ADULT CHANGES IN WEIGHT AND PHYSICAL ACTIVITY IN ASSOCIATION WITH THE RISK OF PANCREATIC CANCER: IN THE VITAL COHORT

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ABSTRACT

Peter S. Samai: Adult Changes in Weight and Physical Activity in Association with the Risk of Pancreatic Cancer: in the VITAL Cohort
(Under the direction of Marilie D. Gammon)

Significance. Pancreatic cancer is the fourth most common cancer-related death in the United States (U.S.); by 2030 this lethal disease is projected to be the second leading cause of cancer-related mortality. Thus, identifying modifiable risk factors for pancreatic cancer is of public health importance.

Innovation. Two modifiable factors that impact pancreatic cancer are obesity and, perhaps, physical activity. Obesity is among the few risk factors that have been consistently associated with pancreatic cancer incidence, whereas the association with physical activity is inconsistent. However, whether age-specific exposures, or adult changes in exposure, are associated with pancreatic cancer is unclear for both exposures. Identification of age-specific risk factors, or adult changes in exposure, could lead to age-specific targeted prevention strategies.

Dissertation Goals. My hypothesis was that age-specific weight and physical activity, and perhaps adult changes, may modulate pancreatic cancer risk. These exposures could plausibly act through several biologic mechanisms, including influencing circulating endogenous hormones, which may in turn impact pancreatic carcinogenesis. Thus, my objectives were to prospectively examine the associations of age-specific weight and physical activity, and adult changes, with pancreatic cancer risk.

Methods. I used the National Cancer Institute-funded VITamins And Lifestyle (VITAL) study. This cohort of ~77,000 men and women in Washington state was recruited in 2000-2002, when participants were aged 55-76 years. Data collection included assessment

of baseline, age-specific, and changes in adult weight and physical activity. Incident pancreatic cancer events (n=280) were identified through linkage to state and national registries after ~10 years of follow-up. Multi-variable Cox proportional hazards models were used to obtain estimates for the pancreatic cancer risk associations.

Results. Pancreatic cancer risk was reduced by ~30-40% in association with adult physical activity undertaken in the 10 years prior to study recruitment, and with physical activity undertaken most days of the week during mid-life. In addition, mid-life adult obesity and weight gain, were associated with ~30-80% elevation in pancreatic cancer risk.

Study Impact. If my results are replicated, targeting middle-aged adult Americans to engage in physical activity most days of the week, and avoid weight gain may be possible risk reduction strategies for this lethal cancer.

For my family- my mother, Paulette Maxine; my sister, Kathryn Elizabeth;
and my father, Peter Kelly. Thank you for your unending love and support,
I carry it in my heart, always.

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LIST OF ABBREVIATIONS

ACS	American Cancer Society
ACSM	American College of Sports Medicine
ADP	Air displacement plethysmography
AICR	American Institute for Cancer Research
AHA	American Heart Association
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CAT	Computed axial tomography
CT	Computed tomography
CPA	Compendium of physical activities
DAGs	Directed acyclic graphs
DXA/DEXA	Dual-energy X-ray absorptiometry
FDA	Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
GI	Glycemic index
HR	Hazard ratio
HNPCC	Hereditary non-polyposis colorectal cancer
IARC	International Agency for Cancer Research
IGFBP1	Insulin-like growth factor binding protein 1
IGF	Insulin-like growth factors
IR	Insulin resistance
k	Kilograms

LAK	Lymphokine-activated killer
LTPA	Leisure-tire physical activity
METs	Metabolic equivalents of tasks
m^2	Meters squared
NCCOR	National Collaborative on Childhood Obesity Research
NCI	National Cancer Institute
NDI	National Death Index
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NK	Natural killer
OPA	Occupational physical activity
OR	Odds ratio
ORCs	Obesity related cancers
PedNSS	Pediatric and Pregnancy Nutrition Surveillance System
RCTs	Randomized control trials
RMR	Resting metabolic rate
RR	Risk ratio
RPA	Recreational physical activity
SAFE	Survey of Activity, Fitness and Exercise
SD	Standard deviations
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic status
TNM	Tumor, Node, Metastasis
TNF-α	Tumor necrosis factor-alpha

TPA	Total physical activity
US	United States
VITAL	VITamins And Lifestyle study
WCRF	World Cancer Research Fund
WHI	Women's Health Initiative
WHO	World Health Organization
YRBSS	Youth Risk Behavior Surveillance System

CHAPTER 1: INTRODUCTION AND BACKGROUND

Pancreatic cancer is the fourth most common cause of cancer deaths in the United States (US), and will account for just fewer than 54,000 new cases in 2017, and just over 43,090 persons in the US will die from the disease, as mortality closely reflects incidence[1]. Age, tobacco smoking, diabetes, a family history of pancreatic cancer, and most recently, obesity, are among the few established risk factors that have been consistently associated with this lethal cancer. Additional modifiable risk factors like physical activity have been inconsistently associated with pancreatic cancer but the exact mechanisms of their underlying relationships remain poorly understood. Identifying and understanding modifiable risk factors of pancreatic cancer, and the timing of these exposures throughout adulthood where they may play an important role, is of critical public health importance, as they potentially lead to age-specific targeted cancer prevention strategies. The importance of studying physical activity timing and weight change is only being exacerbated as the US is experiencing unprecedented increases in the prevalence of obesity across the entire population. Previous studies of obesity, physical activity, and pancreatic cancer have found inconsistent associations, a number of these studies have suffered from small numbers of events and heterogeneous assessments of exposure. Currently, few studies have prospectively examined the effects of changes in weight, and no study has examined adult changes in physical activity levels on the incidence of pancreatic cancer. While increasing physical activity and weight maintenance has been implicated in reducing the risk of developing other cancer types, the impact of these exposures on disease development, and a better reflection of the complexity of energy balance in the US population, remains unclear.

The hypothesis is that adult weight and weight gain is a systematic process; the constitution of elevated adult weight and adult weight gain is primarily adipose tissue, and these adult changes (gains) in weight and physical activity modulate pancreatic cancer risk. These exposures could plausibly be acting through several biologic mechanisms, including influencing levels of circulating endogenous hormones, including the regulation and control of insulin, a hormone secreted chiefly by beta cells in the endocrine pancreas. Thus, the objectives of this dissertation were to prospectively examine the association of adult changes throughout adulthood in weight and physical activity with the subsequent risk of developing pancreatic cancer in a large cohort of adults.

This dissertation used the resources of the National Cancer Institute (NCI)-funded VITamins And Lifestyle (VITAL) study. This cohort of over 77,000 men and women in Washington State was recruited between October 2000 and December 2002, and was originally designed to assess the effect of dietary supplement use and lifestyle exposures on cancer risk in a population of older aged, supplement users identified via a commercial database. Data collection in the VITAL cohort included assessment of baseline, age-specific, and adult changes in weight and physical activity levels throughout adulthood. Cox proportional-hazards models were used to obtain estimates for the association between both adult changes in weight and physical activity and pancreatic cancer risk, after an average 10 years of follow-up using a SEER linkage.

There are few public health messages in the United States regarding the prevention of pancreatic cancer, and it remains a tumor with the poor prognosis and survival. The VITAL study provides exposure information on two potentially modifiable exposures that have been associated with pancreatic cancer, obesity and physical activity. Uniquely, in addition to weight, height, and a validated recent 10-year physical activity assessment at baseline enrollment, VITAL also captured recalled weight at age 18, age 30, and age 45 years and recalled “relative” physical activity levels at age 18, age 30, and age 45 years.

This enabled the creation of several windows of changes in exposure that may inform public health messaging and allowing for more refined messages as to when weight maintenance and/or physical activity level maintenance may be most important in impacting pancreatic cancer risk.

This first chapter of my dissertation highlights the pertinent background information: descriptive epidemiology, underlying biological rationale, and summarize the existing literature concerning the relationships under the proposed study. The chapter consists of four major subsections, 1) epidemiology of pancreatic cancer 2) the epidemiology of obesity 3) the epidemiology of physical activity 4) the epidemiology of weight gain, and a final summary section.

This dissertation utilized a prospective cohort approach that efficiently used the existing resources of the VITAL cohort study assessment of weight and physical activity throughout several ages of adulthood to address the study hypotheses. Innovatively, this dissertation examined windows throughout adulthood where age-specific weight, and weight gain, as well as age-specific physical activity and physical activity changes.

My dissertation findings, if confirmed, have the potential to provide significant insights regarding the etiology of potentially modifiable risk factors for pancreatic cancer and may identify age-specific targets for timed public health messages about those risk factors for prevention of this lethal cancer.

Epidemiology of Pancreatic Cancer

Histology

The common case definition of ductal pancreatic adenocarcinoma is a carcinoma occurring almost exclusively in older adults that is phenotypically similar to pancreatic duct epithelia, with mucin production and expression of characteristic cyto-keratin pattern[2]. The majority of pancreatic ductal adenocarcinomas are found in the “head” of the glad the next most highly localized region being the “tail”. Clinical symptoms include abdominal pain,

unexplained weight loss, jaundice, and pruritus. Identification of localized disease at diagnosis is unusual, tumor spread primarily involves the retroperitoneal fatty tissue, and lymphatic spread is also common. Advanced signs include liver metastasis and progression to adjacent organs.

The TNM classification is used for staging of ductal pancreatic adenocarcinoma. The characteristics of the primary tumor are used to assign a (T) score (Tx: *tumor cannot be assed*, Tis: *carcinoma in situ*, T0: *no evidence of tumor*, T1-4: *size and/or extension of tumor*). Characterization and impact of lymphatic spread associated with disease is used to assign a (N) score (Nx: *cannot be assessed*, N0: *no regional lymph node metastasis*, N1: *regional lymph node metastasis present*, N2: *spread between N1 and N3*, N3: *distant spread or numerous regional spread*). Finally, the presence and degree of metastasis is characterized with an assigned (M) score (M0: *no distant metastasis*, M1: *metastasis present to distant organs*). The stage groupings are then assigned using the combination of these scores[3].

Incidence and Mortality

Approximately 53,670 new cases of pancreatic cancer are estimated in 2017 representing 3% of the incident cancer diagnoses among men and women in that year. Behind cancers of the lung and bronchus, prostate and breast (men, women- respectively), and colon and rectum, pancreatic cancer is estimated to be the fourth most deadly cancer among men and women in the United States[4]. An estimated 22,300 men and 20,790 women will die from pancreatic cancer in 2017, reflecting 7% of cancer related mortality in 2017 among men and women. Since 1998, the incidence of pancreatic cancer has been slowly increasing by 0.8% in men and 1.0% in women, annually[1]. Pancreatic cancer is projected to be the second leading cause of cancer-related mortality in the US by 2030[5].

Using the most recently available SEER 18 Figure 1.1 incidence data (2008-2012), the median age at diagnosis was 71 years; with less than 1% of cases diagnosed under age

20; approximately 11.9% diagnosed between age 20 and 54; 21.5% between 55 and 64; 26.3% between 65 and 74; 26.8% between 75 and 84; and 13.4% among individuals 85 years of age and above. The age-adjusted incidence rate was 12.0 per 100,000 men and women per year, standardized to the US population.

In the United States, the rates of pancreatic cancer are higher among men than women, 13.6 and 10.7 cases per 100,000 persons, respectively. When considering race and ethnicity, the rates of pancreatic cancer are highest among African-American (Black) men and women, 17.1 and 14.8 per 100,000 persons. The rates among US Whites, Hispanics, Asians, and Native Americans are slightly lower.

Due to the lethality of this neoplasm, mortality very closely resembles incidence. The median age of death of 73 years; no deaths from pancreatic cancer under the age of 20; 9.6% between 20 and 54; 19.4% between 55 and 64; 25.8% between 65 and 74; 29.5% between 75 and 84; and 15.7% of deaths among individuals 85 years of age or older. The age-adjusted death rate was 10.9 per 100,000 men and women per year based on the most recent SEER data (2008-2012) in the United States (Figure 1.2). By race, mortality rates follow a similar distribution as incidence rates. The morality rate for all races is 12.6 and 9.6 deaths per 100,000 men and women, respectively in the United States from 2008-2012. Blacks in the United States have the highest mortality rates when compared to other races, 15.0 and 12.3 deaths per 100,000 men and women respectively. Whites are second, 12.5 and 9.4, respectively, followed by Hispanics 9.8 and 7.7, respectively. Due to the asymptomatic nature of the disease and absence of reliable screening the disease lays the largest burden among the elderly. In the same period the mortality rate has increased by 0.4% per year in men and women, while the 5-year survival rate is estimated at 7.3%.

Epidemiology of Pancreatic Cancer: Risk Factors

Age

Cancer represents the sustained unregulated growth of cells in the body; therefore, age is a common risk factor, as tumors require accumulation of this unchecked growth over time. In tumors of the pancreas, age is the most reliable and important known predictor[6].

Sex/Gender

The incidence of pancreatic cancer in the United States is slightly higher in men than women[1].

Race

In the United States, when compared to Whites, Blacks are reported to be at increased risk of pancreatic cancer[4]. The discrepancy is not well understood, and is hypothesized to result from the increased prevalence of tobacco smoking and diabetes among Black men and overweight among both black men and women. Furthermore, among ethic minorities, Blacks are more likely to develop pancreatic cancer than Hispanics and Asians in the United States, and currently have the highest pancreatic cancer rates in the world[7].

Socioeconomic Status

The relationship between socioeconomic status (SES) and pancreatic cancer is inconsistent. Studies from the United Kingdom in the 1930s cite the highest burden of pancreatic cancer in lower socioeconomic class women [8]. In the same population, the distribution of cancer burden flipped in reports from the 1950s and again in 1982, with higher affluent social classes experiencing the most pancreatic cancer [8, 9]. In the United States, the association between SES and pancreatic cancer is equally inconsistent. Some studies have reported increased risk[10], increased risks among socioeconomic subgroups including those employed in higher income jobs, and those with educational attainment [11, 12], or no association at all [13]. More recent cohort studies [14] found no association between education

and pancreatic cancer; yet contemporary case-control studies have found excess risk among low-income men, those with incomes less than $10,000.00 dollars/per year, increasing risks by 80% and 110% in white and black men respectively [15].

Tobacco

Smoking and tobacco use is one of the few, strong, consistently identified risk factors for pancreatic cancer. The International Agency for Cancer Research (IARC) working group concluded that cancer of the pancreas is causally associated with cigarette smoking in 2004 [16], additionally upon quitting smoking relative risks decreased with increased time since quitting smoking. The increased risk associated with tobacco smoking is 77% (RR=1.77 (95%CI=1.38, 2.26), for smokers compared to non-smokers). When individuals who have quit smoking for 10 years are compared to current smokers, the increase in the risk of pancreatic cancer drops to 24% (RR=1.24 (95%CI=0.78, 1.98)) [17]. Similar conclusions were reached in previous sessions of the IARC working group [18]. Despite numerous studies [18] no biologic mechanism has been identified to demonstrate the apparent increase in risk associated with tobacco smoking.

Family History

Familial history of pancreatic cancer is present among 10% of individuals diagnosed with pancreatic cancer [19]. Genetic investigations have identified an autosomal-dominant model of inheritance for one gene [20], with an 18-fold increase in risk accompanying that specific gene mutation; however, the specific gene or genes responsible remains unclear. Pancreatic cancers have also been linked to genetic mutations commonly associated with tumors at other sites. Mutations in DNA mismatch repair genes MLH1 and MSH2 lead to an increased risk of Lynch variant II hereditary non-polyposis colorectal cancer (HNPCC), which has also been associated with pancreatic cancer [21]. BRCA2 mutations in the germ-line have been implicated extensively to cancers of the breast [22] and ovary [23], as they

disrupt regulation of the double-stranded DNA repair, and have also been associated with increased risk of pancreatic cancer [24].

Diet

Diet is a complex exposure when examining any health outcome. In the case of pancreatic cancer, a biologically plausible relationship with diet exists such that the digestion of foods consumed by an individual are controlled via the release of chemicals for digestion from the pancreas[25]. However, unlike other digestive organs like the mouth, esophagus, stomach, colon etc., no food ingested directly contacts the pancreas. A number of studies have examined the relationship between dietary exposures and pancreatic cancer, and a collaborative report between the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) published in 1997 concluded none of the factors examined reached a 'convincing' level of scientific evidence [26]. The report concluded a reduction in risk was 'probable' for fruit and vegetable consumption, and that no increase in risk was 'probable' due to coffee or alcohol consumption. Due to lack of evidence, several items were left unevaluated in this report including sugar, eggs, preparation styles of meats, and fish.

Since the 1997 AICR report, the literature on dietary exposures and pancreatic cancer as expanded dramatically due to the conduct of several large prospective trials, cohort studies, and pooling studies. For example, meat consumption has been associated with increased risks of pancreatic cancer, with positive associations being identified for a variety of types of meat including beef, pork, and chicken [27-30]; however, null associations have been observed by others [31, 32]. Few consistent associations have been observed even when cooking and preparation have also captured in the exposure [33, 34].

Studies examining fruit and vegetable intake have yielded varied results as well. Almost all cohort studies have failed to identify an inverse association, the majority reporting null associations [31, 35, 36], while case-control studies have consistently shown stronger

inverse associations [33, 37-39]. A recent study reported reduced ORs, comparing the highest versus lowest quartile, for total vegetable (OR=0.45 (95%CI=0.32, 0.62)) and total fruit intake (OR=0.72 (95%CI=0.54, 0.98))[40].

Glycemic Index (GI) is a measure of the effects of carbohydrates in food on blood sugar levels or insulin response [41]. Due to the direct relationship between GI and insulin response several studies have hypothesized that increased consumption of high carbohydrates/high glycemic load foods would be associated with increases in the risk of pancreatic cancer. However, studies of pancreatic cancer *in vitro,* have demonstrated that energy density and total energy intake may be drive the relationship [42]. Few studies have consistently observed statistically significant positive associations between glycemic load and pancreatic cancer; however; when examining subpopulations that are overweight and sedentary the results are more consistent [43].

Physical Activity

Sedentary lifestyle (physical inactivity) has an adverse effect on maintaining energy balance, and can create poorer hormone profiles [44]. As shown in Table 2, several studies have examined the association between physical activity and pancreatic cancer; however little consistency has been observed to date. A recent meta-analysis and systematic review reported a summary estimate of twenty-two prospective cohort studies and indicated a 9% reduction in risk (RR=0.91 (95%CI=0.69, 1.19)) when examining total physical activity (TPA). When considering the available cohort studies of occupational physical activity (OPA) only, a stronger and significant reduction was observed, reporting a 14% decrease in pancreatic cancer risk (RR=0.86 (95%CI=0.76, 0.98))[45]. When examining recreational physical activity (RPA) or leisure-tire physical activity (LTPA), a slight 11% reduction in risk was observed when pooling over 20 epidemiologic studies (RR=0.89 (95%CI=0.82, 0.96)); however, when only the cohort studies were considered, the summary effect was non-significantly and slightly reduced by only 4% (RR=0.96 (95%CI=0.91, 1.02))[46].

Obesity

Overweight and obesity in adults is typically defined by body mass index (BMI), which is defined as the ratio of weight in kilograms (kg) to height in meters squared (m^2). As shown in Table 2, the association between body mass and pancreatic cancer has been investigated in a number of independent studies, with several studies reporting positive associations [47, 48], no association [27, 49], and mixed findings [50, 51]. However, recent meta-analyses and pooled studies have consistently reported an increased pancreatic cancer risk of 47% (RR=1.47 (95%CI=1.23, 1.75))[52] with increasing BMI [53-55]. Obesity (BMI≥30.0) at early adulthood has been examined in a pooled analysis of cohort studies and observed similar results (HR=1.43 (95%CI=1.11, 1.85))[56].

Diabetes

In addition to tobacco smoking, diabetes is one of the most thoroughly researched risk factors of pancreatic cancer, with over 30 studies examining the association. Hyperinsulinemia is thought to be the mechanism by which risk increases among those with diabetes due to large flow of blood containing islet hormones entering the exocrine pancreas [57, 58]. Diabetes or impaired glucose tolerance is present in the majority of patients with pancreatic cancer[59-61]. However despite the overwhelming association, the temporality of diabetes onset and pancreatic cancer remains obfuscated by studies implicating diabetes as both a predisposing risk factor of incidence or as a pre-clinical identifier of disease onset[62-64].

Summary

Pancreatic cancer is one of the most deadly cancers in the United States. While consensus exists for a few modifiable risk factors, the exact biological mechanisms by which obesity, diabetes, and tobacco work to increase risk remain largely misunderstood.

Epidemiology of Obesity

The rates of obesity in western societies have risen steadily over the last few decades, according to the WHO, from 1980-2008, worldwide burden (prevalence) of obesity has doubled[65]. While obesity rates appear to be stabilizing, the dominant trend over the last 30 years has been a doubling in the prevalence of obesity worldwide, with the US observing increases of greater than 10% in the prevalence of both “obesity” and “overweight”. The most recent data from the National Health and Nutrition Examination Survey (NHANES) estimate more than one-third of US adults (35.7%) are obese, (68% overweight and obese) and approximately 17% (or 12.5 million) of children and adolescents aged 2-19 years are obese [66]. These numbers have increased dramatically when compared to the numbers just two decades ago (56% adults overweight and obese and only 10% children obese). Resulting obesity-related conditions include heart disease, stroke, type-2 diabetes and some cancers, as well some leading causes of death in the US. Just recently surpassing tobacco use, obesity is now considered to be the number one preventable cause death in the country [67]. Overweight and obesity represent a complex phenomenon; on one hand obesity is clinical endpoint resulting from a complex interaction between individual genes and the environment exhibiting a prolonged exposure to positive energy balance[68]. While at the same time, obesity represents a profound chronic exposure, by which physical weight, altering hormones concentrations, and inducing inflammation, potentiate further adverse health outcomes on the musculoskeletal, endocrine, and immune systems of the body[69-73].

The majority of obesity surveillance in the United States is accomplished through six surveys: the CDC Behavioral Risk Factor Surveillance System (BRFSS), National Health Interview Survey (NHIS), the National Health and Nutrition Examination Survey (NHANES), the CDC Youth Risk Behavior Surveillance System (YRBSS), the Pediatric and Pregnancy Nutrition Surveillance System (PedNSS), and the National Collaborative on Childhood Obesity Research (NCCOR). Each survey uses varying sampling techniques, sampling

frequency, and targets specific populations in order to capture specific information about the current trends of obesity (either through self-reports or more objective measures) informing public health messaging and the creation of guidelines and recommendations. The BRFSS, the NHIS, and NHANES all include adults, and are discussed briefly below.

The BRFSS[74] (Behavioral Risk Factor Surveillance System) is sponsored by the Centers for Disease Control and Prevention (CDC) and is a cross-sectional survey completed by state based health departments via telephone interview. BRFSS respondents represent a probability sample of adults aged 18 or older, with telephones, and (regarding obesity) are asked “How tall they are without shoes?” and to approximate “How much they weight without shoes?”

The NHIS[75] (National Health Interview Survey) is another national cross-sectional household survey conduct by the National Center for Health Statistics along with the CDC. Data collected through the NHIS are commonly used in federal government Department of Health and Human Services for policy and planning. Trained interviewers conduct personal interviews with households and collect information on cancer screening, diet and nutrition, physical activity, and a variety of other health indicators.

The NHANES[76] (National Health and Nutrition Examination Survey) is a series of cross-sectional, nationally representative surveys conducted by the US National Center for Health Statistics along with the CDC. The survey population represents the total national, civilian, non-institutionalized population of the US. Unlike the BRFSS, participants accrued through NHANES undergo a standard physical examination, where (regarding obesity) height and weight are measured by trained technicians.

Obesity Guidelines

“*Obesity is common, serious, and costly”* [77]. The first guidelines drafted in 1998 were developed to address overweight and obesity-conditions responsible for the second leading cause of preventable death in the United States, currently number one. The National Heart,

Lung, and Blood Institute (NHLBI) in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), conducted an extensive literature review focusing solely on evidence based publications and research in order to present a new approach for the assessment of overweight and obesity and establish principles of safe and effective weight loss [78] for research scientists and clinicians in practice. The most recent Dietary Guidelines for Americans have also included recommendations geared more for the general population and public health practitioners. Due to the adverse impact obesity and overweight have on many aspects of health, the key recommendations are to maintain body weight within a healthy range by balancing calories from food and beverages with caloric expenditure, and to prevent gradual weight gain over time, but making subtle decreases in caloric intake while increasing physical activity over time [79]. Some public health messages for Americans do exist regarding the relationship between obesity, weight, and cancer risk reduction, however “Being at a Healthy Weight” (AICR) leaves ample room for improvement. This study may provide insights as to periods of adulthood where the most energy and focus on weight status and physical activity, will be most beneficial to risk reductions for pancreatic cancer.

Obesity Guidelines – Cancer

Obesity is associated with increased risk of several cancers, including post-menopausal breast, esophageal adenocarcinoma, and thyroid cancers, resulting in a moniker of obesity related cancers (ORCs) [80]. Data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) estimated in the US as many as 34,000 new cases of cancer among men and 50,500 new cases in women were due to obesity (4% and 7% respectively). The guidelines for cancer prevention via obesity reduction do not differ from the general guidelines for obesity; however, they are supplemented due to findings from nutritional epidemiologic investigations of cancer indicating that increased consumption of fruits and vegetables, and reduced consumption of

animal fats and sugar sweetened beverages will accomplish the goals of attaining healthy weight while bolstering cancer prevention [79].

Obesity Guidelines – Pancreatic Cancer

Many studies have reported a slight increase in risk of pancreatic cancer among overweight and obese individuals. Minimal public health guidelines or messages exist regarding the prevention of pancreatic cancer. Thus, the results of my dissertation may provide insights to develop age-specific guidelines by identifying age-specific windows throughout adulthood when weight and/or physical activity levels, or changes in these exposures, may most impact the risk of developing pancreatic cancer.

Obesity Measurement

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy, increased risk of poor health outcomes [81]. The amount of body fat is what we are seeking to measure; however, there a several ways by which body fat is measured in scientific research, some of which approximate body fat closely without direct measurement. Thus, the goal in population research is to utilize a measurement that most closely resembles a direct measure of body fat, while remaining feasible for use in a population research setting.

There are several methods to measure obesity including clinical imaging technologies like the X-ray computed tomography (CT) scan, computed axial tomography (CAT) scan, and dual-energy X-ray absorptiometry (DXA/DEXA) scan, and air displacement plethysmography (ADP). The DXA scan uses dual X-ray beams and assesses differences in the density of tissue allowing for the differentiation of muscle, skeletal bone, and fat. The CT uses a single X-ray beam and produces high-resolution cross-sections of the body. Air displacement plethysmography is the newest of these technologies, and uses principles analogous to underwater weighing (densiometry), without requiring the subject to get wet, or exposure to unnecessary radiation [82]. These methods are cumbersome, each requiring

expensive specialized equipment and specific skilled training. After these techniques bioelectrical impedance analysis (BIA) is the next alternative offering a simple, inexpensive, and noninvasive means of assessing body composition [83]. When electricity travels through any matter, the degree to which the strength of the current is affected can be measured, and in the case of lean mass and water BIA can estimate body composition. Finally, in lieu of specialized tools, some anthropometric measurements such as skin-fold thicknesses, or as basic as weight and height can be used to approximate body composition and adiposity, the most common of these the body mass index (BMI).

The body mass index (or Quetelet Index) was originally developed in the 19th century during the social physics movement [84]. Since that time it has been used to compare groups or populations of individuals using their weight adjusted for height. The BMI is the weight of an individual measured in kilograms divided by the square of their height/stature measured in meters (kg/m^2), or weight in pounds divided by the square of height in inches multiplied by a constant of 703 ($[lbs/in^2]x703$)[85]. The resulting calculation produces a continuous index that requires no special tools, techniques, training, and the inputs (weight and height) are easily understood by the general population, and therefore easily administered in population based surveys and questionnaires.

Obesity Biologic Mechanisms

The association between obesity and cancer is well studied in the scientific literature; however, the specific biologic mechanisms linking obesity to cancer are not well understood. Among the many hypotheses for the linkage, three mechanisms in particular arise consistently in discussion of the association: insulin and insulin-like growth factors (IGF), sex hormones, and inflammation. Insulin resistance is an important component all three mechanisms. These candidate mechanisms remain hypotheses as their verifiability is lacking in experimental studies, and they cannot be applied uniformly across all tumor sites. The metabolic dysfunction resulting from the excess accumulation of visceral fat while aging

make studies of change in adulthood valuable, and also implicate why weight maintenance (mitigating the accumulation of excess adipose tissue) is an important public health message for the entire adult population, at each of the levels of adiposity categorization.

Insulin

Insulin is a peptide hormone produced by beta cells in the pancreas[86]. Insulin production regulates glucose metabolism when carbohydrates are consumed by signaling the absorption of glucose from the blood to skeletal muscles. Insulin has a direct relationship with fat tissue by causing fat to be stored in the body rather than used for energy [87]. Hyperinsulinemia results when there are excess levels of insulin circulating in the blood stream, more than would ordinarily be required for the metabolism of the glucose present in the body[88]. The presence of excess accumulated adipose tissue in obesity creates an environment where adipose tissue can secrete metabolites, hormones and cytokines that may contribute to hyperinsulinemia, it is then difficult to determine the causality of if excess adiposity causes hyperinsulinemia, or if the pathophysiology of hyperinsulinemia causes obesity [89]. Even without knowing the true precursor, hyperinsulinemia and obesity exacerbate the effects of the other. Cytokines produced by adipose tissue directly affect insulin secretion [90]. In the presence of excess adipose tissue, adiponectin levels are decreased. The excess production of insulin levels, common in hyperinsulinemia, reduces liver synthesis and blood levels of insulin-like growth factor binding protein 1 (IGFBP1) and IGFBP2, and probably also reduce IGFBP1 synthesis locally in other tissues. Prolonged states of hyperinsulinemia reduce production of IGF binding protein (IGF-BP), normally responsible for occupying IGF-1 receptors, creating a surplus of metabolically active IGF-1 in the blood [91, 92]. These metabolically active receptors are important factors in carcinogenesis.

Sex hormones

Sex hormones oestrogens and androgens exist naturally in the body and are homeostatically regulated by the hypothalamus and anterior pituitary glands in central nervous and endocrine systems[93]. The degree to which this balance is maintained results in the normal function of several endocrine functions throughout adulthood [94]. Obesity can physiologically disturb this balance as the significant accumulation of fat resulting from sustained positive energy balance is known to behave as a hormonally active organ [95]. This visceral adipose tissue produces enzymes that, without the regulation of the central nervous system (CNS), aromatize androgens into extremely metabolically active metabolites, like estradiol [96]. In addition to the indirect deleterious effects this imbalance has on serum concentrations of these hormones, the estradiols are known promoters causing elevated cell replication, while impeding DNA repair and increasing the likelihood of DNA damage among proliferated tumor cells [97].

Inflammation

Inflammation is the body's natural physiological response to insult. When the immune system experiences attack via physical injury or infiltration by a foreign body the inflammatory response is the first step in healing. Obesity can be described as a chronic low-grade state of inflammation, and it is under states of chronic inflammation when this natural response can lead to additional problems[98]. Multiple molecular inflammatory processes begin in presence of excess adipose, increased body mass are likely to contribute to the increased incidence of neoplasia, and worsen a number of metabolic outcomes in obese individuals [99]. The exact mechanisms by which inflammation occures in obesity/metabolic syndrome remains unknown; however, many studies continue to observe the inflammatory immune response in the presence of obesity due to irregular functioning adipose tissue [100].

Obesity Dynamics (Weight Change)

Age-related weight gain can occur due to a natural reduction in resting metabolic rate [101, 102]. Simultaneously, physiologic changes due to aging result in a reduced ability for the body to convert stored fat to energy resulting in additional accumulation of body fat [103, 104]. Additionally, lifestyle changes resulting in more time spent sedentary, without proportional reductions in caloric intake or additions in energy expenditure, result in increased fat storage on the body, reduced muscle mass and a feedback cycle of increasing adiposity. This collection of circumstances describes why adult weight gain, particularly in the US is common. The location and distribution of these newly acquired adipose shows differing patterns between men and women, and between races. Men typically store newly acquired fat in the abdominal area and central torso, resulting in the “apple”, or android, body shape. Women, on the other hand, typically carry this weight gain in the thighs and hips, exhibiting the “pear”, or gynoid, body shape. In general, the preponderance of this weight gain comes in form of visceral adipose tissue [105]. It is because of these physiological phenomena that studies of adult weight gain can be thought to describe the exposure and accumulation of visceral fat.

There are two types of body fat, subcutaneous and visceral. Subcutaneous fat is the adipose located below the skin, and while similarly constituted is not thought to be associated with the endocrine disruption visceral fat can create. Subcutaneous fat is palpable, easily grasped by the palm of your hand, while conversely you cannot reach or see visceral fat; it occupies the space inside the body cavity and encroaches upon the space surrounding the internal organs. When anthropometric measures (such as waist and hip circumferences) are used to reflect weight patterning, it is done in effort to reflect the presence of visceral fat.

Visceral adipose tissue serves an important metabolic regulatory role in the body as it functions as more than an energy storage mechanism [106]. In addition to the metabolism

and function of several key organs like the brain, liver, and pancreas, this highly active tissue secretes cells that play a part in the body's inflammatory immune response as well. Furthermore, when and where throughout adulthood, in the body this tissue is accumulated may exacerbate these already powerful metabolic influences. In general, the higher amount of this tissue, the greater the circulating concentration of free fatty acids; however, studies are beginning to show that the not all visceral fat is the same and the compounded addition of this tissue later in life results in varied patterning (on the body) as well as the development of new adipocyte cells that may vary in size or location, and as a result, vary in function: including the regulation of free floating fatty acid, and liver glucose metabolism [107]. Thus, because weight changes in adulthood signify changes in a person's metabolic and hormonal profile, studies of changes in adulthood are valuable.

Epidemiology of Physical Activity

The first modern epidemiologic writings on the relationship between physical activity and cancer appeared in 1922 when mortality data was evaluated by occupation in Australia, England, and the United States and it was noted in those observations that rates of cancer declined with the increasing amounts of hard labor [108]. Almost a century later in the United States, despite the recommendations of the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and several institutes and academies American College of Sports Medicine (ACSM), American Institute for Cancer Research (AICR), and American Heart Association (AHA), as to the direct health benefits from engaging in regular physical activity, the US is currently the most inactive it has ever been, with more than half of the country failing to meet the current recommendations (Health People 2010) for physical activity according to the Behavioral Risk Factor Surveillance System (BRFSS) [109, 110]. The relationship between physical activity and cancer has been consistently observed for a number of tumor sites[111], including colon[112], post-menopausal breast[113] and the endometrium[114]. The association with pancreatic cancer is less consistent, and the

associations with age-specific physical activity and changes in physical activity have not been previously addressed.

There is a vast literature on the impacts of physical activity on health, accompanying the variability is the terminology used to discuss the exposure. Physical activity is technically defined as any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level [115, 116], exercise is a form of physical activity, but not all physical activity is exercise. Physical inactivity is the phenomena that leads to adverse health effects, and refers to limited participation in, or absence of, activities demanding at least 3.0 metabolic equivalents above resting metabolism [117]. In the United States, the national prevalence of physical activity among adults is monitored using a variety of exposure assessments, including self-report, direct measurement, questionnaires and logs/diaries, often via cross-sectional sampling of the general population. There are four surveys through which the majority of physical activity surveillance is completed in the US: CDC Behavioral Risk Factor Surveillance System (BRFSS), National Health Interview Survey (NHIS), National Health and Nutrition Examination Survey (NHANES), and the CDC Youth Risk Behavior Surveillance System (YRBSS). The YRBSS is conducted biannually, while the others are collected annually, allowing for timely estimates of the distributions of activity levels, modes, and durations, for the general population informing public health messaging and the creation of guidelines and recommendations.

Physical Activity: Guidelines

"Some physical activity is better than none"[118]. This statement was made by the 2008 federal advisory committee on the guidelines for physical activity, and underscores the need for Americans to engage in physical activity. This committee of researchers, scientists, and public health practitioners were evaluating the existing scientific literature where sufficient evidence were available to develop a comprehensive set of specific physical activity recommendations. The "key guidelines for adults" for substantial health benefits included: all

adults should avoid inactivity, all adults should complete at least 150 minutes per week of moderate-intensity (or 75 minutes per week of vigorous-intensity) aerobic exercise in bouts of at least 10 minutes, and adults should do muscle-strengthening activities that are moderate or high intensity involving all major muscle groups on 2 or more days per week [118]. Additional recommendations are available for specific subpopulations like children and adolescents, older adults, and individuals with unique health needs like pregnant women and adults with disabilities or chronic medical conditions.

Physical Activity: Guidelines – Cancer

In 2012, the American Cancer Society (ACS) released a report suggesting generally that Americans "adopt a physically active lifestyle". Specifically, adults in the United States should: 1) Adults should engage in at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week, or an equivalent combination, preferably spread throughout the week, 2) Limit sedentary behavior such as sitting, lying down, watching television, or other forms of screen-based entertainment[119]. The International Agency for Research on Cancer (IARC) concluded that 25% of cancers worldwide are due in part to overweight and obesity [120] and while the burden in the United States is great 45% of men, 38% of women will develop cancer in their lifetimes [121], only 10% to 15% of these cancers have genetic predispositions leaving a substantial majority with etiologies in modifiable lifestyle and environmental factors [120]. Observational studies are often the primary source of evidence examining the association between physical activity and cancer; however, more methodologically rigorous randomized control trials (RCTs) have contributed tremendously with the mechanistic components, including evaluating several specific markers of cancer risk like cytokines and endogenous hormones. The links between physical activity and cancer are more pronounced for tumors of the colon and breast, a variety of studies using different design methods have consistently observed modest inverse associations [122, 123]. The IARC summary report concluded that, across cancers, the most likely mechanism by

which physical activity effects cancer is by meditation of hormonal-metabolic processes and weight control.

Physical Activity: Guidelines – Pancreatic Cancer

According to the Physical Activity Guidelines for Americans committee report (PAGACR), the eight cohort studies and two case-control studies examining the association between physical activity and pancreatic cancer provided enough evidence to suggest that physical activity 'sufficient for weight control' would be associated with reduced incidence [118]. The PAGACR relied on a meta-analysis and systematic review of the association between pancreatic cancer and physical activity[124]. This review contained several studies, of varying designs and physical activity exposure assessments. At the time, a summary review had examined recreational physical activity (RPA), or activity in "leisure time", and observed a modest, but nonsignificant, reduction in risk for the effect of recreational physical activity on pancreatic cancer risk (RR=0.94 (95%CI=0.83, 1.05))[125], the same exposure that will be captured in this dissertation. The physical activity guidelines additionally take into consideration reports of associations between physical activity and pancreatic cancer from studies of occupational physical activity (OPA) and total physical activity (TPA) exposure assessments in making their recommendation that "physical activity (in general) may be beneficial in reducing pancreatic cancer risk"[118]. Recently, however, two systematic reviews and meta-analyses reported summary estimates of the association between physical activity and pancreatic cancer. One examined various measures of physical activity identifying 22 cohort studies and found a reduction in risk of 7% for total physical activity (RR=0.93 (95%CI=0.88, 0.98))[45]. The second study focused on recreational physical activity alone, and identified 21 cohort studies and reported a reduction of 4% (RR=0.96 (95%CI=0.91, 1.02))[46].

Physical Activity: Measurement

There are a variety of methods to measure physical activity, and these methods can be categorized into two groups: indirect and direct. The indirect methods of physical activity measurement include dietary assessment, measured (or estimated) body composition, physiological fitness assessments (or estimated), participation in sports, and occupational classifications. Indirect measures serve as a proxy by which via back calculations using known caloric expenditures or by subject knowledge of repeated tasks/activities in a given sport or occupation, the amount of physical activity experienced by an individual may be estimated. Direct methods of capturing physical activity result in more valid exposure measurements; however; in some contexts, the indirect measurement of physical activity may be the only measure available. The direct measures of physical activity include questionnaire assessments (either self- or interviewer-administered), diary annotations (self- or observer-recorded), and mechanical or electronic monitoring (self- or remote-recorded). Direct measures may be subjective or objective, the study question, population, and resources available dictate the feasibility of implementing a particular measurement tool. Observational epidemiology studies rely commonly on the direct methods of measurement, smaller intervention studies may opt to implement observations of study participants by trained abstractors or fix electronic accelerometers to individuals to objectively measure exposure, while in large population based studies the self-reported survey questionnaire proving to be the most cost-effective manner in which to capture exposure to physical activity, in a standardized manner, by large numbers of individuals.

Research regarding physical activity and cancer, or health in general, did not begin consistently until the late 1970s, the first formal studies examined occupation as a proxy due to the availability of job coding information via the Bureau of Labor Statistics and Census, and the few studies with specific assessments of physical activity only collected information on physical activity in order to control for confounding when examining other exposures. As

interest in the exposure increased, the specificity of the research also increased. Studies began to examine the quality of physical activity by examining the domain, recreational\leisure-time physical activity, occupational physical activity, and the aggregate measure total physical activity.

While the domain in which physical activity occurs is important, contemporary studies of physical activity classifications seek to further quantify the exposure allowing for deeper investigations into the relationship between physical activity and cancer. The additional parameterization of physical activity occurs through implementing the FITT principle (Frequency, Intensity, Time, and Type) [126]. Frequency refers to how often an individual engages in the physical activity (for example, cycling 3 days per week). Intensity refers to the difficulty or exertion during the physical activity (for example, cycling at 80% of peak heart rate, or 5 METs). Time, intuitively, reflects the duration of the physical activity (for example, cycling for 1 hour). Type, the final component of the FITT principle, refers to the specific physical activity chosen, (for example, cycling). In concert these four parameters paint a very vivid (quantitative) characterization of the exposure to physical activity: “cycling for 1 hour, at 80% peak heart rate or 5 METs, 3 days per week,” where previously “leisure-time bike ride” may have been the extent to which exposure to physical activity was captured.

Metabolic Equivalents of Tasks (METs) are the standardized measurement of intensity in physical activity research. One MET theoretically represents the energy required to maintain a body at rest or resting metabolic rate (RMR). The quantity represents a ratio of metabolic rate of energy expenditure while engaging in a specific physical activity compared to a reference metabolic rate, and carries units 1 $kcal \cdot kg^{-1} \cdot h^{-1}$, or 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. The MET is used as a means of expressing the intensity and energy expenditure of activities while controlling for weight. This is primarily because energy expenditure (e.g., in calories or joules) during an activity depends on an individual’s body size; therefore, the energy cost of

the same activity will be different for persons of different weight. The RMR is also dependent on body size, and the use of METs assumes that the ratio of this variability in energy cost to the RMR of each person will remain more or less stable for the specific activity and thus independent of each person's weight.

In order to use MET values one simply calculates the deviation from RMR; however, this is often unnecessary as the Compendium of Physical Activities (CPA) contains MET equivalents for many activities was developed explicitly for use in epidemiologic studies as a component of the Survey of Activity, Fitness and Exercise (SAFE) study in the late 1980s (Haskell, Stanford), and was most recently updated in 2011[127]. Metabolic equivalents of tasks remain the standard intensity measure among population researchers; however, their usage may warrant modification in some populations, as with any relative measure, the validity of MET is based on the referent. The MET RMR used commonly in research is based upon a reference individual male, age 40 years, weighing 70kg, in studies of children or other niche populations where the caloric expenditure for a given activity would reasonably differ substantially from this reference individual obtaining a population specific RMR should be considered.

The values of METs for activities can range from 0.9 (sleeping) to 18 (running approximately 10 mph). Metabolic equivalents are commonly used and interpreted among physical activity researchers, the general population more easily understands characteristics of exercise like the type of activity, the time spent doing it, the distance covered, or how difficult the activity felt. When collecting this information on physical activity intensity, duration, and frequency researchers can then determine the metabolic equivalents. For this reason the physical activity guidelines and physical activity literature communicate using terminology like “sedentary”, “light”, “moderate”, and “vigorous” physical activity, so that the general population can more readily understand guidelines and characterize their individual exposures when surveyed via questionnaire. Light intensity physical activities result in MET

values less than 3.0 (0.9-3.0 METs), these activities include sleeping (0.9), watching television (1.0), desk work (1.8), and walking up to 2.5 mph (2.9). Moderate intensity physical activities have MET values greater than 3.0 but less than 6.0 (3.0-6.0 METs). Bicycling with light effort (3.0), walking 3.0 mph (3.3), and general home calisthenics (3.5) are examples of the types of activities that are classified as moderate intensity. The highest intensity category of MET values carries the label vigorous intensity and these activities have corresponding MET values of 6.0 or greater (6.0-18.0 METs). Jumping rope (10.0), most forms of aerobic exercise, and participation in sports are characterized as vigorous intensity activities.

The most recent estimates of physical activity in the United States found that the percent of adults (18 years of age and older) who meet the Physical Activity Guidelines for aerobic physical activity is 47.0% [128]. The estimated percentage of adults who met the guidelines for muscle-strengthening activity is 22.4%. The final prevalence of note is the percentage of adults failing to meet the guidelines recommendations of both aerobic physical activity and muscle-strengthening activity is 81.2% [129]. As described previously the prevalence can be estimated using several mechanisms [130], but overall the state of physical activity in the United States remains poor, with most of the adult general population failing to meet the current recommendations.

Physical Activity: Biologic Mechanisms

The exact mechanism through which physical activity influences pancreatic cancer is not known. Though several studies have observed an inverse relationship, the evidence from molecular and animal models is also limited. This difficulty is not unique to the study of pancreatic cancer; other tumor sites have experienced the same difficulty in identifying specific mechanisms. More commonly, the literature suggests there may be several biologic processes associated with increased physical activity exposure, and these may be working in concert to impact cancer incidence at varying stages of tumorigenesis [135-137]. These

biologic processes include: 1) energy balance and weight, 2) moderation of sex hormones, 3) inflammatory processes, 4) immune function, and 5) insulin regulation, and each may play an important role in the growth of pancreatic cancers.

Body weight

Energy balance is most commonly cited mechanism by which physical activity may reduce the risk of cancer. As the diet of humans has changed (becoming more calorically dense) and physical activity levels have declined in western societies, the ability of an individual to achieve energy balance has become increasing difficult. Physical activity represents the primary manner in which an individual can increase energy expenditure, and prolonged positive energy balance (more energy intake than expenditure) results in the storage of energy in adipose. Adipose tissue is a metabolically active tissue, the most active being the visceral adipose typically fat accumulated over the central abdomen. This fact is exacerbated by the impact of aging on human physiology where individuals typically gain weight as they age, and the weight gain is predominantly fat. Physical activity is known to preferentially reduce central adiposity, and the additional caloric expenditure over time is known to maintain/reduce weight via neutral/negative energy balance [138].

Sex hormones

Physical activity is associated with circulating levels of sex hormones in both male and females. The mitogenic and proliferative effects of sex hormones implicate their association with carcinogenesis at multiple tumor sites. The presence of estrogen receptors, estrogen binding proteins, and androgen receptors have been demonstrated in human pancreatic adenocarcinomas of ductal origin [139]. In experimental studies using animal models, inhibition as well as growth potentiation of pancreatic cancer has been demonstrated after altering the level of these hormones [140]. Physical activity changes the level of circulating hormone levels in women and over the life course may influence the duration of exposure to estrogens via suppression of gonadal hormones [141]. In males,

physical activity has been shown to impact levels of circulating free [142, 143] and total androgens [144, 145]. However, it should be noted that very high levels of physical activity were required to observe these differences; and it is possible that there may be little benefit conferred among individuals given the lower levels of activity in current recommendations.

Inflammation

While the exact roles that cytokines, transcriptions factors, and pro-inflammatory enzymes are associated with pancreatic cancer are unknown, they have been shown to be associated with the disease, playing key roles in inflammatory response and fibrotic response occurring during healing [146]. Cell damage occurs when cytokines are released during pancreatitis, in the presence of oxidative species [147]. Adipokines are a specific type of cytokines secreted from adipose tissue and several of these polypeptides, including: leptin, adiponectin, tumor necrosis factor-alpha (TNF-α), and interleukin-6,-8 (IL-6. IL-8), and interferon ɣ levels are increased in pancreatic cancer [148, 149]. The literature illustrates the linkage between inflammation and obesity is much better understood; however, the beneficial effects of physical activity on tumorigenesis may exceed the independent effect of weight loss alone. Exposure to prolonged physical activity results in consistent reductions of levels of inflammatory markers TNF-α and IL-6 [136, 150, 151].

Immune function

The immune system is responsible for guarding the body from abnormalities in cell structures and tissues, including cancer cells. When abhorrent cells are not destroyed by the immune system [152], it is also shown that natural killer (NK) cells, lymphokine-activated killer (LAK) cells, cytoxic T-lymphocytes, and macrophages all continue to work inhibiting tumor growth and progression [153]. Physical activity has been shown to initiate immune response in a several studies. The type of response varies with physical activity. Response from physical activity can include the release of pro-inflammatory markers followed by cytokine inhibitors are initiated following activity [154]. This “training” of the immune system via repeated bouts of

physical activity is hypothesized to keep the body more alert to the existence of tumor initiators, developing the immune system [155, 156]. Timing of physical activity throughout life, as well has the type of activity, duration, and intensity all contribute to the benefit conferred. Moderate levels of physical activity are shown to briefly elevate immune function; however, return to their pre-activity levels shortly after completion. The effect of physical activity on immune response is not linear; individuals that are sedentary show a less beneficial response than those individuals who are regularly active, while those that undertake the most difficult and demanding exposures to physical activity can overwhelm the immune response with inflammation [136]. The effects described apply generally across all cancer sites and therefore may play a role in the etiology of pancreatic cancer with respect to physical activity.

Insulin

Insulin is a hormone produced by the pancreas, responsible for regulating carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing energy in the form of glycogen inside these tissues. Insulin is provided within the body in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic [157-159]. With increased production of insulin the concentration of insulin like growth factor binding proteins (IGF-BP) decreases, these binding proteins occupy circulating growth factors associated with tumor cell growth and proliferation [160].

Chronic exposure to excess insulin, or hyperinsulinemia, can lead to an inability for the body to lower glucose effectively; this physiologic condition is described as insulin resistance (IR). Insulin resistance differentially affects the cells involved in glucose synthesis, muscle and tissue result in decreases in storage of glucose as glycogen and triglycerides, while the effect in liver cells results in excess production of glucose production into the blood stream, exacerbating the problem, and creating a negative feedback loop.

Physical activity can affect insulin profiles and therefore insulin resistance in several ways. First, physical activity increases glucose uptake, but musculoskeletal tissues, reducing the excess glucose circulating in the blood, and therefore triggering a halt to insulin excretion by the pancreas. Second, the aforementioned reductions in adiposity reduce the mass of metabolically active tissue responsible for producing growth factors. Finally, as a result of decreased insulin and decreased growth factors, the bioavailability of the existing binding proteins is increased, leaving essentially the same amount circulating at a higher concentration, increasing the efficiency of the "basal" levels of the proteins in the body. The pancreas, and pancreatic cancer, is intimately related to the function and concentration of insulin produced in the body, the exact mechanism remains poorly understood; however, diabetes remains one of the strongest risk factors of the cancer.

Physical Activity: Demographic Predictors

Physical activity represents a complex behavioral exposure, and when conducting scientific investigations regarding this exposure it is important to understand the social, economic, and demographic correlates that may drive participation of this exposure. Physical activity may be conducted individually or in groups, social support from friends or peers has been consistently reported as being strongly correlated with levels of physical activity [131]. Similarly, individual behavioral characteristics such as level-self-control or type-A personality have been consistently associated with physical activity levels [132]. Both higher levels of education and income are each consistently associated with higher levels of physical activity [132, 133]. Males are typically more physically active than females, and individuals identified as White race/ethnicity typically report higher levels of physical activity than non-white counterparts [134].

Physical Activity: Timing/Dynamics

While physical activity represents an important exposure for pancreatic cancer, one aspect of physical activity remains relatively unstudied across the cancer literature: the timing, or dynamics, of physical activity exposures throughout adulthood. As discussed previously, the parameters of the FITT principle are essential to characterizing individual physical activity exposures. The risk of cancer increases with age. Given the discussion above on the mechanisms by which physical activity may affect cancer risk, the next reasonable question should be characterizing physical activity exposure over meaningful epochs of an individual's life. Increasing adult age-specific weight, and the weight gain associated with age as discussed previously, is typically visceral adipose tissue, a metabolically active tissue that in dysfunction creates a carcinogenic environment of inflammation, insulin sensitivity and oxidative stressors. Physical activity is known to affect each of these pathways, and through reduced oxidative stress, reduced inflammation, and improved insulin profiles, physical activity may be viable risk reduction strategy for pancreatic cancer. In addition, understanding if there are important susceptibility windows for this exposure aides in targeting public health messages about the benefits of increasing physical activity.

Summary

In epidemiologic studies, physical activity is measured using a variety of methods and are quantified using the FITT principles and metabolic equivalents of tasks. While the exact relationships are unknown, there are several metabolic an hormonal mechanisms by which increased physical activity may result in an inverse association with incidence of pancreatic cancer. A better understanding of associations with age-specific exposures, and changes in exposure over time, may provide further insights as to physical activity's role in pancreatic cancer etiology.

Adult Changes in Weight and Pancreatic Cancer

As shown in Table 1.2, a number of previous epidemiologic studies have examined whether changes in adult weight – usually from early adulthood (age 20 years, for example) until diagnosis – are associated with the risk of developing pancreatic cancer. A recent study in 2013 reported summary relative risks ranging from 1.15 to 1.53 [161] and concluded that obesity at any age was a source of increased risk. However, when examining prospective studies two have reported results on examining change in weight from early adulthood to study enrollment, a Swedish cohort of twins found a slight increase in risk (RR=1.05 (95%CI=0.87, 1.26))[162], while an American cohort observed a slight decrease (RR=0.97 (95%CI=0.84, 1.12))[163], though both studies estimated confidence intervals contained the null. Few studies to date have focused on whether weight or weight change at specific ages across the adulthood are associated with pancreatic cancer, and using this approach may improve the ability to develop targeted public health messages.

Adult Changes in Relative Physical Activity and Pancreatic Cancer

I was unable to identify epidemiologic studies that focused on changes in physical activity in association with pancreatic cancer. Previous studies of the association between physical activity and pancreatic cancer have generally observed slight decreases in risk (RR=0.96 (95%CI=0.90, 1.02))[45]. Retrospective and case-control studies have more often observed stronger statistically significant results (RR=0.68 (95%CI=0.52, 0.89)); however, these designs suffer from differential error with respect to case-control status. The association of physical activity with pancreatic cancer has been studied using occupational, recreational, and total physical activity exposure assessments. However, among older individuals (incident pancreatic cancer median age 70), particularly those who are white (as in the VITAL cohort) recreational (or leisure time) physical activity assessments have been shown to best characterize an individual's physical activity levels[164-166].

Summary

A number of epidemiologic studies have focused on the issue of whether adult weight gain is associated with pancreatic cancer, but few have examined whether changes during specific ages (e.g., weight gain during early adult life or after age 50 years, for example) are more strongly associated with increased risk. As we age, changes in bodyweight occur, gains in weight typically come in the form of accumulation of visceral adipose, serving as an adverse exposure of several carcinogenic hormones. Increased pancreatic cancer risk has already been associated with BMI and obesity, but this study will examine if the adverse effects of weight gain at various ages throughout adulthood pose additional risk. The association between physical activity and pancreatic cancer is more inconsistent. However, there is biologic plausibility that the beneficial effects of physical activity on mechanisms of carcinogenesis, as well as energy balance are associated with pancreatic cancer risk. Furthermore, no epidemiologic studies have examined the association between changes in physical activity at multiple windows throughout adulthood and pancreatic cancer risk. This information will enhance public health strategies to reduce the risk of pancreatic cancer by targeting of specific adult ages -- or windows of exposure.

Table 1.1 Prospective Studies of Obesity and Pancreatic Cancer

Study	Year	Locale	Study/Population	N(M)	Events (M)	M/F	Age Range	Anthro	Main Finding BMI ≥30 vs BMI <30
Friedman & Van den Eeden et al. [47]	1993	US		2687	450	M/F	15-94	M	1.10 (1.00, 1.22)
Shibata et al. [167]	1994	US		13979	65	M/F	65-85	S	1.22 (0.76, 1.96)
Gapstur et al. [168]	2000	US	Chicago Heart Association	35658 (20475)	139 (96)	M/F	15-90	M	1.38 (0.74, 2.58)
Michaud et al. [169]	2001	US	HPFS	46648	140	M	40-75	S	1.28 (0.98, 1.66)
Michaud et al. [169]	2001	US	NHS	117041	210	F	30-55	S	1.16 (0.98, 1.37)
Isaksson et al. [162]	2002	Sweden	Swedish Twin Study	21884	163	M/F	36-75	S	1.16 (0.87, 1.54)
Stolzenberg-Solomon et al. [170]	2002	Finland	ATBC	29048	172	M	50-69	M	0.87 (0.69, 1.10)
Lee et al. [153]	2003	US	College Alumni Health Study	32687	212	M/F		S	1.07 (0.81, 1.40)
Calle et al. [171]	2003	US	ACS-CPS II Mortality Cohort	900053 (404576)	3558 (1908)	M/F	30-	S	1.17 (1.12, 1.22)
Kuriyama et al. [172]	2005	Japan		27539 (12485)	64 (31)	M/F	40-	S	1.08 (0.64, 1.83)
Patel et al. [163]	2005	US	ACS-CPS II Nutrition Cohort	145627 (69589)	242 (137)	M/F	50-74	S	1.43 (1.19, 1.71)
Sinner et al. [173]	2005	US	Iowa Women's Health	38002	209	F	55-69	S	1.06 (0.88, 1.27)
Batty et al. [174]	2005	UK	Whitehall	17102	147	M	40-64	M	1.06 (0.74, 1.52)
Oh et al. [175]	2005	Korea	KNHIC	781283	466	M	20-	M	0.92 (0.76, 1.10)
Rapp et al. [176]	2005	Austria	VHM&PP	145931 (67447)	129 (64)	M/F	19-94	M	1.30 (0.97, 1.74)
Larsson et al. [177]	2005	Sweden	Swedish Men	45906	75	M	45-79	S	1.34 (0.94, 1.90)
Larsson et al. [177]	2005	Sweden	Swedish Mammography	37147	61	F	49-83	S	1.22 (0.87, 1.70)
Lukanova et al. [178]	2006	Sweden	Northern Sweden Health and Disease	68786 (33424)	63 (22)	M/F	29-61	M	1.05 (0.69, 1.58)
Nothlings et al. [179]	2006	US	Multiethnic	187566 (85650)	475 (246)	M/F	45-79	S	1.06 (0.83, 1.36)
Berrington de Gonzalez et al. [180]	2006	EU	EPIC	438405	324	M/F	19-84	M	1.09 (0.95, 1.24)
Samanic et al. [181]	2006	Sweden	Swedish Construction Worker Cohort	362552	698	M	18-67	M	1.02 (0.91, 1.14)

Table 1.2 Studies of Weight Change and Pancreatic Cancer

Study	Year	Locale	Study/ Population	Design	N(M)	Events (M)	M/F	Age Range	Anthro	Main Finding
Friedman & Van den Eeden et al. [47]	1993	US	Kaiser Permanente	Case Control	2687	450 (??)	M/F	15-94	M	6mo. Gain 10lbs - 0.66 (0.44, 0.99)
Ogren et al. [182]	1996	Sweden	Malmo	Case Control	215	43 (38)	M/F	18-55	S	Since Age30 gain 10kg 1.80 (0.90, 3.60)
Michaud et al. [169]	2001	US	HPFS	Cohort	46648	140	M	40-75	S	+-2.25 kg vs. loss >6.75 kg 1.28 (2.35, 8.84)
Michaud et al. [169]	2001	US	NHS	Cohort	117041	210	F	30-55	S	+-2.25 kg vs. loss >6.75 kg 2.44 (1.46, 4.06)
Isaksson et al. [162]	2002	Sweden	Swedish Twin Study	Cohort	21884	163	M/F	36-75	S	<=1kg 1.02 (0.60, 1.73) 2-5kg ref 6-11kg 1.28 (0.77, 2.14) >=12kg 1.46 (0.87, 2.45)
Patel et al. [163]	2005	US	Cancer Prevention Study- II	Cohort	145627	242	M/F	50-74	S	Age18 to Base M: +13.62kg 1.99 (1.08, 3.65) F: +13.62kg 0.87 (0.50, 1.49)
Verhage et al. [183]	2007	Netherlands	The Netherlands Cohort Study on Diet and Cancer	Case-Cohort	4774	173 (75)	M/F	55-69	S	BMI Age20 1.06 (0.98, 1.14)
Lin et al. [184]	2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	Cohort	110792 (43579)	402	M/F	40-79	S	M: loss>5kg 1.67 (1.10, 2.54) gain>5kg 0.85 (0.49, 1.47) F: loss>5kg 0.41 (0.22, 0.74) gain>5kg 0.93 (0.60, 1.45)
Luo et al. [185]	2008	US	Women's Health Initiative	mRCT-Cohort	161808	251	F	50-79	S	Stable ref Gains 0.9 (0.7, 1.2) Losers 0.7 (0.3, 1.6) Up/Down +- 10lb 1.0 (0.7, 1.3)
*Johansen et al. [186]	2009	Sweden	Malmö Preventive Project	Cohort	33346	183	M/F	40-	S	Gain 10kg age 30 (y/n) 3.6 (1.2-10.1)
Genkinger et al. [52]	2011	POOLED	POOLED	POOLED	846340	2135	M/F	15-107		absolute > 10kg 1.40 (1.13, 1.72) >25kg/m2 early adult and >30kg/m2 at baseline 1.54 (1.24, 1.93)
Stolzenberg-Solomon et al. [161]	2013	US	NIH-AARP Diet and Health Study	Cohort	275,975(165,135)	2122 (1359)	M/F	50-71	S	BMI 18,35,50 HRs 1.15 – 1.53

Table 1.3 Prospective Studies of Recreational Physical Activity and Pancreatic Cancer

Authors	Year	Locale	Study	N (Males)	Events (Males)	Sex	Age	Range	Main Finding Highest vs Lowest Quantile
Nilsen & Vatten [187]	2000	Norway	Nord-Trondelag Health Survey	63374 (31000)	166 (96)	M/F	71m/73f mean	43-93	0.79 (0.50, 1.25)
Michaud et al. [169]	2001	US	HPFS	46648 (44648)	140	M	54 mean	40-75	0.72 (0.40, 1.30)
Michaud et al. [169]	2001	US	NHS	117041 (0)	210	F	43 mean	30-55	0.78 (0.42, 1.45)
Isaksson et al. [162]	2002	Sweden	Swedish Cancer Registry	21884 (9680)	176		56 med		0.65 (0.41, 1.03)
Stolzenberg-Solomon et al. [170]	2002	Finland	ATBC	29048 (29048)	172 (172)	M	58 med	55-62	0.88 (0.65, 1.20)
Inoue et al. [188]	2003	Japan	HERPACC	2200 (1342)	200 (122)	M/F	60m/60f	30-89	0.66 (0.43, 1.01)
Lee et al. [153]	2003	US	College Alumni Health Study	32687 (30385)	212 (?)	M/F	47 mean		1.31 (0.69, 2.49)
Patel et al. [163]	2005	US	ACS-CPS II Nutrition Cohort	145627 (65589)	242 (137)	M/F	63m/62f mean	50-74	1.20 (0.63, 2.29)
Sinner et al. [173]	2005	US	Iowa Women's Health	38002 (0)	209 (0)	F	61f mean	55-69	1.29 (0.93, 1.79)
Berrington de Gonzalez et al. [180]	2006	EU	EPID	438405 (142208)	324 (152)	M/F	61m/63f med	19-84	0.96 (0.66, 1.40)
Luo et al. [185]	2007	Japan	JPHC	99670 (47499)	224 (128)	M/F	51m/52f mean	40-69	1.06 (0.68, 1.65)
Nothlings et al. [189]	2007	US	The Multiethnic Cohort Study			M/F			
Lin et al. [184]	2007	Japan	Japan Collaborative Cohort	110792 (43579)	402 (207)	M/F	57m/57/f mean	40-79	0.98 (0.65, 1.48)
Calton et al. [190]	2008	US	Breast Cancer Detection and Demonstration Project (BCDDP)		70 (0)	F			

Authors	Year	Locale	Study	N (Males)	Events (Males)	Sex	Age	Range	Main Finding Highest vs Lowest Quantile
Yun et al. [191]	2008	Korea	National Health Insurance Corporation	444963 (444963)	349 (349)	M	49 mean	40-	1.00 (0.81, 1.23)
Jiao et al. [192]	2009	US	NIH AARP Diet Health	450416 (263298)	1057 (675)	M/F	62m/61f mean	50-71	0.94 (0.83, 1.06)
Stevens et al. [193]	2009	UK	NHS Central Registry	1200000 (0)	1338 (0)	F	56f		0.97 (0.87, 1.15)
Batty et al. [194]	2009	UK	Whitehall	18863 (18863)	163 (163)	M		40-69	0.76 (0.84, 1.11)
Robsahm et al. [195]	2010	Noway		3428 (1646)	10 (9)	M/F	47.6 median	18-95	1.46 (0.67, 2.68)
Nakamura et al. [196]	2010	Japan	Takayama Study	30826 (14427)	52 (33(	M/F	54m / 55f mean		1.03 (0.41, 2.60)
Heinen et al. [197]	2011	Netherlands	Netherlands Cohort Study	120852 (58279)	408 (217)	M/F	62m /62f mean	55-69	0.80 (0.64, 0.99)
Sormune et al. [198]	2013	Finland	Finnish Cancer Registry	4160 (4160)	27 (27)	M	55 median		1.05 (0.67, 1.65)
Keum et al. [199]	2016	US	HPFS(1986-2012)	51529 (43479)	235 (235)	M	61 mean	40-75	0.95 (0.57, 1.57)

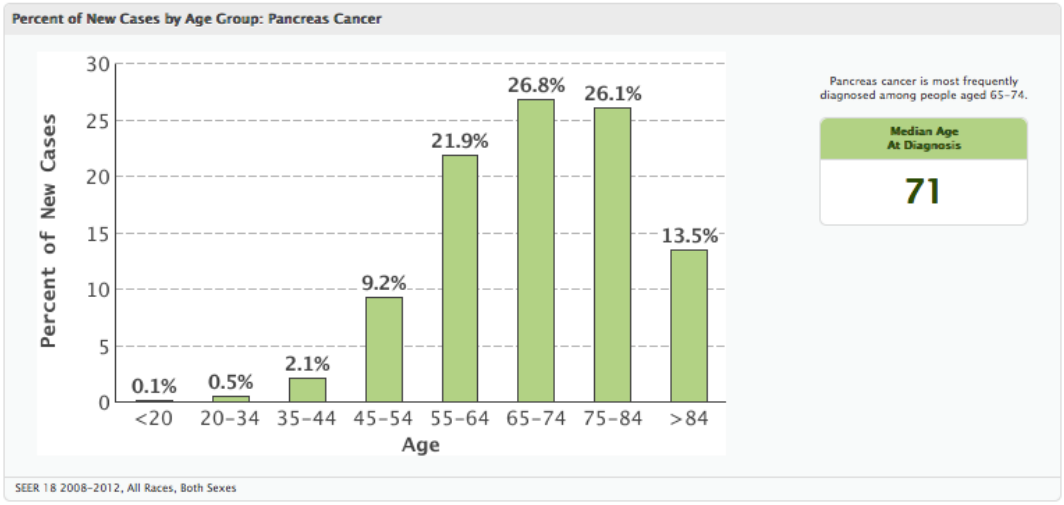

Figure 1.1 SEER Incidences of Pancreatic Cancer by Age

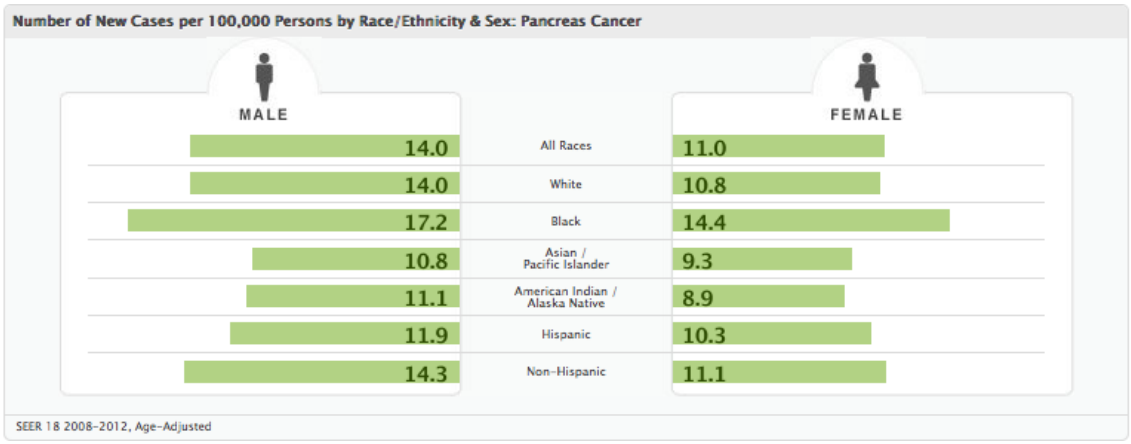

Figure 1.2 SEER Incidences of Pancreatic Cancer by Sex and Race

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CHAPTER 2: RESEARCH METHODS

Overview

As reviewed in Chapter 1 of this dissertation, pancreatic cancer is the fourth most common cause of cancer deaths in the United States (US), accounting for more than 43,090 deaths in 2017[1]. Cigarette smoking, diabetes, and recently, obesity, are the only risk factors that have been consistently associated with pancreatic cancer, while other modifiable risk factors including and physical activity are inconsistently associated. Identifying and understanding the modifiable risk factors of pancreatic cancer – particularly during adulthood – is of critical public health importance, potentially leading to age-specific targeted cancer prevention strategies. The high prevalence of obesity and physical inactivity in the US, and the accompanying adverse metabolic changes that correspond to changes in weight and lack of physical activity during adulthood, emphasize the importance of clarifying associations between pancreatic cancer risk and physical activity or weight change. Previous studies of obesity, but not physical activity, and pancreatic cancer have found consistent associations, although a number of these studies have suffered from small numbers of events and heterogeneous assessments of exposure. Further, studies that have prospectively examined the effects of adult weight have not identified whether adult age-specific weight or adult weight gain may impact pancreatic cancer risk. Finally, no studies have examined whether adult age-specific physical activity or adult changes in physical activity levels are associated with pancreatic cancer.

My hypothesis is that adult age-specific weight, adult age-specific physical activity, adult changes in weight and adult physical activity are associated with pancreatic cancer risk. These associations could plausibly be acting through several biologic mechanisms,

including adverse changes in metabolic profile and influencing levels of circulating endogenous hormones. Thus, the objectives of this dissertation are to prospectively examine the association of adult age-specific and adult changes in weight and physical activity with the subsequent risk of developing pancreatic cancer in a large cohort of adult men and women. My dissertation used the resources of the National Cancer Institute (NCI)-funded VITamins And Lifestyle (VITAL) study. This cohort of over 77,000 men and women in Washington State was recruited between October 2000 and December 2002, and was originally designed to assess the effect of dietary supplement use and lifestyle exposures on cancer risk in a population of older supplement users. Data collection in the VITAL cohort included assessment of baseline, age-specific, and changes in weight and physical activity levels throughout adulthood. Cox proportional hazards modeling was used to obtain estimates for these weight and physical activity exposures in association with pancreatic cancer risk, after an average 10 years of follow-up.

My dissertation findings may provide significant insights regarding the etiology of potentially modifiable risk factors for pancreatic cancer and identify age-specific targets for public health messages for prevention of this lethal cancer.

Lifestyle factors like weight and exercise can have important impacts on the development of disease throughout adulthood. The purpose of this research is to better understand if age-specific weight and physical activity, or changes in these exposures, impact the chance of developing pancreatic cancer.

Specific Aims

Pancreatic cancer accounted for more than 20,000 deaths in both men and women in 2017[2]. No effective screening modality or method of early detection currently exists for the diagnosis of pancreatic cancer, and as a result most diagnoses result in a poor prognosis; for example, even among those diagnosed with a localized tumor, 5- year survival rates are

approximately 20% [3, 4]. Risk factors for pancreatic cancer remain poorly understood, and identifying modifiable risk factors is of critical public health importance.

Obesity, but not physical activity, has been consistently associated with the risk of pancreatic cancer [5]. However, whether age-specific exposures, or changes in these exposures, during adulthood are associated with pancreatic cancer remains unclear The prevalence of obesity and overweight in the US is high [6], current prevalence estimates range from 18.7% to 32% [7]. The continued increases in obesity, the high percentage of adults failing to meet the recommendations for physical activity, and paralleled aging of the US population create a carcinogenic environment, for a number of cancers, including those of the breast [8], endometrium [9] and colon [10], and perhaps the, pancreas. Clarification of whether adult age-specific obesity is associated with pancreatic cancer is an important public health issue.

Increases in adult age-specific weight, and adult weight gain result primarily in centrally deposited adipose tissue, a metabolically active fat mass that is hypothesized to contribute to carcinogenesis by changing levels of endogenous hormones while functioning as an endocrine organ. These exposures are associated with lowering circulating levels of sex hormone-binding globulin, inducing hyperinsulinemia, and increasing insulin-like growth factor-I levels [11-13]. Weight gain is a known risk factor for cancer at other cancer sites [14], yet few studies have attempted to determine if an association exists with pancreatic cancer at specific ages in adulthood. Determining whether age-specific obesity, or weight change (absolute and relative), or patterns of weight change across adulthood are associated with pancreatic cancer will clarify our understanding of disease etiology and improve public health messages.

Some health educators have advocated weight loss as an important goal in reducing an individuals' lifetime cancer risk; however, in both the short- and long-term, recidivism has been reported to be between 60% and 90% [15]. Thus, methods that intervene upon the

concept of weight maintenance – e.g., avoiding weight gain -- may result in better health outcomes, including cancer prevention. Physical activity, a key component energy balance, may therefore play a key role in cancer risk, by aiding in weight control [16] and improving hormonal profiles [17].

For this dissertation, I proposed to evaluate the hypothesis that adult age-specific weight and physical activity, as well as adult changes in weight and physical activity, are associated with the risk of pancreatic cancer.

Specific aims are as follows.

Aim 1. Are recent, age-specific, or changes in weight over adulthood associated with subsequent development of pancreatic cancer? To address this question, I utilized existing data from the VITAL cohort study, which included assessment of self-reported weight at age 18, 30, and 45 years, and at baseline. Specifically, I evaluated the following aims: to examine associations between the incidence of pancreatic cancer after 10 years of follow-up and:

Aim 1a. obesity at baseline, age 18 years, 35 years and 45 years, with each considered in separate models and assessed using the Body Mass Index (BMI), calculated as baseline weight (kg) divided by self-reported usual adult height (m^2);

Aim 1b. absolute adult weight change as well as relative adult weight change since age 18 years, assessed using absolute weight change (kg), calculated as current weight (kg, or weight at age 30 or 45 years, and baseline) minus weight at age 18 (kg), and relative weight change (%);

Aim 1c. weight change patterns across adulthood, considering “weight maintenance (defined as <3% change in weight throughout adulthood)” vs. “constant weight gain” vs. “constant weight loss” vs. “cycling (defined as no consistent pattern)”; and

Aim 1d. timing of relative weight gain across the life course, considering relative weight gain across specific time periods (age 18-30 years, 30-45 years, 45 years-baseline).

Aim 2. Are recent, age-specific, or changes in physical activity during adulthood associated with subsequent development of pancreatic cancer? To address this research question, I utilized data from the VITAL cohort study, which included assessment of self-reported recreational physical activity levels at baseline, and relative physical activity levels at age 18, 30 and 45 years. Specifically, I evaluated the following aims: to examine the associations between pancreatic cancer incidence after 10 years follow-up, and:

Aim 2a. recent activity levels, which were comprehensively assessed over the 10 years prior to baseline, assessed as METs (based on frequency and intensity) along with days per week;

Aim 2b. activity levels at age 18, 30, and 45 years, with PA assessed as days per week with consideration given to meeting the PA guidelines (where 4+ days per week defined as meeting the PA guidelines for cancer vs. <4 days per week); and

Aim 2c. activity level patterns across adulthood (18 to 45 years), considering "physical activity maintenance (defined as the same levels across adulthood" vs. "increasing physical activity" vs. "decreasing physical activity" vs. "no consistent pattern".

Parent Study: the VITAL Cohort

This dissertation used data from the VITamins And Lifestyle Study (VITAL) cohort. Vitamin, mineral, and other dietary supplements are among the most commonly used drugs in the United States [18], with conservative usage estimates among as high as 55 percent of adults. Citing this substantial exposure and recognizing that consumers have little or no scientific validation to guide their use of dietary supplements as they are not regulated by the Food and Drug Administration (FDA) the VITAL study was designed and implemented with the overall aim of investigating associations between these supplements and cancer risk [19]. Adult men and women were recruited in a 13-county area covered by the Washington State Surveillance, Epidemiology, and End Results (SEER) program cancer registry. Names and mailing addresses were identified using a commercial mailing list and individuals aged

50-76 years were mailed a baseline questionnaire. To encourage dietary supplement users to participate the study was marketed openly as a study of supplement use and cancer risk; however, recruitment was not restricted to users of supplements. Between October 2000 and December 2002, 364,418 baseline questionnaires were mailed followed by a reminder post card 2 weeks later, 79,300 (21.8 percent) of the questionnaires were returned, with 77,738 passing subsequent eligibility and quality control checks [19].

Questionnaire data were collected at baseline. The 24-page instrument was entirely self-administered, sex-specific, covering three main portions of the study: supplement use, diet, medical history and risk factor assessment. The supplement use portion of the instrument was the longest as the primary exposure for the parent VITAL study, and had been used previously in supplement studies [19]. Diet was assed using a 120-item food frequency questionnaire adapted from the instrument developed for the Women's Health Initiative (WHI), adding highly supplemented foods [19]. Upon receipt, questionnaires were reviewed prior to optical scanning, where crossed out answers were cleared using a corrective tape, and written answers were coded using internal study protocols.

Characteristics of VITAL

Overall, 79,300 questionnaires were returned (21.8% response, 19.5% men, 24.4% women) of which the 77,738 passed eligibility requirements and internal quality control checks and are presented in Table 2.1.

In addition to baseline age and geographic eligibility criteria, participants must have completed a detailed baseline questionnaire covering supplement use over the past 10 years, diet, physical activity, health history, and cancer risk factors.

The cohort is predominantly female (52%), almost entirely white race (93%), and educated with more than 20% completing high school, 38% completing some college, and 41% graduating from college or university. Smoking history was prevalent in the cohort, with more than half (52.5%) of the cohort self-reported as current smokers or former smokers.

The distribution of body mass index (BMI) was fairly evenly distributed with 33% falling into the “normal” (18.5-<25) category, 41% in the “overweight” (25-<30) category, and 25% of the cohort categorized as “obese” with a calculated baseline BMI greater than 30.0. The cohort could be described as active; and physical activity assed at baseline in (days per week) was also fairly evenly distributed with close to 40% engaging in either “none”, or “1-2” activities per week at baseline, approximately 19% and 30% respectively, and remainder engaging in either “3-4” or “5+” activities, approximately 20% and 31% respectively. Additional baseline characteristics of the VITAL cohort are presented in Table 2.2, and have been previously reported [19].

Exposure Assessment of VITAL

Body mass index (BMI)

In the parent study cohort members were asked to self-report the height at which they were tallest, heaviest weight, and ages at each respectively, as well as their weight at ages 18, 30, and 45. This information was used to compute BMI as weight divided by height squared (kg/m^2), as well as assess change in weight.

Weight gain

Using the self-reported weight as ages: baseline, 18, 30 and 45 years of age, weight gain was be calculated as the difference between age at 18 and each of the ages of recalled, self-reported weight.

Physical activity

Physical activity throughout adulthood may be more strongly related to cancer risk than activity at baseline alone; therefore, the parent study developed a recreational physical activity questionnaire used at baseline to capture activity for the previous 10 years. These questions cover the frequency, duration, and number of years for each of five types of exercise (walking, weight lifting, yoga, mild activities such golf, and moderate/strenuous activities, such as jogging) over the previous 10 years. For walking, there is an additional

question about pace, and for moderate/strenuous exercise the participants can select from among 9 types of activities. Participants were also asked to report the number of days per week (none, 1-3, 4-5, 6-7) they usually exercised at ages 18, 30, and 45. The analysis algorithms computed average MET hours per week (kcal per kg body weight) over the reference period for total-, strenuous-, moderate- and light- activities. The Compendium of Physical Activities is used for the MET score for each type of activity, a common methodology in epidemiologic studies and is discussed in detail previously [20, 21]. In a validation study to assess the measurement characteristics of the physical activity questionnaire the correlation for total 10-year recreational activity between our instrument and a very detailed interview was 0.68 (n=217). In the full cohort, BMI was inversely correlated with 10-year physical activity as assessed by the one-page questionnaire (r = -0.22), a result comparable to other validations between individual BMI and recent physical activity. I additionally checked distributions for outliers and implausible values to ensure that the obtained results are all within plausible ranges of values. There are no validation measures of 10-year physical activity [22]. Ten years of repeated diaries would be informative but not feasible in a study of cancer incidence. However, in a comparison study completed by the VITAL team the study instrument compared favorably representing a valid assessment of recalled physical activity and results are available in detail elsewhere [23].

Outcome Assessment in VITAL

Pancreatic cancer

Incident pancreatic cancer cases were obtained by linking the study cohort to the western Washington SEER cancer registry. SEER data are collected and maintained by the Fred Hutchinson Cancer Research Center (FHCRC) under contract to the SEER Program of the National Cancer Institute. Since 1974, data have been collected on all newly diagnosed invasive and in situ cancers (except non-melanoma skin cancers) occurring in residents of the 13 counties of western Washington State. Cases were ascertained through all hospitals

in the area including pathology, oncology, and radiology departments, as well as from state death certificates. Data routinely collected include demographic characteristics, tumor characteristics, and first course of treatment, and participants were followed up for vital status or death.

Annually, the parent study linked the VITAL cohort to the SEER file containing all cancer diagnoses for the year prior. During each linkage the registry data are estimated to be 97% complete by September for the year before. The parent study has designed and implemented a comprehensive linkage system using data items in common to both the SEER and VITAL datasets, with computerized linkage to identify close probabilistic matches (not exact matches) and final decisions adjudicated by human judgment. Participants may have moved outside of the study area, and the FHCRC/VITAL study staff has addressed the handling of out-migration from the SEER Seattle Puget sound catchment area via a monitored linkage to the US National Change of Address file, and National Death Index (NDI) roster. This is the approach successfully used by the FHCRC for incident cancer outcome ascertainment.

Previous Studies in VITAL

Physical activity has been examined previously in the VITAL cohort for other chronic disease outcomes. For example, activity was assessed in the male cohort and incidence of prostate cancer was measured over follow up. Activity was associated with a 50% increased risk among men who were obese (HR=1.5 (95%CI=0.95, 2.4)), as well in other subgroups, however overall no statistically significant association was observed [24]. Another investigation examined the exposure of physical activity and weight status, increasing MET-hours and sessions per week activity over follow up were inversely related to weight gain after age 45 [25]. Mode of activity was investigated when participants who engaged in yoga were followed for changes in weight status. Yoga practice for four or more years was associated with a

3.1lb lower weight gain among normal weight participants and an 18.5lb lower weight gain among overweight participants [26].

Obesity has been examined previously in the VITAL cohort as well. A cross-sectional examination of 7 serious diseases, 23 medical conditions, and 11 health complaints and baseline BMI found that many variety of the health outcomes on the baseline questionnaire were associated with obesity[27]. In another VITAL investigation, obesity was differentially associated with aggressive and nonaggressive prostate cancer risk, with normal-weight men having a reduced risk (RR=0.69 (95%CI=0.53, 0.93)) and overweight men having an increased risk of aggressive disease (HR=1.77 (95%CI=1.1, 1.8)) [28].

The VITAL cohort has also published on associations with diet, supplement use, lifestyle factors and a number of chronic diseases outcomes including cancer.

Variable Definitions

Outcomes and number of events

The outcome of interest is the incidence of pancreatic cancer. Analyses were limited to first primary pancreatic tumors. Data was linked to the SEER database during the study, and 180 cases were identified through December 2008 and 215 cases through December 2009, the final linkage conducted in 2011 observed 280 cases. These are the most recent data available for my dissertation.

The parent study designed and implemented a comprehensive linkage system, which was largely automated, by using data items common to both sets of data (SEER and VITAL). First, potential matches were identified based on linking the two files several general matching criteria. These included: 1) full social security number (provided by 33-percent of the cohort participants); 2) last four digits of the social security number (36-percent), first five characters of the last name, and date of birth; and 3) “sounds like” based on phonetic sound and accounting for potential variation in spelling the last name; and 4) date of birth. Second, each potential match was ranked electronically to determine whether

it is “good” (several displayed items were common enough to indicate a match), “bad” (not enough displayed items in common to suggest a match), or “needs visual inspection” (some data items in common, but additional visual inspection warranted). The ranking criteria are based on the type and number of other data items that match (name, sex, date of birth, street address, zip code, telephone number, marital status, and birthplace), with the match criteria more conservative for the most general linkage criteria. Third, Fred Hutchinson Cancer Research Center (FHCRC) staff used screens that display all relevant information from VITAL and SEER simultaneously reviewed matches requiring visual inspection. This inspection allowed the use of human judgment for matches not made electronically because of misspellings of names, nicknames, transposition of numbers, and so forth. The linkage described was conducted entirely by the FHCRC staff.

Definition of exposure variables

The primary exposure (predictor) variables in AIM1 were age-specific body mass index (BMI) and weight change assessed via self-reported anthropometry, participants reported height at which they were tallest and their weight at ages baseline, 18, 30, and 45 years. This information was used to compute BMI continuously as weight divided by height squared (kg/m^2) and weight change calculated as weight at an age (30, 45, baseline) minus weight at age 18. The primary exposure (predictor) variables in AIM2 were age-specific and changes in physical activity in MET-hours / week. These estimates were calculated using the analysis algorithms computed average MET hours per week (kcal per kg body weight) over the reference period for total, strenuous, moderate and light activities using the Compendium of Physical Activities. These estimates were calculated for each type of activity, assessed via the baseline recent physical activity (undertaken in the 10 years prior to VITAL recruitment), and age-specific physical activity (number of days per week participating in 20 minutes or more of exercise or sport at age 18, 30, 45 years) [29].

Definitions of change variables

See Table 2.3 for a summary of the variable definitions for body-mass index and physical activity, as well as changes in body-mass index and physical activity. These definitions are also summarized below.

BMI change variables. Using the BMI values and absolute weights (kg) at ages 18, 30, 45 years, and at baseline I calculated absolute change and percent (%) change from pre-baseline (18, 30, 45 years) to baseline BMI. This yielded three different continuous change variables for AIM 1: Age 18 to baseline, Age 30 to baseline, and Age 45 to baseline. These variables were used in models to estimate pancreatic cancer incidence in relation to weight change. Characteristics like consistent “losers”, “gainers”, or “maintainers” of weight and body size over adulthood were also examined for associations with pancreatic cancer risk. All change models used “maintenance” as the referent.

Physical activity (PA) change variables. Using the PA assessment in the baseline questionnaire I ranked participants according to their frequency of PA days for each age of the pre-baseline recall, 18, 30 and 45 respectively. Using these ranks, I can then categorized individuals, for efficiency, into two groups using a simple dichotomization at the median in to “High” and “Low”, resulting in four, now comparable, age windows. With these new categories I then compared each of the age-specific (18, 30, 45) categories ranks, resulting in 4 “individual types”: study participants that were: high and remained high; low and became high; high and became low; or low and remained low, for each age comparison. This yielded three windows of adulthood: age 18 compared to age 30, age 30 comprised to age 45, and age 18 compared to age 45. Using these change classifications, I determined if a type of physical activity change is associated with risk of pancreatic cancer incidence. All change models used “maintenance” as the referent.

Study covariate definitions

This dissertation uses the Directed Acyclic Graphs (DAGs) to identify covariates to be used in a confounder adjustment set. The process involves the enumeration of all the routes (paths) that exist between the nodes of exposure and outcome, and by adjustment (blocking) duplicate paths we aim for the minimum sufficient adjustment set for accounting for any bias due to these covariates. A more thorough discussion of the exact process can be found elsewhere[30, 31]. Producing the most unbiased estimate of the direct effect of the exposure and outcome is the goal, but eliminating all confounding may not be possible. Furthermore, even upon determining a confounder adjustment set, reflective of the literature, distributions of a covariate in the data may not warrant adjustment. It is at that time where a sensitivity analysis of the included covariates effect on change in estimate may further reduce the variables selected for modeling to identify a more parsimonious model, limiting included covariates, to save statistical power.

For my dissertation, select covariates including age, education, race, cigarette smoking, diet (total energy intake, dietary vitamin D, alcohol, fruits and vegetables), health and medical history (diabetes, pancreatitis, family history of pancreatic cancer, NSAID use), were considered as potential confounders using a DAG (see Figures 2.1 and 2.2), and information from a thorough review of the literature review. The DAGs shown in this chapter were then used to create an initial framework describing the association between these covariates and the primary exposures (obesity and physical activity) and the primary outcome (pancreatic cancer).

The final DAG identified confounder adjustment set for aim 1 (obesity and pancreatic cancer risk) included age, sex, total energy intake, race, tobacco smoking, education, physical activity, fruit and vegetable intake. While for aim 2 (physical activity and pancreatic cancer risk), the confounding adjustment set included age, sex, race, education, and tobacco smoking. These variables were defined as follows. Age, a known risk factor for

pancreatic cancer, was modeled continuously. Education (as a marker of socioeconomic status) is potential risk factor, and DAG-identified confounder, was modeled as a three-level categorical variable (high school, some college, college graduate). Cigarette smoking, a known risk factor of pancreatic cancer, was modeled in two levels (never, former/current). It is biologically plausible that BMI and physical activity levels may interact to influence pancreatic cancer risk. However, given the low number of pancreatic cancer events in the parent study, power is insufficient to statistically evaluate this possibility.

Statistical Analysis

All the proposed analyses will be conducted using SAS institute statistical computer software packages (Cary, NC). Data analyses will begin by inspecting the distributions of continuous variables through means, standard deviations (SD), visual assessments with graphs, and error checking for out of range, implausible, and missing values; variables that are skewed will be presented using medians and interquartile ranges. Categorical variables will be examined using frequency tables, accounting for missing or undefined values present in the data. Given the exact relationship between these exposures and the risk of pancreatic cancer in not well characterized, tests for non-linearity will be conducted in continuous models. All data queries and subsequent data changes were catalogued. After these quality control and data cleaning tasks were completed, the analytic datasets were frozen for each manuscript from this dissertation to ensure that all analyses used the same data. Missingness in the data was evaluated for key covariates and potential confounders and effect modifiers to avoid information biases. Analyses were two-sided and statistical significance was set *a priori* at $p \leq 0.05$. Variables included in the proposed analyses were discussed above.

Aims Addressed in the Statistical Analyses

For **Aim 1a.** obesity at baseline, and age-specific obesity, using BMI, calculated as weight (kg.) divided by height (m^2). **Aim 1b.** absolute and relative adult weight change, calculated as current weight (kg) minus weight at age 18 (lbs.) ((Δlbs.-absolute) and the difference between current weight (lbs.) and weight at age 18 (lbs.) divided by weight at age 18 (lbs.) (Δ%-relative). **Aim 1c.,** examined patterning of weight change experienced over the life course using the absolute and relative change measures discussed previously. The last sub-aim component of the first primary aim, **Aim 1d.** used the relative change calculation described in Aim 1b. and constructed variables for windows of weight change through adulthood to examine timing of weight change age 18 to 30, 30 to 45, 18 to 45.

The second aim of this study examined the effect of physical activity on the incidence of pancreatic cancer. **Aim 2a.** used recent physical activity in the 10 years prior to recruitment, and age-specific physical activity, using MET-hours per week. **Aim 2b.** used relative reports by questionnaire as to whether subjects activity levels were higher or lower than the guidelines of activity currently recommended. **Aim 2c.** examined if patterning of change in physical activity impacted the incidence of pancreatic cancer using the age windows of physical activity captured in the questionnaire. These sub-aims are presented further in Table 2.3 below.

Specific Statistical Methods

To address the aims listed above, I estimated hazard ratios (HRs) and their 95% confidence intervals (95%CIs) using multivariable Cox proportional hazard models[32]. These models were used to examine whether recent, age-specific physical activity and weight, and exposure changes are associated with pancreatic cancer incidence. In these models, I used the following categorizations of the exposures. Physical activity (MET-hours per week) and weight change were ranked and categorized into quantiles. Obesity measured as BMI

(kg/m^2) were categorized as “normal” (18.5-25 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2) as this reflects the World Health Organization categorizations [15, 33]. Results of my analyses are described Chapters 3 (Aim 1: obesity) and 4 (Aim 2: physical activity). However, the analysis for examining changes in obesity Aims 1b -1d) yielded inconsistent and unstable results due to small cell counts, and were therefore not included in Chapter 3 but are appended (see Appendix Tables A.1-A.7).

Power

The primary aims of this ancillary study were to measure the associations of obesity and adult weight change and physical activity and adult change in physical activity on the incidence of pancreatic cancer. Power calculations were based on an expected 215 pancreatic cancer deaths, which is less than the actual 280 events observed in the VITAL cohort, in Western Washington State. Assumptions were made in order to estimate study power and they included: 1) 40,250 women and 37,250 men in the study cohort; 2) distributions of body mass index and reported physical activity in the study population (baseline characteristics presented in Table 2.1); 3) deaths rates by age and sex at 60% of the U.S. vital statistics rates for whites; the 60% is an adjustment for the a healthy volunteer effect [34]; 4) a conservative 2% per year loss of participants who move out of the study area [35]; 5) two-sided *p*-value ≤ 0.05. The study will estimate associations discussed in the specific aims using data from a previously constructed cohort. Thus, the study power was computed based on a fixed sample size. The power calculations below use an alpha level of 0.05 to minimize the probability of type I error. All power calculations were conducted using an open source power and sample size calculation package in R, PowerSurvEpi.[36]

For pancreatic cancer incidence-BMI/weight change associations from baseline, my dissertation had 80% power to observe a 47% increased risk (HR=1.47) associated with above-median weight gain when comparing dichotomized weight gain among individuals.

For physical activity and pancreatic cancer associations, my dissertation had 80% power to detect (HR=0.68). ,

For my dissertation, I estimated the effect size at which we have >80% power to detect a statistical significant hazards ratio (HR) to demonstrate the utility of this ancillary study. Effect measures and 95% confidence intervals will be used to quantify associations and estimate precision. Figure 2.3 presents a continuous estimation of power over a range of plausible hazard ratios. Due to limitations in the number of events, there was little power for stratified estimates. It is biologically plausible that BMI and physical activity levels will interact to influence pancreatic cancer risk. However, given the low number of outcome events in the VITAL study, there was insufficient to statistically evaluate this possibility.

Data Interpretation: Study Advantages and Limitations

The results of my dissertation may help understand the effect of obesity and physical activity on the risk of pancreatic cancer. However, as in all observational research, some consideration should be given to interpreting my results in light of potential biases associated with the chosen study population and proposed study methodology.

Data Interpretation: Study Population

The VITAL cohort study population arose from 13 county areas in western Washington State currently covered by the Seattle-Puget Sound SEER cancer registry. The region is predominantly White and as a result the cohort reflects this distribution (93.1% White/Non-Hispanic). The racial and geographic homogeneity of the study population may be of concern when considering the external validity of my results. Little is known about the underlying biological mechanisms of obesity and physical activity on cancer and, similarly, little is known about the etiology of pancreatic cancer. Thus, we cannot exclude the possibility that a genetic susceptibility may exist, which may differ by racial and ethnic groups. Conversely, due to the homogeneous study population, there is little heterogeneity, which increases study power, and the resulting internal validity can be considered high.

VITAL participants were recruited using a commercial mailing database. Review of the existing literature published on VITAL, including the study methods and design paper[19], as well as the preliminary documentation received from the VITAL PI: Emily White, FHCRC do not include specific information regarding the "commercial database" used for cohort recruitment. Given that identification of individuals from a commercial data base favors individuals with a stable residential address, we can infer that the geographic study population favors individuals who are more likely to be white, middle income with a high school education, parous, former smokers, not heavy drinkers, and overweight[37]. The VITAL cohort was recruited using a commercial mailing list, it is unclear the degree to which this recruitment strategy has impacted the prevalence of select characteristics of the study population. There are attributes associated with socioeconomic status, income for example, that are also associated with being on a commercial mailing list: department store catalogs, magazines, retailers would ideally market to individuals with higher income, and who maintain stable addresses. The SEER catchment area and VITAL area in Western Washington state already includes individuals with with higher income and education. Any additional excesses due to the selection process used for VITAL was difficult to ascertain.

Data Interpretation: Exposure Measurement

In the parent VITAL study, participants completed a comprehensive dietary and lifestyle (including body size and physical activity) questionnaire via self-report. Because all exposures in the proposed study are self-reported, all are subject to error in recall. However, height and weight have been shown to be reported fairly accurately (as discussed in more detail below). In contrast, reporting physical activity, especially in early adulthood, is likely to be recalled with less accuracy. Any resulting measurement error is more likely to be non-differential, given the respondents were unaware of their outcome status at baseline.

Alternative, more objective measures, such activity monitors and anthropometric measures collected by trained research staff would have improved the measurements of

exposure understudy. However, a study powered to examine pancreatic cancer incidence prospectively using these exposure measures is resource prohibitive fiscally and economically.

Overall, the data from a recent systematic review reported trends of under-reporting for weight and BMI and over-reporting for height, although the degree of the trend varies for men and women and the characteristics of the population being examined [19]. This should be acknowledged as a limitation; however, likely estimates will be systematically biased toward the null. Studies of self-reported weight often observe underreporting of weight, and given that the exposure, weight, is an acknowledged risk factor of pancreatic cancer it could attenuate results. However, due to prospective cohort design, there is little reason to suggest individuals would differentially recall their weights with any respect to outcome. Furthermore, while their recall may be underreported, when calculating changes, unless there is variability in the degree of their underreporting is occurring, the change value should still reflect a reasonable reflection of their weight change.

My dissertation is one of the first studies to examine these changes in body weight, and the first to consider changes in physical activity. Although the physical activity measurement provides challenges in the use to two different items, a 10-year recent activity assessment at baseline, and age-specific activity (at ages 18, 30, 45 years), I chose to align measures to (current) guidelines for activity resulting in a meaningful discussion on the association of physical activity on pancreatic cancer risk.

Data Interpretation: Outcome Measurement

Pancreatic cancer is a tumor with poor prognosis and a high fatality rate. The SEER registry were linked VITAL cohort to assess new pancreatic cancer diagnoses and death. A potential limitation is the outmigration of participants from the study area, in this circumstance, there is no guarantee cancer deaths would be captured by the study. VITAL

study staff attempted to mitigate the loss of any participants by using change of address records, and by periodically linking the cohort to the US National Death Index file.[38]

Data Interpretation: Power

The statistical power of this study is an issue worth consideration when interpreting the results of this study. While initial estimates suggest this study is powered to observe measureable effect estimates for the study aims, the number of outcome events expected during follow-up was small. Acknowledging this reality, case-control studies have attempted to look at these associations previously with little success and consistency among studies. Therefore implementing a prospective cohort, a superior study design for estimating risk associated with these lifestyle exposures, is necessary. The power to detect the range of effect estimates identified reflect those estimates previously observed in the pancreatic cancer literature for both adverse exposures of obesity, and potential positive effects of physical activity on pancreatic cancer risk, and potentially stronger effects.[39-41]

Data Interpretation: Statistical Analyses

The objectives for aims 1 and 2 were to estimate the association of recent, age-specific, and changes in adult weight and physical activity, respectively, with risk of incident pancreatic cancer. Both primary aims used data from the FHCRC VITAL cohort study baseline study questionnaire exposure assessment and SEER linkages through 2011 for ascertainment of incident pancreatic cancers. The baseline questionnaire asked about a participants tallest height, body weight at age 18, age 30, age 45, and baseline, as well as a validated 10-year recent recreational physical activity assessment, and relative activity measured in days of activity per week, at age 18, age 30, and age 45.

A potential limitation is the high correlation between body weight and physical activity. The study design, and secondary nature of these aims with respect to the primary aims of the parent study limit the emphasis of “adult change” characteristics of these two exposures in the questionnaire. A more consistent exposure measure of physical activity at

earlier ages would allow for comparisons with the “recent” validated 10-year assessment. Additionally, pancreatic cancer is just one of many outcomes followed for and additional covariates that were not adequately captured in the questionnaire (diabetes, medications) would help produce more valid estimates of these associations with pancreatic cancer.

The inclusion of adjustment of baseline characteristics in regression models is commonly thought to improve efficiency and reduce bias when examining the effects of changes in health outcomes. However, in certain circumstances (1- imperfect measurement reliability or 2- changes have already occurred prior to baseline, prior rates of change predict future rates of change, or the exposure is unaffected by baseline) the actual result maybe an increase in the bias to the estimates exceeding any reductions from efficiency. This predicament warrants a careful consideration as to the inclusion of baseline characteristics into any final models, and will be explored empirically using methods previously introduced by Glymour and colleagues[42]. Thus, for the primary analysis I did not include the baseline variable in the models.

Data Interpretation: Sensitivity Analyses

In order to understand potential sources of bias and error in the conduct of these analyses, several sensitivity analyses were explored, as described below.

First, in the obesity analyses, I removed VITAL participants that lost weight throughout the study, there were a small number of these participants, but I did not want to rule out the possibility of some alternative morbidity process or undiagnosed disease. Their removal did not affect the estimates (see Appendix Table A.1) using the original study cohort created quartiles for weight changes or when new quartiles reflecting only participants that gained weight (see Appendix Table A.2) and therefore were no excluded in the presented results.

Second, for both the obesity and physical activity analyses, I considered other potential confounders which were not identified in the final DAG, including Vitamin D.

Addition of these variables did not substantially change estimates; the results for weight change presented age 18 to 45, are presented as a representative example (see Appendix Table A.3).

Third, as a sensitivity analysis for the physical activity analyses, I considered the inclusion of potential causal mediators (obesity and history of diabetes). For example, I included baseline BMI in the analyses of recent physical activity (in the ten years prior to recruitment). I also considered, age-specific BMI for the relative physical activity assessment of exercise sport at age 18, age 30, and age 45 years. But these considerations did not substantially change results (see Appendix Table A.4). Similarly, when I included history of diabetes in the physical activity-pancreatic cancer risk models, the effect estimates were not substantially altered (see Appendix Table A.5, as an example).

Fourth, in the obesity and physical activity analyses, I also considered pack-years of tobacco smoking, to examine whether the magnitude of potential confounding associated with tobacco smoking was attenuated from dichotomization (ever/never). Results for these analyses are presented for 10-year physical activity analyses; no changes were observed (see Appendix Table A.6).

Fifth, in the physical activity analyses, I considered the exposure categorized as tertiles and as quartiles. Both yielded similar results, although the tertiles appeared to be more stable, because of the larger cells counts. The results based on categorizing physical activity levels in tertiles are shown in Chapter 4 of my dissertation, and the results based quartiles are shown are appended (see Appendix Tables A.7).

Conclusions

This dissertation examined whether adult age-specific weight and physical activity, or changes in adult weight or physical activity levels, are associated with the risk of developing pancreatic cancer. These dissertation aims were addressed using existing data from the VITAL cohort, which included multiple assessments of weight and physical activity levels

across adulthood. Standard epidemiologic methods were used to optimize identification of potential high-risk windows of exposure. Few existing studies have examined the risk of pancreatic cancer and associations to these exposures in this manner. The large prospective homogenous cohort design and validated physical activity exposure assessment provided valid results. Additionally, the study of changes in these exposures, allowed for an additional perspective on obesity and physical activity and the results from the proposed dissertation may aid in identifying specific ages during adulthood in which risk reduction strategies focused on weight maintenance and/or increased physical activity levels that could be developed for pancreatic cancer control, a lethal cancer whose mortality is expected to grow in the coming decade[43].

Table 2.1 VITAL Participation

Disposition of questionnaires and response rates in the VITamins And Lifestyle cohort study, Washington State, 2000–2002

	Full mailing list		Returned questionnaires		Response rate (%)
	No.	%	No.	%	
Total	**364,418**	**100**	**79,300**	**100**	**21.8***
Ineligible					
Undeliverable questionnaire	6,900†	1.9			
Deceased	7,300†	2.0			
Duplicate questionnaire	4,700†	1.3	73	0.1	
Age ineligible	4,000†	1.1	844	1.1	
Out of area at baseline	2,600†	0.7	402	0.5	
Transsexual			3	0.0	
Failed quality control checks					
Questionnaire completed by unintended individual			163	0.2	
Excess missing data‡			77	0.1	
Eligible and passed quality control	**338,918†**	**93.0**	**77,738**	**98.0**	**22.9§**

* Percentage of questionnaires returned.

† Estimate based on counts within subsamples or external estimates.

‡ Failed two of three quality control checks.

§ Estimated response rate among eligible individuals.

Excerpted from White et al. 2004 AJE[19]

Table 2.2 VITAL Baseline Characteristics

Selected baseline characteristics of the VITAL cohort		
Characteristic	Group	%
Sex	Male	48.1
	Female	51.9
Age (years)	50 - 59	45.7
	60 - 69	34.7
	>= 70	19.6
Race	Non-Hispanic White	93.1
	Other	6.9
Education	<= High School	20.2
	Some College	38.3
	College Graduate	41.4
Smoking	Never	47.5
	Current or Former	52.5
Body Mass Index (kg/m^2)	18.5 -< 25	33.5
	25 -< 30	41.0
	>= 30	24.6
Physical Activity (days/week)	None	19.4
	1 - 2	30.0
	3 - 4	19.6
	5+	31.0
Fruit + Vegetable	< 5 / day	70.0
	>= 5 / day	30.0
NSAID use	None / low	73.5
	> low	26.5
Screening	No	42.9
	Yes	57.1
	N =	77445

Excerpted from White et al. 2004 AJE[19]

Table 2.3 Variable Construction Summary

Methods	AIM 1: Obesity	AIM 2: Physical Acvitiy
Exposure Assessment in VITAL	Baseline Questionnaire Height Weight at Age 18 Age 30 Age 45 Enrollment (baseline)	Baseline Questionnaire Validated recent 10-year Physical Activity Assessment 5 activities assessed for intensity, frequency, and duration: walking, lifting weights, yoga, mild (bowling/slow dancing/golf), moderate (running, aerobics, folk dancing, swimming, cycling or sports) Recalled relative Physical Activity Assessment PA at Age 18 Age 30 (in days per week) Age 45
Baseline Variable Contruction	Calculate BMI =Weight(kg)/height (m)2	Calculate METs =Intensity X frequency (days per week) X duration (minutes per day) 3 = mild 7 = moderate 9 = intense
Defining Changes	Using BMI and/or Kg weight at Age 18 Age 30 Age 45 Enrollment (baseline) Calculate absolute change and % change from pre-baseline (18, 30, 45 ys) to baseline BMI. Yields 3 different continuous change variables: 18 --> baseline 30 --> baseline 45 --> baseline --> be used in models to predict PanCan incidence in relation to weight change.	Rank participants on PA days for each pre-baseline age Create three age-specific dichotomous quantiles using ranks: High (>median week) vs. low (<median week) Above Guideline (>4) vs. Below (<=4) days per week Three pre-baseline variables: 18 years (high vs. low); 30 years (high vs. low); 45 years (high vs. low) Compare pre-baseline ranks (age 18, 30, 45) Create a 4-level change variable: high to high; low to high; high to low; low to low yields three (18 to 30, 30 to 45, 18 to 45) 4-level change variables --> used to predict PanCan incidence in relation to high vs. low number of days of week engaged in PA
Statistical Models	Baseline BMI and weight 3 continuous change variables: 18 to baseline, 30 to baseline, 45 to baseline	Baseline PA in METs, Relative PA in days/week 3 continuous change variables: 18 to 30, 30 to 45, 18 to 45
Confounders DAG determined	Age, Sex, Race, Energy, Education	Age, Sex, Race, Education
EMM		Explore interaction between baseline BMI & baseline PA

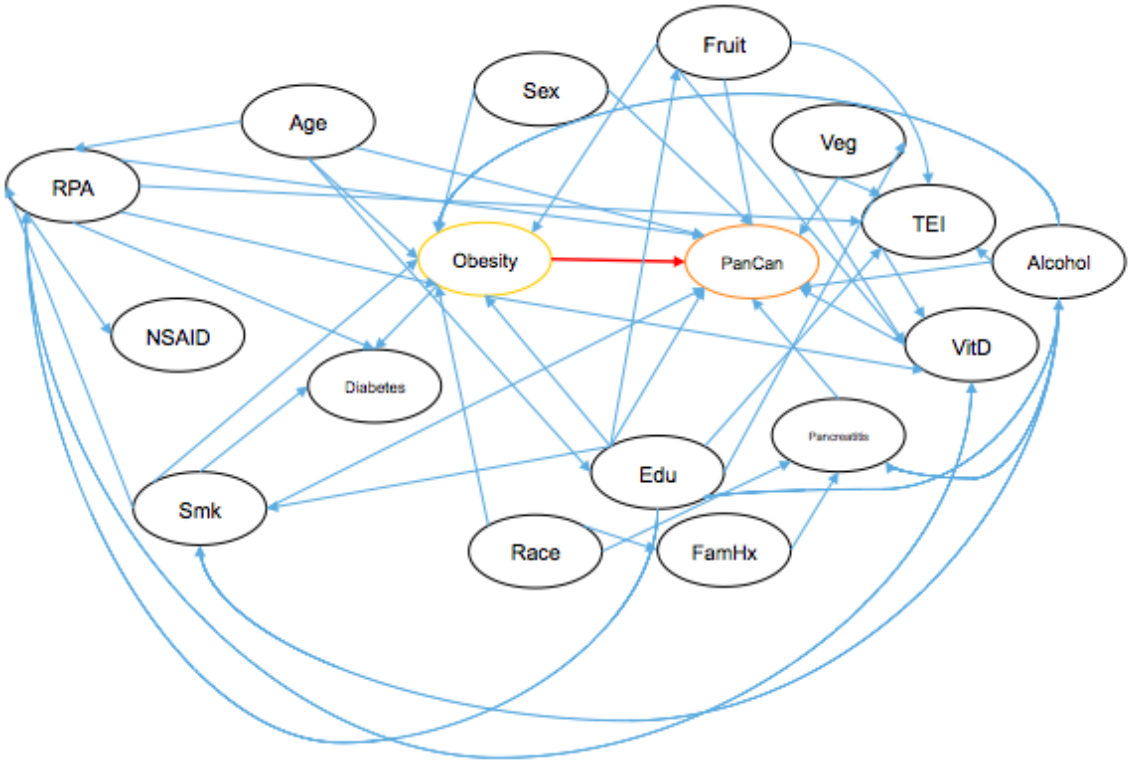

Figure 2.1 Directed Acyclic Graph (DAG) Obesity - Pancreatic Cancer

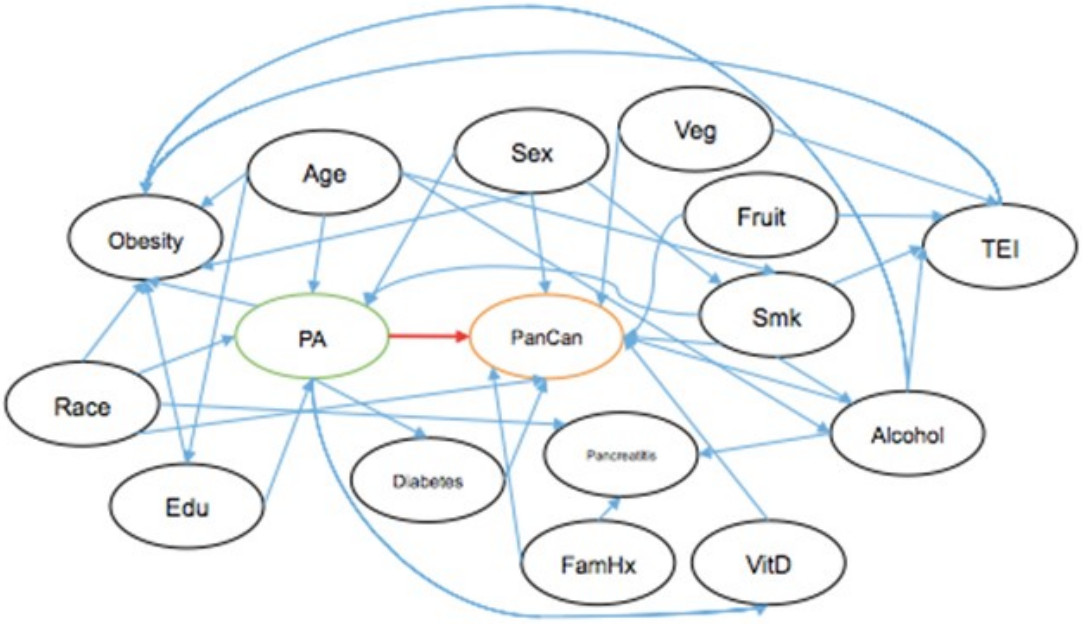

Figure 2.2 Directed Acyclic Graph (DAG) Physical Activity - Pancreatic Cancer

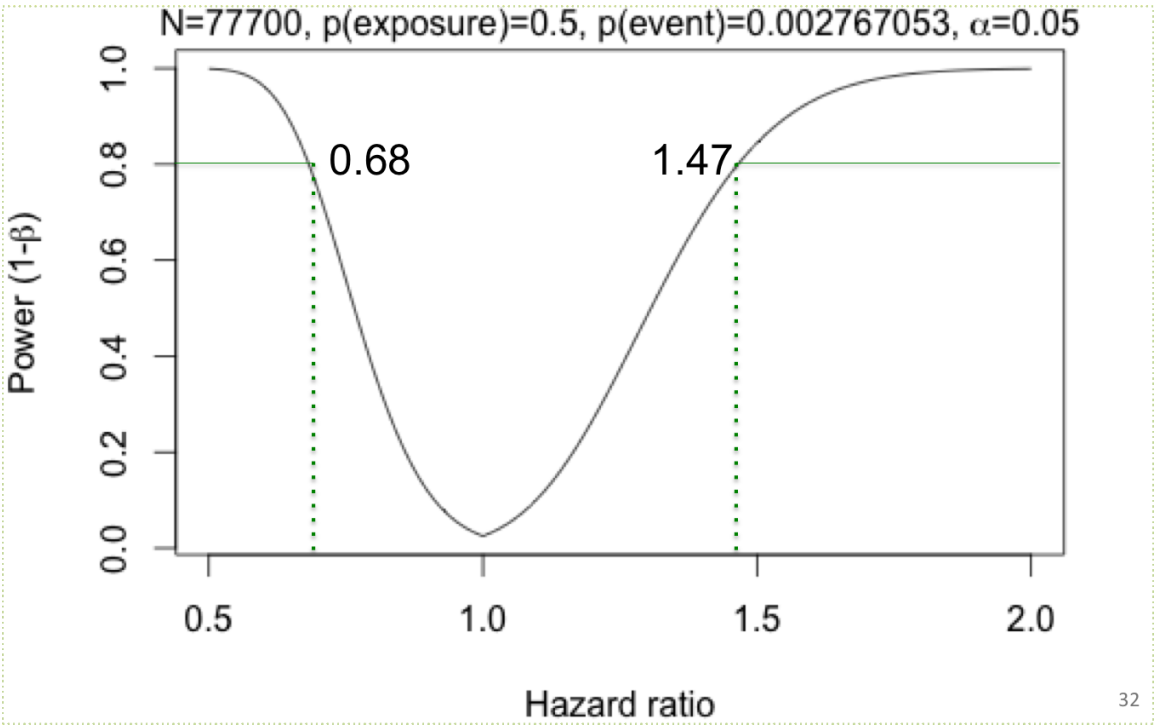

Figure 2.3 Study Power: Cox Proportional Hazards Model

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CHAPTER 3: AGE-SPECIFIC ADULT OBESITY, AND WEIGHT CHANGES IN ASSOCIATION WITH INCIDENT PANCREATIC CANCER IN THE VITAL COHORT

Introduction

Pancreatic cancer will be the twelfth leading cancer diagnosis, and fourth leading cause of cancer-related mortality among men and women in the United States in 2017, with approximately 49,000 deaths estimated[1]. Pancreatic cancer is projected to be the second leading cause of cancer-related mortality by 2030[2]. A pancreatic tumor diagnosis can be highly fatal, the relative one-year survival rate (all stages) is approximately 20%, and the five-year survival rate 7%[1]. Known risk factors for pancreatic cancer include age, sex, and family history. Potentially modifiable risk factors are few, and include tobacco use and obesity. In a previous meta-analysis, obesity, defined as a body mass index > 30.0 kg/m^2, was reported to be associated with an increase in pancreatic cancer incidence by as much as 47%[3], but whether changes in weight across the life course are also associated with elevated risk is understudied[4]. Examination of life course weight/weight changes may help to identify etiologically relevant windows of exposure, and highlight ages at which risk reduction strategies may be most useful.

Weight gain throughout adulthood is common[5], with an average weight gain of 0.5 to 1 kg per year, which may lead to obesity over time[6]. Visceral fat, a component of adult weight gain, is a metabolically active tissue increasing the concentration of circulating endogenous hormones and inflammatory markers[7], creating an environment that promotes carcinogenesis[8]. The pancreas is primarily responsible for secretion of insulin[9] a hormone responsible for the maintenance of blood glucose levels and controlling the proportion of

energy stored as fat during metabolism. Obesity increases the risk of type II diabetes, which in turn is also a risk factor for pancreatic cancer[10].

In the study reported here, we examined whether weight at specific ages during adulthood, or adult weight gain, are associated with increased risk of pancreatic cancer, in a large cohort study of men and women conducted in western Washington state.

Methods

This study uses resources from the National Cancer Institute-funded Vitamin and Lifestyle (VITAL) study cohort. Details regarding the parent study design, including characteristics of the study population, have been published previously[11]. The institutional review boards of the University of North Carolina at Chapel Hill and Fred Hutchinson Cancer Research Center approved this study.

Study Population

The VITAL study cohort includes men and women living in the 13-county region covered by the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry from October 2000 to December 2002. The baseline questionnaire was mailed to 364,418 Washington residents identified through purchased mail business lists. Of these, 77,719 respondents age 50-76 years at baseline who completed and returned the questionnaire met the age- and residency eligibility requirements for enrollment. Participants with complete information on height (at age 18) and weight at baseline were included in the study reported here (N=76,311). Participants provided informed consent before parent study participation.

Outcome Assessment

Follow up via linkage to the Seattle-Puget Sound SEER registry, and the National Death Index (NDI), began at baseline in 2002 and was most recently updated for incident cancers in 2011. Incident cancers for this study were selected using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), codes C250-C269, C25.0-

C25.3, or C25.7-C25.9, reflecting definition codes for pancreatic adenocarcinoma and neuroendocrine tumors. Endocrine pancreatic cancers (C25.4) were excluded, because they may have an alternative etiology[12]. The SEER registry captures cancers from multiple sources, including: all area hospitals; offices of oncologists, pathologists, and radiotherapists; and review of state death certificates. Linkage was accomplished using a ranking of agreement between individual identifiers found in SEER/NDI and VITAL records; including social security number and date of birth. Higher ranked matches using this algorithm were made automatically and study staff visually inspected matches of lower concordance. After ~10 years of follow-up for the 76,311 VITAL study participants in the study reported here, 265 incident pancreatic cancer events were ascertained.

Exposure Assessment

Exposure assessments for this ancillary study are derived from the 24-page gender-specific baseline questionnaire participants completed at enrollment. All responses were processed from the optically scanned questionnaire section on health history and risk factors, diet, and supplement use, from which we derived the primary exposure variables of weight, height, and weight gain, as well as potential confounders (see list below under statistical analysis). Thus, both men and women self-reported height at age 18 years, as well weight at age 18, 30 and 45 years, and current weight (at baseline). Body mass index (BMI) was calculated as weight (kg)/height (m^2). Main exposures for this ancillary study are: BMI calculated at age 18 years, age 30 years, age 45 years, and at baseline enrollment into the cohort; and absolute and relative changes in weight (in pounds) and BMI throughout adulthood (e.g., ages 18 to 30 years, ages 30 to 45 years, age 45 to baseline, and age 18 to baseline). We considered these body size measures in the continuous form, and categorized (using the WHO cut-points for BMI (<18.5 kg/m^2, 18.5 to 25.0 (ref), 25.0 to 30.0, 30+))[13].

Statistical Analyses

Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95%CIs) for the associations between pancreatic cancer risk and age-specific BMI, BMI at baseline, and weight change, with participant age used as the timescale. The proportional hazards assumption was evaluated: using graphical inspections for crossing of the log-log survival curves; and by including a covariate-by-time multiplicative interaction term in each model, and testing parameters for significant p-values (*a priori* alpha=0.05). No violations were detected.

To assess potential confounders of the BMI/weight change-pancreatic cancer relationships, we created a series of directed acyclic graph (DAG)[14], and confounders were selected from a minimum sufficient adjustment set. Results of two models are presented: adjustment for age only; and the fully adjusted model, which additionally adjusted for race (non-white/white), total energy intake (calories per day, continuous), sex (female/male), education attainment (high school or less/some college or more), alcohol (grams per day, in tertiles), recreational physical activity (MET(metabolic equivalent)-hours/week, in tertiles), tobacco smoking (ever/never), fruit and vegetable intake (above median/below median, servings per day). As a sensitivity analysis, we also considered other factors (non-steroidal anti-inflammatory drug use, dietary vitamin D intake, pack-years of cigarette smoking, and history of diabetes) as potential confounders, but were found not to change the effect estimate by >10%[15], and thus were not included in the final models.

All analyses presented were performed using SAS statistical computing software, version 9.4, (SAS Institute, Inc. Cary, North Carolina). All p-values are two-sided, and alpha-level 0.05 was the *a priori* set level for significance.

Results

The distributions of baseline study characteristics of the VITAL respondents, stratified by BMI, are presented in Table 3.1. The study sample includes more female (52%) participants than male (48%), and the average age was 71 years of age. The cohort includes a high percentage of participants who have attended some college (38%), and even larger group who have completed college or other advanced degree (42%). Almost half (47%) of the cohort reported never smoking cigarettes, and a substantial portion of the remaining participants who had smoked had quit more than 10 years prior to enrollment. The majority of the VITAL cohort self-identified as White, Non-Hispanic (93%). At the time of study recruitment, the majority of respondents were either overweight (40%) or obese (25%).

As shown in Table 3.2, BMI at enrollment was associated with an increased risk of pancreatic cancer at all ages. When examining BMI coded continuously, age-adjusted models and multivariable models yielded similar estimates. After adjusting for confounders, the estimated hazard ratios for the association between age-specific BMI (measured continuously, reflecting a 1-BMI unit increase) and pancreatic cancer risk, were slightly elevated (HR=1.05 (95%CI=1.01, 1.09), HR=1.06 (95%CI=1.02, 1.10), HR=1.05 (95%CI=1.02, 1.08), and HR=1.01 (95%CI=0.99, 1.04), for ages 18, 30, 45 years, and baseline, respectively). As also shown in Table 2, increasing the scale to a 5-BMI unit increase resulted in more pronounced effect estimates. When BMI was coded using the World Health Organization (WHO) standardized cut points, a consistent dose-response pattern was observed for each specific age assessed. In multivariable models, overweight (BMI>25 kg/m^2) and obesity (BMI>30 kg/m^2) during early adulthood (age 30 years) was associated with 51% to 82% increased hazard (HR=1.51 (95%CI=1.10, 2.08) and HR=1.82 (95%CI=1.00, 3.31), respectively), when compared to ideal weight (BMI=18.5-25.0 kg/m^2). Similar results were observed at middle adulthood (age 45 years): the hazard ratio was 1.09

(95%CI=0.80, 1.47) for overweight, and 1.80 (95%CI=1.20, 2.71) for obesity. Although the former effect estimate was not statistically significant; the latter was the highest statistically significant relative hazard estimated among the four age periods.

As shown in Table 3.3, continuous weight change, or BMI change, was not significantly associated with an increased rate of pancreatic cancer. When categorized into quartiles, a dose-response pattern was evident, with an increased HR for increases in weight or BMI at almost every adult weight change window. The strongest multivariable-adjusted hazards ratio, with a non-significant increase of 32%, was observed with weight change for adults between the ages of 18 and 45 years (HR=1.32 (95%CI=0.89, 1.96) when comparing the highest quartile to the lowest). Our results did not vary substantially when we removed from the referent category the few individuals who reported weight loss.

Discussion

In a large cohort study conducted among residents of western Washington state, we found the risk of developing pancreatic cancer was significantly higher among the obese, ranging from 30% to 80% for age-specific BMI at early (age 30 years) and middle (age 45 years) adulthood. When we considered changes in adult weight, we observed a non-significant 32% increase in pancreatic risk for weight gain between ages 18 and 45 years. Identification of these patterns may help to guide development of age-specific risk reduction strategies for pancreatic cancer.

Obesity is an established risk factor for pancreatic cancer with relative risks ranging 20%-40% for the association[16], and the magnitude of our finding reported here for baseline BMI is consistent with this range. Also, our findings on age-specific BMI and weight gain confirm previously reported cohort study results by Stolzenberg-Solomon and colleagues[4]. The exact mechanisms underlying the associations between age-specific adult weight/adult weight gain and risk of pancreatic cancer are not well understood[17]. In general, obesity and excess adipose may influence carcinogenesis through proliferation of adipocytes, the

constituent cells of adipose, which can produce estrogen[18], disrupt insulin sensitivity[19], stimulate or prohibit cell growth, affecting tumor aggressiveness[20], create systemic inflammation[21], and disrupt immune response. These processes are dynamic, and thus the timing of these exposures during adulthood may be critical to assessing their impact on cancer risk[22], which may help to refine development of risk reduction strategies.

To examine the complex relationship between obesity and pancreatic cancer incidence there were several challenges. First, we utilized the large VITAL cohort study, which includes 77,000 participants followed for ~10 years, which yielded 280 events identified through the SEER/NDI linkage with 707,384.8 person-years of follow-up. Nonetheless, our study power was limited. Second, it is possible there is error in the measurement of the study outcome, due to outmigration of some cohort members. However, using the NDI would result in identifying deaths due to this highly fatal cancer even if participants had left the western Washington state area. Third, whether to consider a history of diabetes as a confounder or a causal intermediate when examining the association between obesity and pancreatic cancer is not clear. It seems likely that diabetes is on the causal pathway[23], and thus inclusion of this potential causal intermediates in a statistical model would bias the resulting effects estimates[15]. However, our estimates for the obesity-pancreatic cancer association were not substantially changed when we included diabetes in the model as a sensitivity analysis. Fourth, because obesity is not a static exposure, examination of BMI at a single time period (e.g., at the time of recruitment) may mask important considerations regarding the timing of the exposure. The VITAL cohort study retrospectively assessed weight at multiple ages, which allowed examination of associations between age-specific obesity and pancreatic cancer, in addition to the baseline period. Further, we could also examine the association between changes in obesity status among these time points, to facilitate consideration of windows of susceptibility. However, the age windows used in our primary analysis are not of equal duration; instead the number of years

within each window is different, which means that the length of time between “exposure” and the outcome between subjects may vary considerably (just as it does when we consider baseline exposures only). However, identification of specific high-risk ages of weight and weight gain may help to refine public health messages and lend insight into risk reduction strategies.

Conclusions

In a large cohort study, we report that adult obesity at ages 30 and 45 years, and adult weight gain before age 45 years, are associated with ~30-80% increase in pancreatic cancer risk. Our results suggest that prevention of early adult and mid-adult weight gain could be explored as a possible risk reduction strategy for this lethal cancer.

Table 3.1 Selected Baseline Characteristics by Body Mass Index, VITAL Cohort 2000-2011

Characteristic	Total		Body Mass Index (kg/m2) Cat 0: (15.5-<18.5 kg/m2)	%	Cat 1: (18.5-<25.0 kg/m2)	%	Cat 2: 25.0-<30.0 kg/m2)	%	Cat 3: (30.0+ kg/m2)	%
N=	73611		N = 676		N = 24671		N = 30169		N = 18095	
Participants										
Female	37511	51.0	533	78.9	14880	20.9	12555	41.6	9543	52.7
Male	36100	49.0	143	21.2	9791	39.7	17614	58.4	8552	47.3
Events										
Female	124	46.8	3	75.0	41	55.4	49	40.2	31	47.7
Male	141	53.2	1	25.0	33	44.6	73	59.8	34	52.3
Age, mean sd, years										
Female	61.8	7.5	64.4	7.8	62.0	7.6	62.2	7.4	60.8	7.1
Male	62.0	7.4	63.4	7.8	62.8	7.7	62.0	7.4	61.0	7.0
Education										
High school, or less	14428	19.7	175	26.0	4347	17.7	5864	19.5	4042	22.4
Some College, or more	58917	80.3	497	74.0	20215	82.3	24212	80.5	13993	77.6
Energy Intake, mean sd, kcal/d										
Female	1495.6	552.7	1402.3	552.9	1435.3	511.9	1483.5	541.4	1608.7	607.4
Male	2233.8	800.7	2188.3	777.5	2185.6	757.0	2212.9	773.6	2333.2	851.9
Tobacco Smoking										
Never	34687	47.3	304	45.2	12662	51.5	13611	45.3	8110	45.0
Former, Current	38675	52.7	369	54.8	11924	48.5	16452	54.7	9930	55.0

Characteristic	Total		Body Mass Index (kg/m2) Cat 0: (15.5-<18.5 kg/m2)	%	Cat 1: (18.5-<25.0 kg/m2)	%	Cat 2: 25.0-<30.0 kg/m2)	%	Cat 3: (30.0+ kg/m2)	%
Race										
White	68410	93.3	595	89.2	22835	92.9	28183	93.8	16797	93.3
Non-White	453	0.6	72	10.8	1745	7.1	1876	6.2	1212	6.7
Alcohol, mean sd, g/d	8.2	15.5	6.1199	12.6	8.51	14.5	9.20	16.5	6.38	14.8
Vitamin D, mean sd, mcg	5.58	3.8	4.4386	3.5	5.24	3.6	5.74	3.8	5.85	4.0
Fruit Intake, mean sd, servings/d	1.70	1.4	1.82	1.8	1.90	1.5	1.63	1.4	1.55	1.4
Vegetable Intake, mean sd, servings/d	2.30	1.4	2.36	1.8	2.37	1.4	2.24	1.4	2.32	1.4
Non-Steroidal Anti-inflammatory Drugs (NSAID)										
Yes	19179	26.6	122	18.5	5457	22.6	8131	27.6	5469	30.7
No	52932	73.4	537	81.5	18692	77.4	21381	72.5	12322	69.3
History of Diabetes										
Yes	5002	6.8	24	3.6	704	2.9	1653	5.5	2621	14.5
No	68607	93.2	652	96.5	23967	97.2	28515	94.5	15473	85.5

Table 3.2 Hazard Ratios and 95% Confidence Intervals for the Association between BMI at Baseline, Age 45, Age 30, and Age 18 and the Risk of Pancreatic Cancer, VITAL Cohort 2000-2011

Exposure Coding											
		Age-Adjusted					***Full-Adjustment**				
Continuous	units: Δ 1 BMI (kg/m2)	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
	BMI at Baseline	73610	265	1.02	0.99	1.04	66359	233	1.01	0.99	1.04
	BMI at Age 45	73362	263	1.05	1.02	1.08	66137	231	1.05	1.02	1.08
	BMI at Age 30	72763	260	1.05	1.02	1.09	65682	228	1.06	1.02	1.10
	BMI at Age 18	72598	260	1.04	1.00	1.08	65540	229	1.05	1.01	1.09
	units: Δ 5 BMI (kg/m2)						**N**	**Events**	**HR**	**LCL**	**UCL**
	BMI at Baseline						66359	233	1.07	0.94	1.22
	BMI at Age 45						66137	231	1.27	1.09	1.48
	BMI at Age 30						65682	228	1.32	1.11	1.57
	BMI at Age 18						65540	229	1.27	1.03	1.56
		Age-Adjusted					***Full-Adjustment**				
Categorical	units: BMI (kg/m2)	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
BMI at Baseline	Cat 1: (15.5-<18.5 kg/m2)	676	4	1.93	0.71	5.29	567	2	1.17	0.29	4.78
	Cat 2: (18.5-<25.0 kg/m2)	24671	74	1	(ref)		22143	65	1	(ref)	
	Cat 3: (25.0-<30.0 kg/m2)	30169	122	1.37	1.02	1.83	27285	110	1.32	0.96	1.80
	Cat 4: (30.0+ kg/m2)	18095	65	1.36	0.97	1.90	16364	56	1.19	0.82	1.73
BMI at Age 45	Cat 1: (15.5-<18.5 kg/m2)	879	4	1.35	0.50	3.65	744	3	1.24	0.39	3.90
	Cat 2: (18.5-<25.0 kg/m2)	40032	138	1	(ref)		35972	122	1	(ref)	
	Cat 3: (25.0-<30.0 kg/m2)	24303	86	1.18	0.90	1.55	22039	74	1.09	0.80	1.47
	Cat 4: (30.0+ kg/m2)	8149	35	1.83	1.26	2.67	7382	32	1.80	1.20	2.71
BMI at Age 30	Cat 1: (15.5-<18.5 kg/m2)	2645	13	1.47	0.83	2.58	2293	9	1.18	0.60	2.31
	Cat 2: (18.5-<25.0 kg/m2)	51977	167	1	(ref)		46897	148	1	(ref)	

	Cat 3: (25.0-<30.0 kg/m2)	15062	66	1.54	1.16	2.05	13694	59	1.51	1.10	2.08
	Cat 4: (30.0+ kg/m2)	3080	14	1.97	1.14	3.41	2798	12	1.82	1.00	3.31
BMI at Age 18	Cat 1: (15.5-<18.5 kg/m2)	9924	29	0.80	0.54	1.18	8824	23	0.73	0.47	1.12
	Cat 2: (18.5-<25.0 kg/m2)	54571	195	1	(ref)		49372	173	1	(ref)	
	Cat 3: (25.0-<30.0 kg/m2)	6958	31	1.41	0.96	2.06	6303	28	1.40	0.93	2.09
	Cat 4: (30.0+ kg/m2)	1146	5	1.52	0.62	3.69	1041	5	1.65	0.68	4.03

* Adjustments	Race - White (ref), Non-White	Alcohol - g/d tertiles,T1 (ref)
	Total Energy Intake (TEI) - kcal/d, continuous	Fruit / Veg Intake - Above median (ref), Below median
	Sex - Male (ref), Female	Recreational PA - None (ref), tertiles
	Education - Some College, or more (ref), High School, or less	Smoking - Never (ref), Ever

Table 3.3 Hazard Ratios and 95% Confidence Intervals for the Associations between Absolute Changes in Body Weight and the Risk of Pancreatic Cancer, VITAL Cohort 2000-2011

Absolute Weight Change (Difference)

		Age-Adjusted					*Full-Adjustment				
Continuous	units: ∆1lbs.	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
	Age 18 to Baseline	72024	258	1.00	1.00	1.01	65066	228	1.00	1.00	1.00
	Age 18 to Age 45	72544	261	1.01	1.00	1.01	65478	230	1.01	1.00	1.01
	Age 18 to Age 30	72411	258	1.01	1.00	1.02	65362	227	1.01	1.00	1.02
	units: ∆5lbs.						**N**	**Events**	**HR**	**LCL**	**UCL**
	Age 18 to Baseline						65066	228	0.99	0.98	1.02
	Age 18 to Age 45						65478	230	1.03	0.99	1.06
	Age 18 to Age 30						65362	227	1.04	0.99	1.08
		Age-Adjusted					***Full-Adjustment**				
Quantiles	units: ∆lbs.	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
Age 18 to Baseline	Q1: < 19	17714	66	1	(ref)		15893	58	1	(ref)	
	Q2: 19 =< 35	16509	51	0.84	0.58	1.21	14924	45	0.82	0.55	1.21
	Q3: 35 =< 55	18159	72	1.07	0.77	1.49	16449	65	1.03	0.72	1.47
	Q4: 55 >	19642	69	1.01	0.72	1.42	17800	60	0.88	0.61	1.28
Age 18 to Age 45	Q1: < 10	14352	51	1	(ref)		12775	44	1	(ref)	
	Q2: 10 =< 20	15878	53	0.95	0.64	1.39	14324	46	0.93	0.61	1.41
	Q3: 20 =< 35	22007	74	1.01	0.71	1.44	19928	70	1.06	0.72	1.55
	Q4: 35 >	20307	83	1.48	1.04	2.10	18451	70	1.32	0.89	1.96
Age 18 to Age 30	Q1: < 5	17302	67	1	(ref)		15412	57	1	(ref)	
	Q2: 5 =< 10	12752	32	0.64	0.42	0.97	11494	30	0.70	0.45	1.09
	Q3: 10 =< 20	22735	81	0.96	0.70	1.33	20623	72	0.97	0.68	1.39
	Q4: 20 >	19622	78	1.19	0.86	1.65	17833	68	1.13	0.78	1.63

Absolute BMI Change (Difference)

		Age-Adjusted					*Full-Adjustment				
Continuous	units: ∆1 BMI (kg/m2)	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
	Age 18 to Baseline	71302	254	1.00	0.98	1.03	64471	224	0.99	0.97	1.02
	Age 18 to Age 45	71862	257	1.04	1.00	1.08	64909	226	1.03	1.00	1.07
	Age 18 to Age 30	71748	254	1.06	1.01	1.11	64815	223	1.06	1.00	1.11
	units: ∆5 BMI (kg/m2)						**N**	**Events**	**HR**	**LCL**	**UCL**
	Age 18 to Baseline						64471	224	0.97	0.84	1.12
	Age 18 to Age 45						64909	226	1.18	0.98	1.43
	Age 18 to Age 30						64815	223	1.29	0.99	1.68
		Age-Adjusted					***Full-Adjustment**				
Quantiles	units: ∆BMI (kg/m2)	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
Age 18 to Baseline	Q1: < 2.82	17822	66	1	(ref)		16021	57	1	(ref)	
	Q2: 2.82 =< 5.42	17766	53	0.82	0.57	1.17	16139	48	0.83	0.56	1.22
	Q3: 5.42=< 8.55	17878	70	1.06	0.75	1.48	16172	63	1.04	0.73	1.50
	Q4: 8.55 >	17836	65	1.05	0.75	1.48	16139	56	0.96	0.65	1.40
Age 18 to Age 45	Q1: < 1.61	18392	72	1	(ref)		16459	61	1	(ref)	
	Q2: 1.61 =< 3.29	17520	54	0.81	0.57	1.15	15898	50	0.86	0.59	1.25
	Q3: 3.29 =< 5.37	17989	67	1.02	0.73	1.43	16281	61	1.06	0.74	1.52
	Q4: 5.37 >	17961	64	1.17	0.84	1.65	16271	64	1.10	0.76	1.60
Age 18 to Age 30	Q1: < 0.67	18372	74	1	(ref)		16416	63	1	(ref)	
	Q2: 0.67 =< 1.52	16727	45	0.67	0.46	0.97	15124	38	0.64	0.43	0.97
	Q3: 1.52 =< 2.83	18682	65	0.91	0.65	1.27	16933	62	1.00	0.70	1.42
	Q4: 2.83 >	17967	70	1.12	0.80	1.55	16304	60	1.06	0.74	1.53

* Adjustments	Race - White (ref), Non-White	Alcohol - g/d Tertiles T1 (ref)
	Total Energy Intake (TEI) - kcal/d, continuous	Fruit / Veg Intake - Above median (ref), Below median
	Sex - Male (ref), Female	Recreational PA - None (ref), Tertiles
	Education - Some College, or more (ref), High School, or less	Smoking - Never (ref), Ever

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CHAPTER 4: ASSOCIATION OF AGE-SPECIFIC ADULT PHYSICAL ACTIVITY WITH INCIDENT PANCREATIC CANCER IN THE VITAL COHORT

Introduction

To reduce the risk of many cancers, the American Cancer Society (ACS) recommends adults get 150 minutes of moderate intensity, or 75 minutes of vigorous intensity, physical activity per week, spreading that out through most days of the week[1]. The Centers for Disease Control recently reported that some ~21% of adults in the United States (US) meet federal recommendations[2]. It remains unclear overall whether physical activity is inversely associated with pancreatic cancer, moreover, there is not clear evidence available regarding the optimal timing, frequency, or intensity of activity needed to reduce pancreatic risk[3]. In the US, pancreatic cancer is the twelfth most commonly diagnosed cancer and is the fourth leading cause of cancer-related mortality[4]. By 2030, pancreatic cancer is anticipated to be the second leading cause of cancer-related mortality in the US[5].

Physical activity is a key component of energy balance, and thus, physical activity may impact carcinogenesis through its direct relationship to weight and energy balance[6]. Other pathways by which physical activity may reduce the risk of pancreatic cancer include its ability to improve hormone profiles, reduce inflammation, and stimulate the immune system[7].

The goal of the study reported here was to determine whether adult physical activity undertaken in the ten years prior to study enrollment, or the number of days engaged in activity at specific ages, is associated with a reduced risk of pancreatic cancer. We addressed this aim in a large cohort study of middle age and older adults in Western Washington state, who were followed for ~10 years. Identification of specific ages by which

physical activity impacts pancreatic cancer is likely to improve public health messaging.

Methods

This ancillary study uses resources and materials from the National Cancer Institute-funded Vitamins and Lifestyle (VITAL) study cohort. Details regarding the parent study design and methods, including characteristics of the study population, have been published previously[8]. The institutional review boards of the University of North Carolina at Chapel Hill, the Fred Hutchinson Cancer Research Center, and the University of Washington approved this study.

Study Population

In the early 2000s, men and women living in the 13-county region covered by the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry were recruited for participation in VITAL. The baseline questionnaire was mailed to 364,418 Washington residents identified through purchased commercial mail lists. Of these, 77,719 respondents age 50-76 years at baseline who completed and returned the questionnaire met the age- and residency eligibility requirements for enrollment. Study participants provided informed consent before joining the parent study. Only participants (N=76,369) with physical activity information are included in this study.

Outcome Assessment

Follow up via linkage to the Seattle-Puget Sound SEER registry and the National Death Index (NDI) began at baseline and was most recently updated for incident cancers in 2011. Using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), codes C250-C269, C25.0-C25.3, or C25.7-C25.9, reflecting definition codes for pancreatic adenocarcinoma and neuroendocrine tumors, incident tumors for this study were identified. Endocrine pancreatic cancers (C25.4) may have an alternative etiology and therefore have not been included in these analyses[9]. All area hospitals; including, offices of oncologists, pathologists, and radiotherapists; and review of state death certificates were

monitored by SEER staff to facilitate outcome identification. SEER/NDI and VITAL records linkage was accomplished using a ranking of agreement between individual identifiers, including social security number and date of birth. Higher ranked matches using this algorithm were made automatically and study staff visually inspected matches of lower concordance. After ~10 years of follow-up, among the 76,369 VITAL study participants included in the study reported here, 276 first primary pancreatic cancer events were ascertained.

Exposure Assessment

Exposure assessment of physical activity and other potential risk factors for pancreatic cancer are derived from the 24-page gender-specific baseline questionnaire, which was completed by participants in the VITAL cohort at enrollment. All physical activity responses were processed from the optically scanned questionnaire section on health history and risk factors, diet, and supplement use.

Men and women self-completed a validated physical activity instrument[10] and were asked to recall physical activity undertaken in the ten years prior to study recruitment, which we label as 10-year recent physical activity. In the questionnaire, physical activities were categorized as “mild” exercise (walking, lifting weights, yoga) or other “mild” activities (golf, dancing, bowling), or “moderate or strenuous” exercise (running, aerobics, cycling, swimming, or sports). For this study, we also combined all self-reported activities, and categorized as “ALL” physical activity. Responses were converted to metabolic equivalents of tasks (METs) using the method of Ainsworth and colleagues[11]. MET-hours per week (MET-hrs/week) were tertiled, and each tertile was compared to no reported activity; other categories (e.g., quartiles) of physical activity were considered, but results were similar to those shown.

As part of the baseline questionnaire, participants were additionally asked to report the number of days per week they participated in exercise or sports for at least 20 minutes,

at specific ages, including ages 18, 30, and 45 years. Survey responses were recorded in pre-coded categories (no activity, 1 day per week, 2-3 days per week, 4-5 days per week, and 6-7 days per week). To approximate the ACS guidelines[1], we defined most days of the week as 4+ days per week, grouping individuals with responses of 4-5 and 6-7 days, with those reporting no activity as the referent.

Statistical Analyses

We used multivariable-adjusted Cox proportional hazards models, with calendar age as the time scale, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between pancreatic cancer risk and 10-year recent physical activity (MET-hrs/week) at baseline, as well as age-specific physical activity (number of days per week with at least 20 minutes of exercise or sport). The proportional hazards assumption was evaluated using graphical inspections of crossing log-log survival functions, and empirically by including an interaction term for time in the model[12, 13]. No violations were detected.

We used a directed acyclic graph (DAG)[14] to select minimally sufficient sets of confounders. Results of two models are presented: adjustment for age only; and the fully adjusted model [which additionally adjusted for race (non-white/white), sex (female/male), education attainment (high school or less/some college or more), alcohol intake (grams per day, in tertiles), and tobacco smoking (ever/never)]. In a sensitivity analysis, other factors were also considered as potential confounders (non-steroidal anti-inflammatory drug use, tobacco cigarette smoking pack-years, dietary vitamin D intake, BMI, and history of diabetes). We also considered a possible interaction between baseline BMI and physical activity, on a multiplicative scale, by comparing interaction terms from nested models using the log-likelihood test[15]. All analyses presented were performed using SAS statistical computing software, version 9.4, (SAS Institute, Inc. Cary, North Carolina). All p-values included in tables and figures are two-sided, and alpha-level 0.05 was the *a priori* set level for significance.

Results

Baseline characteristics of VITAL participants for these analyses are presented in Table 4.1. The distribution of demographic information, covariates, and potential confounders are shown by level of recent physical activity in the 10 years prior to study recruitment. The cohort included slightly more female participants (51.9%) than males (48.1%), but those in the highest category of physical activity were more likely to be male. Participants reporting higher physical activity levels also reported higher education levels and greater alcohol intake. Ever smokers were more likely to report no physical activity. The relationship between physical activity and energy intake was U-shaped: higher physical activity levels were reported by those reporting high or low energy intakes.

In general, as presented in Table 4.2, physical activity levels (MET-hrs/week) in the 10 years prior to recruitment were inversely associated with the risk of pancreatic cancer after 10-years of follow-up. In the fully-adjusted models (age, race, sex, education, alcohol intake, and tobacco smoking), compared to no physical activity, the hazard for pancreatic cancer risk was non-significantly reduced by 14% percent for the first tertile of activity (HR=0.86 (95%CI=0.60, 1.21)), and significantly reduced by 39% in the second tertile (HR=0.61 (95%CI=0.42, 0.89)) and by 30% in the highest tertile (HR=0.70 (95%CI=0.49, 1.00)). Diabetes and other covariates (non-steroidal anti-inflammatory drug use, tobacco cigarette smoking pack-years, dietary vitamin D intake, and BMI) were also considered as potential confounders, but these factors did not change the effect estimate by >10% (data not shown). We also considered associations stratified by age (<60 vs. 60+), and although cells sizes were limited, results (data not shown) did not differ substantially from those presented. There was no apparent interaction between baseline physical activity and BMI ($p_{interaction}$=0.32), but again, this analysis was exploratory as cell sizes were small.

When we considered intensity of recent physical activity in the 10 years prior to recruitment (MET-hrs/week, tertiled), effect estimates for all three tertiles were below the null

value for moderate, but not intense, activity (Table 4.2). Specifically, for moderate recent physical activity (vs. no activity), we observed: a non-significant 18% reduction in the hazards for the first tertile (HR=0.82 (95%CI=0.54, 1.25); a significant reduction of 49% for the second tertile (HR=0.51 (95%CI=0.32, 0.82)); and a 14% non-significant reduction for the highest tertile of activity (HR=0.86 (95%CI=0.58, 1.30)). For high intensity recent activity (vs. no activity), hazards were non-significantly decreased by 22% and 28% for the first (HR=0.78 (95%CI=0.45, 1.33)) and second tertile (HR=0.72 (95%CI=0.42, 1.23), respectively, but non-significantly increased for the third tertile (HR=1.11 (95%CI=0.69, 1.79).

As shown in Table 4.3, we observed non-significant decreases in the risk of pancreatic cancer in association with increasing days per week of at least 20 minutes of physical activity at ages 30 and 45 years, but not at age 18 years. For example, when we grouped activity undertaken to most (4+) days/week (vs. none), pancreatic cancer risk was reduced for activity at age 45 years by 29% (HR=0.71 (95%CI=0.49, 1.01), and for age 30 years by 16% (HR=0.84 (95%CI=0.57, 1.23)), but the confidence intervals for both estimates included the null value. The hazard for age 18 was not reduced (HR=1.12 (95%CI=0.80, 1.56)).

Discussion

In a large cohort of middle to older adults with an average of 10 years of follow up, we found that increased physical activity levels (MET-hrs/week) in the ten years prior to recruitment was associated with a significant 30-40% reduction in pancreatic cancer risk. We also observed that engaging in at least 20 minutes of physical activity most days per week at ages 30 and 45 years, is associated with about a 15-30% reduction in the risk of pancreatic cancer, although the findings were not statistically significant. For physical activity intensity, inverse associations were consistent for moderate (but not intense) activity levels in the 10 years prior to recruitment, but confidence intervals included the null value. Our

findings, if confirmed, suggest that physical activity undertaken at mid-life or older adults may be a possible risk reduction strategy for pancreatic cancer.

In previous cohort studies, physical activity has been inconsistently associated with reductions in the risk of pancreatic cancer: two independent cohort studies of Dutch and Japanese populations reported modest reductions in risk[16,17], whereas two other cohort studies among Americans failed to observe an association[18,19] A recent meta-analysis on the relationship between recreational physical activity and pancreatic cancer, which included both cohort and case-control studies, did not find an association[20]. As suggested in a recent case-cohort study focused on total physical activity, the timing of the exposure may make a difference[21]. Their hypothesis, that mid-life activity may be more strongly related to risk reduction for pancreatic cancer risk, is consistent with our findings.

As with obesity, there are several mechanisms by which physical activity may play a role in the development of pancreatic cancer. Physical activity lowers the levels of hormones like insulin (secreted by the pancreas) and additional growth factors that hasten tumor development[22]. Inflammation can exacerbate carcinogenesis[23, 24], but physical activity has a beneficial impact on levels of inflammation throughout the body [25, 26]. Additionally, physical activity has been linked to improved immune system response, cell adaptation, and signaling[27]. Pancreatic cancer is additionally an obesity related cancer[28], and physical activity has been successfully linked to several other obesity related tumors including breast[29], colon[30], and endometrial cancers[31]

When examining the relationship between physical activity and pancreatic cancer incidence, there are several potential limitations to consider. First, despite the large number of participants in the parent cohort study, we did not have sufficient number of endpoints to adequately examine patterns of associations. Second, it is possible that there is some measurement error in the study outcome associated with outmigration of study participants. However, this potential bias was mitigated by linking with the NDI. Third, another issue to

consider is whether obesity and/or a history of diabetes are potential confounders or causal intermediates when examining the association between physical activity and pancreatic cancer. It seems likely that physical inactivity precedes both obesity and diabetes, and thus obesity and diabetes should be considered on the causal pathway[32], and thus inclusion of these potential mediators in a statistical model would bias the resulting effects estimates[15]. Yet, in sensitivity analyses, effect estimates for physical activity were not substantially altered when we added BMI or a history of diabetes to our models. Fourth, also of concern are the non-significant elevations in pancreatic cancer risk we noted for the third tertile of intense physical activity undertaken in the 10 years prior to recruitment, which is in contrast to the significant reduced risk observed for the second tertile of moderate activity. The VITAL cohort employed a validated instrument to assess recent physical activity, thus it is possible our observation of an increased risk for the highest level of intense activity is a spurious finding due to small numbers. However, some animal studies show deleterious health effects for intense activity, but beneficial effects for moderate activity[33]. Fifth, another possible limitation of our study is that we did not consider occupational physical activity, which could potentially affect pancreatic cancer[20]. In a study conducted in Switzerland, occupational activity accounted for 36% of all activity among men, but only 2% among women[34]. Thus, to reduce possible misclassification of exposure, future studies among men should also consider occupational physical activity in addition to recreational activity. Sixth, another consideration is the importance of pinpointing the critical exposure time window for physical activity, which may impact public health messaging for risk reduction strategies for pancreatic cancer. Because the age of VITAL participants ranged from 50 to 76 years at recruitment, recent activity in the 10 years prior to recruitment reflects exercise that occurred anywhere from 40 to 76 years of age. Therefore, based on our results, it appears that in our cohort of middle age to older adults, the greatest risk reductions were associated with activity undertaken during mid-life or older. We cannot rule out the possibility that

participants are able to recall recent physical activity levels with more accuracy, than activities from the distant past, although stratifying our results by age (<60 vs 60+) did not reveal any apparent heterogeneity. Thus, additional research is needed where physical activity is assessed among younger individuals, and then the cohort is followed up for cancer development at older ages to determine whether earlier physical activity levels are also associated with pancreatic cancer risk.

Current ACS guidelines recommend 150 minutes of moderate, or 75 minutes of vigorous, aerobic activity per week, spread throughout most days of the week[2]. However, a recent federal report indicates that some 27% of middle-aged Americans are inactive[35]. In our study, we observed a modest non-significant ~15-30% relative reduction in the risk of pancreatic cancer among participants, who at ages 30 to 45 years engaged in at least 20 minutes per day of physical activity of any intensity for four or more days per week (vs. no activity), which is roughly equivalent to (or perhaps below the level) recommended by the ACS. To improve public health messaging, future research should focus on confirming our findings regarding the age, duration, intensity and frequency of activity needed to reduce the risk of pancreatic cancer.

Conclusions

In a cohort of men and women in Western Washington state, recent adult physical activity among middle to older adults was associated with about a 30-40% reduction in subsequent pancreatic cancer risk. Our results, if replicated, suggest that promotion of physical activity during mid-life to older adulthood could be explored as a possible risk reduction strategy for this lethal cancer.

Table 4.1 Selected Baseline Characteristics by Level of Recreational Physical Activity, VITAL Cohort 2000-2011

			Recent (10-year) Recreational Physical Activity (MET-hrs/day)							
Characteristic	**Total**	**%**	**T0: (0 MET-hrs/day)**	**%**	**T1: (0 - 4.229 MET-hrs/day)**	**%**	**T2: (4.229 - 13.125 MET-hrs/day)**	**%**	**T3: (> 13.125 MET-hrs/day)**	**%**
			N=11477		N=21425		N=21346		N=22121	
Participants	76369	--								
Female	39665	51.9	5976	52.1	13103	61.2	11379	53.3	9207	41.6
Male	36704	48.1	5501	47.9	8322	38.8	9967	46.7	12914	58.4
Pancreatic Cancer	276	0.4								
Female	133	0.2	25	48.1	46	55.4	26	41.3	36	46.2
Male	143	0.2	27	51.9	37	44.6	37	58.7	42	53.9
Age, mean, sd, (years)	61.3	7.6	61.9	7.5	61.8	7.4	62.0	7.5	62.1	7.5
Education										
High school, or Less	15121	20.1	3420	30.4	4865	23.1	3886	18.5	2950	13.5
Some College, or More	28751	79.9	7819	69.6	16189	76.9	17094	81.5	18871	86.5
Total Energy Intake, mean, sd, (kcal/d)	1855.1	774.0	1906.4	819.1	1760.3	745.4	1832.3	751.3	1942.7	787.1
Female	1494.6	553.7	1522.8	591.7	1481.7	554.5	1492.7	536.1	1495.0	546.6
Male	2231.8	791.7	2305.8	832.1	2185.5	800.3	2207.3	776.2	2251.0	779.4
Tobacco Smoking										
Never Smoker	36066	47.6	4993	43.9	10436	49.1	10182	48.1	10455	47.6
Former/Current Smoker	39703	52.4	6378	56.1	10818	50.9	11001	51.9	11506	52.4
Race										
White	69959	93.2	10514	93.5	19532	92.7	19520	93.1	20393	93.6
Non-White	5116	6.8	730	6.5	1542	7.3	1447	6.9	1397	6.4
Alcohol, mean, sd, (g/d)	8.17	15.5	7.78	17.5	6.50	13.8	8.00	14.6	10.13	16.3
Dietary Vitamin D, mean sd, (mcg)	5.58	3.8	5.54	3.9	5.32	3.7	5.54	3.7	5.87	3.9
NSAID use										
Yes	19825	26.5	2692	24.0	5329	25.3	5506	26.4	6298	29.1

Characteristic		Total	%	Recent (10-year) Recreational Physical Activity (MET-hrs/day) T0: (0 MET-hrs/day)	%	T1: (0 - 4.229 MET-hrs/day)	%	T2: (4.229 - 13.125 MET-hrs/day)	%	T3: (> 13.125 MET-hrs/day)	%
	No	54965	73.5	8522	76.0	15720	74.7	15386	73.7	15337	70.9
History of Diabetes											
	Yes	5304	7.0	1064	9.3	1844	8.6	1371	6.4	1025	4.6
	No	71064	93.1	10413	90.7	19581	91.4	19975	93.6	21095	95.4

Table 4.2 Recent (10-Year) Recreational Physical Activity and Pancreatic Cancer, VITAL Cohort 2000-2011 (Inactives, Tertiles)

Exposure Coding											
		Age-Adjusted					*Full-Adjustment				
Continuous		**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
	units: Δ 1 MET-hrs/wk										
All		76368	276	1.00	0.99	1.01	74605	270	1.00	0.99	1.01
High	(> 6.0 MET Activities)	76368	120	1.01	0.98	1.02	30306	119	0.98	0.94	1.02
Moderate	(3.0 - 6.0 MET Activities)	76368	171	1.00	0.99	1.02	47073	167	1.00	0.99	1.02
	units: Δ 5 MET-hrs/wk										
All							74605	270	0.98	0.94	1.03
High	(> 6.0 MET Activities)						30306	119	0.99	0.91	1.10
Moderate	(3.0 - 6.0 MET Activities)						47073	167	1.01	0.94	1.08
Categorical											
	units: MET-hrs/wk										
All	No Activity	11476	52	1.00	(ref)		11158	52	1.00	(ref)	
Intensity	T1: >0 -<4.229 MET-hrs	21425	83	0.84	0.59	1.18	20916	82	0.86	0.60	1.21
	T2: 4.229-<13.125 MET-hrs	21346	63	0.62	0.43	0.89	20852	61	0.61	0.42	0.89
	T3: > 13.125 MET-hrs	22121	78	0.72	0.51	1.03	21679	75	0.70	0.49	1.00
High	No Activity	11476	52	1.00	(ref)		11158	52	1.00	(ref)	
Intensity	T1: >0 -<3.281 MET-hrs	6321	20	0.76	0.46	1.28	6190	19	0.78	0.45	1.33
	T2: 3.281 -<9.527 MET-hrs	6563	19	0.68	0.40	1.15	6435	19	0.72	0.42	1.23
	T3: > 9.527 MET-hrs	6621	29	1.07	0.68	1.68	6523	29	1.11	0.69	1.79
Moderate	No Activity	11476	52	1.00	(ref)		11158	52	1.00	(ref)	
Intensity	T1: >0 -<3.5 MET-hrs	11948	41	0.77	0.51	1.16	11691	41	0.82	0.54	1.25
	T2: 3.5 -<11.010 MET-hrs	12241	30	0.54	0.35	0.85	11982	27	0.51	0.32	0.82
	T3: > 11.010 MET-hrs	12468	48	0.84	0.57	1.25	12242	47	0.86	0.58	1.30

* Adjustment Set: Age, Sex, Race, Education, Smoking

Table 4.3 Age-Specific Recreational Physical Activity from Exercise and Sports and Pancreatic Cancer, VITAL Cohort 2000-2011

Exposure Coding											
			Age-Adjusted				*Full-Adjustment				
Categorical		N	Events	HR	LCL	UCL	N	Events	HR	LCL	UCL
	units: days >20 min Exercise/Sport										
		71659									
Age 18	None	18608	61	1.00	(ref)		18188	59	1.00	(ref)	
	1	7878	24	0.95	0.60	1.53	7718	24	0.99	0.62	1.59
	2-3	17831	59	1.02	0.71	1.46	17475	59	1.05	0.73	1.51
	4-5	17406	69	1.21	0.86	1.70	17060	67	1.20	0.84	1.72
	6-7	9936	33	0.98	0.64	1.50	9726	32	0.97	0.62	1.51
	≥ 4 days/week	27341	102	1.12	0.82	1.54	26786	99	1.12	0.80	1.56
Age 30		72221									
	None	16599	61	1.00	(ref)		16211	61	1.00	(ref)	
	1	12677	48	1.13	0.78	1.65	12427	46	1.07	0.73	1.58
	2-3	25446	95	1.14	0.83	1.58	24940	92	1.10	0.79	1.57
	4-5	13426	39	0.92	0.61	1.37	13162	39	0.92	0.62	1.39
	6-7	4073	8	0.58	0.28	1.21	3982	8	0.59	0.28	1.23
	≥ 4 days/week	17498	47	0.83	0.57	1.22	17144	47	0.84	0.57	1.23
Age 45		73358									
	None	17756	74	1.00	(ref)		17332	74	1.00	(ref)	
	1	13608	46	0.85	0.59	1.22	13336	44	0.81	0.56	1.18
	2-3	23645	88	0.92	0.68	1.26	23172	85	0.91	0.66	1.24
	4-5	14160	40	0.72	0.49	1.06	13864	39	0.72	0.49	1.07
	6-7	4189	11	0.63	0.34	1.19	4093	11	0.65	0.35	1.23
	≥ 4 days/week	18348	51	0.70	0.49	1.00	17957	50	0.71	0.49	1.01

* Adjustment Set: Age, Sex, Race, Education, Smoking

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CHAPTER 5: DISCUSSION

Dissertation Goals

Pancreatic cancer is a rarely diagnosed tumor; yet currently it is the fourth leading cause of cancer-related mortality in the United States, and is projected to be the second leading cause of cancer related mortality by 2030[1]. Little is understood regarding the etiology of this tumor, particularly with regard to lifestyle factors that could be intentionally modified in an effort to alter disease risk. Therefore, the purpose of this dissertation was to examine two modifiable age-specific exposures, obesity and physical activity, in association with the risk of pancreatic cancer. Additionally, I sought to explore whether changes in these risk factors throughout adulthood were associated with changes in risk. In order to examine these associations, I used resources from a large cohort of 77,445 men and women, who participated in the Vitamins and Lifestyle (VITAL) study beginning in October 2000 to December 2002, and were then followed for an average of 10 years.

This chapter will provide highlights of the findings from my examination of the associations with pancreatic cancer risk and obesity (Chapter 3) and physical activity (Chapter 4). Additionally this section provides a summary of the study strengths and limitations, including methodological concerns, potential sources of bias, and how these may have impacted the results presented, in order to provide direction for future research focused on obesity, physical activity, and pancreatic cancer risk. Finally, this chapter summarize the potential public health impact of these findings provide.

Summary of Results

Obesity and Pancreatic Cancer Risk

My dissertation confirmed findings from previous studies[2], including a recent pooled analysis of cohorts[3], namely that obesity, classified as a body mass index (BMI) ≥30, is associated with an increased risk of pancreatic cancer. My dissertation presents hazard ratios for several specific time points throughout adulthood, including: ages 18, 30, and 45 years; and age at enrollment at baseline (which ranged from 50 to 76 years), which were consistent with findings from one previous cohort study[2]. The multivariable Cox proportional hazards models of BMI (treated continuously) produced modestly elevated (1- to 6-percent) hazards at all of time windows reported (only the confidence interval for BMI measured at baseline contained the null); changing the scaling did not substantially alter these results. When examining the association using BMI categorized using the common WHO classifications, overweight (BMI$\underline{\geq}$25) and obesity at age 30, and obesity at age 45 were associated with 50- to 80- percent increases in pancreatic cancer risk. Changes within windows were less informative, with the overall trends suggestive that increasing weight (or BMI) through out any window was associated with elevated hazards during the follow-up period; however, for all of these change estimates, the confidence intervals included the null.

Physical Activity and Pancreatic Cancer Risk

The beneficial effects of physical activity on cancer have been consistently documented for several tumor sites[4-6]; however, the relationship between physical activity and pancreatic cancer has not been consistently reported in previous studies[7-10]. Two approaches were used in the VITAL cohort study to assess recreational (leisure-time) physical activity: first, “recent” activity, measured in MET-hrs/week, in the 10 years prior to recruitment; and second, age-specific assessments on the frequency, in days per week, individuals participated in “at least 20 min [or more] of exercise or sports” at ages 18, 30,

and 45 years. First, consistent with a pooled analysis of some previous cohort studies[11], but not others[12, 13], I observed, 30 to 40% reductions in the risk of pancreatic cancer for the upper two tertiles, respectively, of "recent" physical activity in the 10 years prior to recruitment. Second, in the innovative age-specific assessments, the hazards ratios were reduced by 16 to 29% for four or more days per week of exercise or sport at ages 30 and 45 years, respectively, although the confidence intervals did include the null; in contrast, there was no consistent reduction for exercise at age 18 years.

Study Strengths/Limitations and Directions for Future Research

Homogeneous Study Population

The VITAL cohort study population represents a population of men and women living in Western Washington state during the early 2000s. Participants were recruited to the parent study in order to examine the association between vitamins, supplements and lifestyle factors and cancer. The 13-county SEER catchment area used for recruitment is fairly homogeneous demographically. The study population is predominantly White (non-Hispanic). The participants are also highly educated, with modest tobacco smoking exposure history, Supplement use is a health seeking behavior and baseline characteristics of study population corroborate that these data represent a fairly healthy, aged-population in the early 2000s. This homogeneity of the study population increases internal study validity, but may result in a lack of external validity. However, there is little evidence to suggest that the pathophysiology and carcinogenic process of obesity related tumors (like pancreatic cancer) may be differ substantially by race – beyond the differential exposure of excess adipose and the dysfunction associated with it. Nonetheless, given the intriguing associations noted in our homogeneous population, future studies should consider examining these exposures, using the windows of susceptibility approach, in more diverse populations.

Selection Bias

The parent VITAL study was conditioned on supplement use, a characteristic that was oversampled and emphasized in the design. Whether this potential selection bias resulted in a study population with a higher proportion of highly educated whites (and hence less likely to be overweight or inactive) than the general population of the Pacific Northwest, is not apparent. However, the implications of this potential selection bias, given this recruitment/enrollment strategy, should be considered when interpreting the results of this dissertation. Again, future studies should consider examining my dissertation aims in more racially and economically diverse study populations.

Study Power

After an average 10 years of follow-up for the 77,445 male and female participants of the VITAL cohort 280 incident tumors were observed after SEER linkages through 2011. The rarity of pancreatic cancer tumors often presents study power challenges, particularly when considering associations among subgroups or changes over time. Preliminary estimates for each of my dissertation aims showed that study power was adequate. However, even with the large VITAL sample, and extended follow-up for events, several analyses suffered from small cell samples that prohibited clear interpretation. Future studies should consider pooling data from several large cohort studies to increase study statistical power.

Exposure Misclassification

The parent study recruited and collected all information on potential exposures via mailed questionnaire. All of the exposures (and covariates) under study are self-reported, therefore are subject to reporting errors, particularly embellishment associated with the desire to appear more socially acceptable. In addition to being self-reported, these exposures reflect recall of historical periods of each participant’s lives. Participants were asked to recall weight and physical activity, and other lifestyle behaviors up to 50 years ago.

Yet recalling changes in exposures over time is often clouded by current exposure levels. One of the strengths of this dissertation is my use of a cohort study design, which can reduce the differential impact of information bias, as all participants are free from cancer at enrollment, therefore any exposure error is expected to be distributed non-differentially across the entire sample, including the very pertinent bias associated with recall. Nonetheless, future studies should consider recruiting participants at younger ages, and to administer repeated assessments over time at standard intervals, to facilitate accurate reporting of current exposure levels, as well as changes in exposures over time.

Outcome Misclassification

The case definition used in this dissertation sought to capture all pancreatic cancers diagnosed among VITAL subjects during the follow up period. The ICD-O-3 classification system is commonly used to classify tumors and was used to identity all pancreatic cancer outcomes[14]. This ICD-O-3 coding system for pancreatic cancer includes tumors with varying morphology/histology, yet all will be classified at a SEER tumor registry using the same general code. Endocrine pancreatic tumors may have a different etiology[15], and the codes reflecting these tumors were excluded; however, these class of tumors can sometimes, though rarely, be classified using alternative codes that may have met the case definition and were thus inadvertently included in the analyses for my dissertation.

Public Health Impact

Pancreatic cancer is often a highly fatal tumor that is often diagnosed at advanced stage due to lack of efficient screening and asymptomatic presentation. In 2017 it is the fourth leading cause of cancer-related mortality in the United States by 2030 it is projected to become the second leading cause[1]. Identifying modifiable risk factors that may reduce the risk of this lethal cancer is priority. Moreover, understanding when throughout adulthood these exposures may play an increased role in contributing to cancer risk helps both better understand the etiology of this disease while enhancing public health messaging to adults.

Pancreatic cancer incidence may be positively associated with weight and weight change during early and middle adulthood, at age 30 years and age 45 years, respectively. If my dissertation findings are confirmed by others, avoidance of weight gain and increasing physical activity levels are two public health messages, which could be potentially targeted to early and middle age adults in an effort to reduce the risk of developing pancreatic cancer risk.

Conclusions

The two primary goals of this dissertation were to examine adult obesity and weight change, and adult physical activity and physical activity change, in association with risk of developing pancreatic cancer. Findings from this dissertation suggest that increased BMI at ages 30 years and 45 years was associated with an increased risk of pancreatic cancer, and that physical activity at age 45 years may confer reductions in risk, particularly for participating in exercise or sports most days of the week. Given the high national prevalence of overweight and obesity among American adults, and increasing sedentarism[16], potential risk reductions in pancreatic cancer may be attainable by encouraging weight maintenance and increasing physical activity in middle-age adults.

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APPENDIX A: SUPPLEMENTAL TABLES FOR CHAPTER 2

Table A.1 Sensitivity Analysis – Removing Losers of Weight 'Full Cohort Quartiles'

	No Weight Loss* (Full Cohort Quartiles)										
			Age-Adj					*Full-Adj			
	N	Events	HR	LCL	UCL	N	Events	HR	LCL	UCL	
Age 18 to Baseline	67754	238	1.003	0.998	1.007	62260	217	1.003	0.998	1.007	
Age 18 to Age 45	67381	245	1.007	1.002	1.013	61828	224	1.008	1.002	1.014	
Age 18 to Age 30	65084	238	1.009	1.001	1.017	59690	217	1.008	1	1.017	
units: lbs.											
Q1: < 19	67754	238	1	(ref)		62260	217	1	(ref)		
Q2: 19 =< 35			0.909	0.61	1.354			0.91	0.597	1.387	
Q3: 35 =< 55			1.16	0.802	1.68			1.182	0.801	1.744	
Q4: 55 >			1.1	0.757	1.599			1.089	0.733	1.616	
Q1: < 10	67381	245	1	(ref)		61828	224	1	(ref)		
Q2: 10 =< 20			0.909	0.593	1.393			0.892	0.566	1.404	
Q3: 20 =< 35			0.971	0.649	1.452			1.03	0.674	1.575	
Q4: 35 >			1.434	0.964	2.135			1.425	0.93	2.182	
Q1: < 5	65084	238	1	(ref)		59690	217	1	(ref)		
Q2: 5 =< 10			0.546	0.348	0.856			0.591	0.368	0.949	
Q3: 10 =< 20			0.827	0.577	1.184			0.894	0.608	1.316	
Q4: 20 >			1.021	0.71	1.469			1.057	0.71	1.575	
	No Weight Loss* (Full Cohort Quartiles)										
			Age-Adj					*Full-Adj			
	N	Events	HR	LCL	UCL	N	Events	HR	LCL	UCL	
Age 18 to Baseline	67073	234	1.01	0.981	1.04	61680	213	1.011	0.981	1.043	
Age 18 to Age 45	66731	241	1.045	1.006	1.086	61268	220	1.048	1.007	1.091	
Age 18 to Age 30	64471	234	1.062	1.005	1.121	59164	213	1.058	0.998	1.122	
units: BMI											
Q1: < 2.824607	67073	234	1	(ref)		61680	213	1	(ref)		
Q2: 2.824607 =< 5.424926			0.888	0.598	1.318			0.888	0.585	1.347	
Q3: 5.424926 =< 8.554346			1.149	0.792	1.666			1.178	0.796	1.742	
Q4: 8.554346 >			1.146	0.785	1.673			1.151	0.77	1.72	
Q1: < 1.614028	66731	241	1	(ref)		61268	220	1	(ref)		
Q2: 1.614028 =< 3.298322			0.764	0.526	1.111			0.796	0.537	1.181	
Q3: 3.298322 =< 5.374583			0.968	0.679	1.381			1.066	0.735	1.545	
Q4: 5.374583 >			1.121	0.781	1.609			1.116	0.758	1.643	
Q1: < 0.678116	64471	234	1	(ref)		59164	213	1	(ref)		
Q2: 0.678116 =< 1.520481			0.573	0.386	0.852			0.6	0.394	0.915	
Q3: 1.520481 =< 2.834199			0.782	0.545	1.123			0.894	0.612	1.307	
Q4: 2.834199 >			0.962	0.673	1.374			0.977	0.664	1.435	

Table A.2 Sensitivity – Removing Losers of Weight 'Non-Loser Cohort Quartiles'

	No Weight Loss* (New Quartiles)									
			Age-Adj					*Full-Adj		
	N	Events	HR	LCL	UCL	N	Events	HR	LCL	UCL
Age 18 to Baseline	67754	238	1.003	0.998	1.007	62260	217	1.003	0.998	1.007
Age 18 to Age 45	67381	245	1.007	1.002	1.013	61828	224	1.008	1.002	1.014
Age 18 to Age 30	65084	238	1.009	1.001	1.017	59690	217	1.008	1	1.017
units: lbs.										
Q1: < 20	67754	238	1	(ref)		62260	217	1	(ref)	
Q2: 20 =< 37			0.852	0.578	1.256			0.894	0.594	1.347
Q3: 37 =< 57			1.243	0.862	1.794			1.297	0.88	1.913
Q4: 57 >			1.138	0.779	1.664			1.138	0.759	1.706
Q1: < 13	67381	245	1	(ref)		61828	224	1	(ref)	
Q2: 13 =< 23			0.922	0.644	1.319			0.963	0.66	1.405
Q3: 23 =< 36			0.938	0.654	1.345			1.039	0.713	1.513
Q4: 36 >			1.423	1.008	2.009			1.407	0.97	2.041
Q1: < 5	65084	238	1	(ref)		59690	217	1	(ref)	
Q2: 5 =< 10			0.546	0.348	0.856			0.561	0.368	0.949
Q3: 10 =< 20			0.827	0.577	1.184			0.894	0.608	1.316
Q4: 20 >			1.021	0.71	1.469			1.057	0.71	1.575

	No Weight Loss* (New Quartiles)									
			Age-Adj					*Full-Adj		
	N	Events	HR	LCL	UCL	N	Events	HR	LCL	UCL
Age 18 to Baseline	67073	234	1.01	0.981	1.04	61680	213	1.011	0.981	1.043
Age 18 to Age 45	66731	241	1.045	1.006	1.086	61268	220	1.048	1.007	1.091
Age 18 to Age 30	64471	234	1.062	1.005	1.121	59164	213	1.058	0.998	1.122
units: BMI										
Q1: < 3.30013	67073	234	1	(ref)		61680	213	1	(ref)	
Q2: 3.30013 =< 5.69405			0.972	0.664	1.422			0.957	0.641	1.428
Q3: 5.69405 =< 8.78664			1.233	0.862	1.765			1.24	0.852	1.804
Q4: 8.78664 >			1.21	0.838	1.746			1.19	0.807	1.756
Q1: < 2.011908	66731	241	1	(ref)		61268	220	1	(ref)	
Q2: 2.011908 =< 3.486761			0.872	0.606	1.255			0.956	0.653	1.401
Q3: 3.486761 =< 5.578817			1.084	0.764	1.537			1.207	0.836	1.743
Q4: 5.578817 >			1.287	0.905	1.83			1.294	0.885	1.891
Q1: < 0.832036	64471	234	1	(ref)		59164	213	1	(ref)	
Q2: 0.832036 =< 1.700520			0.818	0.562	1.191			0.849	0.571	1.261
Q3: 1.700520 =< 3.040962			1.019	0.715	1.453			1.134	0.785	1.638
Q4: 3.040962 >			1.228	0.868	1.736			1.21	0.834	1.755

Table A.3 Sensitivity Analysis – Adjustments for Additional Confounders (Example- Weight Change 18 to 45):

Hazard Ratios and 95% confidence intervals for the associations between absolute changes in body weight and the risk of pancreatic cancer. (Sensitivity: Vit D, Fruit/Veg, Smoking)

Absolute Weight Change (Difference)

Continuous			***Full-Adjustment**			***Full-Adjustment +Veg/Frt**					***Full-Adjustment +Vit D**				
units: Δlbs.	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
Age 18 to Age 45	66498	237	1.01	1.00	1.01	66498	237	1.01	1.00	1.01	66498	237	1.01	1.00	1.01
Quantiles			***Full-Adjustment**			***Full-Adjustment +Veg/Frt**					***Full-Adjustment +Vit D**				
units: Δlbs.	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
Q1: < 10	12975	44	1	(ref)		12975	44	1	(ref)		12975	44	1	(ref)	
Q2: 10 =< 20	14560	47	0.94	0.62	1.42	14560	47	0.94	0.62	1.42	14560	47	0.94	0.63	1.42
Q3: 20 =< 35	20234	71	1.08	0.74	1.58	20234	71	1.08	0.74	1.58	20234	71	1.08	0.74	1.58
Q4: 35 >	18729	75	1.47	1.01	2.16	18729	75	1.47	1.00	2.15	18729	75	1.47	1.01	2.16
						Fruit = Above Median (ref)					Vitamin D = Above Median (ref)				
						Vegetable = Above Median (ref)									
						***Full-Adjustment +Smoking**					***Full-Adjustment +Veg/Frt Smoking Vit D**				
						N	**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
						12975	44	1	(ref)		12975	44	1	(ref)	
						14560	47	0.97	0.64	1.47	14560	47	0.97	0.64	1.47
						20234	71	1.12	0.77	1.64	20234	71	1.12	0.77	1.64
						18729	75	1.48	1.00	2.17	18729	75	1.48	1.00	2.17

* Adjustments	Race - White (ref), Non-White	Smoking = Never (ref), Former, Current	Fruit = Above Median (ref)
	Total Energy Intake (TEI) - Below Median(ref), Above Median kcal		Vegetable = Above Median (ref)
	Sex - Male (ref), Female		Vitamin D = Above Median (ref)
	Education - Some College, or more (ref), High School, or less		Smoking = Never (ref), Former, Current

Table A.4 RECENT 10-Yr Physical Activity-Pancreatic Cancer Sensitivity

FULL Adjustment: Age*, Sex, Race, Energy, Smoking; + BMI baseline

ALL INTENSITY (FULL)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pmeta3	T1: >0 -<4.22917 MET/hr	1	-0.15523	0.17816	0.7591	0.3836	0.856	0.604 1.214	pmeta3 T1: >0 -<4.22917 MET/hr
pmeta3	T2: 4.22917 -<13.125 MET/hr	1	-0.49053	0.18989	6.6734	0.0098	0.612	0.422 0.888	pmeta3 T2: 4.22917 -<13.125 MET/hr
pmeta3	T3: > 13.125 MET/hr	1	-0.35699	0.18319	3.7977	0.0513	0.700	0.489 1.002	pmeta3 T3: > 13.125 MET/hr

ALL INTENSITY (FULL + BMI cont)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pmeta3	T1: >0 -<4.22917 MET/hr	1	-0.12080	0.18437	0.4293	0.5123	0.886	0.617 1.272	pmeta3 T1: >0 -<4.22917 MET/hr
pmeta3	T2: 4.22917 -<13.125 MET/hr	1	-0.45509	0.19725	5.3229	0.0210	0.634	0.431 0.934	pmeta3 T2: 4.22917 -<13.125 MET/hr
pmeta3	T3: > 13.125 MET/hr	1	-0.30937	0.19186	2.6001	0.1069	0.734	0.504 1.069	pmeta3 T3: > 13.125 MET/hr
pbmi_4		1	0.00990	0.01268	0.6096	0.4349	1.010	0.985 1.035	

HIGH INTENSITY (FULL)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pmeth3c	T1: >0 -<3.28125 MET/hr	1	-0.25494	0.27335	0.8699	0.3510	0.775	0.454 1.324	pmeth3c T1: >0 -<3.28125 MET/hr
pmeth3c	T2: 3.28125 -<9.52778 MET/hr	1	-0.33095	0.27503	1.4480	0.2289	0.718	0.419 1.231	pmeth3c T2: 3.28125 -<9.52778 MET/hr
pmeth3c	T3: > 9.52778 MET/hr	1	0.10816	0.24216	0.1995	0.6551	1.114	0.693 1.791	pmeth3c T3: > 9.52778 MET/hr

HIGH INTENSITY (FULL + BMI cont)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pmeth3c	T1: >0 -<3.28125 MET/hr	1	-0.25540	0.28949	0.7784	0.3776	0.775	0.439 1.366	pmeth3c T1: >0 -<3.28125 MET/hr
pmeth3c	T2: 3.28125 -<9.52778 MET/hr	1	-0.26784	0.28766	0.8669	0.3518	0.765	0.435 1.344	pmeth3c T2: 3.28125 -<9.52778 MET/hr
pmeth3c	T3: > 9.52778 MET/hr	1	0.16879	0.25907	0.4245	0.5147	1.184	0.712 1.967	pmeth3c T3: > 9.52778 MET/hr
pbmi_4		1	0.02478	0.01839	1.8154	0.1779	1.025	0.989 1.063	

MODERATE INTENSITY (FULL)

Analysis of Maximum Likelihood Estimates										
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
pmetm3c	T1: >0 -<3.5 MET/hr	1	-0.19477	0.21187	0.8450	0.3580	0.823	0.543	1.247	pmetm3c T1: >0 -<3.5 MET/hr
pmetm3c	T2: 3.5 -<11.0104 MET/hr	1	-0.66493	0.24065	7.6345	0.0057	0.514	0.321	0.824	pmetm3c T2: 3.5 -<11.0104 MET/hr
pmetm3c	T3: > 11.0104 MET/hr	1	-0.14626	0.20654	0.5014	0.4789	0.864	0.576	1.295	pmetm3c T3: > 11.0104 MET/hr

MODERATE INENSITY (FULL + BMI cont)

Analysis of Maximum Likelihood Estimates										
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
pmetm3c	T1: >0 -<3.5 MET/hr	1	-0.21120	0.22235	0.9022	0.3422	0.810	0.524	1.252	pmetm3c T1: >0 -<3.5 MET/hr
pmetm3c	T2: 3.5 -<11.0104 MET/hr	1	-0.57501	0.24630	5.4502	0.0196	0.563	0.347	0.912	pmetm3c T2: 3.5 -<11.0104 MET/hr
pmetm3c	T3: > 11.0104 MET/hr	1	-0.11198	0.21991	0.2593	0.6106	0.894	0.581	1.376	pmetm3c T3: > 11.0104 MET/hr
pbmi_4		1	0.01538	0.01636	0.8840	0.3471	1.015	0.983	1.049	

Table A.5 Exercise Sport Physical Activity-Pancreatic Cancer Sensitivity

FULL Adjustment: Age*, Sex, Race, Energy, Smoking; + BMI age-specific

Age 18 (FULL)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pes18	1	1	-0.01055	0.24293	0.0019	0.9654	0.990	0.615 1.593	pes18 1
pes18	2.5	1	0.04530	0.18649	0.0590	0.8081	1.046	0.726 1.508	pes18 2.5
pes18	4.5	1	0.18364	0.18348	1.0017	0.3169	1.202	0.839 1.722	pes18 4.5
pes18	6.5	1	-0.03162	0.22532	0.0197	0.8884	0.969	0.623 1.507	pes18 6.5

Age 18 (FULL + BMI18 cont)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pes18	1	1	0.07343	0.24690	0.0884	0.7662	1.076	0.663 1.746	pes18 1
pes18	2.5	1	0.00931	0.19664	0.0022	0.9622	1.009	0.687 1.484	pes18 2.5
pes18	4.5	1	0.22290	0.18981	1.3791	0.2403	1.250	0.861 1.813	pes18 4.5
pes18	6.5	1	-0.07410	0.23721	0.0976	0.7548	0.929	0.583 1.478	pes18 6.5
pbmi18_4		1	0.04022	0.02163	3.4575	0.0630	1.041	0.998 1.086	

Age 30 (FULL)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pes30	1	1	0.07165	0.19667	0.1327	0.7156	1.074	0.731 1.580	pes30 1
pes30	2.5	1	0.09568	0.16699	0.3283	0.5667	1.100	0.793 1.527	pes30 2.5
pes30	4.5	1	-0.07905	0.20685	0.1460	0.7023	0.924	0.616 1.386	pes30 4.5
pes30	6.5	1	-0.53533	0.37672	2.0193	0.1553	0.585	0.280 1.225	pes30 6.5

Age 30 (FULL + BMI30 cont)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pes30	1	1	0.08643	0.20497	0.1778	0.6733	1.090	0.730 1.629	pes30 1
pes30	2.5	1	0.11177	0.17461	0.4098	0.5221	1.118	0.794 1.575	pes30 2.5
pes30	4.5	1	-0.00161	0.21133	0.0001	0.9939	0.998	0.660 1.511	pes30 4.5
pes30	6.5	1	-0.43899	0.37929	1.3396	0.2471	0.645	0.307 1.356	pes30 6.5
pbmi30_4		1	0.05621	0.01749	10.3241	0.0013	1.058	1.022 1.095	

Age 45 (FULL)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pes45	1	1	-0.21299	0.19114	1.2417	0.2651	0.808	0.556 1.175	pes45 1
pes45	2.5	1	-0.09810	0.16012	0.3754	0.5401	0.907	0.662 1.241	pes45 2.5
pes45	4.5	1	-0.32340	0.19919	2.6359	0.1045	0.724	0.490 1.069	pes45 4.5
pes45	6.5	1	-0.42971	0.32372	1.7620	0.1844	0.651	0.345 1.227	pes45 6.5

Age 45 (FULL + BMI45 cont)

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pes45	1	1	-0.19031	0.19705	0.9327	0.3342	0.827	0.562 1.216	pes45 1
pes45	2.5	1	-0.08491	0.16688	0.2589	0.6109	0.919	0.662 1.274	pes45 2.5
pes45	4.5	1	-0.21896	0.20301	1.1633	0.2808	0.803	0.540 1.196	pes45 4.5
pes45	6.5	1	-0.30209	0.32652	0.8560	0.3549	0.739	0.390 1.402	pes45 6.5
pbmi45_4		1	0.04202	0.01499	7.8518	0.0051	1.043	1.013 1.074	

Table A.6 Sensitivity Analysis – Pack-Years of Tobacco Smoke (Recent-10-Yr RPA)

ALL (full adjustment + pack-years (continuous))

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pmeta3	T1: >0 -<4.22917 MET/hr	1	-0.09391	0.17969	0.2731	0.6013	0.910	0.640 1.295	pmeta3 T1: >0 -<4.22917 MET/hr
pmeta3	T2: 4.22917 -<13.125 MET/hr	1	-0.40867	0.19184	4.5381	0.0331	0.665	0.456 0.968	pmeta3 T2: 4.22917 -<13.125 MET/hr
pmeta3	T3: > 13.125 MET/hr	1	-0.26424	0.18555	2.0280	0.1544	0.768	0.534 1.105	pmeta3 T3: > 13.125 MET/hr

HIGH (full adjustment + pack-years (continuous))

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pmeth3c	T1: >0 -<3.28125 MET/hr	1	-0.13475	0.27665	0.2373	0.6262	0.874	0.508 1.503	pmeth3c T1: >0 -<3.28125 MET/hr
pmeth3c	T2: 3.28125 -<9.52778 MET/hr	1	-0.18479	0.27966	0.4366	0.5088	0.831	0.481 1.438	pmeth3c T2: 3.28125 -<9.52778 MET/hr
pmeth3c	T3: > 9.52778 MET/hr	1	0.26644	0.24787	1.1555	0.2824	1.305	0.803 2.122	pmeth3c T3: > 9.52778 MET/hr

MODERATE (full adjustment + pack-years (continuous))

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
pmetm3c	T1: >0 -<3.5 MET/hr	1	-0.09920	0.21433	0.2142	0.6435	0.906	0.595 1.378	pmetm3c T1: >0 -<3.5 MET/hr
pmetm3c	T2: 3.5 -<11.0104 MET/hr	1	-0.55508	0.24358	5.1932	0.0227	0.574	0.356 0.925	pmetm3c T2: 3.5 -<11.0104 MET/hr
pmetm3c	T3: > 11.0104 MET/hr	1	-0.02012	0.21071	0.0091	0.9239	0.980	0.648 1.481	pmetm3c T3: > 11.0104 MET/hr

Table A.7 Quartiles vs Tertiles of Recent 10-Year RPA at Baseline

Exposure Coding		Age-Adjusted					*Full-Adjustment			
Continuous		**Events**	**HR**	**LCL**	**UCL**	**N**	**Events**	**HR**	**LCL**	**UCL**
	units: MET Hrs/wk									
All		276	1.00	0.99	1.01	74605	270	1.00	0.99	1.01
High		276	1.01	0.99	1.02	74605	270	1.01	0.99	1.03
Mod		276	1.00	0.99	1.02	74605	270	1.00	0.99	1.02
Categorical										
All	None	52	1.00	(ref)		11158	52	1.00	(ref)	
	Q1: >0 -<3.025 MET/hr	58	0.78	0.53	1.13	15834	57	0.79	0.54	1.15
	Q2: 2.275 -<6.25 MET/hr	55	0.71	0.49	1.04	15788	55	0.74	0.51	1.08
	Q3: 8.05 -<17.7916667 MET/hr	49	0.63	0.42	0.92	15924	47	0.61	0.41	0.91
	Q4: > 17.7916667 MET/hr	62	0.78	0.54	1.13	15901	59	0.75	0.51	1.09
High	None	208	1.00	(ref)		55457	203	1.00	(ref)	
	Q1: >0 -<2.275 MET/hr	15	0.99	0.59	1.68	4738	15	1.07	0.63	1.80
	Q2: 2.275 -<6.25 MET/hr	9	0.58	0.30	1.14	4820	8	0.55	0.27	1.11
	Q3: 6.25 -<13.8125 MET/hr	29	1.89	1.28	2.79	4685	29	2.00	1.35	2.97
	Q4: > 13.8125 MET/hr	15	1.00	0.59	1.69	4905	15	1.04	0.61	1.77
Mod	None	157	1.00	(ref)		38690	155	1.00	(ref)	
	Q1: >0 -<2.34375 MET/hr	28	0.85	0.57	1.27	8969	28	0.89	0.59	1.33
	Q2: 2.34375 -<6.6354167 MET/hr	24	0.71	0.46	1.09	9081	21	0.65	0.41	1.02
	Q3: 6.6354167 -<14.583333 MET/hr	30	0.89	0.60	1.32	8844	30	0.92	0.62	1.36
	Q4: > 14.583333 MET/hr	37	1.11	0.77	1.58	9021	36	1.10	0.76	1.59