Association of a Healthy Diet Score with prostate cancer severity in newly diagnosed men: A cross-sectional analysis of RADICAL PC

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ABSTRACT

Background: Prostate cancer remains the second most common cause of cancer-related death in men in the United States (Siegel et al. 2017). Observational studies of patients with prostate cancer have found associations between diet and prostate cancer severity, but the evidence is inconsistent or inconclusive. The purpose of this thesis is to implement a validated international healthy diet score and evaluate whether or not it is associated with prostate cancer severity.

Objective: The objectives of this thesis were:

Chapter 1: examine whether an association exists between diet quality, using the validated Healthy Diet Score, and the severity of prostate cancer, and

Chapter 2: examine the agreement between two methods of dietary data collection (an abridged FFQ and a longer previously validated FFQ) with respect to macronutrients and main food groups.

Methods: We used observational data from the Randomized Intervention for Cardiovascular and Lifestyle Risk Factors in Prostate Cancer Patients (RADICAL PC), a multi-centre Canadian prospective cohort study into which men with a new diagnosis of prostate cancer or who were being treated with androgen deprivation therapy were enrolled. To complete objective 1 (Chapter 1) of this dissertation, a cross-sectional analysis was completed using baseline data collected in the RADICAL PC study. In order to evaluate the association of diet with prostate cancer severity, the relationship between the Healthy Diet Score and prostate cancer severity (stage and grade) was assessed. The second objective (Chapter 2) is a comparability sub-study comparing an abridged FFQ with a long, validated FFQ in a subgroup of participant (N=130) enrolled in the RADICAL PC study.

Results:

Chapter 1: In the cross-sectional analysis of baseline data collected in RADICAL PC, a higher diet score was not significantly associated with prostate cancer severity. An association between age and the high-risk prostate cancer category was found to be statistically significant (OR: 1.04, 95%CI 1.02-1.05, p<0.00).

Chapter 2: There was good agreement between the abridged FFQ and long FFQ for carbohydrates, proteins, whole wheat, refined grains, fish, dairy, potatoes, fruits, nuts, and soft drinks (Spearman rank correlation >0.5). Food groups including fried foods, processed meats, vegetables and total fats (nutrients) were found to have moderate correlation (Spearman rank correlation between 0.3-0.5). There was low correlation for legumes, sugars and oils. Bland-Altman plots showed good absolute agreements between the two methods, and reliability test using Spearman's correlation showed moderate to good correlation (0.45 to 0.75 among most food groups.

Conclusion:

There was no clear association between a healthier diet and prostate cancer severity in men with newly diagnosed prostate cancer. There was adequate agreement between the abridged SFFQ and the long FFQ of the expected food groups, and thus the SFFQ can be considered an appropriate tool to use for measuring diet among prostate cancer patients for some food groups and nutrients.

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Completing the class requirements for this program and working in a large clinical trial, designing my own sub-study, and using a large dataset to perform my analysis in Stata while completing the Health Research Methodology program was a completely novel experience and has been an important part of my academic maturation. I am grateful for all my classmates who have all been part of important lessons, lectures, and endless writing dates. I am also thankful for Lorraine, Admissions Coordinator for HRM, who is always there to guide and answer questions for students.

MANUSCRIPT

"Comparability of an abridged Food Frequency Questionnaire (FFQ) to assess diet in prostate cancer patients in the RADICAL PC Study"

-to be submitted

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LIST OF ABBREVIATIONS

ADT: Androgen Deprivation Therapy

BMI: Body-Mass Index

CVD: Cardiovascular Disease

FFQ: Food Frequency Questionnaire

LFFQ: Long Food Frequency Questionnaire

ORs: Odd Ratios

RCT: Randomized Controlled Trial

SFFQ: Abridged or short Food Frequency Questionnaire

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CHAPTER 1: A Cross-Sectional Analysis of Severity of Prostate Cancer and a Healthy Diet Score

1.0 INTRODUCTION AND RATIONALE

Prostate Cancer is the most common cancer among men in Canada with 24,000 diagnosed in 2015 (Siegel et al. 2015). Prostate cancer diagnoses account for 24% of all new cancer cases in men with one in seven Canadian men receiving a diagnosis of prostate cancer during their lifetime (Fradet et al. 2009; Siegel et al. 2015; 2017). After the age of 50, the chances of developing prostate cancer rises rapidly, with the average age of diagnosis approaching 66 years of age (Bashir 2015). As a result of the aging population worldwide and most cases of prostate cancer being diagnosed at ≥ 65, the global burden of prostate cancer is expected to rise exponentially, anticipating nearly 1.7 million new prostate cancer cases around the world and 499,000 deaths by the year 2030 (Bashir 2015).

Many men with prostate cancer have a protracted course following diagnosis, unlike cancers in the lungs and pancreas, which are often discovered at advanced stages yielding shorter life-expectancy and making studies of prevention and therapy response difficult. The recent trend of early diagnosis of prostate cancer makes studies of prevention, survivorship, and therapy response achievable and an opportunity to investigate potential risk factors. Diet is implicated as a modifiable risk factor for prostate cancer and its influence on disease severity at diagnosis is of current interest.

The emphasis of most observational studies of diet and prostate cancer has been on the relationship between diet and the risk of disease progression or recurrence (secondary prevention), with a limited amount of information on the association between diet and the severity of prostate cancer at diagnosis. Some of the existing literature suggests that eating soy protein, green teas, tomatoes (or tomato products) and a low intake of carbohydrates may reduce

the risk of prostate cancer or disease progression. Other studies have found a relationship between high intakes of saturated fats and increased prostate cancer risks. However, there are very few studies that address these beneficial or adverse dietary components concurrently. It is not known whether there is an optimal diet for reducing the risk of prostate cancer severity at diagnosis or for prevention. The objectives of this thesis are therefore to examine the relationship between diet and prostate cancer severity. This study is distinctive from other literature because it will use a Healthy Diet Score in a large sample size of men newly diagnosed with prostate cancer.

For decades, dietary recommendations have focused on consumption of nutrients (eg. fats and carbohydrates) as strategies to reduce chronic disease in populations. In the past two decades, however, the focus of dietary guidelines has shifted from nutrients to foods, given that people's dietary choices are based on food types rather than on specific nutrients (US Department of Agriculture; Tapsell et al. 2016), and since nutrients have many different food sources which may have very different biological effects (e.g. polyunsaturated fat sources include nuts, fish and vegetable oils, which may have differing effects on health). With the exception of the WHO, which still uses nutrients since they make global recommendations, nutrients allow countries to tailor recommendations with local foods. More recently, nutrition research has focused increasingly on dietary patterns (i.e. diet in its totality as opposed to individual foods). There are two major reasons for this shift in focus: 1) the effect of individual foods on health is modest, and so signals are small and statistical power in nutrition studies is limited, whereas the overall diet has a larger impact and associations between overall diet and adverse health outcomes are therefore easier to detect; and 2) recommendations on the overall diet are easier for the public to implement than recommendations on individual nutrients or

specific foods. Despite this recent focus on the overall diet, the optimal diet for populations in chronic disease prevention and recurrence remains unresolved.

One of the largest global diet studies identified eight food groups that were associated with mortality and the incidence of CVD (Yusuf 2004; 2008). The investigators developed a Healthy Diet Score which was strongly predictive of mortality in the PURE study, a prospective cohort study of 140,000 people in 21 countries living on 5 continents, and therefore the only diet score developed in a cohort study of multiple world regions. The PURE Healthy Diet score was validated in 5 independent international studies of more than 100,000 people around the world. The findings were replicated in different world regions and in people with or without vascular disease (presented at the ESC Congress 2018 Aug 28 – manuscript currently under peer review). The PURE healthy diet score was not significantly more predictive of events than the Mediterranean and AHEI scores, but significantly more predictive of events than the DASH score, and substantially more predictive of events than the EAT-Lancet Planetary health score. The PURE diet score is comprised of eight foods that were found to be protective, whereby a higher score reflects a higher intake of these eight foods. The score is comprised of fruit, vegetables, legumes, nuts, fish, dairy (mainly whole fat dairy), unprocessed red meat and poultry. Further explanations of the diet quality score are provided in Chapter 1. Given the increased focus on dietary patterns for chronic disease prevention and treatment and the lack of research examining the association between dietary patterns and prostate cancer severity, I sought to perform analyses to evaluate whether there is evidence for an association between dietary patterns and prostate cancer severity.

There are two chapters to this dissertation which are nested in a large prospective cohort study, RADICAL PC (The Role of Androgen Deprivation Therapy in Cardiovascular Disease –

A Longitudinal Prostate Cancer Study). The first chapter of this dissertation explores the gaps in the literature between diet and prostate cancer stage and grade. It describes the analyses I have undertaken of dietary data collected in the RADICAL PC study. In RADICAL PC, participants provided responses to a food frequency questionnaire as well as an abridged food frequency questionnaire.

Merging the findings and guidelines on diet and prostate cancer creates a foundation that supports focusing on an overall healthy diet. Lifestyle pattern adjustments have the potential to influence a substantially positive change and could be implemented into patient-centered care teaching. By contributing to diet and prostate cancer research and by providing patients with knowledge on what constitutes a healthy diet, the goal is to reduce disease severity for patients affected by prostate cancer.

1.1 OBJECTIVE

Chapter 1: To evaluate the relationship between the Healthy Diet Score (diet quality) and prostate cancer severity among patients enrolled in the RADICAL PC study.

1.2 BACKGROUND

1.2.1 Summary of Relevant Topics

This literature review will address three topics important to this dissertation:

(i) Introduction to prostate cancer, prostate cancer staging, treatment, risk factors (non-modifiable and modifiable risk factors).

(ii) Relevant dietary exposures: Dairy, red meat, fat and vegetables, and the Mediterranean in prostate cancer.

(iii) The evolution of diet research, drawing on the importance of studying overall diet and dietary patterns versus focusing on single nutrients or food items.

In order to review those three topics, the strengths and limitations of several high impact studies and the gaps in literature will be reviewed.

1.2.2 Prostate Cancer in Canada

Prostate cancer is among the top four most commonly diagnosed cancers in Canada, with an estimated diagnosis of 22,900 cases of prostate cancer in 2019 (Canadian Cancer Statistics 2019), trailing only of lung cancer (29,300 cases), breast cancer (27,000 cases), and colorectal cancer (26,300 cases). These four cancers will account for approximately 48% of all new cancers diagnosed in 2019 among Canadians. Figure 1 shows incidence rates of prostate cancer across Canada (excluding Quebec) across time.

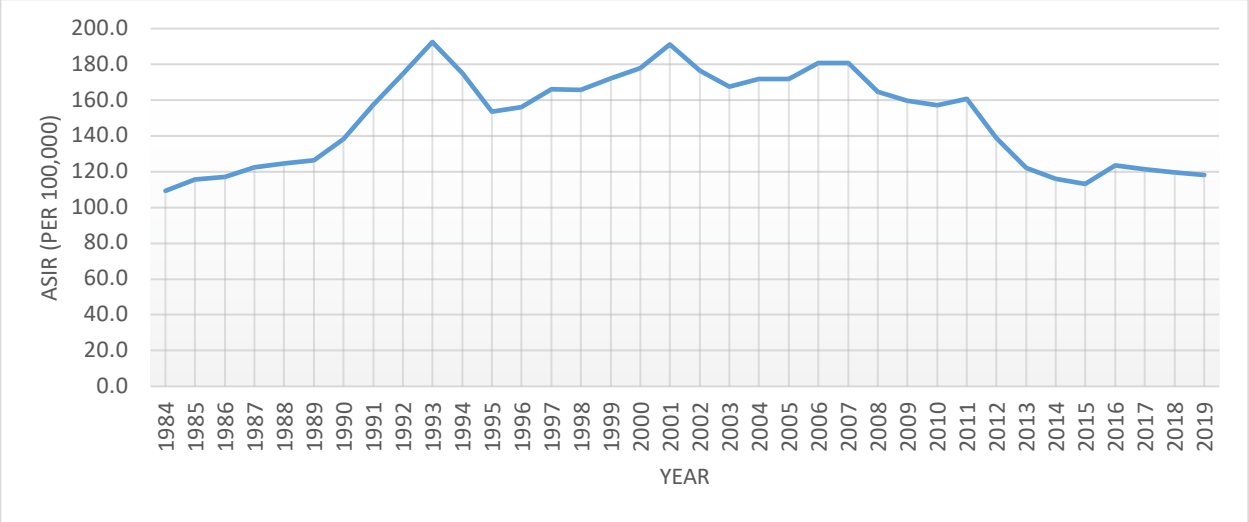

Figure 1: Age-Standardized Incidence rates for prostate cancer in Canada 1984 to 2019 (2015-2019 are predicted values). Created using data from Canadian Cancer Society: Canadian Cancer Statistics 2019.

Although the rate has declined since 2001 (Figure 1), it is still higher than other cancers among men, partially due to advances screening practices, such as the PSA test. Prostate cancer is the most commonly diagnosed cancer in men, accounting for 20.3% of all new cancer cases among men (lung and bronchus is second at 13.2%, colorectal is third at 12.9%). The severity of

PC is described by its grade and stage. Cancer grade is a histological classification scheme. Cancer stage describes the cancer burden and whether it has spread.

1.2.3 Prostate Cancer Severity

There are several scales used to describe the severity of prostate cancer: 1) histologic (Gleason) grade; 2) TNM staging; 3) PC risk as described by D'Amico, et al. The Gleason score is used to classify how aggressive the prostate cancer is by evaluating the cells and assigning a score ranging from 1 to 5. Two different scores are given, one for the first and one the second most common cell patterns, and together these two scores make up the total Gleason Score. Since each individual score ranges from 1 to 5, the total Gleason Score ranges from 2 to 10. Based on this total Gleason Score, a prognostic grade group (I-V) is assigned Pierorazio et al. (2013) using a Gleason Score numbering system from 2 to 10 (Table 1).

Table 1: Prognostic Grade Group based on Gleason scores

Prognostic Grade	Gleason Score
Group I	≤6
Group II	3 + 4
Group III	4 + 3
Group IV	8
Group V	9 or 10

The TNM (Tumour, Node, Metastasis) staging system is also used for classification of prostate cancer. The following Table 2 will summarize the classification system:

Table 2: TNM Staging Classification System for Prostate Cancer (created using data from Canadian Cancer Society 2019)

	Tumour (T)	Node (N)	Metastasis (M)
0	--	Nearby lymph nodes do not contain cancer cells	Cancer has not spread to other parts of the body
1	Cancer is too small to be seen on scan or felt during DRE (classified into a, b, c)	Nearby lymph nodes contain cancer cells	Cancer has spread to other parts of the body outside the pelvis region (a = lymph nodes outside pelvis, b = bone, c = other parts of body).
2	Cancer is completely inside the prostate gland (classified into a, b, c).	--	--
3	Cancer has broken through capsule of the prostate gland (classified into a, b).	--	--
4	Cancer has spread into other bodily organs	--	--

Cancer risk in men with localized prostate cancer can be further characterized using approaches such as the one described by D'Amico, which stratifies patients into three risk categories: (i) low, (ii) intermediate, and (iii) high risk (Thompson et al. 2007; Lowrance et al. 2009) on the basis of the T-stage (described above), the blood concentration of prostate specific antigen (PSA) – a protein synthesized exclusively in the prostate – and the Gleason histological grade.

Table 3: Stratification of Prostate Cancer Severity

	Low	Intermediate	High
Tumour	T1-T2a	T2b	≥Tc2
PSA	< 10 ug/L	10-20 ug/L	≥20 ug/L
Gleason	<6	7	≥8
	< 25%	25-50%	>50%

(D'Amico et al. 1998; Heidenreich et al. 2008; Thompson et al. 2007).

1.2.4 Prostate Cancer Treatment

Treatment options for prostate cancer include: active surveillance, watchful waiting, surgery to remove prostate, external radiotherapy, internal radiotherapy, hormone therapy, chemotherapy, symptom control treatment, high frequency ultrasound therapy, and cryotherapy in some areas.

The most common type of hormone therapy is Androgen Deprovation Therapy (ADT). There are three main options for ADT interventions: (i) surgical castration, (ii) luteinizing hormone-releasing hormone (LHRH) agonist (also called gonadotropin releasing hormone (GnRH)), and (iii) GnRH antagonist. The two types of hormones have slightly varying pathways, but both disrupt the hypothalamic-pituitary-gonadal axis (Zareba 2015). GnRH agonists are the most commonly administered ADT for men with non-metastatic prostate cancer and have demonstrated to improve overall survival when combined with conventional therapy in intermediate-high risk prostate cancer that has not spread beyond the prostate (Yu et al. 2014; Nguyen et al. 2011; Shahinian 2010). Within six months of diagnosis, ADT is prescribed to approximately 40% of patients, and frequently prescribed in patients who have rising levels of PSA following radiation or radical prostatectomy therapy (Shahinian et al. 2010). Clinical progression is a major factor in adjusting treatment for prostate cancer patients, although a small minority also opt for additional preventative treatment despite not meeting clinical criteria for prostate cancer progression. Integrating prevention strategies during active surveillance, such as diet modifications, may reduce morbidity and healthcare costs (Parsons et al. 2017).

1.2.5 Prostate Cancer Risk Factors

The etiology and mechanisms underlying the development of prostate cancer remains uncertain. Risk factors for PC can be categorized into two types; (i) non-modifiable risk factors

and (2) modifiable risk factors. Non-modifiable risk factors include family history, race/ethnicity, and age and modifiable risk factors include diet, physical inactivity, smoking and obesity.

1.2.5.1 Non-Modifiable Risk Factors

(i) Age > 50

Approximately 60% of prostate cancer cases occur in men 65 years or older, and the average age at diagnosis is closer to 66 years of age (Bashir 2015). Data collected in the United States between 2007 and 2011 identified that 0.6% of cases diagnosed with prostate cancer were between the ages of 35-44; ages 45 – 54 were 9.7% of cases; ages 55 – 64 were 32.7% cases; ages 65 – 74 were 36.3% of cases; ages 75 – 84 were 16.8% of the cases; and 85 years or older were 3.8% of cases (Bashir 2015). The incidence rate rises sharply at around age 50, and progresses with age at a faster rate than any other major cancer (Fradet et al. 2009). Data surrounding the diagnosis patterns and age distributions of prostate cancer in Canada are similar to data from the United States.

(ii) Ethnicity

Table 1 is adapted from Fradet et al. (2009) and contains data from the SEER (The Surveillance, Epidemiology, and End Results) registry, showing the highest age-adjusted incidence rates among black men and the lowest rates among Asian/Pacific Islanders and American Indian/Alaskan Natives. Some possible explanations suggest that African-American men have a higher dietary fat intake in comparison to Asian/Pacific Islanders who may have a lower dietary fat intake (Whittemore et al. 1995; Fradet et al. 2009).

Table 4: SEER Incidence rates prostate cancer diagnosed by race in 2001-2005 from the United States National Institutes of Health

Race/Ethnicity	Age-adjusted Rate (per 100,000 men)
All races	163.0
White	156.7
Black	248.5
Asian/Pacific Islander	93.8
American Indian/Alaskan Native	73.3
Hispanic	138

*Adapted from Fradet et al. 2009

Although the SEER incidence rates are surprising in their high age-adjusted rate for blacks versus whites and other races, the difference in incidence rate is probably not due to ascertainment bias, as similar results have also been found in other studies. These results of higher incidence rates among African-Americans are consistent with findings from the CanCHEC study (Sritharan et al. 2017). The CanCHEC study was a large cohort study involving data from the 1991 Canadian Census Cohort and the Canadian Cancer Database (1969-2010), Canadian Mortality Database (1991-2011), and Tax Summary Files (1981-2011). The CanCHEC study identified 37, 695 cases of prostate cancer, with an increased risk of prostate cancer observed in black men compared to Caucasian men (HR: 1.77, 95% CI: 1.66-1.89; fully adjusted). A possible explanation for the increased risk of prostate cancer is related to socioeconomic factors, dietary differences, genetic predisposition, access to health care, and diagnosis disparities. It is important to acknowledge that within Canada the effect of socioeconomic status on healthcare usage and availability has not been ascertained as all Canadians have universal healthcare coverage, potentially reducing associated inequalities between the two countries (Veugelers and Yip 2003).

Disparities in the screening of black men is highlighted in a mixed-methods longitudinal study that identified five major elements that hinder screening for prostate cancer in black men:

lack of communication, lack of knowledge, lack of social support, fear of loss of sexual function and low quality of care (Woods et al. 2004). This explains poor outcomes but does not provide reasoning for high prostate cancer incidence rates.

(iii) Genetics and family history of prostate cancer

Consistent data are available highlighting the familial aggregation of prostate cancer, particularly in a first-degree relative (Bashir et al. 2014; 2015; Carter et al. 1992; Fradet et al 2009; Stanford & Ostrander 2001). Table 2 shows the positive relationship between the risk of prostate cancer and the strength of family history of prostate cancer.

Table 5: Relative risk and Lifetime risk of family history and prostate cancer

Family History	Estimated Relative Risk	Estimated Lifetime Risk (%)
No prostate cancer	1	8
Father diagnosed at or after 60 years	1.5	12
1 brother diagnosed at or after 60 years	2.0	15
Father diagnosed before 60 years	2.5	20
1 brother diagnosed before 60 years	3.0	25
2 male relatives* with prostate cancer	4.0	30
3 or more male relatives with prostate cancer	5.0	35-45

*Adapted from Fradet et al. 2009

Associations of five genetic loci with prostate cancer have been identified. The use of a genome-wide scan has identified region 8q24 as associated with higher risk of prostate cancer (Fradet et al. 2009). A small study completed by Ribeiro et al. (2012) was the first to provide evidence of differential gene expression in periprostatic adipose tissue of obese patients and prostate cancer aggressiveness. The study by Ribeiro et al. (2012) has been credited with providing a new perspective on prostate cancer progression and the microenvironment because they included 46% well-characterized genes in the array expression in periprostatic adipose tissue, which is comparable to omental adipose tissue (Lughezzani 2012, Ribeiro et al. 2012). Prior to his study, there was scarce data available on periprostatic adipose tissue. His findings

identified 34 differently expressed genes, for the first time, when comparing periprostatic adipose tissue of obese and overweight non-diabetic men to lean men (Ribeiro et al. 2012).

1.2.5.2 Modifiable Risk Factors

(i) Smoking

Cigarrette smoke is speculated to increase the risk of prostate cancer by altering the circulation of steriod hormones, particularly lowering bioavailable estradiol levels and increasing the bioavailable testosterone levels (Plaskon et al. 2003). Regulated levels of testosterone are necessary for normal prostate growth and development, and any alterations in testosterone could be associated with tumour growth. A meta-analysis of 24 prospective cohort studies with 26,000 prostate cancer cases found a modest 9-30% increase in both incident and mortality specific prostate cancer among current smokers (Huncharek et al. 2010). They found no associations between smokers (current or former) and prostate cancer incidence. The included studies did have broad categories of pack-years for former and current smokers (Huncharek et al. 2010).

(ii) Physical Inactivity

Given the widely accepted health benefits of regular physical activity, there is still interest in confirming an association between prostate cancer incidence and physical activity. However, whether physical activity reduces the risk of prostate cancer remains inconclusive (Benke et al. 2018). A meta-analysis that included 48 cohort studies and 24 case-control studies with a total of 151,748 PC cases with a mean age of 61 (Benke et al. 2018) showed no association between physical inactivity and prostate cancer incidence. They did find a reduced risk of prostate cancer mortality with increased physical activity, which is consistent among other studies (Benke et al. 2018; Kenfield et al. 2011). It is possible that physical inactivity does not increase risk, and physical activity reduces risk. However, it is also possible that due to the

latent of prostate cancer it is possible that the induction period of physical activity exposure and prostate cancer occurrence was missed.

(iii) Obesity

Excess weight may impact cancer related mortality, including prostate cancer mortality (Lew & Garfinkel 1979; WCRF 2014). The current recommendations for decreasing risk of PC include maintaining a healthy weight, eating healthy, and being physically active (WCRF 2014). Though many meta-analyses report a positive association between prostate cancer risk and high BMI, and most experts agree that obesity is a risk factor for prostate cancer, it is important to note that some heterogeneity between studies still exists (Allott et al. 2013; Cao et al. 2011; Discacciati et al. 2012; Hu et al. 2014; Keum et al. 2015; Macinnis et al. 2006; Renehan et al. 2008; Zhang et al. 2015). Studies also vary in their definition of obesity and overweight patients, making comparisons between studies complicated (Calle et al. 2003).

The Cancer Prevention Study II (CPS-II) done between 1982 and 1998 was the largest prospective study (900,000 participants; 45% men) that examined the relationship between body-mass index (BMI) and (any) cancer death during a follow-up of 16 years (32,303 deaths, 4,004 or 12% from prostate cancer) (Calle et al. 2003). The American Cancer Society outlines the methodology of this study and includes all questionnaires that were used. The patients of the CPS-II study received a baseline questionnaire in 1982 and Lifelink questionnaire 10 years later in 1998. The LifeLink questionnaire is named after the LifeLink cohort which was initiated in 1998 with the goal of collecting and storing blood samples and includes demographic, clinical and nutrition data. The researchers were unable to support an association for risk of prostate cancer with a high BMI but reported an increase in of death from prostate cancer patients with higher BMI (P-trend <0.001) (Calle et al. 2003). Mortality from prostate cancer included 1,971

deaths in the BMI grade 1 overweight category (25.0-29.9 kg/m^2 (RR: 1.08; 95% CI: 1.01-1.15)), 311 deaths in the grade 2 overweight category (30.0-34.9 kg/m^2 (RR: 1.20 (95%, CI 1.06-1.36)), and 41 deaths in the grade 2 overweight (35.0-39.9 kg/m^2 (RR: 1.34 (95%, CI 0.98-1.83)). The authors included numerous potential confounders in data analysis, including age, race (white, black or other), smoking (never, former, current), education (< high school, high school, some college, college), physical activity (none, slight, moderate, heavy), alcohol use (none, <1 drink/day, 1 drink/day, >2 drinks/day), marital status (not married, married), current aspirin use (use or nonuse), crude index of fat consumption, and vegetable consumption.

Another large-scale cohort study of participants in the Norwegian screening program included 950, 000 men between the ages of 20-74 years of age followed for 21 years. This screening program was compulsory for individuals over the age of 15 and enrolled 1.7 million people between 1963 and 1975. The cohort study identified 33, 300 (3.5%) with a diagnosis of prostate cancer cases when it was linked to the Cancer Registry of Norway and the Death Registry at Statistics Norway (Engeland et al. 2003). All enrolled individuals were followed until death or emigration from Norway. To assess prostate cancer risk and obesity, only verified prostate cancer cases were included and all diagnosis prior to height/weight measurements were excluded. Out of the recruited patients, only seven were lost to follow-up, 58.3% were alive and had no diagnosis of prostate cancer, 38.2% died, and 3.5% had a verified diagnosis of prostate cancer.

Table 6: Relative Risk of Prostate Cancer from Cox Regression Analysis by age and BMI or height

Variable	Age (years)							
	50-59 (1813 cases)		60-69 (9511 cases)		70-79 (15429 cases		80-89 (6432 cases)	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
BMI (kgm^{-2})								
<18.50	0.82	0.41-1.65	0.89	0.65-1.22	0.80	0.62-1.02	1.05	0.76-1.47
18.50 – 24.99	1	Referent	1	Referent	1	Referent	1	Referent
25-29.99	1.13	1.02-1.25	1.04	1.00-1.09	1.07	1.04-1.11	1.07	1.02-1.13
≥30.00	1.58	1.29-1.94	1.00	0.91-1.10	1.07	1.00-1.14	1.04	0.93-1.15
Height (cm)								
<160	0.45	0.17-1.19	0.45	0.32-0.64	0.70	0.59-0.82	0.63	0.50-0.79
160-169	0.83	0.72-0.97	0.88	0.83-0.93	0.92	0.89-0.96	0.84	0.80-0.89
170-179	1	Referent	1	Referent	1	Referent	1	Referent
180-189	1.03	0.92-1.14	1.09	1.04-1.15	1.07	1.02-1.11	1.02	0.95-1.11
≥190	0.85	0.60-1.21	1.33	1.13-1.56	1.01	0.83-1.24	1.03	0.66-1.60

**adjusted for birth cohort and age at measurement
(Engeland et al. 2003)

The authors also explored the relationship between BMI and age groups by stratified analyses on attained age and age at measurement. The authors reported excess risk of prostate cancer in obese men irrespective of age, however, there was a higher obesity-associated risk in men who were youngest at the time of measurement (Engeland et al. 2003). Among 50 to 59-year-olds, overweight men (BMI ≥ 30.0 kg/m^2) had a RR of 1.58 (95% CI: 1.29-1.94) when compared to men who were in the normal BMI range in that age group. Overall, there was a modest increase in the risk of prostate cancer by increase of BMI.

A large Swedish retrospective cohort study of 135, 006 construction workers (2368 cases; 1.8%) enrolled between 1971 and 1975 and followed for 20-years examined body size (BMI) and prostate cancer (Andersson et al. 1997). This retrospective cohort study is the largest that solely focuses on prostate cancer patients and obesity as a risk factor. The BMI reference

category was <22.1 kg/m^2, and compared the following categories for incidence of prostate cancer: (i) 22.1-24.1 kg/m^2 (499 cases) RR: 1.09 (95%, CI 0.94-1.26), (ii) 24.2-26.2 kg/m^2 (676 cases) RR: 1.10 (95%, CI 0.96-1.26), and (iii) >26.2 kg/m^2 (899 cases) RR: 1.13 (95, CI 0.99-1.29), with P for trend = 0.10. The risk of prostate cancer mortality was significantly higher in all BMI categories that were above the reference category of <22.1 kg/m^2 with RR: 1.4, 95% CI: 1.09-1.81 in the highest category (>26.2 kg/m^2). Andersson et al. (1997) predicted that this trend could be explained with associations of high levels of estrogen and lower levels of testosterone and sex hormone-binding globulin in obese participants. The physiological mechanisms of levels of endocrine aberrations, fat distribution and hormone metabolism are still unclear. All other anthropometric measurements, weight, height and lean-body-mass, had a positive association with risk of prostate cancer that was statistically significant (Andersson et al. 1997).

In 2012 Allott and colleagues published an important review of the existing literature in prostate cancer and obesity and concluded that obesity was associated with aggressive prostate cancer, and a modest association with prostate cancer risk (Allott et al. 2013). This review included 97 RCTs, prospective population-based studies, systematic reviews, and meta-analyses of case-control studies and reviews. The review by Alott (2012) found three meta-analyses that reported a positive association between obesity and prostate cancer incidence . The studies had modest RRs from 1.01 (95% CI, 1.0-1.02 per 1 kg/m^2 increase in BMI (Bergstrom et al. 2001), and RR 1.05 (95% CI, 1.01-1.08 (MacInnis and English 2006), and RR 1.03 (95% CI, 1.0-1.07) per 5 kg/m^2 increases in BMI (Renehan et al. 2008). Looking more closely at the individual studies included in the three meta-analyses, it became evident that they were strikingly different (Allott et al. 2013). They varied in sample size quite drastically, with two out of three (MacInnis and English 2006, Renehan et al. 2008) meta-analyses obtaining over 50% of their patients from

one aforementioned Norwegian study (Engeland et al. 2003). The third meta-analysis obtained more than half of its cases from a Swedish registry, also discussed above (Andersson et al. 1997). These two Scandinavian studies are major contributors to the positive association findings between obesity and risk of prostate cancer and influenced the authors to explore the data further by separating it into geographical areas. The researchers found unique patterns between distinct geographic regions. In North America, studies show no effect of obesity on prostate cancer risk (RR: 1.0; 95% CI: 0.96-1.03), and European and Australian studies show a modest, yet significantly positive, association of prostate cancer and obesity (RR: 1.04; 95% CI: 1.01-1.07), per 5kg/m^2 increase in BMI (Allott et al. 2013). A possible explanation could be the lower rate of PSA screening in Europe and prostate cancer may be diagnosed at more advanced stages. Obese men tend to have lower PSA values (7% lower for BMI: 25-30kg/m^2, 14% lower in BMI: 30-35kg/m^2, 18% lower in BMI >35kg/m^2) compared to normal weight patients (BMI: <25kg/m^2) and this may reduce PSA-driven biopsy rates and cause detection bias (Hekal and Ibrahiem 2010). Some other possible explanations for a potential association between obesity and risk of prostate cancer could be biological body changes that are common in obese patients (eg. insulin resistance, cell migration, inflammation, angiogenesis), as well as a change in adipokine levels that are also related to prostate cancer aggressiveness (Di Francesco and Tenaglia 2014).

(vi) Diet

Prostate cancer has a long latency period and there is little information on dietary patterns prior to or at the time of prostate cancer diagnosis. Most of the foods generally recommended for various chronic diseases, such as fruits, vegetables, legumes, nuts, and fish, are good candidates to be assessed as protective foods for prostate cancer. Other foods are more controversial and

there are no obvious conclusions on recommendations of consumption, such foods include dairy and meats.

In a prostate cancer summary report completed in 2014, the World Cancer Research Fund (WCRF) reviewed 104 global studies (~9 million patients) and compared to their report from the "2007 Second Export Report" to evaluate how prostate cancer recommendations have changed. Diet as a risk factor was a major focus of their review and provides insight to current expert opinions. According to the WCRF 2014 report, there is limited evidence that draws conclusions about any one specific type of food item, nutrient or supplement with a decreased or increased risk of prostate cancer. In 2007 they stated in their report that there is strong evidence that diets high in calcium have an increased risk of prostate cancer, in their recent 2014 report this changed to limited evidence. Similarly, they downgraded their conclusion from strong evidence that selenium and lycopene lower the risk of prostate cancer to limited evidence (WCRF 2014). Instead of focusing on any particular food item, the new recommendations to reduce the risk of prostate cancer are to eat a healthy diet, be physically active, and maintain a healthy weight. As a result of these conclusions, studies have begun to review overall diet. Diet as a modifiable risk factor is a major topic of this dissertation and will therefore be discussed in detail in section 1.2.6.

1.2.6 The Evolution of Diet Research in Prostate Cancer

Dietary intake has always been of relevance for many cancers as well as other major diseases, namely cardiovascular disease and lately, mental health. Diet plays a major role in our society and as such, the trends of diet research are quite complex. Specific nutrients, food items and supplements, to either treat, prevent or reduce the risk of prostate cancer have continuously engaged the interest of researchers and patients. Some of these findings have helped influence

current recommendations of what food groups/items are an important part of a healthy diet. However, recently, there has been an emergent trend in diet and disease research that focuses on overall dietary eating patterns and promotes long-term healthy eating habits.

To begin reviewing the vast available literature, this section will summarize findings from individual food items and groups that were considered vital topics in prostate cancer diet research (dairy, red meat, fat and vegetables), followed by a summary on available research on the Mediterranean diet and prostate cancer, and finally, a discussion on studies that looked at overall dietary eating patterns and prostate cancer. This includes one major high impact RCT on diet and prostate cancer (Parsons et al. 2018), and a few prospective studies.

1.2.6.1 Dairy

There are many studies of specific food items or food groups. Dairy has been one of those food items that has captivated the curiosity of researchers and the current recommendations regarding dairy have considerably changed in the last decade.

Harrison et al. published the largest meta-analysis on high milk intake and increased risk of prostate cancer including 172 studies (RCTs, observational, biomarker, animal models and genetic studies) (Harrison et al. 2017). They extracted the data from all included studies, combining similar studies together and concluded that there was some evidence that risk of prostate cancer increased with insulin-like growth factor-I (IGF-I) (OR 1.09; 95% CI 1.03, 1.16, n=51 studies). However, authors found that the evidence was not strong enough because studies that investigated the association between IGF and milk did not have sufficient data to perform a meta-analysis, and thus were unable to calculate a combined effect estimate and make definitive conclusions (Harrison et al. 2017). It is important to note that authors did not differentiate between assessment methods, all types of questionnaires were included regardless of their

validity in the population being studied. Additionally, measurement errors and other diet and lifestyle confounders may impact study results.

In their 2014 report the WCRF and American Institute for Cancer Research amended their conclusions in 2007 Second Export Report, in which they stated that high intakes of dairy are associated with an increased risk of prostate cancer (WCRF 2014). They showed a 7% increased risk per 400 g of dairy products consumed per day in prostate cancer risk (RR 1.07; 95% CI 10.2-1.12). When stratified by prostate cancer type (non-advanced, advanced, fatal), there was no association per 400 g of increased consumption. The panel concluded that the evidence for increased risk of prostate cancer with higher consumption of dairy as a whole food is limited (WCRF 2014).

1.2.6.2 Red Meat

A popular topic in diet research is meat (processed and unprocessed) and prostate cancer risk, and much like dairy, results from studies are very inconsistent. In one cohort study 940 men completed an FFQ (validated and based on Willet/National Cancer Institute Diet History Questionnaire) with 137 food items. Participants with higher intake of total red meat had a marginally greater risk of high-grade prostate cancer with a Gleason ≥4+3 (top vs. bottom quartile, adjusted OR 1.66; 95% CI 0.93-2.97. p=0.05). Similarly, consuming well and very well-done meat (OR 1.72; 95% CI 0.99-3.01) showed an increased risk of high-grade prostate cancer (Wilson et al. 2016). One of the main study limitations is lack of information about participants pre-diagnostic PSA screening (which can often lead to healthier behaviours).

A pooled analysis of 15 prospective cohort studies that included over 52,000 prostate cancer cases calculated study-specific relative risks and pooled the data using a random effects model (Wu et al. 2016). They applied the following inclusion criteria (i) at least one publication

on any diet and cancer association, (ii) assessment of long-term diet, (iii) validation of the dietary assessment method or a closely related dietary instrument, (iv) at least 50 incident cases of prostate cancer (Wu et al. 2016). The data showed no associations between total red (RR 0.99; 95% CI 0.94-1.03), unprocessed red (RR 1.02; 95% CI 0.98-1.06), and processed read meat (RR 1.04; 95% CI 1.01-1.08) for risk of prostate cancer (Wu et al. 2016). The prospective design, large sample size and minimization of selection bias strengthen this study. Their major limitation was not accounting for cooking methods of different meats, i.e. frying versus baking. The WCRF (2007; 2014) concluded in both reports there are no conclusions/limited evidence regarding whether being exposed to high intakes of red meat contributes to the prostate cancer incidence rate or progression.

A recent publication provided recommendation based on the Nutritional Recommendations (NutriRECS) guideline development process, which is a rigorous systematic review methodology and GRADE methods to rate certainty of evidence for each outcome (Johnston et al. 2019). They concluded with weak recommendations that people continue with their current consumption of both processed and unprocessed red meats stating five main reasons for their findings: (i) the certainty of evidence for adverse health outcomes associated with meat consumption was low to very low with similar effect estimates for red meat and processed meat, (ii) small or no risk reduction based on realistic decrease of three servings of red or processed meat weekly, (iii) if the very small exposure effect is true, based on how omnivores value their meat consumption, a small associated risk will likely not inspire a reduction of red meat or processed meat, and (iv) the panel considered health outcomes exclusively, and disregarded environmental and animal welfare (Johnston et al. 2019).

1.2.6.3 Fats

Whether fats are good or bad has been disputed for some time now. Some recent studies focused on reducing saturated fat to 10% of energy, which is aligned with current recommendations for healthy eating promotion. A small prospective case-control study of 384 men diagnosed with prostate cancer between 1990 to 1992 with a mean follow-up of 5.2 years used a diet history questionnaire (different from the FFQ) and a trained nutritionist to keep track of diet (Fradet et al. 1999). They focused on total energy from fat and found that men in the upper tercile had three times the risk of dying from prostate cancer (HR=3.13, 95%, CI 1.28-7.67) and recommend reducing fat to reduce the risk from dying from prostate cancer (Fradet et al. 1999). Since then, fats have become a debated topic. The Canadian Food Guide was updated for the first time 12 years, and now recommends only 2-3 Tbsp of oils and fats per day. Although the recommendations are high for vegetables and fruits, some recent studies have challenged their recommendation for fats.

Fats can be divided into three main categories: unsaturated fats, saturated fats (eg. Coconut oil), and trans fats. Unsaturated fats are further split into monounsaturated (eg. Avocados, almonds, peanuts, olive and canola oil) and polyunsaturated fats (eg. fish, sunflower, walnuts, flax seeds). One prospective Health Professionals Follow-up Study initiated in 1986 included 51,529 males between 40 and 75 years of age and introduced PSA screening in 1994 (Richman et al. 2013). Men were asked biannually whether they had a diagnosis of prostate cancer and completed annual FFQ's. The Health Professionals Follow-Up Study included a total of 4,577 men who had no previous history of cancer (except non-melanoma skin cancer), but who developed prostate cancer after enrolment into the study. Cox proportional hazards

regression models were used to evaluate the relationship between saturated, monounsaturated, polyunsaturated, trans, animal, and vegetable fat intakes, with lethal prostate cancer and all-cause mortality. The consumption of vegetable fat intake (oil-based dressing, margarine, mayonnaise, nuts) was found to be associated with a lower risk of 13% all-cause mortality (HR: 0.87; 95% CI: 0.72, 1.05) and 29% lower risk of lethal prostate cancer (HR: 0.71; 95% CI: 0.50, 1.00) (Richman et al. 2013). Patients who increased their nut intake by one serving daily post diagnosis were suggestively associated with a 11% lower risk of death (HR:0.89; 95% CI: 0.79, 0.99) and an 18% lower risk of lethal prostate cancer (HR: 0.82; 95% CI: 0.67, 1.01). A similar magnitude of association was found with replacing animal fat with vegetable fat, however, it was not statistically significantly (HR: 0.76, 95% CI: 0.52, 1.10, p-value: 0.14). It is unclear whether patients were advised to increase their intake of vegetable fat or in any other way alter their diet post diagnosis. However, the authors did conclude that their study findings merit counselling men to increase their vegetable fat intake and follow a "heart healthy diet" post diagnosis.

1.2.6.4 Vegetables

Whether vegetables have an impact on prostate cancer progression or incidence is also inconclusive. The Epic study is a large prospective cohort study in which the relationships between dietary and lifestyle factors, and cancer and other chronic diseases are examines. An analysis of EPIC specifically on prostate cancer risk and fruit and vegetable intake was performed. The highest level of intake of fruit was associated with a significantly reduced risk of prostate cancer (HR=0.91; 95% CI 0.83-0.99, p=0.01), but no associations with vegetables and prostate cancer incidence were demonstrated. Others found an association with some vegetables, but acknowledge that the evidence is limited and requires a prospective methodology with a larger sample size (Chan et al. 2009). Most studies evaluate subtypes of fruits and vegetables and

prostate cancer risk and progression, such as citrus fruits or leafy vegetables. There a few methodological limitations; in particular, diet in most populations is not isolated and can be influenced by many confounders. It is difficult to conclude with certainty that a specific vegetable or a precise type of fat alone are contributing as risk factors or impacting prostate cancer progression. This is evident in studies that look at different diets that are similar, but have some variations, such as the difference between the Mediterranean diet and the prudent diet (Castello et al. 2018).

1.2.6.5 The Mediterranean Diet

Arguably, the Mediterranean diet has been one of the most increasingly relevant nutritional topics in the last few years, and it has been in the spotlight for many diseases including prostate cancer. Most study findings appear to favour the Mediterranean diet. The trend has also played a role in nutrition and prostate cancer research, yielding strong evidence supporting associations between foods typical of a Mediterranean diet and prostate cancer risk and progression. In the Health Professionals Follow-up Study, 47,867 men were followed between 1986 and 2010, during which 4538 were diagnosed with prostate cancer (Kenfield et al. 2013). Their diets were evaluated using a validated FFQ, where the mean Pearson correlation of all foods comparing the FFQ and diet records was 0.63 and 73% of food items had a correlation of ≥ 0.50, which is well in the acceptable range of a dietary tool validation study. They used a diet score to indicate whether adherence to the Mediterranean diet was low, moderate, or high. In order to obtain the diet score, the total points were added for specific food groups considered to be a part of a Mediterranean diet. One point for being above the median of each of the following: vegetables, fruits and nuts, legumes, cereals, fish and seafood, fat, and alcohol. One point for being below the median for each of the following: red and processed meats, and dairy products.

The authors observed a 22% reduced risk of overall mortality in men with prostate cancer (HR: 0.78; 95% CI, 0.67-0.90) in participants who had a high adherence to the Mediterranean diet (scores 6-9) compared to participants with a low adherence (scores 0-3). The major limitation of this study design was that they were unable to evaluate whether a change in diet happened before and after diagnosis (Kenfield et al. 2013).

The Prostate Cancer Project (PCaP) evaluated the difference between the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet scores with respect to prostate cancer aggressiveness (Schneider et al. 2019). The authors found that higher Mediterranean diet scores were inversely associated with aggressive prostate cancer (OR 0.66; 95%, CI 0.46-0.95), concluding that a Mediterranean diet may reduce the odds of prostate cancer that is highly aggressive (Schneider et al. 2019). These two studies are not isolated in their results, studies by Erdrich et al. (2015), Bray et al. (2010) and an RCT done by de Lorgeril et al. in 1988 had the same conclusions. The Mediterranean diet has additionally played a role in other outcomes for patients with prostate cancer, such as sexual and urinary function. These outcomes are considered patient-important outcomes, since many patients with prostate cancer experience either sexual and/or urinary dysfunction post treatment (average age of participants=68) (Bauer et al. 2018).

Most of these studies examined the Mediterranean diet against either food groups or a diet that is drastically different. Cestello et al. (2018) did a multicase-control study in Spain across seven provinces (2008-2013) with 754 cases with a Gleason score ≥6, and 1,277 controls (ages 38-85). They identified three types of diets: “Western,” “Prudent,” and “Mediterranean.” A Western diet is high fat dairy, refined grains, processed meat, sweets, caloric drinks, convenience foods and sauces, and low intakes of low-fat dairy products, vegetables, fruits, whole grains, and

juices. The prudent pattern is a high intake of low-fat dairy products, whole grains, vegetables, fruits, and juices. The Mediterranean diet was classified as high intake of fish, vegetables, boiled potatoes, legumes, fruits, olive oil and olives (Castello, et al. 2018). They interviewed all their participants in a face-to-face interview to collect sociodemographic information and a medical history, and assessed diet using an FFQ that was previously validated that was sent home with patients and returned by mail (Castello et al. 2018). Importantly, a bivariate analysis found no difference between adherence to the three diets between controls and cases. They found that high adherence to the Mediterranean diet was associated with a lower risk of Gleason score >6. They assessed this by dividing the Gleason score ≥6 cases into quartiles, quartile 3 versus 1 had a RR of 0.66 (95%, CI 0.46-0.96) and quartile 4 versus 1 had a RR of 0.68 (95%, CI 0.46-1.01), p-trend = 0.024 (Castello et al. 2018). There is an overlap between the prudent and the Mediterranean dietary pattern, yet the prudent diet showed no effect. This is a key conclusion from this study as it points to looking at dietary patterns rather than foods. The additions to the Mediterranean diet that differ from the prudent diet is fish, boiled potatoes, olive oil and olives. Studying a dietary pattern that is well balanced and promotes a healthy lifestyle is easier to promote to patients. Knowledge translation is a large part of research, the end goal being improvement of patient care and reducing disease burden on the individual patient and society. These conclusions are the rationale for using diet scores of main food groups for this dissertation rather than focusing on single food items.

1.2.6.6 Dietary patterns in prostate cancer

RCT studies are accepted as the strongest evidence-based research method in determining a cause-disease relationship, however, methodological design issues arise when attempting a dietary intervention RCT. Monitoring dietary intervention often involves a higher frequency of

check points, such as interacting with patients regularly, offering dietary counselling, and sometimes providing feedback recurrently. Patient adherence to dietary interventions and monitoring dietary adherence is also complicated. The higher frequency of check points requires substantially more involvement when compared to some other RCT studies that place patients on a surgical intervention or a new medication that yields higher adherence to the intervention than a dietary intervention would (Crichton et al. 2012). Due to these methodological restrictions, it is difficult to establish a definite causal relationship between diet and prostate cancer incidence and progression.

One successfully implemented RCT with a dietary intervention investigates the influence of a "healthy diet" in reducing morbidity to prevent clinical progression. This recently completed RCT (Parsons et al. 2018) was a phase III clinical trial testing the efficacy of a high-vegetable diet to prevent cancer progression in patients with prostate cancer who are currently on active surveillance. Preliminary evidence implies that an increased intake of vegetables, and decreased intake of fats in patients with prostate cancer may lead to progression-free survival (Frattaroli et al. 2008; Parsons et al. 2018; Richman et al. 2012; Richman et al. 2013). In the Men's Eating and Living (MEAL) study (CALGB 70807 [Alliance]) participants with prostate cancer were randomized to a validated diet counselling intervention or the control group that received no diet counselling. Between 2011 and 2015 464 participants with a mean age 64 (SD 6.4) years and mean PSA concentration of 4.9 (SD 2.1) ng/mL were randomized. The total vegetable servings increased and fat calories decreased in the intervention group at two time points; 12 and 24 months. This is the largest study that randomized prostate cancer patients to a dietary intervention. They were able to show feasibility of implementing a phase III clinical trial for diet and prostate cancer with an intervention predicted to prevent disease progression (Parsons et al.

2018). They presented their results at the 2018 AUA meeting, but have not published their results in a journal yet. They found no difference between the intervention and the control for time to progression (HR 0.96; 95% CI 0.75-1.24). Likewise, they no difference in the risk of serum PSA ≥ 10 ng/mL and PSA doubling time < 3 years (HR 0.86; 95% CI 0.65-1.13) (presented by Parsons in San Diego AUA 2018). The authors concluded that no effects were seen after two years of this dietary intervention, but that it was a successful behavioural intervention and that long-term effects are unclear.

A number of prospective studies have explored diet in prostate cancer using FFQ's. One study analysed patients enrolled in the PCaP (North Caroline-Louisiana Prostate Cancer Project) population-based, cross-sectional study of risk of highly aggressive prostate cancer in African American/Black or Caucasian American/White men (Arab et al. 2013). The goal of PCaP was to analyse the effect of adherence to the WCRF lifestyle recommendations, which was not previously analysed, and address the relationship between prostate cancer aggressiveness and lifestyle (diet and exercise) changes. The WCRF had 7 recommendations: (1) maintain BMI within normal range 21-23, (2) Engage in at least 60 minutes of moderate or 30 minutes of vigorous physical activity daily, (3a) limit consumption of energy-dense foods, (3b) avoid sugary drinks, (4a) eat at least 5 servings of non-starchy vegetables and fruits every day, (4b) eat at least 25 g of unprocessed grains/cereals and legumes per day, (5) eat less than 500 g (18 oz) of red meat per week, (6) limit alcohol intake to 2 drinks per day for men and 1 drink per day for women, and (7) limit sodium intake to less than 2.4 g per day. Patients were eligible if they were between 40 and 79 years of age, self-identified as "white/Caucasian American" or "black/African American," and were able to complete the questionnaire in English. Participants completed questionnaires on prostate cancer characteristics, demographics, lifestyle, clinical

characteristics, and nutrition. In total 2,212 newly diagnosed participants were enrolled between 2004 and 2009. Gleason scores, TNM stage, and serum from the PSA test were used to estimate prostate cancer aggressiveness. Patients were categorized as either 1) highly aggressive (Gleason sum ≥8, or PSA >20ng/ml, or Gleason sum ≥7 and clinical stage cT3-cT4) or 2) low aggressiveness (Gleason sum<7, clinical stage cT1-cT2, and PSA <10ng/ml). The Dietary History Questionnaire, similar in format to the FFQ primarily used in North America (Kelemen et al. 2003), was implemented to determine adherence to the WCRF recommendations for reducing prostate cancer aggressiveness. Adherence for each recommendation was assigned a binary code 1 = adherence, and 0 = did not adhere to guideline.

The analysis involved a total adherence score from 0 to 9, with 9 being completely adherent to recommendations. This was done for a planned risk model analysis for high adherence to the recommendations and prostate cancer aggressiveness. An adjusted multivariate logistic regression model was used to evaluate adherence for each of the 9 WCRF recommendations. They adjusted for study location (either in Louisiana or North Carolina), level of education, age of diagnosis, and smoking (Arab et al. 2013). A higher total adherence score was inversely associated with the occurrence of highly aggressive prostate cancer (OR: 0.87; 95% CI: 0.79-0.96) (Arab et al. 2013). The analysis demonstrated a correlation between eating energy-dense foods (classified as > 125 kcal/100g) and an increased risk of prostate cancer aggressiveness (Arab et al. 2013). The strongest contributors to decreased risk of highly aggressive tumors was consumption of ≤125 kcal/100 g non-beverage food per day (OR: 0.71; 95% CI: 0.51, 0.99) and <500 g of red meat/week (OR: 0.77; 95% CI: 0.61, 0.98). There was no difference between patients who had 5 servings of fruits/non-starchy vegetables and patients who did not adhere (< 5 servings of fruits/non-starchy vegetables) to the WCRF 4a recommendation

(OR: 1.01; 95% CI: 0.80, 1.28). However, there were not enough research participants who had an adherence scores of 7 or higher, and a risk model at the high end of the adherence program was not established. Of all participants, <5% were compliant with the recommended maintenance of a BMI of 21-23 kg/m^2, and subjects not within the range were considered nonadherent. Overall, authors predicted a 38% increased risk of prostate cancer tumor aggressiveness if the adherence was <4 out of 9 compared to an adherence of ≥ 4 (Arab et al. 2013).

A recent review by Peisch et al. (2017) summarizes existing evidence while looking at diet and lifestyle factors of patients with prostate cancer post diagnosis. The study by Peisch et al. (2017) focused on factors commonly investigated in patients with prostate cancer, such as BMI, smoking, dairy/calcium, red meat, etc. The following table is a summary of their findings:

Table 7: Selected risk factors and risk of prostate cancer progression (Peisch et al. 2017)

Increased Risk	Decreased Risk
BMI ****	Physical Activity ****
Smoking ****	Fish **
Dairy/calcium **	Tomatoes/Lycopene **
Processed red meat *	Vegetable fat **
Eggs/choline *	Cruciferous vegetables **
Poultry (w/ skin) *	Coffee *
Animal fat/saturated fat *	Soy *
Selenium supplementation *	Tea *

* Number of asterisks indicates the assessment of *strength of evidence,* not the magnitude of effect. A greater number of * indicates greater confidence in association (Peisch et al. 2017).

1.2.7 Defining a Healthy Diet

The studies above either reviewed different types of diet (i.e. Western, Mediterranean) or the percentage of energy intake between different groups and the association between diet and

disease (Dehghan et al. 2012; Dehghan et al. 2018; Igbal et al. 2008; Mente et al. 2009; Mente et al. 2017; Miller et al. 2017). The are some clear limitations of only focusing on one food item, primarily, longevity. Participants have a hard time adhering to diets asking for specific nutrient changes during the course of a study, and it increases in difficulty if advising for long-term changes. Recent findings from the PURE study by Mente, Dehghan, and Miller (2017, 2018) have been rudimentary in the definition of a "healthy balanced diet" and the methodology behind developing the diet score (section 2.8). The healthy balanced diet will include (i) fruits, (ii) vegetables, (iii) legumes, (iv) nuts, (v) fish, (vi) dairy, (vii) unprocessed red meat, and (viii). Avoiding extreme levels of intakes of any food groups and focusing on a balanced lifestyle (Dehghan et al.2017; Mente et al. 2017; Miller et al. 2018). The current literature reaffirms that balanced nutrition plays a significant role in overall healthy lifestyle habits and prostate cancer. Nutrition is potentially one of the most modifiable risk factors and is implicated in prostate cancer progression/stage as well as prostate cancer risk factors.

1.2.8 Healthy Diet Score

The eight foods associated with lower mortality (fruits, vegetables, dairy, unprocessed red meat, poultry, fish, legumes, and nuts) are used to calculate the diet quality score based on recent findings published and presented at the ESC Congress (28 Aug 2018). These findings justify the use of this particular diet quality score and the definition of a *healthy balanced diet.* Every participant is given a score of either 0 or 1 for each of the eight foods, where a score of 0 indicates an intake of the food that is below the median for the RADICAL PC cohort, and a score of 1 indicates an intake of the food that is equal to or above the median. The score for each food item is added to calculate a total score ranging from 0 to 8 points; higher scores are characteristic of a healthier diet. These scores are then separated into four categories (0-3, 4, 5, 6-8). This data

could not be distributed into equal quintiles, as done in the PURE study (ESC Congress 2018). Additionally, the data was also divided into tertiles (low quality diet: 0-3, intermediate quality diet: 4-5, high quality diet: 6-8).

1.2.9 Literature Summary

Although prostate cancer has a high prevalence, it has a long latency period with increased survivorship and clearly defined stages of progression. Nutritional research on prostate cancer predominantly focused on nutrients and individual food items and only recently have a few studies emerged with dietary patterns or studies that review the effect of specific diets on prostate cancer progression. It remains unknown whether there is an optimal recommended diet that can reduce prostate cancer incidence and decrease prostate cancer severity at diagnosis. Nutritional studies in prostate cancer are feasible, as established by the feasibility study of an RCT of prostate cancer patients and diet adherence, and are of interest to patients and the medical community.

1.3 HYPOTHESIS

We hypothesized that in newly diagnosed prostate cancer patients, a healthier diet score is associated with lower prostate cancer severity.

1.4 METHODS

1.4.1 Research Question

(1) In prostate cancer patients in the RADICAL PC study at baseline, is a healthier diet (higher Healthy Diet Score) associated with lower prostate cancer severity?

1.4,2 Study population

The RADICAL PC study was previously described in the introduction of this thesis. This analysis will include baseline data across all 15 Canadian sites involved in the RADICAL PC

study, including: Juravinski Hospital, St. Joseph's Hospital (Hamilton), Queens University, London Health Sciences (twosites), Jewish General, Laval University, CHUM, Ottawa, McGill University, UHN, Niagara Health, Woodstock Hospital, Grand River Hospital and Vancouver General. Recruitment for the study began October-2015. and this analysis includes patients until August-2019. All research assistants on the study receive the same comprehensive training from the coordinating centre. The data from each site is transferred electronically to the coordinating centre at Population Health Research Institute (Hamilton ON), and underwent quality control checks by the local study team. All participants provided informed consent, which was approved by their local board of ethics. The protocol and provisional approval were done by the Hamilton Health Sciences Research Ethics Board (HiREB).

1.4.3 Baseline data description

Information on participants medical history, medications, exercise, demographic and other anthropometric data was collected at baseline along with a SFFQ (see Appendix III for the SFFQ used in RADICAL PC and Chapter 2 for the Comparability Study done to evaluate the use of the SFFQ). RADICAL PC also collected grip strength, blood pressure, and Cardiovascular important data, which is not covered in the scope of this dissertation. The SFFQ at baseline was completed by a total of N =2,243 participants across all sites.

1.4.4 Data Management

All data management and analysis were completed in STATA IC 14.2 College Station, TX 77845. Data was extracted from iDataFax into a .dta file for STATA. All visits (i.e. 3,6-month follow-up etc.) were discarded and only baseline data was reviewed. Patients were categorized into PC1 (observational) or PC2 (RCT), stratified by prostate cancer severity (Table 3: Stratification of Prostate Cancer Severity), and given a Healthy Diet Score (as described in

section 2.8). Additionally, data was cleaned and organized for ethnicity, education, smoking, diabetes, BMI (calculated weight kg/height m^2), categorized into obesity (underweight <18.5kg/m^2, healthy BMI 18.5-25 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m^2), categorized into Gleason Scores (≤6, 3+4, 4+3, 8, "9 or 10"), PSA at enrollment and PSA categories (≤10, 10-20, >20), and Clinical Stage (i.T0 ii. T1, T1a, T1b, T1c iii. T2, T2a, T2b, T2c iv. T3, T3a, T3b, T4).

Data preparation for the nutritional data is described in detail in Chapter 2 (section 2.4.7), with the exception of one additional step. Frequency of consumption was calculated (not extracted by data management team as in Chapter 2) as follows:

Table 8: Conversion of Response from iDataFax to Frequency of Consumption

Response in iDataFax	Calculation	Frequency of Consumption
1 = never or <1/month	1x0	=0
2 = 1-3/month	2/30.5	= 0.0657
3 = 1/week	1/7	= 0.1429
4 = 2-4/wk	3/7	= 0.4286
5 = 5-6/wk	5.5/7	= 0.7857
6 = 1/day	1x1	= 1
7 = 2-3/day	1x2.5	= 2.5
8 = >4/day	1x4	= 4

1.4.5 Statistical Analysis Plan

Descriptive statistics were used to describe the specific characteristics of the baseline data and presented as mean, standard deviation, and percentage. The descriptive and anthropometric data is available in Table 9 for all baseline characteristics of participants in RADICAL PC. To analyze whether an association exists between high risk prostate cancer and a low Healthy Diet Score, a Logistic Regression was done. The patients were placed into two groups of prostate cancer risk: (i) Low & Intermediate Risk and (ii) High Risk and were compared against the

categorical values of the Healthy Diet Score. The Healthy Diet Score was analyzed individually, grouped by four categories and tertiles. The following co-variates were adjusted for: age, tobacco (never, former, current; categorical), diabetes (yes or no), BMI (healthy 20-25 kg/m^2, underweight <20 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m2; categorical), and education (< High School, High School, > High School; categorical).

1.5 RESULTS

As previously explained, the diet score uses the median grams per day to classify a participant as "healthy" or "unhealthy" for that group (Table 9). Participants were considered healthy if they were at or above the median, and unhealthy if they were below the median.

Table 9: Median intake of Grams per Day for Food Groups in the Healthy Diet Score

Food Group	Median intake (grams)
Fruits	125
Vegetables	107.15
Legumes	18.01
Nuts	4.29
Fish	12.52
Dairy	267.89
Red Meats	28.58
Poultry	42.68

Using these classifications of healthy versus unhealthy for the 8 food groups that are part of the Healthy Diet Score, participants were given a total score out of 8.

Table 10: Number of participants in individual Healthy Diet Score for RADICAL PC baseline data

Diet Quality Score	Number of Participants (%)
0	25 (1.2)
1	86 (4.1)
2	173 (8.3)
3	322 (15.4)
4	441 (21)
5	454 (21.7)
6	358 (17.1)
7	180 (8.6)
8	54 (2.6)
Total	2,093

The cohort was then stratified for their individual Healthy Diet Score by four categories (taking into consideration the uneven distribution of data in individual scores, perfect quintiles were not obtainable).

Table 11: Healthy Diet Score in Four Categories for RADICAL PC baseline FFQ

Healthy Diet Score	Frequency (%)
0-3	606 (28.9)
4	441 (21.1)
5	454 (21.7)
6-8	592 (28.3)
Total	2,093

For the purpose of this dissertation, I also explored the results of the Healthy Diet Score in tertiles (taking into consideration the uneven distribution of data in individual scores, perfect tertiles were not obtainable), which gave three categories of the Healthy Diet Scores: (i) low, (ii) intermediate, and (iii) high.

Table 12: Healthy Diet Score in Tertiles for RADICAL PC baseline FFQ

Healthy Diet Score	Frequency (%)
Low (0-3)	606 (28.9)
Intermediate (4-5)	895 (42.8)
High (7-8)	592 (28.3)
Total	2,093

The following table summarizes the demographic information of all participants in RADICAL PC:

Table 13: Descriptive and anthropometric data from RADICAL PC baseline visit

Diet Quality Score in Four Categories	0-3 (%)	4 (%)	5 (%)	6-8 (%)	Total
Age			68 (7.8)		2,091
BMI					
Healthy (20-25 kg/m^2)	115 (27.5)	79 (18.9)	102 (24.4)	122 (29.2)	418
Underweight (<20 kg/m^2)	4 (18.2)	7 (31.8)	6 (27.3)	5 (22.7)	22
Overweight (25-30 kg/m^2)	270 (27.5)	212 (21.5)	211 (21.5)	290 (29.5)	983
Obese (>30 kg/m^2)	209 (32.8)	135 (21.2)	128 (20)	166 (26)	683
					2,093
Diabetes					
Yes	495 (28.2)	369 (21)	394 (22.5)	497 (28.3)	1,755
No	111 (32.8)	72 (21.3)	60 (17.8)	95 (28.1)	338
					2,093
Employment					
Employed	237 (28.8)	173 (21)	180 (21.8)	234 (28.4)	824
Not Employed	369 (29.2)	266 (21)	273 (21.5)	358 (60.5)	1,266
					2,090
Education					
< High School	84 (34.4)	58 (23.8)	58 (23.8)	44 (18)	244
High School	199 (35.6)	128 (22.9)	112 (20)	120 (21.5)	559
> High School	322 (25.1)	251 (19.6)	282 (22)	427 (33.3)	1,282
					2,085
Ethnicity					
Caucasian	545 (29.2)	394 (21.1)	409 (21.9)	519 (27.8)	1,867
Non-Caucasian	60 (27.7)	45 (20.7)	44 (20.3)	68 (31.3)	217
					2,084
Tobacco					
Never	216 (24.8)	184 (21.1)	190 (21.8)	281 (32.3)	871
Former	307 (30.2)	212 (20.9)	223 (21.9)	274 (27)	1,016
Current	82 (40)	45 (21.9)	41 (20)	37 (18.1)	205
					2,092

Alcohol					
Never	64 (31.5)	51 (25.1)	45 (22.2)	43 (21.2)	203
Current	476 (28.3)	352 (20.9)	360 (21.4)	492 (29.3)	1,680
Former	65 (31.3)	37 (17.8)	49 (23.6)	57 (27.4)	208
					2,091
Physical Activity IPAQ Score					
Low	165 (35.6)	114 (24.6)	104 (22.4)	81 (17.5)	464
Moderate	220 (30.5)	135 (18.7)	164 (22.7)	203 (28.1)	722
High	200 (25)	163 (20.4)	163 (20.4)	274 (34.3)	800
					1,986
Income					
None & < $20,000	41 (41.8)	16 (16.3)	23 (23.5)	18 (18.4)	98
$20-49,000	150 (36.9)	92 (22.7)	77 (19)	87 (21.4)	406
$50-74,000	129 (30)	94 (21.9)	98 (22.8)	109 (25.4)	430
>$75,000	239 (24.2)	191 (19.3	221 (22.4)	338 (34.2)	989
					1,923
Living					
Alone	118 (37.1)	64 (20.1)	62 (19.5)	74 (23.3)	318
Not Alone	488 (27.5)	377 (21.2)	392 (22.1)	518 (29.2)	1,775
					2,093

Additionally, Table14 is a summary of prostate cancer characteristics of participants in RADICAL PC:

Table 14: Prostate Cancer characteristics data from RADICAL PC baseline visit

Diet Quality Score in Four Categories	0-3 (%)	4 (%)	5 (%)	6-8 (%)	Total
PSA at baseline					
≤10 ng/mL	387 (29.3)	277 (21)	285 (21.6)	371 (28.1)	1,320
>10 and ≤20 ng/mL	127 (28.5)	85 (19)	98 (22)	136 (30.5)	446
>20 ng/mL	87 (27.8)	76 (24.3)	67 (21.4)	83 (26.5)	313
					2,079
Prostate Cancer Prognostic Grade					
Group I (≤6)	90 (29.5)	59 (19.4)	55 (18)	101 (33.1)	305
Group II (3 + 4)	248 (31.1)	175 (21.9)	175 (21.9)	200 (25.1)	798
Group III (4 + 3)	124 (28.4)	101 (23.2)	94 (21.6)	117 (26.8)	436
Group IV (8)	69 (25.3)	52 (19)	68 (24.9)	84 (30.8)	273
Group V (9 or 10)	64 (25.5)	47 (18.7)	60 (23.9)	80 (31.9)	251
					2,063
Prostate Cancer Stage					
1 (T1, T1a, T1b, T1c)	238 (30.2)	159 (20.2)	167 (21.2)	224 (28.4)	788
2 (T2, T2a, T2B, T2c)	218 (29.7)	166 (22.6)	160 (21.8)	191 (26)	735
3 (T3, T3a, T3b, T4)	99 (25.2)	82 (20.9)	85 (21.6)	127 (32.3)	393
					1,916

A total sample of N=1,948 participants was included in the final analysis. These participants had a response to prostate cancer severity and completed the FFQ. A chi^2 test was not statistically significant for prostate cancer risk categories and the Healthy Diet Scores Categorized into four categories.

Table 15: Chi-Square Table of Prostate Cancer Risk Categories and Healthy Diet Score into Four Categories

Prostate Cancer Risk Category	Healthy Diet Score Categories into Four Categories				Total
	0-3 (%)	4 (%)	5 (%)	6-8 (%)	
Low & Intermediate	346 (30.8)	237 (21.1)	220 (19.6)	320 (28.5)	1,123
High	256 (27)	201 (21.3)	228 (24.1)	261 (27.6)	946
Total	602 (29.1)	438 (21.2)	448 (21.6)	581 (28.1)	2,069

Pearson $Chi^2(4)$ Statistic = 7.461 p-value = 0.059

A chi^2 test was not statistically significant for prostate cancer risk categories and the Healthy Diet Scores categorized into three categories.

Table 16: Chi-Square Table of Prostate Cancer Risk Categories and Healthy Diet Score in Three Categories (low, intermediate, and high)

Prostate Cancer Risk Category	Healthy Diet Score Categories in Tertiles			Total
	Low quality Diet (Scores 0-3) (%)	Intermediate Quality Diet (Scores 4-5) (%)	High Quality Diet (Scores 6-8) (%)	
Low & Intermediate	346 (30.8)	457 (40.7)	320 (28.5)	1,123
High	256 (27)	429 (45.4)	261 (27.6)	946
Total	602 (29.1)	886 (42.8)	581 (28.1)	2,069

Pearson $Chi^2(2)$ Statistic = 5.227 p-value = 0.073

The estimated odds ratio (ORs) of high prostate cancer risk per unit increase in the Healthy Diet Score and their corresponding 95% CIs were calculated using a logistic regression model, which is reported in Table 17. The overall model is not statistically significant.

Table 17: Logistic Regression of Prostate Cancer Severity and individual Healthy Diet Scores (0-8) for N=2,069

	ORs	SD	z	p>z	95% CI	
Healthy Diet Scores	1.03	0.027	1.19	0.232	0.98	1.08

* Log likelihood = -1425.827, LR chi2(1) = 1.43, Prob > chi2 = 0.232

The estimated ORs of having high-risk prostate cancer and their corresponding 95% CIs for categories of the Healthy Diet Scores into four categories (0-3, 4, 5, 6-8) for an increment of one point were computed using a logistic regression model. Included were terms for age, tobacco (never, former, current; categorical), diabetes (yes or no), employment (yes or no), ethnicity (Caucasian or non-Caucasian), BMI (healthy 20-25 kg/m^2, underweight <20 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m^2; categorical), education (< High School, High School, > High School; categorical), cardiovascular disease at baseline (yes or no), income (none & <20k, 20-49k, 50-74k, >75k), categorical), living alone (yes or no), and physical activity (low, moderate, high), the results are reported in Table 18.

Table 18: Logistic Regression of Prostate Cancer Severity and Four Categories of the Healthy Diet Scores (0-3, 4, 5, 6-8) and covariates for N=1,775

	ORs	p>z	95% CI	
Healthy Diet Score				
Category 1: Score = 0-3	1		Referent	Referent
Category 2: Score = 4	1.21	0.16	0.93	1.61
Category 3: Score = 5	1.41	0.01	1.08	1.86
Category 4: Score = 6-8	1.13	0.37	0.87	1.45
p-for-trend = 0.21				
Age	1.03	0.00	1.01	1.04
Tobacco				
Never	1		Referent	Referent
Former	0.96	0.67	0.78	1.17
Current	1.09	0.65	0.76	1.54
Diabetes	1.16	0.28	0.89	1.51
Employment	0.92	0.49	0.73	1.16
Ethnicity	0.89	0.49	0.65	1.23
BMI				
Healthy (20-25 kg/m^2)	1		Referent	Referent
Underweight (<20 kg/m^2)	0.93	0.89	0.37	2.41
Overweight (25-30 kg/m^2)	1.11	0.44	0.86	1.43
Obese (>30 kg/m^2)	1.13	0.38	0.86	1.49
Education				
< High School	1		Referent	Referent
High School	0.96	0.79	0.68	1.34
>High School	1.01	0.93	0.74	1.40
Cardiovascular Disease	1.11	0.46	0.85	1.45
Income				
None & < $20,000	1		Referent	Referent
$20-49,000	1.06	0.81	0.66	1.69
$50-74,000	0.96	0.87	0.60	1.53
>$75,000	0.75	0.23	0.47	1.19
Living Alone	1.05	0.74	0.79	1.38
Physical Activity				
Low	1		Referent	Referent
Moderate	1.01	0.91	0.79	1.31
High	0.81	0.11	0.63	1.05

*Log likelihood = -1198.42, Prob > chi2 =0.0003, LR chi2(13) = 50.28

Similarly, the ORs of having high-risk prostate cancer and their corresponding 95% CIs for categories of the Healthy Diet Scores in tertiles (low 0-2, intermediate 3-5, and high 6-8) using a logistic regression model is reported in Table 16. Adjustment is made for the following co-variates: age, tobacco (never, former, current), diabetes (yes or no), employment (yes or no), ethnicity (Caucasian or non-Caucasian), BMI (healthy 18.5-25 kg/m^2, underweight <18.5 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m2), education (< High School, High School, > High School), cardiovascular disease at baseline (yes or no), income (none & <20k, 20-49k, 50-74k, >75k), categorical), living alone (yes or no), and physical activity (low, moderate, high):

Table 19: Odds Ratios for High-Risk Prostate Cancer for Three Categories of the Healthy Diet Scores (low 0-3; intermediate 4-5; high 6-8) and covariates for N=1,748

	ORs	p>z	95% CI	
Healthy Diet Score				
(0-3)	1		Referent	Referent
(4-5)	1.32	0.02	1.05	1.66
(6-8)	1.12	0.37	0.87	1.46
p-for-trend = 0.39				
Age, year	1.03	0.00	1.01	1.04
Tobacco				
Never	1			
Former	0.96	0.67	0.78	1.17
Current	1.08	0.65	0.76	1.54
Diabetes	1.16	0.29	0.89	1.51
Employment	0.92	0.49	0.73	1.16
Ethnicity	0.89	0.49	0.65	1.23
BMI				
Healthy (20-25 kg/m^2)	1		Referent	Referent
Underweight (<20 kg/m^2)	0.93	0.89	0.36	2.40
Overweight (25-30 kg/m^2)	1.10	0.46	0.86	1.42
Obese (>30 kg/m^2)	1.12	0.40	0.85	1.49
Education				
>High School	1		Referent	Referent
High School	0.95	0.79	0.68	1.34
>High School	1.02	0.92	0.74	1.40
Cardiovascular Disease	1.11	0.44	0.85	1.45
Income				
None & < $20,000	1			
$20-49,000	1.05	0.83	0.66	1.68
$50-74,000	0.95	0.84	0.59	1.52
>$75,000	0.75	0.22	0.47	1.19
Living Alone	1.05	0.74	0.79	1.39
Physical Activity				
Low	1		Referent	Referent
Moderate	1.02	0.89	0.79	1.31
High	0.82	0.12	0.63	1.05

* Log likelihood = -1180.79, LR chi2(16) = 41.83, Prob > chi2 = 0.0004

Additionally, a logistic regression of the dependent variable (prostate cancer risk category) and each term age, tobacco (never, former, current), diabetes (yes or no), employment (yes or no), ethnicity (Caucasian or non-Caucasian), BMI (healthy 18.5-25 kg/m^2, underweight

<18.5 kg/m^2, overweight 25-30 kg/m^2, obese >30 kg/m2), education (< High School, High School, > High School), cardiovascular disease at baseline (yes or no), income (none & <20k, 20-49k, 50-74k, >75k), categorical), living alone (yes or no), and physical activity (low, moderate, high) was calculated. A statistically significant relationship was between the high-risk prostate cancer category and age (OR: 1.03, 95%CI 1.01-1.04 p<0.00) was found.

1.6 DISCUSSION

No significance between the high-risk prostate cancer category and a lower quality diet measured by the Healthy Diet Score may be due to a few plausible explanations. Without a definitive consensus on whether diet has an effect on prostate cancer risk based on current literature, these findings can be influenced by numerous factors that make them both different and similar to existing literature.

A recent RCT previously described that randomized prostate cancer patients to a healthy diet intervention versus a control (MEAL study) also found no effects after two years of the dietary intervention (Parsons et al. 2018). Their diet was a high vegetable diet controlled using an RCT design, which results in stronger interpretations regarding cause and effect, whereas no interpretation of cause and effect can be drawn from a cross-sectional analysis. In comparison, the observational data of this dissertation uses a Healthy Diet Score, the median of the population being analysed, and uses categories of food groups that are broad and balanced. The MEAL study also measured serum PSA and this dissertation analysis used the prostate cancer risk stratification to compare prostate cancer severity. The MEAL study implements a high vegetable and a decrease of fat diet, specifically the intervention arm was assigned a diet counsellor that encouraged seven servings of fruit and vegetables (1 serving = half a cup of raw or cooked vegetables or fruits; therefore 3.5 cups/day) that included at least two servings of cruciferous

vegetables and tomatoes. It is unclear whether the MEAL study will report other dietary factors such as dairy and meat, which may also have a role in prostate cancer progression. Some other drawbacks of this methodological design are that specifically looking at very high intakes of vegetables and low intakes of fat is not easily sustainable in patients long-term. Unfortunately, the CDC reported in 2015 that approximately 9.3% of people living in the United States consume the recommended 1.5-2 cups of servings of vegetables. If approximately 90% of the population are unable to abide to portions that are half the recommended portions of the MEAL dietary intervention, it may not be a realistic advice for the general population. Recent discussion has focused on food affordability and taking into consideration economic dimensions of people's lives when designing studies and offering dietary guidelines. This is a strength of the analysis done for the purpose of this dissertation, as it takes into consideration overall dietary intake (fats, vegetables, dairy, meat etc.) and portrays a more realistic and obtainable dietary goal. These are notable differences between the studies that do not allow for a direct comparison, but the MEAL study also reported surprising findings of no effect between diet and prostate cancer severity. Diet has been consistently implicated in prostate cancer for some time, but it is still unclear what dietary factors are protective of prostate cancer and have an effect on severity.

The PCaP (Prostate Cancer Project) was previously described in two sections*, 1.2.6.5 The Mediterranean Diet* and *1.2.6.6. Dietary patterns in prostate cancer* (Arab et al. 2013). These two studies were more comparable in their methodological design to this dissertation in their means to assess diet and prostate cancer, since they explored diet without an intervention. The WCRF lifestyle guidelines include both diet and exercise in their seven recommendations and the Healthy Diet Score only considers diet using the median intake of the RADICAL PC baseline participants, which is a major difference. As a reminder, the WCRF recommendations included:

(1) maintain BMI within normal range 21-23, (2) Engage in at least 60 minutes of moderate or 30 minutes of vigorous physical activity daily, (3a) limit consumption of energy-dense foods, (3b) avoid sugary drinks, (4a) eat at least 5 servings of non-starchy vegetables and fruits every day, (4b) eat at least 25 g of unprocessed grains/cereals and legumes per day, (5) eat less than 500 g (18 oz) of red meat per week, (6) limit alcohol intake to 2 drinks per day for men and 1 drink per day for women, and (7) limit sodium intake to less than 2.4 g per day. Authors predicted a 38% increased risk of prostate cancer tumor aggressiveness if the adherence was <4 out of 9 compared to an adherence of that was ≥ 4 (Arab et al. 2013). The WCRF adherence score considers BMI, alcohol and sodium intake, two of which are included as potential confounders in the analysis of this dissertation using the Healthy Diet Score, with the exception of sodium intake, which was not reported in the SFFQ. Another major limitation of using the WCRF guidelines is that they exclude discussion of recommendations of fat and dairy intake, which are major sources of dietary intake in North America.

The PCaP database was also used by Schneider et al. (2019) to evaluate differences between the Mediterranean diet and the DASH score. They found that high Mediterranean diet scores was inversely associated with high aggressive prostate cancer (OR: 0.66; 95% CI: 0.46, 0.95) compared to low Mediterranean diet scores. They also found an inverse association between DASH scores and prostate cancer aggressiveness (OR: 0.76; 95% CI: 0.55,1.06). The Mediterranean diet is based on eating patterns in the Mediterranean regions, however, the DASH (Dietary Approaches to Stop Hypertension) diet score was originally developed to decrease hypertension. The Healthy Diet Score was evaluated in people with or without vascular disease and found that it was not significantly more predictive of cardiovascular events than the Mediterranean diet, but it was significantly more predictive of events than the DASH score (ESC

Congress 2019 Aug 28). One major methodological weakness in the PCaP database is that dietary data was only collected for the year prior to diagnosis and that 359 participants who had highly aggressive prostate cancer were excluded due to no information on covariates. It is also important to note that the nature of cancer causation is different than for cardiovascular disease, particularly, there is evidence that most exposures are proximal to diagnosis, though not exclusively (Willett2013).

A cross-sectional analysis is often used to examine associations and provide information about prevalence, but does have limitations. An important limitation of cross-sectional analysis is reverse causality. Individuals with more severe prostate cancer could have attempted to provide healthier eating options or been more conservative with answers regarding unhealthy eating habits. This could particularly impact patients enrolled into RADICAL PC since they are not all new diagnosis patients. Patients are included in RADICAL PC if they are diagnosed within one year, their first initiation of ADT, or within 6 months of ADT or planned start of ADT for the first time within one month of enrollment. Patients that were diagnosed with prostate cancer a year ago, or more had sufficient time to change their diet and adopt healthier eating habits. Although this may be beneficial for the overall health of the patient, unfortunately this is a major limitation for a cross-sectional analysis. The opposite may be true for patients with less severe prostate cancer, who may be less likely to adjust their diet.

The results of this study could potentially have been impacted by recall bias, which is a known potential limitation of FFQ's as well as cross-sectional studies. Individuals with severe prostate cancer may report less accurate reports of their eating habits. Generally, a large sample size is required for a cross-sectional study and studies examining prostate cancer, which is a commonly occurring cancer, but still considered a rare disease. Large sample sizes do have cost

implications, but in the case of the RADICAL PC dataset, it is possible to repeat this cross-sectional analysis once the study has reached completion and recruited to the full sample size.

Cross-sectional significance tests can be helpful in determining whether data are unlikely under the null hypothesis of no effect (to determine whether an effect exists), but non-significant findings do not support the converse interpretation. The finding of an association between age and the high-risk prostate cancer category is helpful in data validation, since it is supportive of available literature for high-risk prostate cancer and age.

CHAPTER 2: Comparability of an abridged Food Frequency Questionnaire (FFQ) to assess diet in prostate cancer patients: A sub-study of RADICAL PC

2.0 INTRODUCTION AND RATIONALE

The measurement of diet is challenging, particularly in large epidemiological studies (Willett 1987). Since the consumption of foods varies widely among different individuals and also changes on a daily basis, diets are difficult to measure. Dietary assessment tools aim to obtain information regarding energy or nutrient intake habits using tools that document types of food as well as frequency of consumption. The most commonly used tool is the Food Frequency Questionnaire (FFQ). Chapter 2 of this dissertation will evaluate an abridged FFQ as a tool used to study diet in prostate cancer patients. Specifically, I will evaluate methodological considerations by assessing agreement of daily intakes of food groups and nutrients between the abridged FFQ and the validated (Kelemen et al. 2003) longer version of the FFQ. Chapter 1 describes the RADICAL PC study in more detail, as well the relationship between diet and prostate. In the second chapter of my thesis, I performed analyses comparing the abridged with the full food frequency questionnaires to understand whether the abridged food frequency questionnaire is an adequate tool to describe dietary patterns. In the comparability sub-study, the FFQ and abridged FFQ were administered to consenting participants (N=130) in RADICAL PC. Briefly, RADICAL PC 1 and 2 are a prospective cohort study and randomized controlled trial, respectively. RADICAL PC explores cardiovascular disease among prostate cancer patients with a proposed follow-up of three years. Patients who agreed to participate in RADICAL PC at St. Joseph's Hospital in Hamilton were asked if they wanted to participate in the nutritional sub-study.

An FFQ is not the most precise measurement tool compared to diet records or 24-hr recalls, but it is the most commonly used tool due to its simplicity. A review of how

questionnaires are developed, validated, and used, stated that many papers do not indicate the intended use of the particular FFQ and a group of experts felt that other studies used an inappropriate FFQ (Cade et al. 2012; Kelemen et al. 2003). Some examples include the use of an FFQ in a small sample size, for *absolute* intakes, and using an FFQ that was developed for another country with different eating habits or amending an FFQ without validation. Therefore, it is imperative to assess an amended questionnaire in the population of its intended use to ensure the FFQ's ability to be used as a tool to evaluate the particular diet and disease relationships. For instance, the questionnaire should reflect specific food types typically consumed in the region where it will be implemented and to reflect foods implicated in the diet-disease relationship, if possible.

The FFQ in the RADICAL PC study will be used to assess the relationship between diet and prostate cancer and CVD. Since this study is being conducted in Canada the long FFQ validated by Kelemen et al. (2003) can be implemented. A comprehensive FFQ covers the consumption of beverages and foods over a certain time period and can be used to describe a population intake over time. Questionnaires can range anywhere from 5-350 questions, and a more detailed questionnaire is closer to the more precise method of the diet recall or 24-hr diet records. However, due to the length of the questionnaire and the additional time requirements of participants in the study, an abridged version was considered likely to be helpful. The abridged FFQ decreases the time requirement from approximately 45 minutes (long FFQ) to 10-15 minutes (SFFQ). The successful comparability of the abridged FFQ allows the questionnaire to be used in RADICAL PC and supports achieving the primary objective of this dissertation discussed in Chapter 1.

2.1 OBJECTIVES

Chapter 2: To compare an abridged food frequency questionnaire with a validated, full-length food frequency questionnaire in the assessment of the daily intake of food groups and nutrients among men with prostate cancer enrolled in the RADICAL PC study.

2.2 BACKGROUND

There are three main ways of collecting dietary data (1) FFQs, (2) Diet Records, and (3) 24-diet recalls. In depth interviews is also a potential means of collecting dietary information, though less common, and scarcely used in large epidemiological studies due to cost and time requirements. The FFQ records the frequency of consumption of specific food items daily, weekly, or monthly, and provides an estimate of nutritional intake for a specified amount of time. The specific period of time is based on the study, but long-term dietary intake is a more accurate predictor of disease-diet relationships than short-term dietary intake (Willett 1987). Measuring diet twice a year will account for major seasonal changes, captures an extensive overview of dietary habits and is biologically significant (Willett 1987). Most epidemiological studies will examine dietary patterns over an extended period of time, rather than one specific time point. Diet Records ask participants to keep a prospective record of what they eat for a specified amount of time (usually up to one week). The 24-hour diet recalls ask participants to recall what they consumed in the last 24 hours. With the evolution of diet-disease study methodologies, the need for evaluation tools grows concurrently. FFQ's are now the primary technique for assessing diet-disease relationships in epidemiological studies and numerous FFQ's have been developed for many populations and countries (Dehghan M. et al. 2012a).

The initial development of an FFQ is based on the specified population and is then validated for use within that population. For instance, the FFQ's used by the PURE study were

developed and validated in different countries and/or regions, depending on the location of the specific study site. The validation of the FFQ is essential because diet assessments must take cultural considerations into account in order to avoid biased estimates or false associations (Dehghan M. et al. 2005, Dehghan M. et al. 2012a, Dehghan M. et al. 2012b, Dehghan M. et al. 2012c). If a questionnaire has already been developed, validated and only requires amendments, then a comparability study can be conducted using the validated questionnaire and the amended questionnaire. This dissertation uses a Short FFQ (SFFQ) that has been abridged from a previously validated FFQ in the PURE study (Chapter 1). The next sections of this dissertation will discuss the steps taken to develop and validate the original long version of the FFQ, followed by a discussion of the comparability model used to assess the abridged FFQ used in the Chapter 1 analysis and RADICAL PC study.

2.2.1 Development of the FFQ

The FFQ is either developed or adapted. Over 50% of food questionnaires are adapted from questionnaires by Block et al. (1986) and Willett et al. (1987). The process of developing and validating a new questionnaire is as follows:

i) Assess diet intake of the population in question (24-hour diet recalls, or diet records, or interviews),
ii) Identify a food list using the assessment
iii) Develop a questionnaire (FFFQ) using the food list
iv) Concurrently implement the questionnaire (FFQ) with 24-hour diet recall or diet records in a new sample

v) Analysis of validity and reliability of developed questionnaire versus 24-hour diet recall (Bharathi et al. 2008, Block et al. 1986, Cade et al. 2002, Willett et al. 1988).

This process is done when there is a requirement for a questionnaire in a new population for a novel research topic. The development of the FFQ for the PURE study began as a pilot between the years of 1995 and 1996 in Hamilton, Ontario, Canada. An introduction letter and invitation to participate was mailed out to 522 households in their native language (English, south Asian, Chinese, Europeans). A follow-up phone called assessed eligibility (based on ancestry to include multicultural populations of Canada) and a follow-up visit was scheduled in clinic where a 24-hour recall was administered. Two weeks after their clinic visit, two more 24-hour recalls were administered via telephone or a take-home four-day Diet Record was mailed to the participant.

<u>24-Hour Diet Recall:</u>

The 24-hour diet recall is a method used for assessing complete dietary intake for a specific time point. The participant is asked to recall what they consumed in the last 24-hours and details about their food preparation and the ingredients used. There are two options for collection of 24-hour Diet Recalls. The first uses an unstructured approach, in which the participant is simply asked to recall everything they consumed, all food preparation and ingredients. The participant is not further directed or assisted. The second approach is a "meal plan" approach, during which the participant is asked to recall everything they consumed during each specific meal and between meals, as well as preparation and ingredients. A study by Subar et al. (2007) investigated the two versions of collecting 24-hour Diet Recalls, "unstructured" versus "meal plan," and found that participants preferred the "meal-plan" option and were able to

remember more variations of foods and provide greater detail. The 24-hour Diet Recall done in the PURE study for the development of the FFQ used a "meal plan" approach for conducting interviews. The 24-hour diet recall is now also done with computer assisted programs that ask the participants questions in a similar manner to an interviewer. Since participants rely on memory, there is more potential for errors (Willett 2007).

The main advantage of the 24-hour Diet Recall is that patients are not given a take-home task and that data is easily obtained. The disadvantage is that that sources of error stem from self-interpretation of questions, using memory, and perception of portion sizes. Additionally, it is a report of a single day of diet intake and cannot describe a typical diet. Some studies have done multiple 24-hour Diet Recalls in order to obtain up to seven days of data, however, this becomes very time consuming for study teams, burdensome on participants, and is not always feasible.

Diet Records:

Diet Records ask the participant to self-report all foods and beverages consumed prospectively during a specified amount of time, this method is often referred to as the gold standard (Willett 2013). The Diet Record method involves training participants prior to completing food records, which prepares them with an understanding of the level of detail required for food descriptions (Bingham et al. 1988). Participants are provided supplemental information that include examples, for instance a person consuming lasagna and milk would list all the ingredients in lasagna and how it was prepared. There is no perfect methodological design that collects dietary intake, but Diet Records have the smallest degree of error (Willet 2013). Diet Records are advantageous because they are open-ended and, not dependent on memory like 24-hour diet recall, because participants are instructed to make notes prospectively throughout the day as they consume foods. For instance, participants are instructed to complete a Diet

Record of what they consumed for breakfast immediately after breakfast. The disadvantages are that participants may not follow these instructions and may change what they eat during record keeping. This could introduce bias and incorrectly report a typical daily intake. Training participants is also difficult, both due to understanding and inability to provide participants with needed assistance on site when they are completing the Diet Records on their own. This method relies on having literate participants, which could be a limitation for some studies.

The main difference is that Diet Records require participants to be trained in advance and they are asked to report consumption prospectively and independently into a food diary format at home for a specified amount of time (i.e. 4 – 7 days). They are not provided with assistance and researchers rely on participants completing the Diet Records. During a 24-hour recall, participants are interviewed about what they consumed the previous day and must rely on memory of details of ingredients and portion sizes.

Continuing with the above example of the first FFQ developed for the PURE study, 29 South Asian (17 m), 25 Chinese (15 m), and 20 European (9 m) provided complete 24-hour diet recall in clinic with specific questions about portion size as well as details of type of foods consumed (Kelemen et al. 2003). This data was used to develop a food list, which is a unique list of commonly consumed food items using all the interviews done on each participant in the particular population being studied. Once all the data points were collected, local community members were consulted to review the results and assist with identifying any missing food items with face validity. These dietary patterns were then used to compile a food lists for rural and urban areas (Kelemen et al. 2003). A total of 74 patients were used to develop food lists for the Canadian FFQ. This initial survey was useful in determining that existing FFQs could not be used in this population because they excluded common food items reported in the pilot study.

Frequency of reporting was tallied, average portion sizes, and common units of measurements were determined, and a novel questionnaire was developed. Once the questionnaire was successfully developed, the researchers could perform the validity and reliability test.

Consequently, the next FFQs for the PURE study were all created to be applicable to the specific area where they would be implemented: Colombia {cite}, India (Bharathi et al. 2008) Poland {cite}, Argentina {cite}, etc. The process of creating these other questionnaires mirrored the aforementioned methodology done in Hamilton, Ontario and the results were FFQs reflective of the populations of interest.

2.2.2 Nutrient Database (NDB)

A nutrient database provides nutritional profile of food items. In Canada, two sources are most commonly used to create a nutrient database and define portion sizes: the United States Department of Agriculture (USDA) food composition database and Canadian Nutrient File. These databases have an extensive list of food items categorized both by type and specific brands available for purchase in Canada. The nutrient profiles from the United States Department of Agriculture and Canadian Nutrient File provide nutrient values for each food item of an FFQ, for example whole milk, 2% milk, chocolate milk, skim milk etc. Some examples of what is included in the nutrient profile is as follows: energy, lipids, carbohydrates, fiber, sugar, saturated fats, Vit B6, Vit B12, potassium, Zinc etc. North American studies tend to use these databases, and having the same resource for obtaining nutrient values and portion sizes makes comparisons between different studies with similar methodological design possible.

Continuing with the PURE example, portion sizes were chosen based on participants estimates (cup, spoons, tablespoon etc.) and the questionnaire was formatted so participants could select daily, weekly, monthly or yearly averages intakes. The US Department of

Agriculture nutrient database and the 1991 Canadian Nutrient File were used to derive the nutrient composition for the FFQ food items from the Canadian PURE study. Researchers also used brand names that participants recorded in Diet Records and obtained additional nutrient information from these products.

2.2.3 Validity and Reproducibility

The assessment of how well an FFQ measures true dietary intake is usually done through a two-step process of validity and reproducibility. Reproducibility of a questionnaire measures the consistency of multiple administrations to the same person, but at different time points. Validity evaluates a questionnaires ability to measure the aspect of diet it was proposed to measure (Willett 2013). Participants report consumption per day, per week, per month or per year in an FFQ and concurrently complete either a 24-hour diet recall or Diet Records. The daily frequency of consumption and daily nutrient intake is calculated based on response for food items and portion sizes. The amount of nutrients, or amount or frequency of consumption of food items are then compared between the FFQ and the "gold standard" multiple 24-hour recalls or multiple days of diet records.

Walter Willet (2013) states that there are seven approaches to evaluating dietary questionnaires:

Table 20: Approaches, Definitions and Limitations to Evaluating Dietary Questionnaires

Approach	Definition	Limitation
Comparison of means	Comparing mean nutrient intakes of an FFQ with values derived from another source, which can provide some insight as to whether questionnaires are comprehensive.	Comparison of means provides no information on portion sizes of two questionnaires and this method cannot discriminate among participants. It is also important to note whether mean intake is important for

		the particular nutrition-disease relationship.
Proportions of total intake	Proportions of total intake (of a food or nutrient) can be used to evaluate the completeness of a questionnaire, this is generally done when comparing a compressed questionnaire to a comprehensive questionnaire.	This gives limited information on questionnaire performance because high or low nutrient percentage (from proportions of total intake) is not directly indicative of an effective or ineffective questionnaire.
Reproducibility	The ability to successfully reproduce a questionnaire from one time point to another is useful as an initial analysis of performance, but never done independently to as a measure of validity.	A low level of reproducibility may be indicative of that the questionnaire fails to provide an adequate long-term intake measurement. Although people's diet changes over time, it should generally not impact the timeframe of a reproducibility FFQ being implemented. A low degree of reproducibility may be suggestive that long-term intakes are not adequately measured.
Validity	This method compares a questionnaire to a more accurate method (gold standard) among individuals. Diet Records likely have the least errors because they are open ended (do not rely on memory, fixed lists and therefore differ from the FFQ). The alternative is 24-hour recall, which relies on memory and is not optimal, but sometimes done in populations that are not motivated or illiterate.	Since no method of dietary data collection is absolute, it is important that the two methods of data collection differ. This can often be a limitation due to feasibility.
Comparison with biochemical markers	Using biochemical markers to evaluate the performance of a questionnaire is essentially uncorrelated with errors to any FFQ.	The most obvious limitation is feasibility to check every marker for all dietary components to obtain complete nutritional intake. Biochemical markers may

		differ among individuals in how they are metabolised and absorbed.
Correlation with psychological approach	This is a qualitative analysis of a dietary questionnaires' ability to predict an established relationship between a nutrient intake and a psychological response.	There is not much data on this method and it is rarely used. The major limitation that established relationships between nutrient intake and a psychological response are scarce.
Ability to predict disease	This qualitative method requires an established relationship between a disease and a nutrient (or dietary factor).	This is limited by shortage of evidence that has been able to establish definitive causal relationships between diet and disease.

A combination of validity and reproducibility is commonly used to evaluate the performance of new FFQ's. The validation of FFQ's is performed by comparison of the nutrient quantities ascertained through the FFQ with the quantities of the same nutrient quantities estimated by Diet Records with reproducibility being evaluated at a secondary time point. Correlation coefficients that are considered acceptable fall between the ranges of 0.5 to 0.7. This is lower than correlation ranges in a laboratory setting, but similar to other validity correlation of other measurements in epidemiology studies (Willet 2013). Questionnaires are considered to have a low correlation if their range is between 0.3 and 0.5 (Cade et al. 2002; Rohrmann & Klein 2003). For example, comparing vegetable intakes from diet records (detailed, open-ended) to a single question about how often any type of vegetable is consumed on an FFQ may lead to a low correlation between 0.3 to 0.5. Reproducibility is generally the last step, and serves as an assessment of consistency of the same questionnaire across time (Mayer-Davis et al. 1999). The minimally accepted time interval between questionnaires is four weeks, although some markers are highly variable over time, such as cholesterol, (Willet 2013). Due to the variability in each individual's intake of particular nutrients over time, most questionnaires are done 3-8 months

apart (i.e. not so close together that they are likely to recall their previous responses, but not so far apart that dietary patterns are likely to change). Following along with the PURE example, FFQ 1 and FFQ2 is compared at two different time points. Time point one (FFQ1) is the baseline collection and time point two is done between 6-8 months (FFQ2).

2.2.4 Comparability Model

The length of a full FFQ can negatively impact participant motivation to complete the study visit, as well as increasing burden and decreasing focus (Willett 2013). An abridged FFQ (SFFQ) is beneficial for studies that are not assessing the total diet of their participants, but rather focusing on food groups such as fat or carbohydrate intakes, such as when investigating Coronary Heart Disease or different types of Cancer (Rohrmann and Klein 2003). SFFQ's have also been successfully used in other large epidemiological studies. Willett and other experts (2013) state that analysis of total diet is ideally performed using Diet Records or at the very least a full FFQ, but recognize that there are limitations to attempting to apply this method broadly across studies. Most large long-term epidemiological studies do not have resources to dedicate to Diet Record data collection and analysis. Diet Records need to be collected 4-7 days and are open-ended, therefore, yielding an extensive number of food items requiring immense data analysis resources. Most studies investigating prostate cancer are interested in food groups or specific food items, and a SFFQ is sufficient, particularly, since the SFFQ is accompanied with the added benefits of decrease of patient burden.

A comparability model can be applied to assess the agreement between two measurement methods or tools that are similar, particularly, between a validated instrument and its amended form. The FFQ that was validated with Diet Records for the PURE study was abridged to compose the SFFQ for data collection in the RADICAL PC study and the cross-sectional

analysis done in Chapter one of this dissertation. The comparability model is implemented in order to determine whether the SFFQ provides a comprehensive and specific enough measurement tool to assess diet-disease relationship, (Dehghan M. et al. 2017a). The comparability model is successful when participants complete both sets of questionnaires (FFQ and SFFQ) at the same time-point. The correlation coefficient (r) is used to assess the relationship between the FFQ and the abridged SFFQ to determine whether the two measurements are in adequate agreement.

2.3 HYPOTHESIS

The hypothesis is that there is adequate agreement (0.3-0.5) in main food groups, proteins, carbohydrates, and total fats between the SFFQ and the LFFQ.

In the long and the abridged FFQ participants are asked to estimate their dietary intake over the past year and therefore, since both tools assess the same time horizon, we postulate that the correlation is moderate (between 0.3 and 0.5) (Cade et al. 2012; Rohrmann & Klein 2003). Alternatively, a questionnaire that asks patients to give estimates over the past year compared to a 24-hour recall (long versus short time horizon), would be expected to have estimates closer to 0.3. A modest correlation around 0.3 is adequate to broadly stratify large numbers of people into categories of intake to assess associations between diet and health outcomes of large epidemiological studies, given that large numbers of people can drown out random measurement error (assuming that measurement error is random and not systematic).

2.4 METHODS

2.4.1 Sub-Study Design

The prospective nutritional sub-study was conducted at St. Joseph's hospital in Hamilton, Ontario. The sub-study for FFQ and abridged (SFFQ) comparability received ethics approval

from Hamilton Integrated Research Ethics Board (HiREB). Patients who meet eligibility criteria and provided informed consent for RADICAL-PC are eligible to be included in the sub-study. The participants in the sub-study will follow the protocol for RADICAL PC1 or PC2.

Each participant completed one FFQ and one SFFQ concurrently at baseline and one FFQ and one SFFQ concurrently during the 6-month follow-up. Patient recruitment was completed within one year between October 2016 and September 2017 based on the calculated sample size (section 2.4.4). Patients were considered lost to follow-up if they were not reached within one month of the planned 6-month phone call date after numerous attempts were made to contact the patient. Two patients provided consent and completed their baseline questionnaire in the Urology clinic, but were not successfully reached the next day for the FFQ/SFFQ data collection. An additional 18 patients were lost to follow-up at the time of the 6-month follow-up questionnaire.

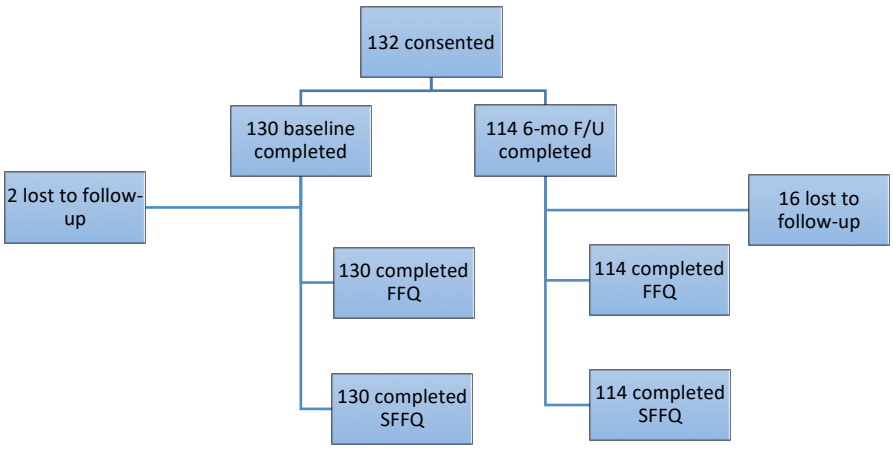

Figure 2: Recruitment flow-chart

The questionnaires were administered by trained research personnel who followed the instructions outlined at the top of the FFQ's. The FFQ includes a total of 161 questions and is 11

pages in length. The answer choices are in quantities per day, week, month or year, and each food item has three options for portion sizes. The SFFQ includes a total of 50 questions and is two pages in length. The answer choices are 1-3 times per month, 1 per week, 2-4 times per week, 5-6 times per week, 1 per day, 2-3 times per day, or >4 times per day. Full versions of the SFFQ and the FFQ are provided in Appendix III and Appendix IIII, respectively. The following section (2.4.2) provides details of the difference between the two questionnaires and explanations of groupings that were created during the process of abridging the FFQ.

2.4.2 Short FFQ Design

A comparison was performed between the SFFQ (50 questions) and the FFQ (161 questions). The SFFQ was amended by removing food items from the FFQ that were not components of the main food groups, and creating food groups (Table 21 and Table 22) rather than having individual food items listed. The groupings were done to shorten the FFQ and decrease the time required to complete the questionnaire using the guidelines from previously amended FFQ's (Willet 2013; Cade et al. 2012; Rohrmann & Klein 2003; Dehghan et al. 2017). The groupings of items are identified in Table 21. Column A depicting the groups in the SFFQ and column B shows what food items from the long FFQ were used to compose the groupings in the SFFQ:

Table 21: Groupings of food items for the abridged FFQ

A) FOOD GROUPINGS IN SFFQ	B) FOOD ITEMS FROM FFQ
SKIM MILK OR LOW-FAT MILK	2% milk
	1% milk
	Skim milk
EGGS	Fried
	Hard boiled
	Omelet
	Poached
	Scrambled
RED MEAT	Ground beef

	Regular beef
	Steak
	Pot roast
	Pork
	Ham
	Veal
	Lamb
FRUITS (FRESH)	Apple
	Banana
	Watermelon
	Kiwi
	Orange
	Tangerine
	Grape
	Melon
	Peach
	Apricot
	Plum
VEGETABLE (FRESH/RAW)	Carrot
	Broccoli
	Cabbage
	Cauliflower
	Brussel sprouts
	Corn
	Peas
	Dark leafy vegetables
	Cucumber
	Lettuce
	Tomatoes
	Onion
	Beets
	Sweet potato
	Root vegetable
	Yellow squash
	Summer squash
	Green pepper
	Asparagus
	Avocado
	Other vegetables (mushrooms, celery, artichokes)
	Pickles
FRIED VEGETABLES	Sautéed peppers
	Sautéed onions
	Sautéed vegetable mix
FRIED FOODS	McDonalds (chicken fingers)

	Burger King (medium fries)
	Chinese egg rolls
PASTRIES	Toaster pastries
	Apple pie
	Blueberry pie
	Cherry pie
	Chocolate chip cookies
	Cookies, molasses
	Cookies, oatmeal
	Pound cake
	Fruitcake
	Sponge cake
	Doughnuts (chocolate)
	Doughnuts (plain)
PROCESSED MEAT	Bacon
	Hamburger
	Sausage
	Lunch meat
NUTS	Almonds
	Walnuts
BEANS & OTHER PULSES	Kidney beans
	Baked beans
	Chickpeas
	Pinto beans
	Navy beans
COLD CEREAL	Bran/granola cereals
	Whole wheat cereals
	Sugar coated cereals (Frosted flakes, fruit loops)
	No sugar cereal (corn flakes, rice krispies)
BUTTER	Butter on breads, rolls, or boiled rice
	Butter on vegetables (excluding use in baked & mixed dishes)
MARGARINE	Margarine on breads, rolls, or boiled rice
	Margarine on vegetables (excluding use in baked & mixed dishes)

There are also groups (Table 22) that were divided into low and regular fat in the long FFQ and were averaged out in the abridged FFQ, they are as follows:

Table 22: Groupings of low/regular fat within the long FFQ for the abridged FFQ

LONG FFQ	SHORT FFQ
Cottage cheese, ricotta cheese	**CHEESE (SOFT)**
Crème cheese	
Sour crème, whipping cream	
Cheese (regular fat, natural and processed)	**CHEESE (HARD)**
Cheese (part-skim, natural and processed)	
Yogurt (plain, regular fat)	**YOGURT**
Yogurt (plain, low fat)	
Yogurt (fruit-flavoured, regular fat)	
Yogurt (fruit-flavoured, low fat)	
Pizza, no meat	**PIZZA**
Pizza, meat	
Macaroni, spaghetti, boiled	**PASTA/RICE**
Pasta with tomato sauce, no meat	
Pasta with cream sauce no meat	
Pasta with cheese/meat	
Steamed rice	
Fried rice	

Items that were not a component of the main food groups were removed. The following items were removed: candy, tofu or tempeh, peanut butter, jam, syrup, honey, gravy, chocolate syrup, strawberry syrup, berry syrup, ketchup, mustard, mayonnaise, wheat bran, wheat germ, mustard, soy sauce, fresh garlic, chilies, list of juices, soup, meat stew, chili con carne, salad dressing, pickled meat or fish, crackers, crisp snacks, and alcohol. These food items were removed because they were not part of the major food groups and were not considered important food items for the evaluation of the disease-diet relationship for the RADICAL PC study. Items were also removed because they were not commonly consumed, and would not greatly impact the estimates of intake in a large epidemiological study. Removing food items known to be less common in the general population, or amending a long FFQ from individual food items to an aggregation of food groups, is a practice often done for abridged questionnaires (Dehghan M. et al. 2017a).

The last five questions of the questionnaire were not specific to food items. They were as follows:

#45 How often do you eat meals at a fast food/non-fast food restaurant?

#46 How often do you consume canned foods (any type)?

#47 How often do you consume frozen foods/meals?

#48 What type of oil do you use for cooking most often (chose one response only)?

i) Soya Oil

ii) Sunflower seed oil

iii) Olive oil

iv) Canola oil

v) Corn oil

vi) Vegetable oil

vii) Coconut oil

viii) Other

ix) None

#49 Have you changed your diet during the last year? No or Yes, if Yes, due to health conditions? No or Yes

#50 Are you on a special diet? No or Yes, if yes, what diets are you currently following (check all that apply)?

i) Diabetic diet

ii) Low fat diet

iii) Low salt diet

iv) Weight reducing diet

v) High nuts diet

vi) High olive oil diet

Data on alcohol were collected in the other baseline questionnaires as part of the RADICAL PC study, and thus it was repetitive to include these questions in the amended SFFQ. The other items were found to contribute no significant value in the estimates of daily intake (Dehghan M. et al. 2017a).

2.4.3 FFQ Comparability

The long FFQ has been previously validated against the gold standard: a 24-hour diet recall and Diet Records (Dehghan et al. 2012b). Since the SFFQ is an abridged version of the FFQ (Dehghan et al. 2012a; Dehghan et al. 2012b), the goal is to assess comparability between the SFFQ and the long FFQ and its reproducibility (Dehghan M. et al. 2017a). A nutrient database was previously constructed for the FFQ and the same format was used to create a nutrient database for daily nutrient intakes for the SFFQ (Dehghan M. et al. 2017a). Section 2.2.2 provides a description of what a nutrient database is and how it is created. Food items that were measured by the SFFQ and FFQ were each grouped into 10 food groups (Table 6). To report daily nutrient intake of an individual, reported frequency was merged with the Nutrient Database (NDB), an example calculation is provided in section 2.4.6.

Table 23: Food groups for FFQ and SFFQ

Food groups	Food items
Whole grains	Whole grains Whole wheat bread, 60% whole wheat bread, whole wheat bread rolls, bran or oat muffins
Refined grains	Refined grains White bread, bread rolls, boiled rice
Total meats	Total meats Ground beef, steak, pork chop, veal, lamb, bacon, fried chicken, chicken, and turkey
Fish and seafood	Fish and seafood Steam baked fish, battered fish fried, canned fish, seafood, salted fish, and fish
Dairy products	Dairy products Whole milk, 2% milk, 1% milk, skim milk, cottage cheese, cream cheese, cheese regular, cheese part-skim, sour cream, yogurt plain regular fat, yogurt plain low fat, yogurt fruit flavored, yogurt fruit flavored low fat
Raw vegetables	All types of vegetable consumed raw
Fruits	Fruits All types of fruit, fruit juice and dried fruits
Nuts	All nuts
Tea and coffee	Tea and coffee Tea and coffee
Soft drinks	All types of soft drinks

2.4.4 Sample Size Calculation

Sample size for FFQ reproducibility and validity studies are generally between 50 and 100 people (Cade et al. 2002, Steinemann et al. 2017). The primary analysis is the correlation between the FFQ and the SFFQ. Comparing between two similar methods of dietary data collection requires a correlation coefficient of 0.5 to conclude adequate agreement (Cade et al. 2002; Rohrmann & Klein 2003). A power of 80% was chosen and the sample size calculation was performed in STATA:

H0: 0.3

Ha: 0.5

Power: 0.8

N = 120

According to Serra-Majem et al. (2009) and Willett & Lenart (1998), a sample size for validation and comparability studies involves correlations for many nutrients and is therefore, less

straightforward. These authors estimated that an adequate sample size is between 100 and 200 individuals.

2.4.5 Inclusion Criteria/Exclusion criteria

Inclusion Criteria

The only inclusion criteria for the nutritional sub-study done within RADICAL PC was that the participant gave consent to participating in the large cohort study. On the consent form there was a separate question asking about their willingness to participate in the sub-study, which would involve one additional diet questionnaire at two time points. Participants had the option of accepting or declining this additional sub-study of RADICAL PC at the time of consent into cohort study.

The following are the inclusion and exclusion criteria for RADICAL PC:

A man with a diagnosis of PC that is:

a) New, defined as a diagnosis within year 1 of baseline visit OR
b) ADT treatment for the first time *before* month 1 of baseline visit OR
c) ADT treatment for the first time *after* month 1 of baseline visit

Exclusion Criteria

a) Unwilling to provide consent OR
b) Are < 45 years of age
c) See a cardiologist early
d) On the following regime: Aspirin, Statin, ACE-I or ARB AND exercise ≥ 4 times per week

A sample of the consent form is provided in the Appendix II

2.4.6 Reliability

Two time points can provide an evaluation of questionnaire performance. This is usually not done in a short time frame (days or weeks), but rather with a longer interval between questionnaires (3-6 months) (Willett 2013). Using a longer interval between the two questionnaires, responses are likely to show true changes in dietary intake that contribute to reliability.

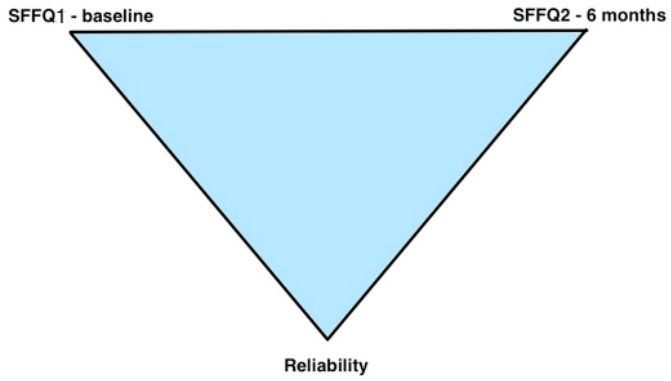

Figure 3: Reliability model

Questionnaire was the same at baseline and 6-month interval, first the short FFQ and then the long FFQ were administered to patients who provided consent in the RADICAL PC sub-study.

2.4.7 Data Preparation

Statistical software package STATA version 14.0 was used for data analysis. All study data collection is done using the software iDataFax, including patient demographics, RADICAL PC specific outcomes, and data collection for the nutritional sub-study.

The following outlines the procedures taken to prepare the data for analysis:

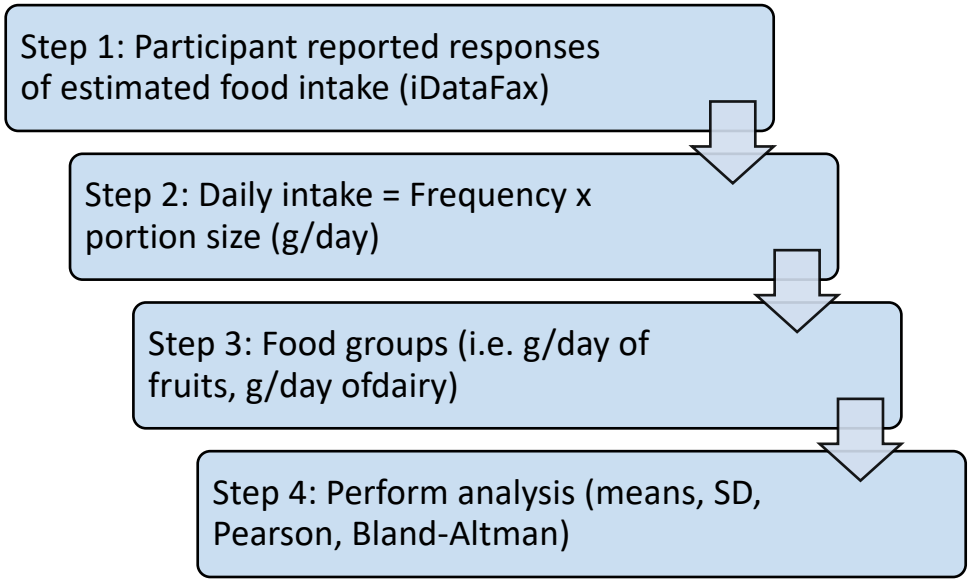

Figure 4: The FFQ Comparability Analysis Flow-Chart

Step 1

The participant reported responses were extracted from the iDataFax database. Participants responded to the FFQ by estimating their food item intake either daily, weekly, monthly or yearly. This estimated frequency of consumption is then converted to a daily intake for food items that are reported weekly, monthly, or yearly. For example, if a participant reports 1 egg each week:

1 egg x 52 weeks = 52 eggs/year

52/365 = 0.142 frequency of consumption of egg/day

OR

1 egg/week

1/7 = 0.142 frequency of consumption of egg/day

Step 2

Once the frequency is acquired, the frequency is converted to grams per day using the portion sizes obtained from the NDB (section 2.2.2) by multiplying the frequency by the portion size (g). For example, referring back to the egg example:

0.142 frequency of consumption of egg/day

1 egg = 50 g (average portion size obtained from NDB)

0.142 x 50 = 7.12 g/day

Step 3

Different food items are compiled into their assigned groups to assemble a total gram per day for each food group. See Table 20 for Food Groups. Main food groups (starches, meats, meats, fruits, vegetables, and soft drinks) are an important part of being able to assess the correlation and agreement between the two questionnaires. The total amount of grams of each food group of the SFFQ is compared to the long FFQ in addition to a comparison of macro-nutrients. It is not possible to compare all individual food items of the long FFQ to the short FFQ since the abridged version removed several food items (Table 18).

Step 4

The proposed statistical analyses (Spearman's correlation, mean, SD, Bland-Altman) are also completed in STATA version 14.0 using the data extracted and converted steps 1 through 3.

Table 24: Structure of data extraction, conversion and grouping

Type	File	Extracted		Converted		Grouped	
		Baseline	6-month	Baseline	6-month	Baseline	6-month
Short	Daily intake	√	√	√	√	√	√
	Nutrients	√	√	n/a	n/a	n/a	n/a
Long	Daily intake	√	√	√	√	√	√
	Nutrients	√	√	n/a	n/a	n/a	n/a

** n/a: not applicable

This data was analyzed using the Spearman's method to evaluate whether both instruments rank people in the same way. Dehghan et al. (2017) also recommends assessing the level of agreement and whether the estimated measures of the two methods were dependent on the magnitude of measurements using the Bland-Altman plot method (Bland & Altman 1986). Correlation allows us to identify the relationship between one variable and another, but the Bland-Altman method is recommended for comparability (agreement), as it estimates the agreement between two quantitative methods of measurement (Giavarina 2015). The Bland-Altman plot constructs limits of agreement in order to quantify agreement between the FFQ and SFFQ (Dehghan 2012b; Giavarina 2015).

2.5 RESULTS

A total of 132 participants consented to the RADICAL FFQ sub-study and two did not complete the FFQ for a total of 130 participants. All participants reported living at home (versus retirement home, hospice etc).

Table 25: Demographic Characteristics of Participants in the Comparability Sub-Study. The data presented are mean±standard deviation or count (percentage)**.**

Characteristic	Overall (n=130)
Age in years; mean (SD)	60.27 ±6.39
Highest level of education achieved	
< high school; n (%)	17 (13)
High school; n (%)	36 (28)
College; n (%)	31 (24)
University; n (%)	43 (33)
Trade school; n (%)	3 (2)
Employment	
Employed with income; n (%)	60 (46)
Employed without income; n (%)	1 (<1)
Retired; n (%)	68 (52)
Homemaker; n (%)	1 (<1)
Physical activity	
Days walked; mean (SD)	1.97 (2.51)
Days moderate; mean (SD)	0.80 (1.80)
Days vigorous; mean (SD)	0.42 (1.33)
Smoking	
Never; n (%)	56 (43)
Current; n (%)	12 (9)
Former; n (%)	62 (48)
Alcohol	
Never; n (%)	9 (7)
Current; n (%)	109 (84)
Former; n (%)	12 (9)
BMI (kg/m^2); mean (SD)	27. 40 (3.82)

Nearly all participants were either never smokers (43%) or former smokers (48%), and most participants were currently consuming alcohol (84%), *Table 25.*

Table 26: Mean, SD and estimated correlation (Spearman's) of main food groups.

Food Item	Short FFQ		Long FFQ		Energy adjusted Spearman	Spearman (rho)
	Mean (g)	STD	Mean (g)	STD		
Whole Wheat	25.83	29.07	44.81	72.88	0.57**	0.76**
Refined Grains	103.41	70.26	106.79	71.85	0.75**	0.78**
Meats	94.32	49.09	62.38	34.25	0.45*	0.47*
Processed meats	24.31	37.92	12.64	11.48	0.49*	0.57**
Fish	9.84	9.86	19.31	17.39	0.79**	0.85**
Dairy	311.39	241.93	324.73	249.80	0.76**	0.87**
Vegetables	106.62	69.33	257.34	145.74	0.32*	0.31*
Potatoes	33.81	27.72	24.88	21.97	0.83**	0.88**
Legumes	14.37	15.86	16.24	18.12	0.28	0.28
Fruits	175.14	123.42	174.36	122.10	0.73**	0.74**
Nuts	9.78	10.14	10.05	13.08	0.58**	0.74**
Soft drinks	81.33	149.63	107.62	218.19	0.54**	0.76**
Fried Foods	36.36	35.27	80.19	53.23	0.24	0.34*
Sugar	13.22	17.01	141.47	123.73	0.10	0.18
Oil	30.53	24.09	7.29	6.69	0.17	0.23

** indicates correlation greater than 0.5
* indicates weak correlation 0.3-0.5

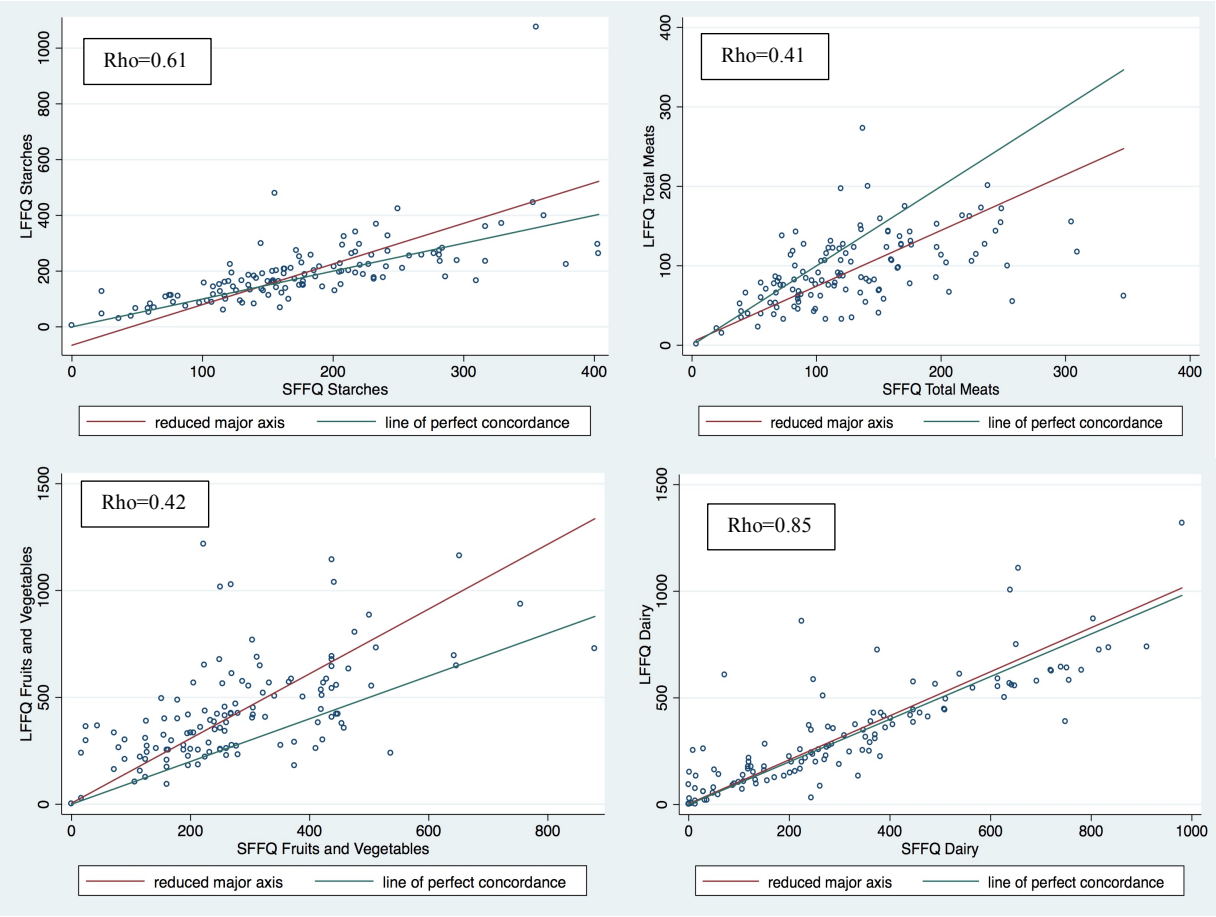

Figure 5: Scatter plots for LFFQ and SFFQ of starches (whole wheat, refined grains, legumes, potatoes), Total Meats (meat, processed meat, fish), Fruits and Vegetables, and Dairy

The mean and standard deviation for each food group was computed for the SFFQ and the FFQ and can be seen in Table 23.

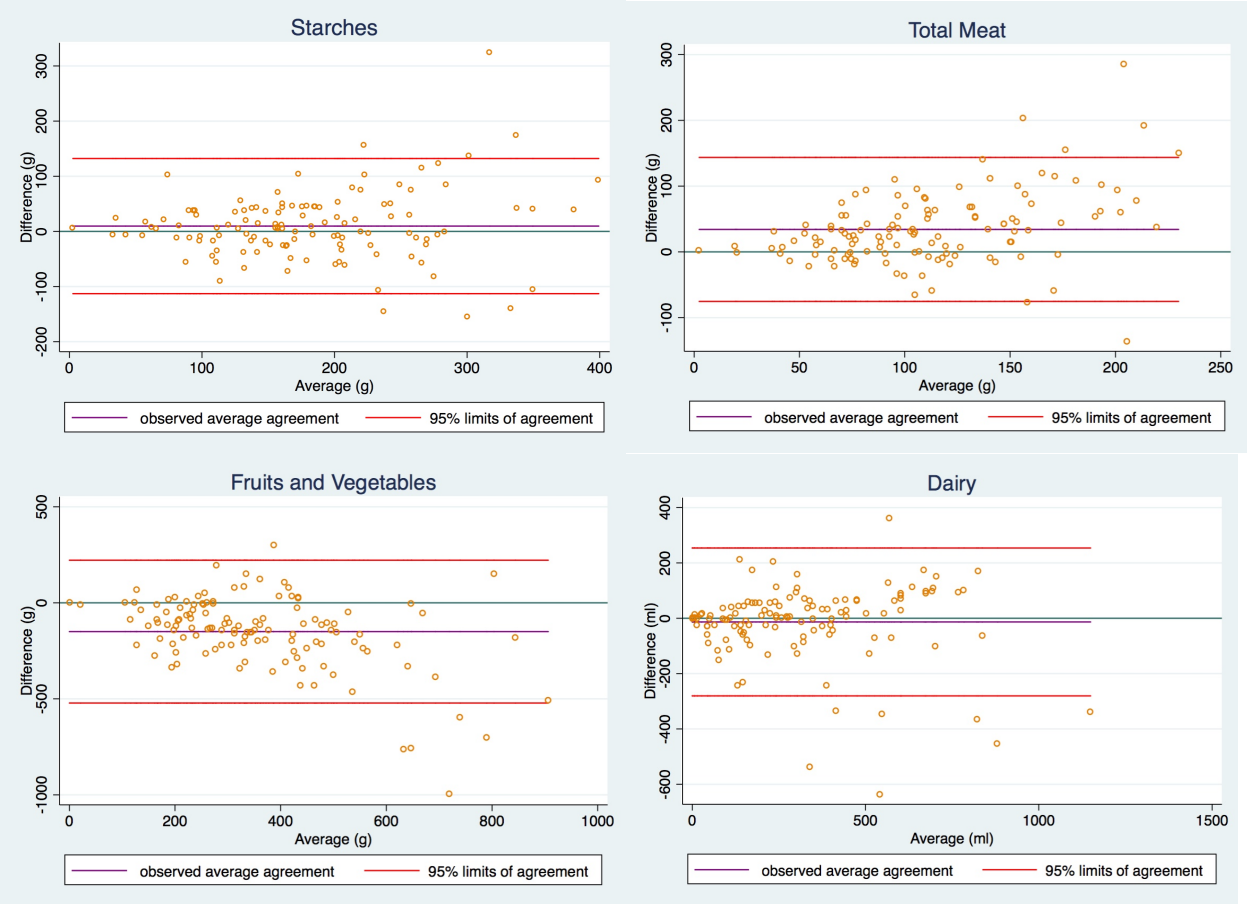

Figure 6: Bland-Altman plots of agreement between SFFQ and LFFQ for starches, total meats, fruits and vegetables, and dairy. The difference of means estimates of each FFQ is plotted.

The level of agreement can be measured using the Bland-Altman plots of agreements reported in Figure 5 for food groups and Figure 6 for nutrients.

Table 27: Macro Nutrients Protein, Carbohydrate, and Total fats Mean, SD, and estimated correlation (Spearman's)

Food Item	Short FFQ		Long FFQ		Energy adjusted Spearman	Spearman (rho)
	Mean	STD	Mean	STD		
Protein	63.25	19.24	70.19	21.86	0.41*	0.68**
Carbohydrates	137.17	41.19	209.65	77.32	0.38*	0.57**
Total Fats	60.78	25.65	50.90	19.80	0.10	0.47*

** indicates correlation greater than 0.5
* indicates weak correlation 0.3-0.5.

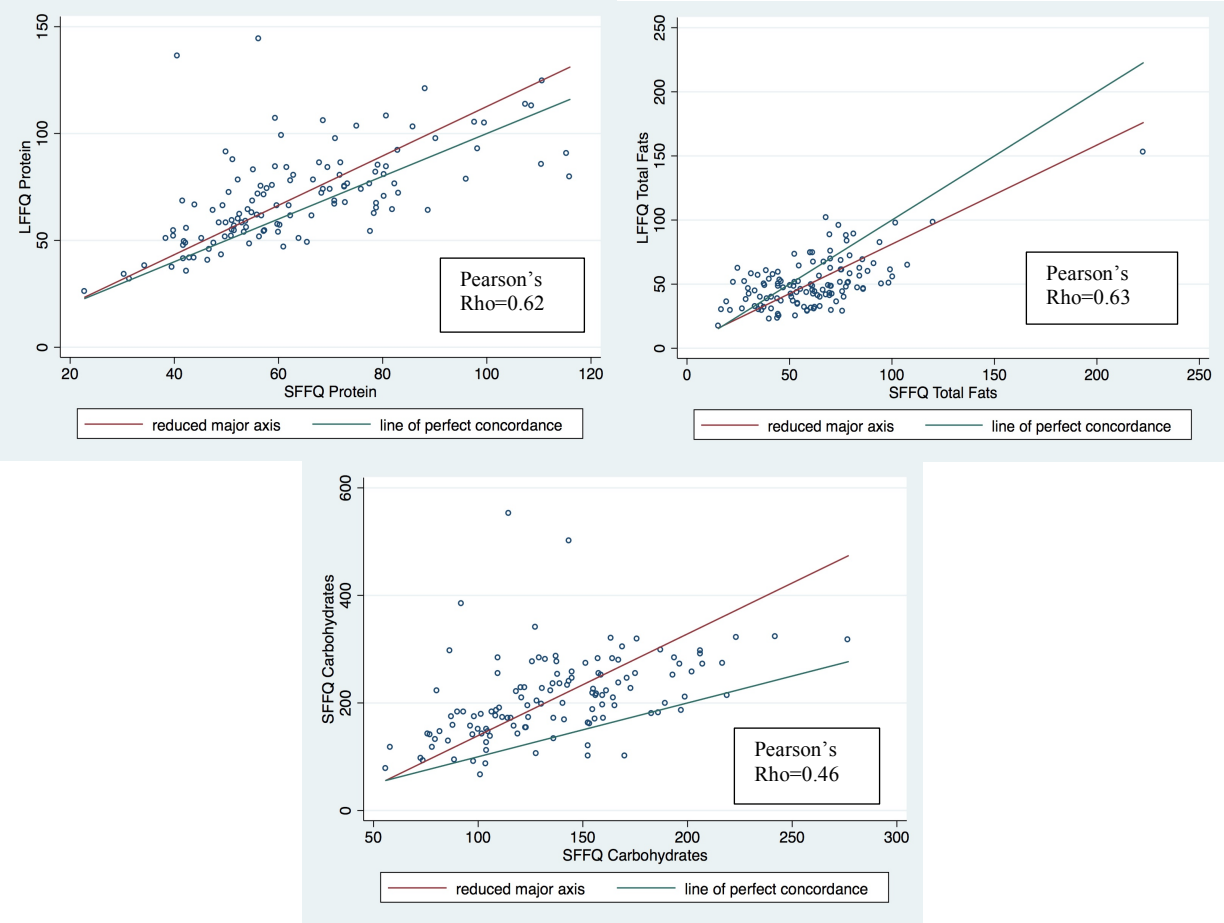

Figure 7: Scatter plots for LFFQ and SFFQ of proteins, total fats, and carbohydrates.

The mean and standard deviation for each nutrient (protein, carbohydrate, total fats) was computed for the SFFQ and the FFQ and can be seen in Table 24.

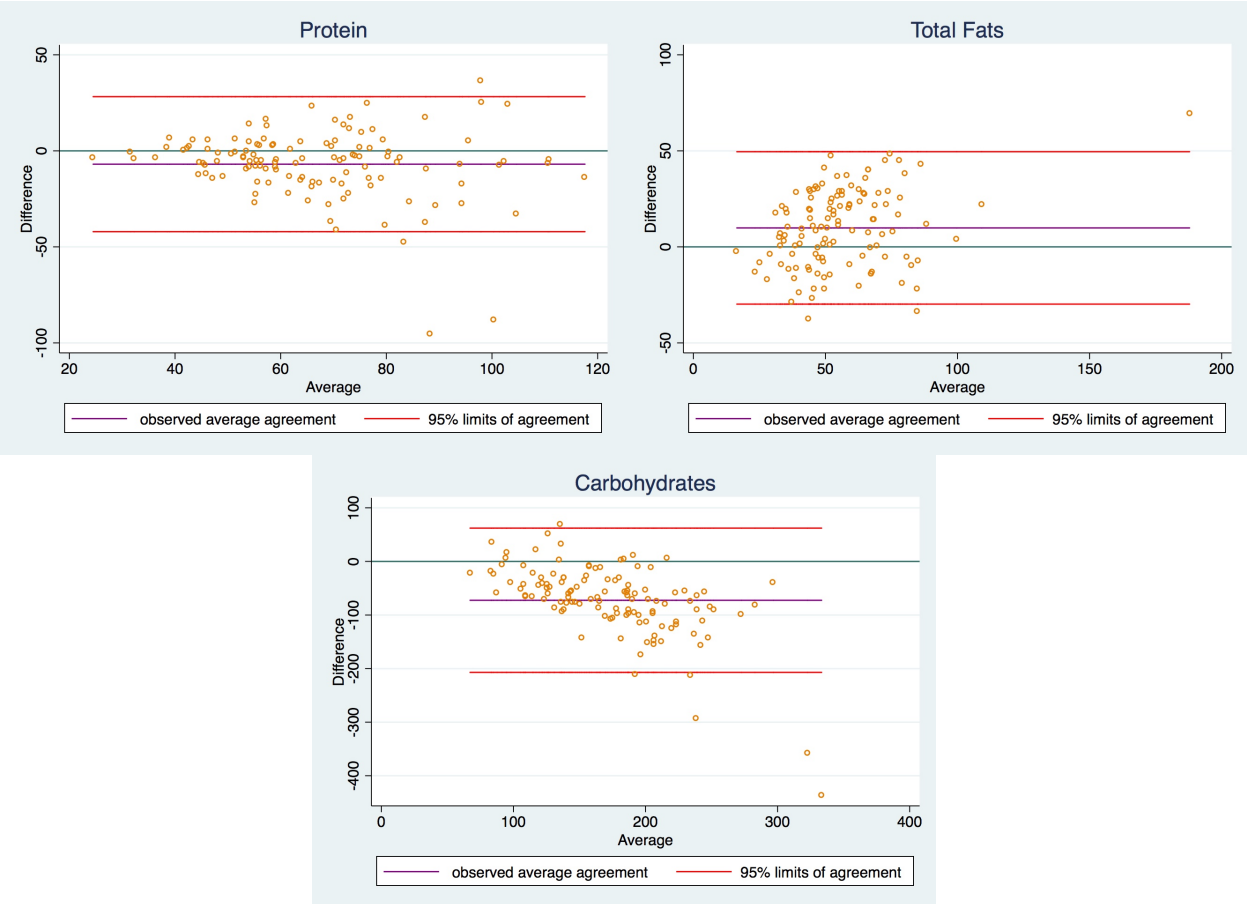

Figure 8: Bland-Altman plots of agreement between SFFQ and LFFQ for protein, total fats, and carbohydrates. The difference of means estimates of each FFQ is plotted.

Reliability Testing

Reliability testing is done to determine the process of reproducibility of the FFQ in order to deem the FFQ as valid. This is done by assessing diet over time in an FFQ to evaluate performance and discover any discrepancies.

Table 28: Reliability of the FFQ

Food Item	Short FFQ Baseline		Short FFQ 6-mo		Spearman (rho)
	Mean (g)	STD	Mean (g)	STD	
Whole Wheat	25.83	29.07	22.55	26.51	0.66**
Refined Grains	103.41	70.26	110.66	81.50	0.58**
Meats	94.32	49.09	96.10	54.09	0.45*
Processed meats	24.31	37.92	25.51	37.67	0.60**
Fish	9.84	9.86	10.27	9.72	0.61**
Dairy	311.39	241.93	272.57	217.59	0.75**
Vegetables	106.62	69.33	108.82	82.16	0.47*
Potatoes	33.81	27.72	32.23	25.93	0.62*
Legumes	14.37	15.86	11.15	14.74	0.28
Fruits	175.14	123.42	173.79	125.08	0.54**
Nuts	9.78	10.14	10.59	10.31	0.49*
Soft drinks	81.33	149.63	72.98	195.26	0.66**
Fried Foods	36.36	35.27	48.96	56.82	0.46*
Sugar	13.22	17.01	12.22	19.02	0.64**
Oil	30.53	24.09	26.46	18.47	0.46*

There were strong correlations above 0.5 for whole wheat, refined grains, processed meats, fish, dairy, potatoes, fruits, soft drinks, and sugar for the reliability test. Moderate correlation (0.3-0.5) was found among meats, vegetables, legumes, nuts, fried foods, and oil. There was poor correlation (0.28) among legumes between the two questionnaires.

2.6 DISCUSSION

This analysis sought to compare estimates of food intakes measured by the long and abridged FFQ for individuals enrolled in the RADICAL PC study. Overall, the results indicate good agreement between the two questionnaires and are in keeping with findings of other

comparability studies (Dehghan et al. 2017). The expected range of correlation values (0.3-0.5) when assessing an abridged questionnaire to a longer version were observed and are acceptable for use in large epidemiological health studies to evaluate diet and health outcomes (Cade et al. 2002; Rohrmann & Klein 2003). A key component of a large epidemiological studies is that bigger sample sizes can drown out error and thus a less conservative correlation range is accepted. The Bland-Altman (1986) method was used to assess absolute agreement and found acceptable agreement among main food groups and nutrients, indicating that the SFFQ is an adequate tool to measure diet in prostate cancer patients. Testing the reliability of the FFQ was done by comparing two separate time points (6 months apart). The Spearman correlations were between moderate to good at a range of 0.45 to 0.75, with the exception of legumes which had a correlation of 0.28. Overall the SFFQ administered in the RADICAL PC study had good reliability.

Unlike most epidemiological studies with aims to identify a causal relationship, diet is not one single exposure, but rather a complex set of continuous variables (Willetts 1987). The study of diet and PC may evaluate overall diet, specific nutrients, food groups or even specific items. Each approach has its advantages and disadvantages, but nearly all are considered continuous variables. The ability to describe dietary factors as either being absent or present is rarely a possibility, which is defined in the Bradford Hill criteria for proving causality (Willett 1987; Hill 1962). Instead of looking for whether an effect exists (absence or presence), dietary factors are evaluated using dose-response relationships, which are not always linear (Willett 1987). Further challenges of nutritional epidemiology are the variations in nutritional intakes of individuals, which are not entirely consistent within a population regardless of similarities in culture and habits. Food composition, preparation, behavioural patterns, and ultimately a

difference in total intake will impact the ability to draw definitive relationships, resulting in underestimates of associations (Willett 1987). Additionally, diet is not typically compared across populations, and a diet-disease relationship in one population may not have any associations in another population (Willett 1987), this concern is generally addressed by adjusting the FFQ used to collect data. This is not to say that diet is an exposure that is impossible to measure, but an exposure that requires flexibility in how its measurements are assessed.

One limitation of this study is the length of time it takes to complete the baseline visit and 6-month visit when participants have to complete the long and the abridged FFQ at one timepoint. This may result in increased patient fatigue and burden and thus resulting in less accurate results, and it may also lead to participants not wanting to repeat both questionnaires at the 6-month follow-up. Implementing a shorter FFQ that is less time consuming and burdensome to patients will have positive effects on study feasibility and likelihood of patient participation. Particularly in this population were approximately 46% of participants are still employed and do not wish to stay long after their clinic visit for study purposes or answer lengthy questionnaires over the phone. Conversely, an increased amount of food items included in the FFQ may increase accuracy of diet measurements or creating a more compact questionnaire may results in decreased accuracy (Dehghan et al. 2017). This particular patient group and RCT has main objectives (CVD and ADT) that do not involve a complete diet history, but rather involve a large sample size, which will assess long-term habitual food consumption and thus an abridged SFFQ is adequate. When implementing FFQ's into a population, all these factors need to be taken into consideration, weighing the benefits and risk of bias when deciding what type of intake assessment tool will be used. The most important factor should be the specific hypothesis of the study. The FFQ should be comprised of information that takes into consideration the hypothesis

in question, in the case of this SFFQ, it was specifically amended to fulfill dietary objectives of RADICAL PC. Given the high number of participants in large epidemiological studies, FFQ's are considered to be adequate tools for assessing diet-disease relationships assuming that proper methods to evaluate validation or comparability were conducted (Willett 2013). Therefore, having agreement between a validated questionnaire and one that has undergone any changes (such as being abridged) is valuable for studying diet and disease relationships.

3.0 FINAL CONCLUSIONS AND RECOMMENDATIONS

3.1 Summary and Interpretation of Results Chapter 1

In conclusion, there was no relationship between diet and prostate cancer, and no association between the high-risk prostate cancer category and a poor-quality diet using the Healthy Diet Score. As anticipated, there was an association between the high-risk prostate cancer category and age.

3.2 Summary and Interpretation of Results Chapter 2

In conclusion, the abridged SFFQ for prostate cancer patients was found to be an adequate tool for measuring dietary intake of certain food groups and nutrients. Overall agreement was found among the two questionnaires using the Spearman's rank correlation and Bland-Altman plots. Reliability was also adequate when checked at two different time points 6 months apart.

3.3 Recommendations

A simple recommendation would be to repeat this analysis in RADICAL PC once the study is complete and has a more robust sample size. At this time point, it might be possible to separate patients into time diagnosed. As for future recommendations, it would be really interesting to have a sample size of patients who have a new diagnosis of prostate cancer and to complete an FFQ with participants at time of diagnosis. There may be some practical limitations to this setup to consider. The Healthy Diet Score should also be reviewed in a study not impacted by temporality.

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Appendix I: RADICAL PC Protocol

The Role of Androgen Deprivation Therapy in CArdiovascular Disease – A Longitudinal Prostate Cancer Study (RADICAL PC1)
&
A RAndomizeD Intervention for CArdiovascular and Lifestyle Risk Factors in Prostate Cancer Patients (RADICAL PC2)

RADICAL PC1 is a prospective cohort study of men with a new diagnosis of prostate cancer
RADICAL PC2 is a randomized, controlled trial of a systematic approach to modifying cardiovascular and lifestyle risk factors in men with a new diagnosis of prostate cancer

Principal Investigator: Dr. Jehonathan Pinthus
Co-Investigators: Dr. Himu Lukka, Dr. Darryl Leong, Dr. Laurence Klotz
Project Office: RADICAL PC Project Office, Population Health Research Institute
Hamilton General Hospital Campus, DBCVSRI, 237 Barton St E, Hamilton, ON
Study Size: 6000 patients

Primary Objective for RADICAL PC1:
1. To determine the prevalence of cardiovascular risk factors and disease, and the incidence of major adverse cardiovascular events
2. To measure the relationship between ADT with major adverse cardiovascular events
3. To identify factors that are independently associated with the development of cardiovascular disease

Primary Objective for RADICAL PC2:
1. To determine whether a systematic cardiovascular and lifestyle risk factor modification strategy, as compared with usual care, improves a) the cardiovascular risk profile b) cognitive function c) physical function
2. To estimate the incremental cost-effectiveness ratio of a systematic cardiovascular and lifestyle risk factor modification strategy

Inclusion Criteria:
1. A man with a diagnosis of prostate cancer that is either:
a) new (i.e. the diagnosis was made within 1 year of the enrollment visit) **or**
b) treated with ADT for the first time within 6 months prior to the enrollment visit **or**
c) to be treated with ADT for the first time within 1 month after the enrollment visit

Exclusion Criteria:
1. Patients will be excluded if they fulfill any of the following:
a) are unwilling to provide consent or
b) are <45 years of age

2. Patients will be eligible for RADICAL PC1, but will not be eligible for RADICAL PC2 if they:

a) see a cardiologist every year or

b) are undertaking ALL of the following: aspirin use, statin use, systolic blood pressure ≤130mmHg

Appendix II: Informed Consent for RADICAL PC & Nutritional sub-study

Participation Information Sheet for the RADICAL PC1 Study

Title of the Study: The Role of Androgen Deprivation Therapy In CArdiovascular Disease – A Longitudinal Prostate Cancer Study (RADICAL PC1)

Principal Investigator:
Dr. Jehonathan Pinthus
Associate Professor
Department of Urology and Surgical Oncology
Hamilton Health Sciences / McMaster University

Co-Principal Investigators:
Dr. Himu Lukka
Professor
Department of Oncology, Division of Radiation Oncology
Hamilton Health Sciences / McMaster University

Dr. Darryl Leong
Assistant Professor
Division of Cardiology, Department of Medicine
Hamilton Health Sciences / McMaster University

Locally Responsible Principal Investigator:
Dr. Bobby Shayegan (St. Joseph's Healthcare)

Funding Source:
Funding has been provided by Prostate Cancer Canada through the Movember Foundation for Clinical Trials in Prostate Cancer.

INVITATION TO PARTICIPATE IN THE RADICAL PC TRIAL

You are being invited to participate in a research study conducted by Dr. Bobby Shayegan and his colleagues at St. Joseph's Healthcare because you have been diagnosed with prostate cancer and you may be at risk of developing cardiovascular disease (such as a heart attack or stroke). Cardiovascular disease is common in men with prostate cancer.

In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form will give you detailed information about the research study.

Once you understand the study, you will be asked to sign this form if you wish to participate. Please take your time to make your decision. Feel free to discuss participating with your friends and family, and/or your physician or surgeon. Please ask the study doctor or study staff to explain anything you do not understand before signing this consent form. Make sure all your questions have been answered to your satisfaction before signing this document.

STUDY SPONSOR

This is an investigator-initiated study and the sponsor is the Population Health Research Institute of McMaster University, which is a not-for-profit academic research institute in Hamilton, Ontario.

WHY IS THIS RESEARCH BEING DONE?

Cardiovascular disease is a common occurrence in men with prostate cancer. This research aims to 1. Explore why some men with prostate cancer develop cardiovascular disease, and in particular, determine whether one type of treatment for prostate cancer called Androgen Deprivation Therapy (ADT) contributes to the risk of cardiovascular disease, and 2. Whether the risk of cardiovascular disease can be reduced in men with prostate cancer.

WHAT DOES TAKING PART IN THE STUDY INVOLVE?

You are invited to participate in RADICAL PC1.

RADICAL PC1 is an observational study in which you will receive your usual care and information on your health will be collected.

For RADICAL PC1, the research team will visit you during one of your regularly scheduled hospital/clinic visits to collect information about your health during an initial baseline visit, a 12 month visit, and a 24 month visit. Information will be collected about your medical history, current medications, physical measurements and results of routine blood and urine tests. You will be asked to complete 7 short questionnaires about your ability to perform tasks, ability to concentrate, erectile function, mood, diet, physical activity, and general well-being. You will be asked to perform a 6-minute walk test, where the distance you can walk (at your own pace) over 6-minutes will be measured.

If you consent to participate in the Food Frequency Sub-study, you will be asked to complete a longer version of the Food Frequency Questionnaire, which will take approximately 15 additional minutes to complete. The longer version of the Food Frequency Questionnaire will be administered at your regular scheduled study baseline visit, and you will receive an additional telephone call 6 months after your baseline visit to complete it a second time. The Food Frequency Sub-study will include approximately 100 participants at St. Joseph's Healthcare Hamilton.

If your participation lasts longer than 24 months you will also have a close-out visit which will be your final visit. At this visit, information will be collected about your current medication use, physical measurements, results of routine blood tests and negative health outcomes.

Whenever possible, we will try to schedule your study visit with any of your regularly scheduled clinic or hospital visits. The visit should only take approximately 30 minutes or less.

The expected duration of your participation in the study is 2-4 years.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?
RADICAL PC1 is an observational trial, therefore there are minimal risks and discomforts.

HOW MANY PEOPLE WILL BE IN THIS STUDY?
In total, we plan to recruit approximately 2000 patients to participate in this study of which approximately 100 patients will be enrolled from St. Joseph's Healthcare.

WHAT ARE THE POSSIBLE BENEFITS FOR ME AND/OR FOR SOCIETY?
We cannot promise any personal benefit to you from your participation in this study. However, potential benefits include the possibility of preventing death and disability from cardiovascular disease.

Your participation may help other people undergoing treatment in the future. Information gathered from this study will help the RADICAL PC trial researchers to determine whether ADT use might accelerate coronary artery disease in some men, who may benefit from closer monitoring or strategies to reduce their risk of a heart attack or other complication.

IF I DO NOT WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?
It is important for you to know that you can choose not to take part in the study. Choosing not to participate in this study will in no way affect your usual care or treatment.

WHAT INFORMATION WILL BE KEPT PRIVATE?
Your information will be kept in strict confidence and will not be shared with anyone except with your consent or as required by law. This information will be used only for medical research purposes. All personal information such as your name, address, phone number, and family physician's name will be removed from the records and will be replaced with a number. A list linking the number with your name will be kept in a secure place, separate from your file. The records, with identifying information removed will be securely stored in a locked office in the research office on a secure password-protected server. The information for this research study will be retained for 25 years.

For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of the Hamilton Integrated Research Ethics Board or a representative from the national regulatory authority or the sponsor, may consult your research information and medical records for verification of study procedures and/or information without violating your confidentiality to the extent permitted by applicable laws and regulations. However, no records which identify

you by name or initials will be allowed to leave St. Joseph's Healthcare. By signing this consent form, you authorize such access.

If the results of the study are presented or published, your name will not be used and no information that discloses your identity will be released or published without your specific consent to the disclosure. However, it is important to note that this original signed consent form and the information which follows may be included in your health record.

CAN PARTICIPATION IN THE STUDY END EARLY?

Your participation in this study is entirely voluntary. You may refuse to take part in the study, or you may stop participation at any time, without affecting future treatment, and without penalty or loss of benefits to which you would otherwise be entitled. You have the option of removing information that was already collected at any time after your consent is withdrawn. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

WILL I BE PAID TO PARTICIPATE IN THIS STUDY?

No. Participants will not be compensated for participating in this study.

WILL THERE BE ANY COSTS?

Your participation in this research project will not involve any additional costs to you. You will receive the treatments free of charge.

IF I HAVE ANY QUESTIONS OR PROBLEMS, WHOM CAN I CALL?

If you have any questions or concerns about this study now or later or if you think you have a research-related injury, please feel free to contact the Principal Investigator, Dr. Bobby Shayegan, at 905-522-1155 ext 33982, or one of the Co-Investigators, Dr. Edward Matsumoto, at 905-522-1155 ext. 36186, or Dr. Anil Kapoor, at 905-522-1155 ext. 33218, or the Research Nurse, Sarah Karampatos, at 905-522-1155 ext. 32134. If you feel you have a significant research-related injury that requires immediate or urgent medical attention, do not hesitate to call or go to the closest emergency department.

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call the Office of the REB Chair, HIREB at 905.521.2100 x 42013

II. Consent Statement for RADICAL PC1 trial

I therefore certify the following:

- I have read pages 1 through 6and understand the study involves research. I understand the purpose of the study as well as the potential benefits and risks of participating in the study.

- I have had the opportunity to ask questions. All my questions have been answered to my satisfaction.

- I understand that I am free to withdraw from this study at any time without the need to give reasons and without affecting my future treatment. Similarly, should I choose not to participate in this study in the first place, that decision would not make a difference to my medical treatment.

- I also grant auditors from the national regulatory authority, the sponsor or the Research Ethics Board direct access to my original medical records for verification of clinical trial procedures and/or information to the extent permitted by applicable laws and regulations.

I agree to participate in this study and I understand that I will receive a signed copy of this form.

1. **I agree to provide my provincial health card number for future research linking my health outcomes with administrative health databases. I understand my personal health information will remain confidential.**

   ☐ **YES** ☐ **NO**

2. **I agree to participate in the Food Frequency Sub-study and understand that I will receive an additional 6 month telephone follow-up visit.**

   ☐ **YES** ☐ **NO**

_____

Name of Participant (please print)

_____

Name of Legally Authorized Representative (please print if applicable)

_____ _____

Signature of Participant or Legally Authorized Representative Date

CONSENT FORM ADMINISTERED AND EXPLAINED IN PERSON BY:

_____
Name and title (please print)

_____ _____
Signature Date

SIGNATURE OF INVESTIGATOR:
In my judgment, the participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent to participate in this research study.

_____
Name of Investigator (please print)

_____ _____
Signature of Investigator Date

Appendix III: SFFQ

RADICAL PC **FFQ Short - Reference Page 1**

1) Whole milk:	Includes milk produced by mammals with 3.25% fat or more
2) Skim milk/low fat milk	Includes milk produced by mammals and cream is partly or completely removed
3) Soy milk	Plant based drink produced from soybean
4) Almond milk	Plant based drink, mixture of almond and water
5) Eggs	Raw/frozen/boiled eggs, fried eggs, quiche, omelet, sugared/salted eggs, duck eggs
6) Chicken with skin	All cuts of chicken, Cornish hen, canned chicken, all with skin
7) Chicken without skin	All cuts of chicken, Cornish hen, canned chicken, skin completely removed
8) Red meat with fat	Includes all ground beef, all other cuts of beef and all cuts of veal, goat, mutton, pork, lamb, all types with fat
9) Red meat without fat	Includes all ground beef, all other cuts of beef and all cuts of veal, goat, mutton, pork, lamb, all types visible fat removed
10) Fish, cooked	Includes fresh-water and sea-water fish; canned fish
11) Fish, fried	Includes fresh-water and sea-water fish; fried in pan with oil
12) Fish, salted	Includes dried fish; preserved fish with salt
13) Whole grains bread	Includes whole wheat flour breads; whole wheat chapatti, corn/hominy/masa harina/corn flour/maize
14) Refined grains:	Includes white flour bread; white flour chapatti
15) Fruit, fresh	Includes any type of fruit freshly consumed
16) Fruit, frozen	Includes any type of fruit packaged and frozen
17) Vegetable, fresh	Include all types of fresh vegetables; lettuce, broccoli, cauliflower, spinach, bok choi; choi sum, collards, mustard or turnip greens; asparagus
18) Vegetables, frozen	Includes any vegetables packaged and frozen
19) Vegetables, cooked	Includes any cooked vegetables
20) Vegetables, fried	Includes any fried vegetables
21) Vegetables, stir fried	Includes any vegetables fried rapidly over high heat while stirring briskly
22) Soft drink, regular	Includes sweetened cola, non-cola beverages, tonic water, instant ice tea
23) Soft drink, diet	Includes unsweetened cola, non-cola beverages, tonic water, instant ice tea
24) Fried foods	Includes French fries, potato chips, onion rings, samosas, papad, pakoras; sev; fried won ton, egg roll
25) Pastries	Includes cakes, pies, pastries, cookies, brownies, burfi/ladoo, rasgulla/gulab jamun, halwa, shameia, mohalabeia, Chinese sweet buns, sweet bean desserts, burritos with fruit
26) Rice, pasta	Include any type of cooked, fried, stir fried rice, whole wheat pasta, fresh pasta
27) Processed meat	Include hamburger, hot dog, sausages, bacon, wiener, luncheon meat

RADICAL-PC **Food Frequency Questionnaire (English, Page 1 of 2)** CRF 55

DataFax #009 Plate #055

☐ Baseline ☐ 3 Month ☐ 6 Month ☐ 12 Month ☐ 18 Month ☐ 24 Month ☐ 36 Month ☐ Close-Out

Patient ID# ☐☐☐☐☐☐ **Initials** ☐☐☐ *F/M/L*

Baseline Visit: in the past year, on average, how often have you consumed the following foods?

3 Month Visit onwards: Since your last visit, how often have you consumed the following foods and drinks?

Food / Drink	Avg Serving	Never, <1/month	1-3/mo	1/wk	2-4/wk	5-6/wk	1/day	2-3/day	>4/day
1. Whole milk	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
2. Skim milk or low fat milk	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
3. Soy milk	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
4. Almond milk	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
5. Eggs	1	☐	☐	☐	☐	☐	☐	☐	☐
6. Chicken with skin	90-120 g	☐	☐	☐	☐	☐	☐	☐	☐
7. Chicken without skin	90-120 g	☐	☐	☐	☐	☐	☐	☐	☐
8. Red meat with fat	90-120 g	☐	☐	☐	☐	☐	☐	☐	☐
9. Red meat without fat	90-120 g	☐	☐	☐	☐	☐	☐	☐	☐
10. Fish, cooked	1 fillet	☐	☐	☐	☐	☐	☐	☐	☐
11. Fish, fried	1 fillet	☐	☐	☐	☐	☐	☐	☐	☐
12. Fish, salted	20 g	☐	☐	☐	☐	☐	☐	☐	☐
13. Whole wheat/multigrain bread	1 slice	☐	☐	☐	☐	☐	☐	☐	☐
14. White bread	1 slice	☐	☐	☐	☐	☐	☐	☐	☐
15. Fruits (fresh)	1 medium	☐	☐	☐	☐	☐	☐	☐	☐
16. Fruits (frozen)	1/2 cup	☐	☐	☐	☐	☐	☐	☐	☐
17. Vegetables (fresh/raw)	1/2 cup	☐	☐	☐	☐	☐	☐	☐	☐
18. Vegetables (frozen)	1/2 cup	☐	☐	☐	☐	☐	☐	☐	☐
19. Vegetables (cooked)	1/2 cup	☐	☐	☐	☐	☐	☐	☐	☐
20. Vegetables (fried)	1/2 cup	☐	☐	☐	☐	☐	☐	☐	☐
21. Vegetables (stir-fried)	1/2 cup	☐	☐	☐	☐	☐	☐	☐	☐
22. Soft drink (regular)	1 glass/can	☐	☐	☐	☐	☐	☐	☐	☐
23. Soft drink (diet)	1 glass/can	☐	☐	☐	☐	☐	☐	☐	☐
24. Fried foods (potatoes etc.)	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
25. Pastries, industrial bakery products such as cake, donuts or cookies	1 piece	☐	☐	☐	☐	☐	☐	☐	☐
26. Rice, pasta	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
27. Processed meats (cold cuts, sausage and bacon)	90-120 g	☐	☐	☐	☐	☐	☐	☐	☐

28) Cream	Include fat removed from milk
29) Butter	Include solid dairy product made by churning fresh or fermented cream or milk
30) Margarine	Include a butter substitute made from vegetable oils or animal fats
31) Cheese, hard	Include Cheddar, Emmental, Gruyere, Gouda, Edam etc.
32) Cheese, soft	Include cream cheese, Brie, Havarti, etc.
33) Yogurt	Include any type with or without fat
34) Olive oil	Include any type used for salad dressing or cooking
35) Nuts	Includes peanuts, almonds, walnut, sunflower seeds, cashews, and all other nuts and seed
36) Cold cereal breakfast	Include raisin bran, corn flake, bran flake, wheat flake, puffed rice, puffed wheat
37) Oatmeal, cooked	Include ground oat cooked for breakfast
38) Organ meats	Include organ meats from all animals, liver, kidney, brain, spleen, heart
39) Seafood	Include shrimp, crab, lobster, muscle, etc.
40) Beans and other pulses	All legumes (non-sprouted), tofu, soy protein isolated, soy meal, soy flour, soy protein concentrate, dried beans, lentils, peas, dals, soups (split pea), baked beans, tofu/soybean curd
41) Potatoes	Boiled potatoes, potato flour, mashed potatoes made from real potatoes or granules
42) Pizza	All-dressed, pepperoni, plain pizza, and calzone
43) Sugar	All types white and brown sugars
44) Dried fruits	Includes dried apricot, plum, peaches

RADICAL-PC **Food Frequency Questionnaire (English, Page 2 of 2)** CRF 56

☐ Baseline ☐ 3 Month ☐ 6 Month ☐ 12 Month ☐ 18 Month ☐ 24 Month ☐ 36 Month ☐ Close-Out

DataFax #009 Plate #056

Patient ID# ☐☐☐☐☐☐ **Initials** ☐☐☐ *F/M/L*

Baseline Visit: in the past year, on average, how often have you consumed the following foods?

3 Month Visit onwards: Since your last visit, how often have you consumed the following foods and drinks?

Food / Drink cont'd	Avg Serving	Never, <1/month	1-3/mo	1/wk	2-4/wk	5-6/wk	1/day	2-3/day	>4/day
28. Cream	1 Tablespoon	☐	☐	☐	☐	☐	☐	☐	☐
29. Butter	1 Tablespoon	☐	☐	☐	☐	☐	☐	☐	☐
30. Margarine	1 Tablespoon	☐	☐	☐	☐	☐	☐	☐	☐
31. Cheese (hard)	30 g	☐	☐	☐	☐	☐	☐	☐	☐
32. Cheese (soft)	30 g	☐	☐	☐	☐	☐	☐	☐	☐
33. Yogurt	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
34. Olive oil	4 Tablespoons	☐	☐	☐	☐	☐	☐	☐	☐
35. Nuts	30 g	☐	☐	☐	☐	☐	☐	☐	☐
36. Cold breakfast cereals	30 g	☐	☐	☐	☐	☐	☐	☐	☐
37. Oatmeal (cooked)	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
38. Organ meat	60 g	☐	☐	☐	☐	☐	☐	☐	☐
39. Seafoods (shrimp, crab, etc.)	60 g	☐	☐	☐	☐	☐	☐	☐	☐
40. Beans and other pulses (cooked)	1 cup	☐	☐	☐	☐	☐	☐	☐	☐
41. Potatoes (boiled, cooked)	1 medium	☐	☐	☐	☐	☐	☐	☐	☐
42. Pizza	1 slice	☐	☐	☐	☐	☐	☐	☐	☐
43. Sugar (white, brown)	1 tsp	☐	☐	☐	☐	☐	☐	☐	☐
44. Dried fruits (e.g. apricot, plum, etc.)	30 g	☐	☐	☐	☐	☐	☐	☐	☐
45. How often do you eat meals at a fast food/ non-fast food restaurant?		☐	☐	☐	☐	☐	☐	☐	☐
46. How often do you consume canned foods (any type)?		☐	☐	☐	☐	☐	☐	☐	☐
47. How often do you consume frozen foods/meals ?		☐	☐	☐	☐	☐	☐	☐	☐

48. What type of oil do you use for cooking most often (*choose one response only*)?

☐ Soya oil ☐ Sunflower seed oil ☐ Olive oil ☐ Canola oil

☐ Corn oil ☐ Vegetable oil ☐ Coconut oil ☐ Other ☐ None

49. Have you changed your diet during the last year? ☐ No ☐ Yes → If yes, was it due to health conditions? ☐ No ☐ Yes

50. Are you on a special diet? ☐ No ☐ Yes → If yes, what diets are you currently following *(check all that apply)*?

☐ Diabetic diet ☐ Low fat diet ☐ Low salt diet

☐ Weight reducing diet ☐ High nuts diet ☐ High olive oil diet

Appendix IIII: FFQ

RADICAL PC **FFQ - Reference Page 1**

Please note: If the participant is required to complete this questionnaire at home for reasons such as time constraint, the Coordinator will instruct the participant to complete all questions and return it to the site (either via mail or in person), in a timely manner. Once the participant returns the questionnaire, the Coordinator will ensure all questions have been completed appropriately. If there are any omissions or errors, the Coordinator will follow up with the participant via telephone for the necessary corrections. All corrections will be dated an initialed by the Coordinator at the time of the correction. The Coordinator will also make note at the bottom of the questionnaire the date it was returned and the method (ie: mail or in-person). The Coordinator will sign and date the bottom of the CRF. If the participant has signed and dated the questionnaire, the Coordinator will ensure the Coordinator's name is entered into DataFax, not the participant's name, to ensure privacy.

FFQ-Ref

RADICAL PC **Food Frequency Questionnaire (English, Page 1 of 11)** CRF 36

DataFax #009 Plate #036

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

BEVERAGES	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
1. WHOLE MILK (HOMO) (as beverage or in cereal, but not in coffee or tea)					1 cup (250ml)	S	M	L
2. 2% MILK (includes Lactaid) (as beverage or in cereal, but not in coffee or tea)					1 cup (250ml)	S	M	L
3. 1% MILK (as beverage or in cereal, but not in coffee or tea)					1 cup (250ml)	S	M	L
4. SKIM MILK (as beverage or in cereal, but not in coffee or tea)					1 cup (250ml)	S	M	L
5. COFFEE, regular (brewed or instant)					1 cup (250ml)	S	M	L
6. COFFEE, decaffeinated					1 cup (250ml)	S	M	L
7. TEA, regular (Red Rose, Salada)					1 cup (250ml)	S	M	L
8. MILK in Tea and Coffee Please mark type:								
Homo milk					2 tbsp (30ml)	S	M	L
2% or 1%					2 tbsp (30ml)	S	M	L
Skim					2 tbsp (30ml)	S	M	L
9. CREAM in Tea and Coffee Please mark type:								
Coffee cream					1 tbsp (15ml)	S	M	L
Half & Half					1 tbsp (15ml)	S	M	L
Non dairy creamer					1 tbsp (15ml)	S	M	L

DataFax #009 Plate #037

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

BEVERAGES cont.	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
10. SUGAR or HONEY (in Tea and Coffee)					1 tsp (1 pack)	S	M	L
11. COLAS, non-dietetic (Coca Cola, Pepsi)					1 can (355ml)	S	M	L
12. OTHER SOFT DRINKS, (non-dietetic, 7-Up)					1 can (355ml)	S	M	L
13. DIET COLAS					1 can (355ml)	S	M	L
14. ORANGE, GRAPEFRUIT JUICE					3/4 cup (175ml)	S	M	L
15. APPLE, GRAPE JUICE					3/4 cup (175ml)	S	M	L
16. OTHER JUICES (pineapple, cranberry)					3/4 cup (175ml)	S	M	L
17. FRUIT DRINK (iced tea, lemonade)					1 cup (250ml)	S	M	L
18. VEGETABLE JUICE (excluding clamato juice)					3/4 cup (175ml)	S	M	L
19. CHOCOLATE MILK, HOT CHOCOLATE					1 cup (250ml)	S	M	L
20. MILK SHAKE					1 cup (250ml)	S	M	L
21. YOGURT DRINK					1 cup (250ml)	S	M	L
22. BEER, ALE					1 bottle (355ml)	S	M	L
23. WHITE WINE					5 oz (150ml)	S	M	L
24. RED WINE, SHERRY, PORT					5 oz (150ml)	S	M	L
25. SPIRITS, Liquor only					1.5 oz (45ml)	S	M	L

DataFax #009 Plate #038

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
DAIRY PRODUCTS	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
26. EGG, boiled, poached					1 egg	S	M	L
27. EGG, fried, scrambled, omelette					1 egg	S	M	L
28. COTTAGE CHEESE or RICOTTA CHEESE					1/2 cup (125ml)	S	M	L
29. CREAM CHEESE					2 tbsp (30ml)	S	M	L
30. CHEESE, regular fat, natural and processed					1 slice (30gm)	S	M	L
31. CHEESE, part-skim, natural and processed					1 slice (30gm)	S	M	L
32. SOUR CREAM, WHIPPING CREAM					1 tbsp (15ml)	S	M	L
33. YOGURT, plain, regular fat					3/4 cup (175ml)	S	M	L
34. YOGURT, plain, low fat					3/4 cup (175ml)	S	M	L
35. YOGURT, fruit-flavoured, regular fat					3/4 cup (175ml)	S	M	L
36. YOGURT, fruit-flavoured low fat					3/4 cup (175ml)	S	M	L
MIXED DISHES, PIZZA AND PASTA								
37. SOUP, creamed					1/2 cup (125ml)	S	M	L
38. SOUP, not creamed					1/2 cup (125ml)	S	M	L
39. PIZZA, no meat					1 medium slice	S	M	L
40. PIZZA, with meat					1 medium slice	S	M	L
41. MACARONI, spaghetti, boiled					1 cup	S	M	L
42. PASTA WITH TOMATO SAUCE, no meat					1 cup	S	M	L

RADICAL PC **Food Frequency Questionnaire (English, Page 4 of 11)** CRF 39

DataFax #009 Plate #039

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
43. PASTA WITH CREAM SAUCE no meat					1 cup (250ml)	S	M	L
44. PASTA WITH CHEESE/MEAT					1 cup (250ml)	S	M	L
45. MEAT STEW with carrots, potato, other vegetables					1 cup (250ml)	S	M	L
46. CHILI CON CARNE					1 cup (250ml)	S	M	L
VEGETABLES, PEAS AND BEANS								
47. POTATOES, boiled, mashed or baked					1 medium (1/2 cup)	S	M	L
48. FRENCH FRIES and FRIED POTATOES					1 cup or small McDonald's	S	M	L
49. CARROTS, raw or boiled					1 medium (1/2 cup)	S	M	L
50. BROCCOLI					1/2 cup (125ml)	S	M	L
51. CABBAGE, COLESLAW					1/2 cup (125ml)	S	M	L
52. CAULIFLOWER					1/2 cup (125ml)	S	M	L
53. BRUSSEL SPROUTS					1/2 cup (125ml)	S	M	L
54. CORN, fresh, frozen or canned					1 cob or 1/2 cup	S	M	L
55. PEAS, FRESH LIMA BEANS					1/2 cup	S	M	L
56. DRIED BEANS or LENTILS (kidney beans, chickpeas)					1/2 cup	S	M	L
57. GREEN BEANS/SNAP BEANS					1/2 cup (125ml)	S	M	L
58. DARK LEAFY VEGETABLES (example spinach, collards, kale mustard greens), cooked					1/2 cup (125ml)	S	M	L
59. CUCUMBER					1/2 cup (125ml)	S	M	L

DataFax #009 Plate #040

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

VEGETABLES, PEAS AND BEANS cont.	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
60. LETTUCE					1 cup (250ml)	S	M	L
61. TOMATOES, fresh					1 medium	S	M	L
62. ONIONS, raw or cooked					1/2 cup (125ml)	S	M	L
63. BEETS, boiled or pickled					1/2 cup (125ml)	S	M	L
64. SWEET POTATOES, baked					1 medium (1/2 cup)	S	M	L
65. OTHER ROOT VEGETABLES (turnips, parsnips, yams, radish, rutabagas, leeks), raw or cooked					1/2 cup (125ml)	S	M	L
66. YELLOW SQUASH, winter type					1/2 cup (125ml)	S	M	L
67. SUMMER SQUASH, ZUCCHINI, EGGPLANT					1/2 cup (125ml)	S	M	L
68. GREEN PEPPER, raw or cooked					1/2 cup (125ml)	S	M	L
69. ASPARAGUS					4 stalks	S	M	L
70. AVOCADO					1/2 medium	S	M	L
71. OTHER VEGETABLES (celery, mushrooms, artichokes), raw or cooked					1/2 cup (125ml)	S	M	L
72. BEAN SPROUTS, ALFALFA SPROUTS					1/2 cup (125ml)	S	M	L
73. PICKLES, RELISH					1 dill (2 tbsp)	S	M	L
74. BUTTER on vegetables (excluding use in baked & mixed dishes)					1 tsp or 1 pat	S	M	L
75. MARGARINE on vegetables (excluding use in baked & mixed dishes)					1 tsp or 1 pat	S	M	L
76. KIND OF OIL USED IN SALADS (excluding bottled dressings)					1 tsp	S	M	L

Specify: _____

DataFax #009 Plate #041

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
VEGETABLES, PEAS AND BEANS cont.	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
77. KIND OF FAT USED IN COOKED VEGETABLES Specify: _____					1 tsp	S	M	L
78. SALAD DRESSING, creamy-type					1 tbsp (15ml)	S	M	L
79. SALAD DRESSING, oil/vinegar type (French, Italian)					1 tbsp (15ml)	S	M	L
MEATS								
80. GROUND BEEF as hamburger, meat loaf, in casseroles					3" patty (90gm)	S	M	L
81. ROAST BEEF					medium	S	M	L
82. STEAK					medium	S	M	L
83. POT ROAST					medium	S	M	L
84. PORK CHOP					medium	S	M	L
85. BAKED HAM					medium	S	M	L
86. VEAL					medium	S	M	L
87. LAMB					medium	S	M	L
88. BACON					2 strips	S	M	L
89. HOT DOGS, weiners					1 hot dog	S	M	L
90. SAUSAGES (including pork, link sausages)					1 medium or 2 links	S	M	L
91. LUNCHEON HAM, CORNED BEEF					1 slice (30gm)	S	M	L
92. OTHER LUNCHEON MEAT (includes salami, bologna)					1 slice (30gm)	S	M	L
93. LIVER					medium	S	M	L

DataFax #009 Plate #042

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
MEATS cont.	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
94. FRIED CHICKEN (includes chicken nuggets), CHICKEN WINGS					medium or 4 wings	S	M	L
95. CHICKEN, TURKEY, roasted oven baked					medium	S	M	L
96. FISH, steamed, baked (fresh or frozen)					medium	S	M	L
97. FISH, fried, battered, fish sticks					medium (5 fish sticks)	S	M	L
98. CANNED FISH					1/2 can (50ml)	S	M	L
99. SEAFOOD, meat only (includes crab, lobster, shrimp)					medium	S	M	L
100. SALTED/DRIED MEAT or FISH					medium	S	M	L
101. PICKLED MEAT or FISH					medium	S	M	L
BREADS, CEREALS AND GRAINS								
102. WHITE BREAD					1 slice	S	M	L
103. WHOLE WHEAT BREAD, 100% (includes dark rye)					1 slice	S	M	L
104. WHOLE WHEAT BREAD 60% (includes light rye)					1 slice	S	M	L
105. BREAD ROLLS (white flour), kaisers, bagels, hamburger/ hot dog buns					1 medium	S	M	L
106. BREAD ROLLS (whole wheat), kaisers, bagels					1 medium	S	M	L
107. BRAN/GRANOLA CEREALS Specify usual type:_____					3/4 cup (175ml)	S	M	L
108. WHOLE WHEAT CEREALS (Shreddies) Specify usual type:_____					1 cup (250ml)	S	M	L
109. SUGAR COATED CEREALS (Frosted Flakes, Fruit Loops) Specify usual type:_____					1 cup (250ml)	S	M	L

DataFax #009 Plate #043

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
BREADS, CEREALS AND GRAINS cont.	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
110. NO SUGAR CEREALS (Corn Flakes, Rice Krispies) Specify usual type:_____					1 cup (250ml)	S	M	L
111. COOKED CEREALS (porridge, oatmeal, dalia, bulgar) Specify usual type:_____					1 cup (250ml)	S	M	L
112. SUGAR on cereal (white, brown)					1 tsp	S	M	L
113. CRACKERS (soda or snack type)					2 crackers	S	M	L
114. BRAN or OAT MUFFINS					1 small or 1/2 lrg	S	M	L
115. OTHER MUFFINS, FRUIT BREADS					1 small or 1/2 lrg	S	M	L
116. RICE, boiled					small (1/2 cup)	S	M	L
117. FRIED RICE, plain or pulao (with vegetables)					small (1/2 cup)	S	M	L
118. BUTTER on breads, rolls or boiled rice					1 tsp or 1 pat	S	M	L
119. MARGARINE on breads, rolls or boiled rice					1 tsp or 1 pat	S	M	L
120. CRISP SNACKS (popcorn, potato chips, nachos)					1/2 cup (125ml)	S	M	L
FRUITS								
121. APPLE, PEAR					1 medium	S	M	L
122. CITRUS FRUITS (oranges, clementines, grapefruit)					1 orange or 2 clementines or 1/2 grapefruit	S	M	L
123. BANANA					1 medium	S	M	L
124. GRAPES					1/2 cup (125ml)	S	M	L
125. BERRIES (strawberries, raspberries)					1/2 cup (125ml)	S	M	L
126. PEACH, PLUM, NECTARINE					1 medium peach or 1 large plum	S	M	L

DataFax #009 Plate #044

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
FRUITS cont.	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
127. CANTELOUPE					1 slice (1/2 cup)	S	M	L
128. WATERMELON, HONEYDEW					1 wedge or 1 cup (250ml)	S	M	L
129. MANGO, PAPAYA					1/2 mango or 1/2 cup	S	M	L
130. ALL OTHER FRUIT (such as pineapple, kiwi)					1 slice (1/2 cup)	S	M	L
131. CANNED FRUIT					1/2 cup (125ml)	S	M	L
132. DRIED FRUIT (such as raisins, dates)					1 tbsp raisins or 2 dates	S	M	L
DESSERTS AND SWEETS								
133. CAKES					1 slice or 2" x 4" x 1"	S	M	L
134. DOUGHNUTS, SWEET ROLLS					1 doughnut or 1 sweet roll	S	M	L
135. ICE CREAM					1/2 cup (125ml)	S	M	L
136. SHERBET, POPSICLES, FREEZIES					1/2 cup or 1 popsicle	S	M	L
137. PUDDING					1/2 cup (125ml)	S	M	L
138. PIES and TARTS, danish					1 slice or 1/6 pie	S	M	L
139. COOKIE					1 cookie	S	M	L
140. CHOCOLATE (includes chocolate candy, bar)					1 small-size bar or 45 gm or 5 chocolates	S	M	L
141. CANDY, no chocolate					2 candies	S	M	L
MISCELLANEOUS								
142. TOFU or TEMPEH					1/2 cup (125ml)	S	M	L
143. PEANUT BUTTER					1 tbsp (15ml)	S	M	L

DataFax #009 Plate #045

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

MISCELLANEOUS cont.	How often? *Write in* **ONE** *column only*				Average Serving	Your Serving Size		
	Per Day	Per Week	Per Month	Per Year or Never		Less Than Average (small)	Average (medium)	More Than Average (large)
144. JAM, SYRUP, HONEY (not used in beverages)					1 tsp	S	M	L
145. GRAVY					1 tbsp (15ml)	S	M	L
146. CHOCOLATE SYRUP, STRAWBERRY SYRUP					1 tbsp (15ml)	S	M	L
147. KETCHUP					1 tbsp (15ml)	S	M	L
148. SAUCES, white, cream on vegetables, meats					2 tbsp (30ml)	S	M	L
149. MAYONNAISE on sandwiches					1 tbsp (15ml)	S	M	L
150. NUTS					2 tbsp (30ml)	S	M	L
151. WHEAT BRAN					1 tbsp (15ml)	S	M	L
152. WHEAT GERM					1 tbsp (15ml)	S	M	L
153. MUSTARD					1 tsp	S	M	L
154. SOY SAUCE, in cooking, added to food					1 tsp	S	M	L
155. FRESH GARLIC (includes use in cooking)					1/2 tsp	S	M	L
156. CHILIES, green, red					1 small	S	M	L
157. ADDED SALT AT TABLE, on raw or cooked dishes					2 sprinkles	S	M	L
158. SUGAR SUBSTITUTES (such as Equal, Nutrasweet)					1 pak or 1 tablet	S	M	L

159. How often do you use coconut oil in cooking or coconut milk (liquid removed from shredded coconut which has been soaked in water)?

☐ often ☐ sometimes ☐ never

DataFax #009 Plate #046

☐ Baseline ☐ 24 Month
☐ 12 Month ☐ Close-Out

Patient ID# Centre # Patient # **Initials** F/M/L **Date form completed:** year/month/day

160. What type of the following items do you use? *(Please mark one box per line)*:

a) butter:	☐	regular	☐	light	☐	both	☐ none
b) margarine:	☐	regular	☐	light	☐	both	☐ none
c) mayonnaise:	☐	regular	☐	light	☐	both	☐ none
d) cream cheese:	☐	regular	☐	light	☐	both	☐ none
e) salad dressing:	☐	regular	☐	calorie-wise	☐	both	☐ none
f) sour cream:	☐	regular	☐	light	☐	both	☐ none

161. a) Are you currently on a special diet?

☐ Yes ☐ No

→ b) If YES, what type of diet? _____

c) If YES, how long have you been on that special diet? ☐☐ Years ☐☐ Months

Name of person administering questionnaire: _____
Full Name