Biomarkers Prev.* 2019;28(2):258-64. doi: 10.1158/1055-9965.EPI-18-0622.
50. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, Courneya KS. Physical Activity and Survival After Prostate Cancer. *Eur Urol.* 2016;70(4):576-85. doi: 10.1016/j.eururo.2015.12.032.
51. Bonn SE, Sjolander A, Lagerros YT, Wiklund F, Stattin P, Holmberg E, et al. Physical activity and survival among men diagnosed with prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2015;24(1):57-64. doi: 10.1158/1055-9965.EPI-14-0707.
52. Wang Y, Jacobs EJ, Gapstur SM, Maliniak ML, Gansler T, McCullough ML, et al. Recreational Physical Activity in Relation to Prostate Cancer-specific Mortality Among Men with Nonmetastatic Prostate Cancer. *Eur Urol.* 2017;72(6):931-9. doi: 10.1016/j.eururo.2017.06.037.
53. Bonn SE, Holmberg E, Hugosson J, Balter K. Is leisure time sitting associated with mortality rates among men diagnosed with localized prostate cancer? *Eur J Cancer Prev.* 2019. doi: 10.1097/CEJ.0000000000000523.
54. • U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd edition. Washington, DC: U.S. Department of Health and Human Services;

2018. These are the latest guidelines from the US Department of Health and Human Services for physical activity, which includes recommendations for prostate cancer survivors.

55. Steinberger E, Kollmeier M, McBride S, Novak C, Pei X, Zelefsky MJ. Cigarette smoking during external beam radiation therapy for prostate cancer is associated with an increased risk of prostate cancer-specific mortality and treatment-related toxicity. *BJU Int.* 2015;116(4):596-603. doi: 10.1111/bju.12969.

56. Rieken M, Shariat SF, Kluth LA, Fajkovic H, Rink M, Karakiewicz PI, et al. Association of Cigarette Smoking and Smoking Cessation with Biochemical Recurrence of Prostate Cancer in Patients Treated with Radical Prostatectomy. *Eur Urol.* 2015;68(6):949-56. doi: 10.1016/j.eururo.2015.05.038.

57. Joshu CE, Mondul AM, Meinhold CL, Humphreys EB, Han M, Walsh PC, et al. Cigarette smoking and prostate cancer recurrence after prostatectomy. *J Natl Cancer Inst.* 2011;103(10):835-8. doi: 10.1093/jnci/djr124.

58. Pickles T, Liu M, Berthelet E, Kim-Sing C, Kwan W, Tyldesley S, et al. The effect of smoking on outcome following external radiation for localized prostate cancer. *J Urol.* 2004;171(4):1543-6. doi: 10.1097/01.ju.0000118292.25214.a4.

59. Riviere P, Kumar A, Luterstein E, Vitzthum LK, Nalawade V, Sarkar RR, et al. Tobacco smoking and death from prostate cancer in US veterans. *Prostate Cancer Prostatic Dis.* 2020;23(2):252-9. doi: 10.1038/s41391-019-0178-6.

60. Gong Z, Agalliu I, Lin DW, Stanford JL, Kristal AR. Cigarette smoking and prostate cancer-specific mortality following diagnosis in middle-aged men. *Cancer Causes Control.* 2008;19(1):25-31. doi: 10.1007/s10552-007-9066-9.

61. Pantarotto J, Malone S, Dahrouge S, Gallant V, Eapen L. Smoking is associated with worse outcomes in patients with prostate cancer treated by radical radiotherapy. *BJU Int.* 2007;99(3):564-9. doi: 10.1111/j.1464-410X.2006.06656.x.

62. Merrick GS, Butler WM, Wallner KE, Galbreath RW, Lief JH, Adamovich E. Effect of cigarette smoking on biochemical outcome after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys.* 2004;58(4):1056-62. doi: 10.1016/j.ijrobp.2003.08.021.
63. Moreira DM, Aronson WJ, Terris MK, Kane CJ, Amling CL, Cooperberg MR, et al. Cigarette smoking is associated with an increased risk of biochemical disease recurrence, metastasis, castration-resistant prostate cancer, and mortality after radical prostatectomy: results from the SEARCH database. *Cancer.* 2014;120(2):197-204. doi: 10.1002/cncr.28423.
64. Oefelein MG, Resnick MI. Association of tobacco use with hormone refractory disease and survival of patients with prostate cancer. *J Urol.* 2004;171(6 Pt 1):2281-4. doi: 10.1097/01.ju.0000125123.46733.93.
65. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34. doi: 10.3322/caac.21551.
66. Sato N, Shiota M, Shiga KI, Takeuchi A, Inokuchi J, Tatsugami K, et al. Smoking effect on oncological outcome among men with prostate cancer after radical prostatectomy. *Jpn J Clin Oncol.* 2017;47(5):453-7. doi: 10.1093/jjco/hyx013.
67. Miller KD, Goding Sauer A, Ortiz AP, Fedewa SA, Pinheiro PS, Tortolero-Luna G, et al. Cancer Statistics for Hispanics/Latinos, 2018. *CA Cancer J Clin.* 2018;68(6):425-45. doi: 10.3322/caac.21494.
68. Chinea FM, Patel VN, Kwon D, Lamichhane N, Lopez C, Punnen S, et al. Ethnic heterogeneity and prostate cancer mortality in Hispanic/Latino men: a population-based study. *Oncotarget.* 2017;8(41):69709-21. doi: 10.18632/oncotarget.19068.
69. Ngo TC, Lee JJ, Brooks JD, Nolley R, Ferrari M, Presti JC, Jr. Smoking and adverse outcomes at radical prostatectomy. *Urol Oncol.* 2013;31(6):749-54. doi: 10.1016/j.urolonc.2011.06.013.

70. Oh JJ, Hong SK, Jeong CW, Byun SS, Lee SE. Significance of smoking status regarding outcomes after radical prostatectomy. *Int Urol Nephrol*. 2012;44(1):119-24. doi: 10.1007/s11255-011-9964-3.
71. Bonn SE, Wiklund F, Sjolander A, Szulkin R, Stattin P, Holmberg E, et al. Body mass index and weight change in men with prostate cancer: progression and mortality. *Cancer Causes Control*. 2014;25(8):933-43. doi: 10.1007/s10552-014-0393-3.
72. Bhindi B, Kulkarni GS, Finelli A, Alibhai SM, Hamilton RJ, Toi A, et al. Obesity is associated with risk of progression for low-risk prostate cancers managed expectantly. *Eur Urol*. 2014;66(5):841-8. doi: 10.1016/j.eururo.2014.06.005.
73. Narita S, Mitsuzuka K, Yoneyama T, Tsuchiya N, Koie T, Kakoi N, et al. Impact of body mass index on clinicopathological outcome and biochemical recurrence after radical prostatectomy. *Prostate Cancer Prostatic Dis*. 2013;16(3):271-6. doi: 10.1038/pcan.2013.16.
74. Ho T, Gerber L, Aronson WJ, Terris MK, Presti JC, Kane CJ, et al. Obesity, prostate-specific antigen nadir, and biochemical recurrence after radical prostatectomy: biology or technique? Results from the SEARCH database. *Eur Urol*. 2012;62(5):910-6. doi: 10.1016/j.eururo.2012.08.015.
75. Kane CJ, Im R, Amling CL, Presti JC, Jr., Aronson WJ, Terris MK, et al. Outcomes after radical prostatectomy among men who are candidates for active surveillance: results from the SEARCH database. *Urology*. 2010;76(3):695-700. doi: 10.1016/j.urology.2009.12.073.
76. van Roermund JG, Hinnen KA, Battermann JJ, Witjes JA, Bosch JL, Kiemeny LA, et al. Body mass index is not a prognostic marker for prostate-specific antigen failure and survival in Dutch men treated with brachytherapy. *BJU Int*. 2010;105(1):42-8. doi: 10.1111/j.1464-410X.2009.08687.x.
77. King CR, Spiotto MT, Kapp DS. Obesity and risk of biochemical failure for patients receiving salvage radiotherapy after prostatectomy. *Int J Radiat Oncol Biol Phys*. 2009;73(4):1017-22. doi: 10.1016/j.ijrobp.2008.05.041.

78. Jayachandran J, Banez LL, Aronson WJ, Terris MK, Presti JC, Jr., Amling CL, et al. Obesity as a predictor of adverse outcome across black and white race: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database. *Cancer*. 2009;115(22):5263-71. doi: 10.1002/cncr.24571.
79. Davies BJ, Smaldone MC, Sadetsky N, Dall'era M, Carroll PR. The impact of obesity on overall and cancer specific survival in men with prostate cancer. *J Urol*. 2009;182(1):112-7; discussion 7. doi: 10.1016/j.juro.2009.02.118.
80. van Roermund JG, Kok DE, Wildhagen MF, Kiemeneij LA, Struik F, Sloot S, et al. Body mass index as a prognostic marker for biochemical recurrence in Dutch men treated with radical prostatectomy. *BJU Int*. 2009;104(3):321-5. doi: 10.1111/j.1464-410X.2009.08404.x.
81. Efstathiou JA, Skowronski RY, Coen JJ, Grocela JA, Hirsch AE, Zietman AL. Body mass index and prostate-specific antigen failure following brachytherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;71(5):1302-8. doi: 10.1016/j.ijrobp.2007.11.073.
82. Magheli A, Rais-Bahrami S, Trock BJ, Humphreys EB, Partin AW, Han M, et al. Impact of body mass index on biochemical recurrence rates after radical prostatectomy: an analysis utilizing propensity score matching. *Urology*. 2008;72(6):1246-51. doi: 10.1016/j.urology.2008.01.052.
83. Hisasue S, Yanase M, Shindo T, Iwaki H, Fukuta F, Nishida S, et al. Influence of body mass index and total testosterone level on biochemical recurrence following radical prostatectomy. *Jpn J Clin Oncol*. 2008;38(2):129-33. doi: 10.1093/jjco/hym162.
84. Freedland SJ, Sun L, Kane CJ, Presti JC, Jr., Terris MK, Amling CL, et al. Obesity and oncological outcome after radical prostatectomy: impact of prostate-specific antigen-based prostate cancer screening: results from the Shared Equal Access Regional Cancer Hospital and Duke Prostate Center databases. *BJU Int*. 2008;102(8):969-74. doi: 10.1111/j.1464-410X.2008.07934.x.

85. Stroup SP, Cullen J, Auge BK, L'Esperance JO, Kang SK. Effect of obesity on prostate-specific antigen recurrence after radiation therapy for localized prostate cancer as measured by the 2006 Radiation Therapy Oncology Group-American Society for Therapeutic Radiation and Oncology (RTOG-ASTRO) Phoenix consensus definition. *Cancer*. 2007;110(5):1003-9. doi: 10.1002/cncr.22873.
86. Spangler E, Zeigler-Johnson CM, Coomes M, Malkowicz SB, Wein A, Rebbeck TR. Association of obesity with tumor characteristics and treatment failure of prostate cancer in African-American and European American men. *J Urol*. 2007;178(5):1939-44; discussion 45. doi: 10.1016/j.juro.2007.07.021.
87. Efstathiou JA, Chen MH, Renshaw AA, Loffredo MJ, D'Amico AV. Influence of body mass index on prostate-specific antigen failure after androgen suppression and radiation therapy for localized prostate cancer. *Cancer*. 2007;109(8):1493-8. doi: 10.1002/cncr.22564.
88. Montgomery RB, Goldman B, Tangen CM, Hussain M, Petrylak DP, Page S, et al. Association of body mass index with response and survival in men with metastatic prostate cancer: Southwest Oncology Group trials 8894 and 9916. *J Urol*. 2007;178(5):1946-51; discussion 51. doi: 10.1016/j.juro.2007.07.026.
89. Strom SS, Kamat AM, Gruschus SK, Gu Y, Wen S, Cheung MR, et al. Influence of obesity on biochemical and clinical failure after external-beam radiotherapy for localized prostate cancer. *Cancer*. 2006;107(3):631-9. doi: 10.1002/cncr.22025.
90. Siddiqui SA, Inman BA, Sengupta S, Slezak JM, Bergstralh EJ, Leibovich BC, et al. Obesity and survival after radical prostatectomy: A 10-year prospective cohort study. *Cancer*. 2006;107(3):521-9. doi: 10.1002/cncr.22030.
91. Bassett WW, Cooperberg MR, Sadetsky N, Silva S, DuChane J, Pasta DJ, et al. Impact of obesity on prostate cancer recurrence after radical prostatectomy: data from CaPSURE. *Urology*. 2005;66(5):1060-5. doi: 10.1016/j.urology.2005.05.040.

92. Strom SS, Wang X, Pettaway CA, Logothetis CJ, Yamamura Y, Do KA, et al. Obesity, weight gain, and risk of biochemical failure among prostate cancer patients following prostatectomy. *Clin Cancer Res.* 2005;11(19 Pt 1):6889-94. doi: 10.1158/1078-0432.CCR-04-1977.
93. Freedland SJ, Grubb KA, Yiu SK, Humphreys EB, Nielsen ME, Mangold LA, et al. Obesity and risk of biochemical progression following radical prostatectomy at a tertiary care referral center. *J Urol.* 2005;174(3):919-22. doi: 10.1097/01.ju.0000169459.78982.d7.
94. Freedland SJ, Isaacs WB, Mangold LA, Yiu SK, Grubb KA, Partin AW, et al. Stronger association between obesity and biochemical progression after radical prostatectomy among men treated in the last 10 years. *Clin Cancer Res.* 2005;11(8):2883-8. doi: 10.1158/1078-0432.CCR-04-2257.
95. Freedland SJ, Aronson WJ, Kane CJ, Presti JC, Jr., Amling CL, Elashoff D, et al. Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the Shared Equal Access Regional Cancer Hospital database study group. *J Clin Oncol.* 2004;22(3):446-53. doi: 10.1200/JCO.2004.04.181.
96. Amling CL, Riffenburgh RH, Sun L, Moul JW, Lance RS, Kusuda L, et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. *J Clin Oncol.* 2004;22(3):439-45. doi: 10.1200/JCO.2004.03.132.
97. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin.* 2021;71(1):7-33. doi: 10.3322/caac.21654.
98. American Cancer Society, Cancer Facts and Figures 2021.
<https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf> (2021). Accessed 09/07/2021.
99. American Cancer Society, Cancer Facts and Figures 2019-2021.
<https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer->

[treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf](#) (2019). Accessed 01/28/2022.

100. Negoita S, Feuer EJ, Mariotto A, Cronin KA, Petkov VI, Hussey SK, et al. Annual Report to the Nation on the Status of Cancer, part II: Recent changes in prostate cancer trends and disease characteristics. *Cancer*. 2018;124(13):2801-14. doi: 10.1002/cncr.31549.

101. Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. *Cancer Epidemiol Biomarkers Prev*. 2016;25(1):16-27. doi: 10.1158/1055-9965.EPI-15-0578.

102. Langlais CS, Graff RE, Van Blarigan EL, Palmer NR, Washington SL, 3rd, Chan JM, et al. Post-Diagnostic Dietary and Lifestyle Factors and Prostate Cancer Recurrence, Progression, and Mortality. *Curr Oncol Rep*. 2021;23(3):37. doi: 10.1007/s11912-021-01017-x.

103. Hu FB, Willett WC. Current and Future Landscape of Nutritional Epidemiologic Research. *JAMA*. 2018;320(20):2073-4. doi: 10.1001/jama.2018.16166.

104. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002;13(1):3-9.

105. Kenfield SA, Batista JL, Jahn JL, Downer MK, Van Blarigan EL, Sesso HD, et al. Development and Application of a Lifestyle Score for Prevention of Lethal Prostate Cancer. *J Natl Cancer Inst*. 2016;108(3). doi: 10.1093/jnci/djv329.

106. Shams-White MM, Brockton NT, Mitrou P, Romaguera D, Brown S, Bender A, et al. Operationalizing the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Cancer Prevention Recommendations: A Standardized Scoring System. *Nutrients*. 2019;11(7). doi: 10.3390/nu11071572.

107. Shams-White MM, Romaguera D, Mitrou P, Reedy J, Bender A, Brockton NT. Further Guidance in Implementing the Standardized 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Score. *Cancer Epidemiol Biomarkers Prev*. 2020;29(5):889-94. doi: 10.1158/1055-9965.EPI-19-1444.

108. McCullough ML, Patel AV, Kushi LH, Patel R, Willett WC, Doyle C, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. *Cancer Epidemiol Biomarkers Prev.* 2011;20(6):1089-97. doi: 10.1158/1055-9965.epi-10-1173.
109. Van Blarigan EL, Fuchs CS, Niedzwiecki D, Zhang S, Saltz LB, Mayer RJ, et al. Association of Survival With Adherence to the American Cancer Society Nutrition and Physical Activity Guidelines for Cancer Survivors After Colon Cancer Diagnosis: The CALGB 89803/Alliance Trial. *JAMA Oncol.* 2018;4(6):783-90. doi: 10.1001/jamaoncol.2018.0126.
110. Lubeck DP, Litwin MS, Henning JM, Stier DM, Mazonson P, Fisk R, et al. The CaPSURE database: a methodology for clinical practice and research in prostate cancer. CaPSURE Research Panel. *Cancer of the Prostate Strategic Urologic Research Endeavor. Urology.* 1996;48(5):773-7.
111. Willett W. *Nutritional Epidemiology.* 3 ed. Oxford University Press; 2013.
112. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc.* 1993;93(7):790-6.
113. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. *Am J Clin Nutr.* 1999;69(2):243-9. doi: 10.1093/ajcn/69.2.243.
114. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol.* 1992;135(10):1114-26; discussion 27-36. doi: 10.1093/oxfordjournals.aje.a116211.
115. U.S. Department of Agriculture, Agricultural Research Service. FoodData Central, 2019. <https://fdc.nal.usda.gov/>.

Accessed January 12, 2022.

116. Chasan-Taber S, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA, Giovannucci E, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology*. 1996;7(1):81-6.
117. Pickles T, Liu M, Berthelet E, Kim-Sing C, Kwan W, Tyldesley S. The effect of smoking on outcome following external radiation for localized prostate cancer. *J Urol*. 2004;171(4):1543-6. doi: 10.1097/01.ju.0000118292.25214.a4.
118. Rieken M, Shariat SF, Kluth LA, Fajkovic H, Rink M, Karakiewicz PI, et al. Association of Cigarette Smoking and Smoking Cessation with Biochemical Recurrence of Prostate Cancer in Patients Treated with Radical Prostatectomy. *Eur Urol*. 2015;68(6):949-56. doi: 10.1016/j.eururo.2015.05.038.
119. Negrón R, Vásquez A, Nieves M, Guerrios L, Irizarry-Ramírez M. Body mass index affects the diagnosis and progression of prostate cancer in Hispanics. *Ethn Dis*. 2010;20(1 Suppl 1):S1-168-72.
120. Kane CJ, Im R, Amling CL, Presti JC, Jr., Aronson WJ, Terris MK, et al. Outcomes after radical prostatectomy among men who are candidates for active surveillance: results from the SEARCH database. *Urology*. 2010;76(3):695-700. doi: 10.1016/j.urology.2009.12.073.
121. Bonn SE, Sjölander A, Lagerros YT, Wiklund F, Stattin P, Holmberg E, et al. Physical activity and survival among men diagnosed with prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):57-64. doi: 10.1158/1055-9965.Epi-14-0707.
122. Epstein MM, Kasperzyk JL, Mucci LA, Giovannucci E, Price A, Wolk A, et al. Dietary fatty acid intake and prostate cancer survival in Örebro County, Sweden. *Am J Epidemiol*. 2012;176(3):240-52. doi: 10.1093/aje/kwr520.
123. Tat D, Kenfield SA, Cowan JE, Broering JM, Carroll PR, Van Blarigan EL, et al. Milk and other dairy foods in relation to prostate cancer recurrence: Data from the cancer of the prostate strategic urologic research endeavor (CaPSURE™). *Prostate*. 2018;78(1):32-9. doi: 10.1002/pros.23441.

124. Langlais CS, Chan JM, Kenfield SA, Cowan JE, Graff RE, Broering JM, et al. Post-diagnostic coffee and tea consumption and risk of prostate cancer progression by smoking history. *Cancer Causes Control*. 2021;32(6):635-44. doi: 10.1007/s10552-021-01417-1.
125. National Death Index. National Center for Health Statistics, Centers for Disease Control and Prevention, Department of Health and Human Services; 2021.
<https://www.cdc.gov/nchs/ndi/resources.htm> Accessed January 13, 2022.
126. Klein JP, Moeschberger ML. *Survival Analysis: Techniques for Censored and Truncated Data*. Berlin/Heidelberg, Germany: Springer; 2003.
127. Harel O, Mitchell EM, Perkins NJ, Cole SR, Tchetgen Tchetgen EJ, Sun B, et al. Multiple Imputation for Incomplete Data in Epidemiologic Studies. *Am J Epidemiol*. 2018;187(3):576-84. doi: 10.1093/aje/kwx349.
128. Rubin DB. Inference and Missing Data. *Biometrika*. 1976;63(3):581-92.
129. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243-74. doi: 10.3322/caac.21142.
130. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *Int J Cancer*. 2007;121(7):1571-8. doi: 10.1002/ijc.22788.
131. Kensler KH, Rebbeck TR. Cancer Progress and Priorities: Prostate Cancer. *Cancer Epidemiol Biomarkers Prev*. 2020;29(2):267-77. doi: 10.1158/1055-9965.EPI-19-0412.
132. Cespedes EM, Hu FB. Dietary patterns: from nutritional epidemiologic analysis to national guidelines. *Am J Clin Nutr*. 2015;101(5):899-900. doi: 10.3945/ajcn.115.110213.
133. Giovannucci E. A framework to understand diet, physical activity, body weight, and cancer risk. *Cancer Causes Control*. 2018;29(1):1-6. doi: 10.1007/s10552-017-0975-y.
134. Sfanos KS, De Marzo AM. Prostate cancer and inflammation: the evidence. *Histopathology*. 2012;60(1):199-215. doi: 10.1111/j.1365-2559.2011.04033.x.

135. Nguyen DP, Li J, Tewari AK. Inflammation and prostate cancer: the role of interleukin 6 (IL-6). *BJU Int.* 2014;113(6):986-92. doi: 10.1111/bju.12452.
136. Vignozzi L, Maggi M. Prostate cancer: intriguing data on inflammation and prostate cancer. *Nat Rev Urol.* 2014;11(7):369-70. doi: 10.1038/nrurol.2014.143.
137. Ahearn TU, Peisch S, Pettersson A, Ebot EM, Zhou CK, Graff RE, et al. Expression of IGF/insulin receptor in prostate cancer tissue and progression to lethal disease. *Carcinogenesis.* 2018;39(12):1431-7. doi: 10.1093/carcin/bgy112.
138. Albanes D, Weinstein SJ, Wright ME, Mannisto S, Limburg PJ, Snyder K, et al. Serum insulin, glucose, indices of insulin resistance, and risk of prostate cancer. *J Natl Cancer Inst.* 2009;101(18):1272-9. doi: 10.1093/jnci/djp260.
139. Chan JM, Stampfer MJ, Ma J, Gann P, Gaziano JM, Pollak M, et al. Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. *J Natl Cancer Inst.* 2002;94(14):1099-106.
140. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science.* 1998;279(5350):563-6.
141. Tabung FK, Smith-Warner SA, Chavarro JE, Wu K, Fuchs CS, Hu FB, et al. Development and Validation of an Empirical Dietary Inflammatory Index. *J Nutr.* 2016;146(8):1560-70. doi: 10.3945/jn.115.228718.
142. Tabung FK, Wang W, Fung TT, Hu FB, Smith-Warner SA, Chavarro JE, et al. Development and validation of empirical indices to assess the insulinaemic potential of diet and lifestyle. *Br J Nutr.* 2016:1-12. doi: 10.1017/S0007114516003755.
143. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol.* 2013;63(5):800-9. doi: 10.1016/j.eururo.2012.11.013.
144. Livingstone MB, Black AE. Markers of the validity of reported energy intake. *J Nutr.* 2003;133 Suppl 3:895S-920S. doi: 10.1093/jn/133.3.895S.

145. Michels KB, Willett WC. Self-administered semiquantitative food frequency questionnaires: patterns, predictors, and interpretation of omitted items. *Epidemiology*. 2009;20(2):295-301. doi: 10.1097/EDE.0b013e3181931515.
146. Yuan C, Spiegelman D, Rimm EB, Rosner BA, Stampfer MJ, Barnett JB, et al. Validity of a Dietary Questionnaire Assessed by Comparison With Multiple Weighed Dietary Records or 24-Hour Recalls. *Am J Epidemiol*. 2017;185(7):570-84. doi: 10.1093/aje/kww104.
147. Roach M, 3rd, Hanks G, Thames H, Jr., Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65(4):965-74. doi: 10.1016/j.ijrobp.2006.04.029.
148. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiology*. 2011;22(4):582-5. doi: 10.1097/EDE.0b013e31821db37e.
149. Li R, Chambless L. Test for additive interaction in proportional hazards models. *Ann Epidemiol*. 2007;17(3):227-36. doi: 10.1016/j.annepidem.2006.10.009.
150. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*. 1992;3(5):452-6.
151. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *ASA*. 1999;94(446):496-509.
152. . World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project Expert Report 2018 Diet, nutrition, physical activity, and prostate cancer Available at dietandcancerreport.org.
153. Vigneri R, Goldfine ID, Frittitta L. Insulin, insulin receptors, and cancer. *J Endocrinol Invest*. 2016;39(12):1365-76. doi: 10.1007/s40618-016-0508-7.
154. Belfiore A. The role of insulin receptor isoforms and hybrid insulin/IGF-I receptors in human cancer. *Curr Pharm Des*. 2007;13(7):671-86. doi: 10.2174/138161207780249173.

155. Aroke D, Folefac E, Shi N, Jin Q, Clinton SK, Tabung FK. Inflammatory and Insulinemic Dietary Patterns: Influence on Circulating Biomarkers and Prostate Cancer Risk. *Cancer Prev Res (Phila)*. 2020;13(10):841-52. doi: 10.1158/1940-6207.CAPR-20-0236.
156. Fu BC, Tabung FK, Pernar CH, Wang W, Gonzalez-Feliciano AG, Chowdhury-Paulino IM, et al. Insulinemic and Inflammatory Dietary Patterns and Risk of Prostate Cancer. *Eur Urol*. 2021;79(3):405-12. doi: 10.1016/j.eururo.2020.12.030.
157. McMahon DM, Burch JB, Hebert JR, Hardin JW, Zhang J, Wirth MD, et al. Diet-related inflammation and risk of prostate cancer in the California Men's Health Study. *Ann Epidemiol*. 2019;29:30-8. doi: 10.1016/j.annepidem.2018.10.008.
158. Tabung FK, Satija A, Fung TT, Clinton SK, Giovannucci EL. Long-Term Change in both Dietary Insulinemic and Inflammatory Potential Is Associated with Weight Gain in Adult Women and Men. *J Nutr*. 2019;149(5):804-15. doi: 10.1093/jn/nxy319.
159. Shi N, Aroke D, Jin Q, Lee DH, Hussan H, Zhang X, et al. Proinflammatory and Hyperinsulinemic Dietary Patterns Are Associated With Specific Profiles of Biomarkers Predictive of Chronic Inflammation, Glucose-Insulin Dysregulation, and Dyslipidemia in Postmenopausal Women. *Front Nutr*. 2021;8:690428. doi: 10.3389/fnut.2021.690428.
160. Lee DH, Giovannucci EL, Tabung FK. Insulin-related dietary indices predict 24-h urinary C-peptide in adult men. *Br J Nutr*. 2020:1-8. doi: 10.1017/S0007114520002184.
161. Liu L, Nishihara R, Qian ZR, Tabung FK, Nevo D, Zhang X, et al. Association Between Inflammatory Diet Pattern and Risk of Colorectal Carcinoma Subtypes Classified by Immune Responses to Tumor. *Gastroenterology*. 2017;153(6):1517-30 e14. doi: 10.1053/j.gastro.2017.08.045.
162. Tabung FK, Noonan A, Lee DH, Song M, Clinton SK, Spakowicz D, et al. Post-diagnosis dietary insulinemic potential and survival outcomes among colorectal cancer patients. *BMC Cancer*. 2020;20(1):817. doi: 10.1186/s12885-020-07288-0.

163. Jin Q, Shi N, Aroke D, Lee DH, Joseph JJ, Donneyong M, et al. Insulinemic and Inflammatory Dietary Patterns Show Enhanced Predictive Potential for Type 2 Diabetes Risk in Postmenopausal Women. *Diabetes Care*. 2021;44(3):707-14. doi: 10.2337/dc20-2216.

Funding

Crystal S. Lenglais was funded by the National Institutes of Health (NIH) National Cancer Institute (NCI) grant F31CA247093 and the University of California San Francisco (UCSF) Prostate Cancer Program Pilot Award.

Additional funding sources for the co-authors of this work include:

- NIH/NCI R01CA181802, R01CA207749, K07CA197077, and K01CA211965.
- Movember Foundation
- Prostate Cancer Foundation

The CaPSURE study was funded by the United States Department of Defense Prostate Cancer Research Program (W81XWH-13-2-0074 and W81XWH-04-1-0850) and the UCSF Goldberg-Benioff Program in Translational Cancer Biology.

Publishing Agreement

It is the policy of the University to encourage open access and broad distribution of all theses, dissertations, and manuscripts. The Graduate Division will facilitate the distribution of UCSF theses, dissertations, and manuscripts to the UCSF Library for open access and distribution. UCSF will make such theses, dissertations, and manuscripts accessible to the public and will take reasonable steps to preserve these works in perpetuity.

I hereby grant the non-exclusive, perpetual right to The Regents of the University of California to reproduce, publicly display, distribute, preserve, and publish copies of my thesis, dissertation, or manuscript in any form or media, now existing or later derived, including access online for teaching, research, and public service purposes.

DocuSigned by:

Crystal Lenglais

C0CA1A3BFFC8463...

Author Signature

3/9/2022

Date