Inflammatory Potential of Diet And Pancreatic Cancer Risk: Interaction And Mediation Analysis In Two Prospective Cohorts

Jiali Zheng
University of South Carolina

Follow this and additional works at: https://scholarcommons.sc.edu/etd

Part of the Epidemiology Commons

Recommended Citation

This Open Access Dissertation is brought to you by Scholar Commons. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Scholar Commons. For more information, please contact dillarda@mailbox.sc.edu.
INFLAMMATORY POTENTIAL OF DIET AND PANCREATIC CANCER RISK: INTERACTION AND MEDIATION ANALYSIS IN TWO PROSPECTIVE COHORTS

by

Jiali Zheng

Bachelor of Science
Shanghai Jiao Tong University, 2010

Master of Public Health
University of Nebraska Medical Center, 2013

Submitted in Partial Fulfillment of the Requirements
For the Degree of Doctor of Philosophy in
Epidemiology

The Norman J. Arnold School of Public Health
University of South Carolina
2017

Accepted by:
Susan E. Steck, Major Professor
Anwar T. Merchant, Committee Member
Jiajia Zhang, Committee Member
Michael D. Wirth, Committee Member
Rachael Z. Stolzenberg-Solomon, Committee Member
Cheryl L. Addy, Vice Provost and Dean of the Graduate School
DEDICATION

This dedication is dedicated to my parents and my grandma who have been supporting and encouraging me, and helping me overcome many challenges during my entire doctoral study. I also want to dedicate my dissertation to my mentor Dr. Susan Steck who has afforded me four-year systematic, comprehensive and high-quality doctoral training. I am truly grateful to those invaluable opportunities Dr. Steck provided me in my graduate study to improve my research ability and experience and promote my independence in my focused research area of diet and cancer prevention.
ACKNOWLEDGEMENTS

I would first acknowledge my parents for their dedicated contributions to my graduate study by financially and spiritually supporting me in a foreign country and encouraging and helping me to overcome challenges. I want to especially thank my grandma who raised me up and taught me to be strong, always work as hard as I can and be grateful to people who helped me or are willing to help me. I think I could not have been able to achieve my goal without these good moral characters and personality.

I would like to thank my mentor and dissertation chair Dr. Susan Steck, whose mentorship in my entire doctoral study have been invaluable and gradually developed my research ability in every aspect of conducting an independent nutrition and cancer epidemiology study, and also helped me with my career development. I highly appreciate so many opportunities Dr. Steck provided me in grant writing, manuscript development and publication, research proposal formation and presentations in many national and local conferences. I also would like to extend my gratitude to my committee members for their expertise and support readily provided to me.

My dissertation research was supported and funded by the Support to Promote Advancement of Research and Creativity (SPARC) grant by the University of South Carolina Office of the Vice President for Research. I am grateful also to the two large cohort studies I used to produce this work, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial and the National Institutes of Health American Association of Retired Persons Diet and Health Study.
ABSTRACT

Background: Inflammation plays a pivotal role in pancreatic cancer etiology and can be modulated by diet. We aimed to examine the association between inflammatory potential of diet, assessed with the Dietary Inflammatory Index (DII™), and pancreatic cancer risk in two prospective cohorts, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study. We explored effect modification by important inflammation-related lifestyle factors, and investigated whether type-2 diabetes mediated the association in a pooled analysis of both studies.

Methods: A total of 101,449 and 533,286 participants aged between 50 to 78 years at baseline were included in the analytical cohort of PLCO and NIH-AARP, respectively. Energy-adjusted DII (E-DII) scores were computed based on food and supplement intake. Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatic cancer by E-DII quintiles with participants in the lowest E-DII quintile (most anti-inflammatory scores) as the referent. We estimated natural direct effect, natural indirect effect, and marginal total effect of both categorical and continuous E-DII scores on pancreatic cancer with type-2 diabetes as a mediator using causal mediation approach. Results: A total of 328 and 3,338 pancreatic cancer cases were identified in the PLCO and NIH-AARP, respectively. There was no significant association between dietary inflammatory potential and pancreatic cancer risk in either the PLCO or NIH-AARP. However, time significantly
modified the association in PLCO (P-interaction=0.02). An inverse association in the first four years of follow up was observed (HR_{Q5vsQ1}=0.55; 95% CI=0.32-0.95; P-trend=0.15), while there was a positive trend among those with ≥4 years of follow-up (HR_{Q5vsQ1} =1.36; 95% CI=0.85-2.17; P-trend=0.03). Type-2 diabetes significantly mediated the E-DII and pancreatic cancer association (P<0.05). **Conclusion:** Findings from these two large prospective cohorts did not support the association between inflammatory potential of diet and pancreatic cancer risk. Reverse causality owing to undetected disease may account for the inverse association observed in the first four years of follow-up in the PLCO. Type-2 diabetes explained an underlying mechanism through dietary inflammatory potential to pancreatic cancer development.
# TABLE OF CONTENTS

DEDICATION ................................................................................................................... iii

ACKNOWLEDGEMENTS ............................................................................................... iv

ABSTRACT ......................................................................................................................... v

LIST OF TABLES .............................................................................................................. x

CHAPTER 1: INTRODUCTION ........................................................................................ 1
  1.1 Statement of the problem ..................................................................................... 1
  1.2 Purpose and objectives ......................................................................................... 4
  1.3 Significance and relevance of the dissertation research ....................................... 7
  1.4 Dissertation outline .............................................................................................. 8

CHAPTER 2: BACKGROUND ........................................................................................ 10
  2.1 Relationship between chronic inflammation and pancreatic cancer .......... 10
  2.2 Relationship between diet and chronic inflammation ........................................ 14
  2.3 Other inflammation-related lifestyle factors: Obesity, type-2 diabetes, smoking, NSAIDs use .............................................................. 27
  2.4 Risk factors for pancreatic cancer ...................................................................... 30
  2.5 Summary of dietary factors and pancreatic cancer risk in the PLCO and NIH-AARP Studies ............................................................... 54

CHAPTER 3: METHODS ................................................................................................ 62
  3.1 Statement of research aims and hypotheses ....................................................... 62
  3.2 Description of the study population ..................................................................... 63
  3.3 Diet assessment .................................................................................................. 66
3.4 Covariates assessment ................................................................. 72
3.5 Effect measure modifiers assessment ............................................. 73
3.6 Outcomes assessment ................................................................. 74
3.7 Statistical analysis ...................................................................... 76

CHAPTER 4: INFLAMMATORY POTENTIAL OF DIET AND RISK OF PANCREATIC CANCER IN THE PROSTATE, LUNG, COLORECTAL AND OVARIAN (PCLO) CANCER SCREENING TRIAL ..................................................... 84

4.1 Abstract .................................................................................. 85
4.2 Introduction ............................................................................. 86
4.3 Materials and methods .............................................................. 87
4.4 Statistical analysis ................................................................... 91
4.5 Results .................................................................................... 93
4.6 Discussion ............................................................................... 95
4.7 Conclusion .............................................................................. 101

CHAPTER 5: INFLAMMATORY POTENTIAL OF DIET, INFLAMMATION-RELATED LIFESTYLE FACTORS AND RISK OF PANCREATIC CANCER: RESULTS FROM THE NIH-AARP DIET AND HEALTH STUDY ......................... 110

5.1 Abstract .................................................................................. 110
5.2 Introduction ............................................................................. 111
5.3 Methods ................................................................................ 113
5.4 Statistical analysis ................................................................... 118
5.5 Results .................................................................................... 121
5.6 Discussion ............................................................................... 122
5.7 Conclusion .............................................................................. 127

CHAPTER 6: MEDIATION EFFECT OF TYPE-2 DIABETES IN THE ASSOCIATION BETWEEN DIETARY INFLAMMATORY POTENTIAL AND PANCREATIC
CANCER RISK: A POOLED ANALYSIS OF THE PLCO CANCER SCREENING TRIAL AND NIH-AARP DIET AND HEALTH STUDY ............................................ 141

6.1 Abstract ............................................................................................................ 141
6.2 Introduction ...................................................................................................... 142
6.3 Methods .......................................................................................................... 144
6.4 Statistical analysis ......................................................................................... 152
6.5 Results ............................................................................................................ 156
6.6 Discussion ...................................................................................................... 159
6.7 Conclusion ...................................................................................................... 163

CHAPTER 7: DIETARY INFLAMMATORY POTENTIAL AND PANCREATIC CANCER RISK: DISCUSSION OF STUDY RESULTS OF INTERACTION AND MEDIATION ANALYSES IN TWO PROSPECTIVE COHORTS.............................. 176

7.1 Summary of results........................................................................................ 176
7.2 Comparisons of dissertation findings with previous studies ................. 177
7.3 Potential mechanisms of action................................................................. 178
7.4 Strengths and limitations........................................................................... 180
7.5 Public health implications........................................................................ 183
7.6 Implications for future research ................................................................. 184
7.7 Conclusion..................................................................................................... 185
7.8 Acknowledgements .................................................................................... 186
REFERENCES ....................................................................................................... 188
LIST OF TABLES

Table 2.1 Summary table for associations between dietary factors and pancreatic cancer in the PLCO and NIH-AARP .................................................................55

Table 4.1 Baseline characteristics of 101,449 subjects in the PLCO Cancer Screening Trial cohort by quintiles of E-DII from food plus supplement.................................102

Table 4.2 Association between E-DII from food plus supplement and pancreatic cancer risk among 101,449 subjects in the PLCO Cancer Screening Trial ...........................104

Table 4.3 Stratified analyses of E-DII from food plus supplement and pancreatic cancer risk by follow-up time (i.e. <4 and >=4 years) among 101,449 subjects in the PLCO Cancer Screening Trial .................................................................105

Table 4.4 Association between E-DII from food only and pancreatic cancer risk among 101,449 subjects in the PLCO Cancer Screening Trial .............................................106

Table 4.5 Association between E-DII from food only and pancreatic cancer risk by follow-up time (i.e. <4 and >=4 years) among 101,449 subjects in the PLCO Cancer Screening Trial .................................................................................................................107

Table 4.6 Comparison of important demographic and lifestyle characteristics between study sample and excluded sample in the PLCO Cancer Screening Trial .........................108

Table 5.1 Baseline characteristics of 533,286 subjects in the NIH-AARP Diet and Health Study by quintiles of E-DII .................................................................................129

Table 5.2 Hazard ratios of pancreatic cancer by quintiles of E-DII score among 533,286 subjects in the NIH-AARP Diet and Health Study ..............................................................132

Table 5.3 Hazard ratios of pancreatic cancer by quintiles of E-DII score among 533,286 subjects in the NIH-AARP Diet and Health study, stratified by inflammation-related lifestyle factors ..........................................................................................................................134

Table 5.4 The association between E-DII quintiles and risk of pancreatic cancer by cancer stage in the NIH-AARP Diet and Health Study ..........................................................136

Table 5.5 The association between E-DII quintiles and risk of pancreatic cancer by cancer grade in the NIH-AARP Diet and Health Study ..........................................................137
Table 5.6 Multivariable-adjusted HRs of lag time analysis of E-DII and pancreatic cancer risk after excluding subjects with follow-up<5 years ......................................................138

Table 5.7 Multivariable-adjusted HRs of sensitivity analysis of adding pancreatic cancer death cases with imputed incident time to the first incident pancreatic cancer ...............139

Table 5.8 Multivariable-adjusted HRs of sensitivity analysis of adding pancreatic cancer death cases with imputed incident time to incident primary pancreatic cancer ...............140

Table 6.1 Baseline characteristics of 269,641 subjects by quintiles of E-DII in the pooled mediation cohort of the PLCO Cancer Screening Trial and NIH-AARP Diet and Health Study ..........................................................................................................................164

Table 6.2 Study-specific natural direct effect, natural indirect effect, and marginal total effect of E-DII on pancreatic cancer risk with incident type-2 diabetes as mediator .................................................................166

Table 6.3 Pooled PLCO and NIH-AARP natural direct effect, natural indirect effect, and marginal total effect of categorized E-DII on pancreatic cancer risk with incident type-2 diabetes as mediator, using random effects model .................................................................167

Table 6.4 Study-specific and random effects model pooled natural direct effect, natural indirect effect, and marginal total effect of one-unit increase in centered E-DII and E-DII z-score on pancreatic cancer risk with type-2 diabetes as mediator .................................................168

Table 6.5 Natural direct effect, natural indirect effect, and marginal total effect of the categorized E-DII on pancreatic cancer mediated by type-2 diabetes using primary data of 269,641 subjects from the PLCO and NIH-AARP .................................................................170

Table 6.6 Natural direct effect, natural indirect effect, and marginal total effect of one-unit increase in centered E-DII and E-DII z-score on pancreatic cancer risk with type-2 diabetes as mediator using primary data of 269,641 subjects from the PLCO and NIH-AARP .................................................................171

Table 6.7 Comparison of important demographic and lifestyle characteristics between study sample and excluded sample in the pooled PLCO Cancer Screening Trial and NIH-AARP ..........................................................................................................................172

Table 6.8 Hazard ratios of pancreatic cancer by quintiles of E-DII score from food and supplement in the pooled mediation cohort of 269,641 subjects .................................................174
CHAPTER 1

INTRODUCTION

1.1 Statement of the problem

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States among both men and women and has the highest case-fatality rate among major cancers with 7% 5-year survival rate for all stages combined.\(^1,2\) Most pancreatic cancer (95%) are cancers of the exocrine pancreas, which produces enzymes to digest food. Neuroendocrine tumors (5%) are much rarer, and have a younger median age at diagnosis and better prognosis than exocrine pancreatic cancer.\(^1\) Because there is so far no reliable screening method for early detection, pancreatic cancer is often diagnosed at an advanced stage when survival statistics are even worse (2% 5-year survival for patients diagnosed at distant stage).\(^1\) Thus, identifying modifiable risk factors for pancreatic cancer is an important strategy for reducing the burden of this disease.\(^3\) The main risk factors include age, cigarette smoking, diabetes, family history, obesity, and chronic pancreatitis, though taken together these risk factors do not explain all of the risk for this malignancy.\(^4\) There is biologic evidence showing chronic inflammation is related to pancreatic cancer development, and substantial amount of studies support that some dietary factors could increase cancer incidence or mortality risk through modulating inflammation.\(^5\) Thus, understanding the effect of dietary inflammatory potential on pancreatic cancer development may help guide dietary intervention strategies and clinical guidelines for preventing this cancer.
Many dietary factors, such as saturated fat and fruits and vegetables, have been shown to affect inflammation through pro-inflammatory or anti-inflammatory mechanisms. A Western style diet characterized by greater intake of pro-inflammatory foods which are high in sugar, refined grains, red and processed meats, and fried foods can increase pro-inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). In contrast, the Mediterranean diet, high in whole-grains, fruit, green vegetables, and fish, and low in red meat and butter, with moderate alcohol and olive oil intake, has been associated with reduced chronic inflammation. However, most often nutrients or dietary components have been studied separately for their potential association with pancreatic cancer and inconsistent results have been found. A dietary pattern approach, which takes into account the complex interactions among dietary components, has advantages over individual foods or nutrients when being studied for associations with disease risk. Given the fact that no nutrient is consumed alone but in conjunction with other nutrients or non-nutrient components of food, several dietary patterns or indices such as the Healthy Eating Index (HEI) have been studied in relation to PanC. However, these dietary indices are limited by the relatively small numbers of dietary components and lack of focus on specific biologic pathways for explaining their mechanism. Until the dietary inflammatory index (DII™) was developed based on extensive review of research articles published through 2010 on the effect of dietary parameters on six well established inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF-α and CRP), none of these a priori indices had focused on inflammation as a main mechanism explaining diet’s effects on disease. The DII calculated with dietary data from different dietary assessment tools has been construct-
validated where higher DII scores (representing more pro-inflammatory diets) were found to be positively associated with higher inflammatory biomarker levels.\textsuperscript{23-30} Higher DII scores also have been associated with increased risk of different types of cancer in multiple studies.\textsuperscript{31-33,34-37}

Given the role of inflammation in pancreatic carcinogenesis, a dietary index with inflammation as the underlying biological mechanism and which assesses the inflammatory potential of the entire diet, has advantages for its potential association with pancreatic cancer compared to other dietary patterns focused solely on a specific food item or more general dietary guidelines. Among the literature, only two case-control studies have examined the association between the DII and pancreatic cancer. One study conducted in Italy between 1991 and 2008 with 326 incident cases and 652 controls reported a positive association between the DII and pancreatic cancer.\textsuperscript{38} Another case-control study with 817 cases and 1,756 controls in the US by Antwi et al. reported a 2.54-fold excess odds of pancreatic cancer among subjects in the highest quintile of DII compared to those in the first quintile (odds ratio (OR)\textsubscript{Q5vsQ1}=2.54, 95% confidence interval (CI)=1.87-3.46, P-trend<0.0001).\textsuperscript{39} Given the possibility of selection bias and inextricable recall bias of diet measurement in case-control studies, a prospective cohort study design may be a more appropriate study design compared to case-control design on this research topic.

Although two case-control studies found a significant positive association between dietary inflammatory potential and pancreatic cancer, little is known about the mechanism underlying the pathway from dietary inflammatory potential to pancreatic cancer development. Type-2 diabetes has been shown to have a positive relationship with
pancreatic cancer. Recent data from pooled analyses reported concordant findings, showing that diabetics had 40% to 90% increased pancreatic risk compared to non-diabetics. Given the strong positive association between type-2 diabetes and pancreatic cancer and the inflammatory nature of diabetes, type-2 diabetes may play a role as a mediator linking the dietary inflammatory potential to pancreatic cancer development.

1.2 Purpose and objectives

We used data from two large, nationally representative, prospective cohort studies [i.e. the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study] with rich dietary and other comprehensive covariate information to examine the inflammatory potential of diet and pancreatic cancer association in a prospective manner. We also investigated effect modification by inflammation-related lifestyle factors including body mass index (BMI), cigarette smoking, alcohol drinking, diabetes history, and non-steroidal anti-inflammatory drug (NSAIDs) use. As it is unclear whether diets with high inflammatory potential increase the risk of pancreatic cancer through occurrence of type-2 diabetes mellitus, we also conducted a causal mediation analysis with combined PLCO and NIH-AARP data to examine whether incident type-2 diabetes was playing a role as a mediator in the causal pathway between dietary inflammatory potential and pancreatic cancer and if so, what was the mediation proportion of diabetes. Our three specific aims were as follows:

Aim 1: Examine the association between inflammatory potential of diet and pancreatic cancer in the PLCO and examine effect modification by sex and BMI.
PLCO is a randomized controlled trial with the aim to assess if cancer screening tests can reduce cancer mortality. Briefly, a total of 154,897 eligible participants (76,682 men and 78,215 women), aged 55–74 years, were enrolled into the trial from 1993 to 2001 from ten centers across the US and randomized based on sex and age group into either a control arm (77,453 participants) where usual care was received, or an intervention arm (77,444 participants) where screening exams for prostate, lung, colorectal or ovarian cancers were received. In general, a majority of recruited participants were non-Hispanic white, married or living as married, had higher education level than some college, were overweight at baseline, and above 85% of female participants were postmenopausal. We calculated the energy-adjusted DII (E-DII) score for each subject using dietary data from the Diet History Questionnaire (DHQ) and calculated BMI at baseline to examine its effect modification on the E-DII and pancreatic cancer relationship. We hypothesized that higher E-DII scores were associated with higher risk of developing pancreatic cancer and that associations were stronger among males and overweight or obese subjects.

**Aim 2:** Examine the association between inflammatory potential of diet and pancreatic cancer in the NIH-AARP and examine effect modification by sex and inflammation-related lifestyle factors including BMI, cigarette smoking, alcohol drinking, diabetes history, and NSAIDs use. The NIH-AARP Diet and Health Study was initiated to examine a number of important diet and cancer hypotheses. The initial study population of this cohort was 567,169 eligible study participants (340,148 men and 227,021 women) after excluding respondents whose responses on the questionnaire were not reliable. Participants were 50 to 71 years old with mean age of 62 years at baseline.
and lived in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, or Louisiana) or two metropolitan areas (Atlanta, Georgia or Detroit, Michigan). Participants are predominantly white and have higher education level than the general US population. The percentage of current smokers in the NIH-AARP are lower than national estimates. We hypothesized that a pro-inflammatory diet (i.e., higher E-DII score) was associated with increased risk of pancreatic cancer. As more pancreatic cancer cases were available in the NIH-AARP dataset than the PLCO, we a priori proposed to examine more effect modifiers in these analyses than in Aim 1, including sex, BMI, cigarette smoking, alcohol drinking, diabetes history, and NSAIDs use. We hypothesized that males, overweight or obese individuals, individuals with previous smoking history, high level of alcohol drinking, those who had presence of diabetes history, or less frequent NSAIDs use would have an enhanced effect of E-DII on pancreatic cancer risk compared to their counterparts.

Aim 3: Investigate causal mediation by type-2 diabetes in the association between inflammatory potential of diet and pancreatic cancer in PLCO and NIH-AARP pooled analysis. We first conducted a causal mediation analysis to investigate the causal mediated effect of type-2 diabetes on the pathway from E-DII to pancreatic cancer risk in PLCO and NIH-AARP studies separately. Given that PLCO and NIH-AARP studies had very similar food frequency questionnaire (FFQ) and other covariate information as well as study population demographics, and for the purpose of increasing pancreatic cancer cases and incident type-2 diabetes cases, we combined primary data from these two cohorts into a single dataset after demonstrating that there was no significant heterogeneity between two studies. We hypothesized that incident type-2
diabetes played a role as a mediator in the DII and pancreatic cancer association in both
cohorts and the pooled analyses.

1.3 Significance and relevance of the dissertation research

1.3.1 Public health and clinical impact

Pancreatic cancer is a highly malignant cancer with low survival chance and no reliable
screening method. Findings from this dissertation had both clinical and public health
significance. Quantifying the effect of inflammatory potential of diet on pancreatic cancer
risk and the interactive effects of important inflammation-related lifestyle factors is
crucial, not only for healthy people who may reduce their chance of developing
pancreatic cancer through modulating dietary inflammation, but also important for those
who are already at risk of this malignancy such as obese or diabetic individuals. By
elucidating the role that type-2 diabetes may play in the pathway of DII and pancreatic
cancer, we may better understand the mechanism through which dietary inflammatory
potential could lead to development of pancreatic cancer. Findings of mediation analyses
also may provide clinical evidence and guidance to identify possible intermediate
biomarkers to screen high risk population of developing pancreatic cancer, especially for
those who consume more pro-inflammatory diets. In addition, it could help with the
design and guidance of an effective dietary intervention to reduce risk of pancreatic
cancer through intervening on type-2 diabetes.

1.3.2 Scientific relevance or significance

This dissertation work was significant in the following aspects: (1) Use of data
from two large, well-characterized prospective cohorts minimized the recall and selection
bias that may exist in a typical case-control study. Aims 1 and 2 were the first two studies
to investigate the inflammatory potential of diet and pancreatic cancer association in a prospective manner with adequate number of pancreatic cancer cases and with comprehensive dietary factors and covariates assessed before pancreatic cancer onset; (2) the joint effect of E-DII and other common inflammation-related lifestyle factors on pancreatic risk was examined in a prospective study for the first time, and (3) this was the first mediation analysis with the method of pooling studies to examine the mediated effect of type-2 diabetes on the pathway from DII to a cancer endpoint.

1.4 Dissertation outline

Chapter 1 provides a brief overview of the problem of interest with an introduction to the relationships between diet/dietary patterns and inflammation, and between inflammation and pancreatic cancer. We also present the tentative scope of the dissertation: three aims with respective hypothesis. Chapter 1 concludes with the clinical and public health relevance of the dissertation as well as scientific significance. Chapter 2 provides a detailed overview of the previous literature with aspects related to the dissertation work including the biological mechanisms of chronic inflammation and pancreatic cancer; biological and epidemiological perspectives of the association between dietary factors and inflammation; an overview of dietary patterns research and introduction to a few a priori dietary patterns; and current evidence of risk factors for pancreatic cancer as well as summary of study results related to diet and pancreatic cancer risk in the PLCO and NIH-AARP. Chapter 3 provides a description of the methods used for each aim which includes study population description, variable information, and statistical analysis methods. Chapters 4 to 6 include detailed manuscripts for each aim. Chapter 7 is the synthesis and discussion for my overall
dissertation.
CHAPTER 2

BACKGROUND

2.1 Relationship between chronic inflammation and pancreatic cancer

2.1.1 Biological mechanism for chronic inflammation and cancer

Inflammation, a crucial function of the innate immune system, protects against pathogens and initiates specific immunity.\textsuperscript{49} Acute inflammation is a rapid and self-limiting process during which chemical mediators are induced in a tightly regulated sequence, and immune cells move in and out of the affected area, destroying infectious agents, repairing damaged tissue, and initiating a specific and long-term response to the pathogen.\textsuperscript{49} Acute inflammation is not regarded as a risk factor for the development of neoplasia, although many of the same molecular mediators are generated in both acute and chronic inflammation.\textsuperscript{50} Frequent acute inflammation results in unresolved wound healing with consequent chronic inflammation. Chronic inflammation could be caused by a variety of factors, including bacterial, viral, and parasitic infections, chemical irritants, and non-digestible particles. Chronic exposure to inflammatory mediators including metabolites of arachidonic acid, cytokines, chemokines, and free radicals leads to increased cell proliferation, mutagenesis, oncogene activation, and angiogenesis. The ultimate result is the proliferation of cells that have lost normal growth control.\textsuperscript{50} Several lines of evidence, including general or cell-specific gene inactivation and population-based studies, support the view that inflammation plays an important role in cancer causation which include the following: (1) many cancers arise at sites of chronic
inflammation, and chronic inflammation increases cancer risk, (2) immune cells with the function to mediate chronic inflammation are found in cancers and they promote growth of tumor, (3) cancers could produce chemical mediators that regulate inflammation, (4) development of experimental cancers are inhibited after deletion or inhibition of inflammatory mediators, (5) genetic variation of inflammatory genes can alter susceptibility to and severity of cancer, and (6) the long term use of NSAIDs reduces the risk of some cancers. The types of chronic inflammation that lead to cancer are varied. In some cases, the inflammation initiation factors are known which may include chronic bacterial and parasitic infections, chemical irritants, and non-digestible particles. In animal cancer models, these cells and mediators of chronic inflammation act as tumor promoters for malignant progression of Barrett’s esophagus and esophageal cancer, inflammatory bowel disease, gastric cancer, liver cancer and colon cancer. In other cases, the underlying cause of the chronic inflammation is complex due to the diversity of inflammatory reactions that is dictated by the primary stimulus as well as by exogenous and endogenous modifying signals. At one end of the spectrum, type 1 inflammation, characterized by granuloma formation, is elicited by intracellular pathogens. At the other extreme, inflammatory reactions to parasites are characterized by eosinophil and mast cell infiltration and by extensive tissue remodeling (type 2 inflammation).

More recently, the role of inflammation in cancer development was highlighted by Brucher and Jamall who proposed a new paradigm for the epistemology of the origin of cancer. They stated that less than 10% of all cancers are hereditary. According to their view, the origin of cancer follows a sequence of events beginning with (1) a pathogenic stimulus which can be biologic or non-biologic (including diet), (2) followed
by chronic inflammation from which fibrosis develops, with associated changes in the cellular microenvironment if the inflammation does not resolve, (3) a pre-cancerous niche then develops which triggers a chronic stress escape strategy that transforms a normal cell to a cancer cell if the chronic stress does not resolve. Based on this hypothesis, we have a better chance to reduce cancer burden in the nation should we intervene to reduce chronic inflammation which may be triggered by potentially modifiable risk factors such as diet.

2.1.2 Relationship between chronic inflammation and pancreatic cancer development

Inflammation has been identified as a significant factor in the development of solid tumor malignancies including pancreatic cancer. Both hereditary and sporadic forms of chronic pancreatitis are associated with an increased risk of developing pancreatic cancer. The combined increase in genomic damage and cellular proliferation, both of which are involved with inflammation, transform normal pancreatic cells to a malignancy. Cytokines, reactive oxygen species, and mediators of the inflammatory pathway (e.g., nuclear factor-κB (NF-κB) and cyclooxygenase-2 (COX-2)) have been shown to increase cell cycling, cause loss of tumor suppressor function, and stimulate oncogene expression, all of which may lead to pancreatic malignancy. Like other tumor types, pancreatic cancer has been shown to overexpress COX-2, a modulatory molecule in inflammation and carcinogenesis which has been implicated in the positive regulation of growth and tumorigenesis. Systemic low-grade chronic inflammation in addition to local inflammation in the pancreas is involved in the pathogenesis of pancreatic cancer. Using laser-capture microdissection (LCM), gene array, and
immunohistochemistry, some researchers found the potential inflammatory components in epithelial and stromal cells that may contribute to both chronic pancreatitis and pancreatic cancer, illustrated as follows: (1) increased expression of IL-8, an activator of the inflammatory factor NF-κB, (2) decreased expression of IκB (an inhibitor of NF-κB) in chronic pancreatitis ductal cells compared with normal ducts, (3) increased expression of tumor related genes including S100A4, cyclin E1, and epidermal growth factor (EGF) receptor, and (4) expression of matrix metalloproteinase 2, a pro-invasive factor for tumor cells.61

Epidemiology studies have reported associations between certain chronic inflammatory biomarkers and pancreatic cancer risk with inconsistent results. Several hospital-based case–control studies showed that CRP levels, an acute phase protein produced in the liver which is part of the systemic inflammatory response to the tumor, were significantly higher in pancreatic cancer cases compared with controls.62-64 In addition, serum levels of IL-6 and TNF-α have been repeatedly reported in several case-control studies to be significantly higher among pancreatic cancer patients than healthy controls. 62-66 One study also found significantly higher levels of IL-8 and macrophage inflammatory protein-3α in sera of pancreatic adenocarcinoma patients compared to healthy controls.67 However, two nested case-control and two prospective cohort studies reported no association or weak inverse associations between pre-diagnostic CRP and pancreatic cancer,68-71 while three studies have reported positive point estimates.69-71 Only one study examined pre-diagnostic IL-6 and TNF-α receptor levels in relation to pancreatic risk, and neither biomarker was reported to be significantly associated with pancreatic cancer.69 The inconsistent results across studies may be due to differences in
study designs, populations, different confounding factors, or statistical power.

Other evidence that supports a relationship between inflammation and pancreatic cancer is demonstrated by NSAID’s effect to reduce its risk. One meta-analysis involving 7,252 pancreatic cancer cases and more than 120,000 healthy control subjects showed that high-dose aspirin intake was marginally associated with decreased risk for pancreatic cancer in the overall analysis (OR=0.88, 95% CI=0.76-1.01) and stratified analysis for Americans showed a similar result (OR=0.82, 95% CI=0.65-1.02).72

2.2 Relationship between diet and chronic inflammation

2.2.1 Biological mechanisms linking diet and chronic inflammation

Dietary factors have consistently been shown to affect inflammation, through both pro-inflammatory and anti-inflammatory mechanisms. Dietary components that are beneficial against carcinogens seem to have multiple mechanisms of action and many share a common mechanism of reducing inflammation, often via the NF-κB pathway.73 NF-κB is a transcription factor that activates expression of multiple genes related to inflammation and is also upregulated in response to oxidative stress.74 Another well-accepted mechanism for a protective effect of diet against inflammation is that healthy diets can reduce obesity and insulin resistance75 which are factors likely to initiate inflammation,76,77 and decrease oxidative damage78 and change gene expression.79 Many dietary components in mammals including folate, vitamin B6, vitamin B12, betaine, methionine and choline can induce changes in deoxyribonucleic acid (DNA) methylation.79 A lot of dietary factors including fruits and vegetables,80,81 isoflavones (such as genistein and diadzein),82,83 flavonols (such as kaempferol and quercetin),84 stilbenes,85 curcumin,86 isothiocyanates,87 and omega-3 fatty acids88 have been shown to have anti-
cancer ability though decreasing pro-inflammatory cytokines, suppressing the activity of NF-κB, or promoting antioxidant defense.

2.2.2 Relationship between individual dietary factors and chronic inflammation

Several studies have investigated the association between an individual dietary factor and inflammatory biomarkers. Factors that were reported to be associated with lower inflammation levels included fruits and vegetables, omega-3 polyunsaturated fatty acids (PUFAs), fiber, whole grains, moderate alcohol intake, vitamin E, vitamin C, β-carotene, anthocyanin and flavonols. On the contrary, some dietary factors were observed to be related to higher inflammation levels which included saturated fat, high daily intake of carbohydrate from honey, sucrose, or high-fructose corn syrup, high dietary glycemic index (GI) and/or glycemic load (GL), animal protein and meat protein, as well as total protein intake within an energy-restricted diet.

2.2.3 Relationship between dietary patterns and chronic inflammation

2.2.3.1 An overview of dietary pattern research and different types of dietary patterns

The traditional nutritional epidemiological studies usually focused on the relation between specific nutrients, food items, or food groups and disease, but people consume a wide variety of food items, not isolated nutrients or foods. Additionally, impacted by different living environmental conditions, religions, personal preferences, food availability, economical statuses and many other cultural factors, people may have culture-specific dietary patterns. Dietary pattern research thus provides a more comprehensive scope to examine diet-disease associations than an individual food or
nutrient approach. The dietary pattern approach has several advantages over the traditional individual food/nutrient approach which have been discussed as follows:115-120

(1) biologically, nutrients may interact with each other via impacting bioavailability and absorption; single nutrient-based research does not consider the complex interactions among nutrients; (2) increased consumption of one food item may be always associated with reduced consumption of other food items since the total energy intake is considered to be stable; (3) many nutrients, especially macronutrients such as fat, and total energy are highly correlated and studying their separate effects may produce a collinearity issue in the statistical model; (4) the effect of a single nutrient may be too small to be detected but the cumulative effects of multiple nutrients in a dietary pattern may be sufficiently large to be identified; (5) analysis of individual nutrients may be confounded by dietary patterns; and (6) analysis of a large number of individual nutrients or food groups may produce significant associations simply by chance.

There are basically two broad categories of dietary pattern approach: the \textit{a priori} dietary pattern which is also known as index-based or score-based dietary pattern, and the \textit{a posteriori} dietary pattern which is also known as a data-driven approach. Both index-based and data-driven dietary patterns take into account the whole diet instead of a single nutrient, thus overcoming most limitations of single nutrient research, and results are more meaningful and interpretable. There are both strengths and limitations of each approach. The index-based approach is analytically simple to compute, and easily reproducible and can be comparable across different studies because it provides a standardized assessment of a set of recommendations which allows researchers to define criteria exactly the same way.13 However, scores that dichotomize components (met or
not met) do not consider the full range of amount of foods consumed. Those that include a range of points for each component do consider variability in intake of foods but not amounts at the extremes. The scoring algorithm of the index is based on the underlying dietary guidelines, which are generally not targeted at certain type of disease. Subjectivity may be introduced during index construction in terms of the selection of foods for inclusion, number of foods or nutrients being selected, scoring algorithm, and interpretation of the result. Also, the equally weighted diet components implies that each component is equally related to health, which may not be the case.

The data-driven methods can be broadly grouped into two categories: data-driven, outcome independent and data-driven, outcome dependent. Factor analysis and cluster analysis are two data-driven, outcome independent methods to identify dietary patterns, because both are derived from analysis of dietary data (factor analysis examines correlations between food group variables and finds linear combinations of those variables that explain overall variance in the data so it is a continuous variable; and cluster analysis identifies clusters of individuals with similar dietary patterns according to food groups defined by investigator so it is a categorical variable) and both are derived independent of their potential relationship to a health outcome. Therefore, the resulting factors or clusters may be significantly associated with a health outcome, but the interpretation does not mean that this factor or cluster necessarily represents the dietary pattern most associated with disease. Another limitation of factor analysis is subjectivity introduced at multiple levels including food groups determination, the number of factors, names of the factors (often called patterns), and treatment of input items (e.g., whether to use grams, servings, percent energy or standardized intake). Unless methods of collecting
the data are comparable and food group construction is standardized, results are not comparable across studies. In addition, factors are not mutually exclusive and therefore do not represent the entire eating pattern for a group of individuals. Another challenge both factor and cluster analysis face is that the population under study can dramatically affect results because patterns are derived based on data variability under the study population. It is almost unlikely that the exact same pattern could be identified by using another population, therefore generalizability of the results and reproducibility is necessarily limited. Reduced rank regression (RRR) and classification and regression tree analysis (CART) are two data-driven, outcome dependent methods. RRR is typically used to identify combinations of food that explain the most variation in a set of intermediate health biomarkers and in subsequent confirmatory analysis it links the pattern to the outcome of interest. CART is an emerging method and it makes determinations in stepwise fashion, first determining which dietary component explains the most variation in the health outcome and then determining which component explains the next most variation based on value for the initial component, until the last component is reached. Results from RRR and CART are reproducible across studies to the extent that study population exhibit the same relationship between diet and health outcome.

Regarding the relationship of dietary patterns and inflammation, the Western-type diet, which is typically defined as high in refined grains, red and processed meat, high-fat dairy, sweets and desserts, fries and soft drinks has been associated with higher levels of CRP and IL-6. In a cross-sectional study with 486 healthy Iranian women, higher Western pattern score was associated with elevated CRP (beta=0.08, P<0.001), serum amyloid A (SAA) (beta =0.11, P<0.05), and IL-6 (P<0.001). In contrast, the
As my dissertation focuses on an a priori dietary pattern as exposure, I mainly describe in the following sub-sections a few selected well-established a priori dietary patterns including introduction of each dietary pattern’s scoring algorithm and its association with inflammatory biomarkers and some disease outcomes.

2.2.3.2 Healthy Eating Index

The HEI was developed by the US Department of Agriculture (USDA) to measure concordance with the Dietary Guidelines for Americans (DGA) and the Food Guide Pyramid. The overall structure of HEI included 10 components: five food groups (grains, vegetables, fruits, milk and meat), four nutrients (percent energy from total fat, percent energy from saturated fat, cholesterol intake, sodium intake), and the number of different kinds of foods in person’s diet over a 3-day period. Recipe ingredients of mixed food item were allocated to appropriate food groups. The exact score assigned to a person in every component of HEI was determined by the number of servings the individual consumed per day for a given energy intake. For example, the recommended dietary allowance (RDA) for total energy for a 40-year-old woman is 2,200 kcal and the USDA food guide pyramid indicated that four servings of vegetables per day are recommended at this energy level. Thus, a woman of 40-year-old should have at least four servings of vegetables per day to obtain the maximum score of 10 in this category. Each of the 10 components has a score ranging from 0 to 10, so the total
index score is 100. If an individual consumed the recommended number of servings for each food component or met the recommended guidance for nutrient intake, then this individual would receive a score of 10 for this component. A score of 0 was assigned to people who had no serving within a food group or below the criteria for minimum score of 0 for nutrients intake. Between 0 and 10, the score of each component was calculated proportionately.¹³¹

Some studies have investigated the association of the HEI score and inflammation with the main findings showing that the HEI score was not associated with systemic inflammation biomarkers such as CRP,⁷,¹³²,¹³³ SAA¹³³ and IL-6.⁷,¹³²,¹³³ Only one cross-sectional study using data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that higher HEI score predicted lower CRP level among 8719 disease-free adults (P-trend=0.04).¹³⁴ HEI only weakly predicted major chronic disease risk in men but not in women and it generally did not predict cancer risk in men or women.¹³⁵,¹³⁶ The HEI’s low predictive ability for chronic inflammation and chronic disease outcomes could be improved had it distinguished between unsaturated and saturated fats, the form of carbohydrates, or protein sources.¹³⁷ These limitations were addressed by the development of an alternate HEI (AHEI) with the goal to capture specific dietary pattern and eating behavior consistently associated with lower chronic disease risk in clinical and epidemiological investigations. AHEI has 9 components, and compared to the original HEI, the AHEI removed potato and potato products from the vegetable component; whereas HEI considered all types of meat, AHEI gave more credit for consuming white over red meat (included a component: white to red meat ratio). AHEI also included a separate component for beneficial non-meat protein sources which
were nuts and soy products and gave credit for higher cereal fiber intake in the grain category. The ratio of polyunsaturated to saturated fat was included in AHEI to capture beneficial effects of unsaturated oils which was not considered in HEI; moderate alcohol consumption and a long-term multivitamin use were also added into the AHEI. Except for the multivitamin use (contributing either 7.5 points for regular use >5 years and 2.5 points for all others), the other 8 components of AHEI were assigned a score from 0 to 10. All individual component scores were summed for a total AHEI score ranging from 2.5 (worst) to 87.5 (best).\textsuperscript{135,137} A study comparing the disease predictive ability of the HEI and AHEI using same study population and during same follow up periods found that the AHEI was nearly twice as predictive of overall chronic disease risk as was the HEI and most of additional reduction of risk resulted from reduction in cardiovascular disease (CVD) risk.\textsuperscript{138} However, AHEI was more predictive of CVD risk than cancer risk, perhaps because CVD outcome is more homogeneous than is cancer outcome.\textsuperscript{138} The association between AHEI and plasma concentrations of inflammation biomarkers was assessed in two studies with main findings showing higher AHEI scores were associated with lower inflammatory biomarker levels such as IL-6 and TNF-α.\textsuperscript{7,139}

Since DGA are issued every 5 years by the USDA and U.S. Department of Health and Human Services, the HEI-2005\textsuperscript{14} and HEI-2010\textsuperscript{140} reflected the dietary recommendations from 2005 edition of the Dietary Guidelines and the 2010 edition, respectively. The HEI-2010 keeps several features of the 2005 version: (1) it has 12 components, many unchanged, including 9 adequacy (adequacy items are those higher intake indicate higher score) and 3 moderation components (those reverse scored food items); (2) it uses an energy density approach to set standards, e.g., nutrients are adjusted
for total energy as a percent of calories; and (3) the standards for the maximum scores are the least-restrictive (easiest to achieve) recommendations among those that vary by energy level, sex, and/or age. Changes to the HEI-2010 include: (1) Greens and Beans replaces Dark Green and Orange Vegetables and Legumes because Greens and Beans are considered as the subgroups for which intakes are furthest from recommended levels; (2) Seafood and Plant Proteins has been added to capture specific choices from the protein group; (3) Fatty Acids, a ratio of poly- and mono-unsaturated to saturated fatty acids, replaces Oils and Saturated Fat to acknowledge the recommended beneficial effect of replacing saturated fat with mono-and polyunsaturated fatty acids; and (4) a moderation component, Refined Grains, replaces the adequacy component, Total Grains, to reflect the recommendation of restricting the over-consumption of refined grains. The HEI-2010 allows for flexibility in food choices and lack of any one commodity does not prevent from having a perfect HEI-2010 score. In contrast to the adequacy components of the HEI-2010 where assigning the minimum score of zero was determined by no intake, the 85th percentile of the 2001–2002 population distribution of 1-day intakes is used for the minimum score of zero for those moderate components because these components are reverse-scored and there is no clear scientific evidence to specify how high of an intake deserves a score of zero. Although the suitability of the HEI-2010 for ethnic and cultural groups has not yet been determined, the index would be expected to be useful for assessing the diets for subpopulations for which the DGA are appropriate.

HEI-2005 was found to have an inverse association with CRP. The higher HEI-2005 score was found to be related to lower risk of colorectal cancer, reduced symptoms of depression, lower risk of cardiovascular risk factors, reduced risk of
overall chronic diseases,\textsuperscript{146} and lower risk of stroke.\textsuperscript{147} HEI-2010 was also found to be related to lower risks of all-disease mortality, cardiovascular disease mortality, and cancer mortality in the low-income Southeast US population.\textsuperscript{148} Among specific cancer types, an inverse association was found for HEI-2010 with risk of melanoma,\textsuperscript{149} lung cancer,\textsuperscript{150} and colorectal cancer.\textsuperscript{151}

\textbf{2.2.3.3 Dietary Approaches to Stop Hypertension (DASH)}

The DASH-style diet was initially developed in the middle 1990s to lower blood pressure and prevent hypertension in the US. It is a healthy dietary pattern that contains 8 components: fruits, vegetables, whole grains, low-fat dairy products, legumes and nuts, sodium, red and processed meat, and sugar-sweetened beverages.\textsuperscript{152} There are several versions of DASH scoring algorithms: one version assigns scores from 1 to 5 to each quintile of component intake (higher quintile of recommended food items intake receive higher point while higher quintile of undesired food items intake was assigned lower score)\textsuperscript{153} with total score ranging from 8 to 40; a second version has minimum and maximum component scores between 0 and 10 with total score from 0 to 80;\textsuperscript{154} while a third version has 11 components with scores from 0 to 1 assigned to each component thus making total DASH score from 0 to 11.\textsuperscript{155} A recent meta-analysis of twenty-two randomized clinical trials that investigated the effect of DASH diet intervention on CVD risk factors reported that compared to control, DASH diet significantly decreased systolic blood pressure (BP), diastolic BP, the concentrations of total cholesterol and low-density lipoprotein.\textsuperscript{156} Importantly, the beneficial effects of the DASH diet are not limited to BP and CVD risk factors, some studies have reported significant improvements in weight loss,\textsuperscript{157} insulin sensitivity,\textsuperscript{158,159} inflammation,\textsuperscript{160,161} and oxidative stress.\textsuperscript{159} The DASH
diet has been shown to be associated with reduced risk of several inflammation-related chronic diseases such as type-2 diabetes,\textsuperscript{154,162,163} colorectal cancer,\textsuperscript{164} all cancer mortality,\textsuperscript{165} heart disease and stroke,\textsuperscript{153,166} and all-cause mortality.\textsuperscript{165} In a NIH-AARP study followed from 1995 to 2006, Miller et al. compared four DASH indices defined by Dixon (7 food groups, saturated fat, and alcohol), Mellen (9 nutrients), Fung (7 food groups and sodium), and Günther (8 food groups) with regard to their associations with colorectal cancer risk.\textsuperscript{167} They concluded that higher scores of all four indices were consistently associated with reduced risk of colorectal cancer in men and higher scores on three of the indices (except the Dixon defined index) were associated with reduced risk among women.\textsuperscript{167}

\textbf{2.2.3.4 Mediterranean Diet Score (MDS)}

The Mediterranean diet score (MDS) was originally developed by Trichopoulou et al.\textsuperscript{168} to measure the degree of adherence to the traditional Mediterranean diet. It includes eight components and a score of 1 is assigned to beneficial food items including vegetables, legumes, fruits, cereal and ratio of monounsaturated fat to saturated fat for which the consumption is at or above the sex-specific median, and 0 is assigned to consumption of these foods below sex-specific median. For components presumed to be unhealthy (meat and meat products, milk and dairy products), people whose consumption is at or above the sex-specific median are assigned 0, and people with consumption below the sex-specific median are assigned a score of 1. For ethanol consumption, a score of 1 is assigned for moderate ethanol consumption and 0 is assigned to heavy drinkers. The total score ranged from 0 (minimal adherence) to 8 (maximal adherence). Trichopoulou et al. later updated the original version of MDS to include fish intake and defined
moderate ethanol consumption as 10 to 50 grams per day for men and 5 to 25 grams for women, which made the total score between 0 to 9.\textsuperscript{169} Different definitions of moderate ethanol consumption were included in other studies.\textsuperscript{170,171} There were several Mediterranean dietary indices constructed based on the original MDS and used to evaluate their associations with health outcomes, such as the adapted composite Mediterranean diet score (MED) considering different health effects of cereal and grain products,\textsuperscript{172} the alternate MED (aMED) which was adapted to the American population,\textsuperscript{173} and the Mediterranean style-dietary pattern score (MSDPS).\textsuperscript{174,175} Increasing evidence suggests that bioactive and nutrient-dense components contained in the Mediterranean diet are modulators of insulin resistance, can exert beneficial effects on blood pressure, improve atherogenic dyslipidemia, beneficially influence metabolic pathways or attenuate the inflammatory burden.\textsuperscript{176,177} The Mediterranean diet could protect against diseases associated with chronic inflammation, including metabolic syndrome,\textsuperscript{178,179} atherosclerosis and CVD,\textsuperscript{180,181} cancers,\textsuperscript{182} diabetes,\textsuperscript{177} and obesity.\textsuperscript{183,184} The MDS has been associated with lower chronic systemic inflammation markers, such as IL-6 and CRP.\textsuperscript{7,185,186} A study to compare and evaluate the reliability of ten Mediterranean diet indices showed these indices had acceptable performance in measuring the adherence to the Mediterranean diet.\textsuperscript{187} The components that had strongest correlation with the core of Mediterranean diet were monounsaturated-to-saturated fatty acid ratio, fruit, and vegetables. In order to improve the concordance between the indices, further research was suggested to standardize the number of components and the scoring criteria.\textsuperscript{187}
2.2.3.5 Dietary inflammatory index (DII)

The development and construct validation of the DII have been described previously. In short, the 45 food parameters (i.e., DII components) were assigned inflammatory effect scores based on research summarizing findings from 1,943 articles published through 2010 describing the relationship between the food parameters and six inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP). A representative world database (i.e., dietary intake from 11 populations around the world) was created that provided a mean intake and standard deviation for each food parameter. To calculate an E-DII score, this global mean dietary intake after energy adjustment was subtracted from the actual food intake value from a specific study, and divided by its standard deviation. This z-score is then converted to a percentile (in order to minimize the effect of outliers or right-skewing) and centered by doubling the value and subtracting 1. The product of the transformed z-score and inflammatory effect score for each DII component was calculated and summed across all components to create the overall E-DII score for an individual. The E-DII score characterizes an individual’s diet on a continuum from maximally anti-inflammatory to maximally pro-inflammatory, with a higher E-DII score indicating a more pro-inflammatory diet and a lower E-DII score indicating a more anti-inflammatory diet.

The DII has been construct validated with dietary data from different dietary assessment tools, where higher DII scores were found to be positively associated with higher inflammatory biomarkers levels. Higher DII scores have previously been associated with some inflammation-related diseases such as colorectal cancer reported in the Iowa Women’s Health Study, NIH-AARP study, the Women’s Health Initiative, and others.
and the Bellvitge Colorectal Cancer Study;\textsuperscript{32} prostate cancer among French middle-aged adults\textsuperscript{189} and Jamaican men\textsuperscript{190} as well as Italian men;\textsuperscript{191} prostate cancer mortality among patients with aggressive cancer,\textsuperscript{192} esophageal squamous cell cancer,\textsuperscript{193,194} gastroesophageal junctional adenocarcinoma,\textsuperscript{195} endometrial cancer,\textsuperscript{36} ovary cancer,\textsuperscript{196} dyspnoea and radiological evidence of emphysema among heavy smokers,\textsuperscript{197} breast cancer death\textsuperscript{198} and incidence,\textsuperscript{193} myocardial infarction,\textsuperscript{199} ulcerative colitis,\textsuperscript{200} previously diagnosed circulatory conditions,\textsuperscript{201} hepatocellular cancer,\textsuperscript{202} metabolic syndrome and associated traits including higher blood pressure and triglycerides and lower HDL-cholesterol,\textsuperscript{26,203} depression,\textsuperscript{204} asthma.\textsuperscript{205} Higher DII scores were more likely to be observed among shift workers especially rotating shift workers.\textsuperscript{206} The higher DII was also associated with larger BMI, waist circumference and waist to height ratio in a population sample at high CVD risk,\textsuperscript{207} lower scores on other dietary indices,\textsuperscript{208} decreased cognitive functioning,\textsuperscript{196} lower fetal growth and breast feeding failure,\textsuperscript{209} lower bone mineral density,\textsuperscript{210} lower lung function,\textsuperscript{205} higher risk of incident cardiovascular diseases,\textsuperscript{211,212} higher CVD mortality,\textsuperscript{193,213,214} and higher cancer mortality and all-cause mortality.\textsuperscript{213-216} As mentioned previously, the DII has been associated with pancreatic cancer in two case-control studies.\textsuperscript{38,39}

2.3 Other inflammation-related lifestyle factors: Obesity, type-2 diabetes, smoking, NSAIDs use

Obesity is an inflammatory condition, often associated with the development of adipose tissue inflammation, resulting in metabolic dysfunction and an increased risk for developing multiple chronic diseases.\textsuperscript{217} In addition to excess fat storage in adipose tissue, obesity is also associated with fat storage in other tissues including liver and
skeletal muscle, which may lead to insulin resistance and stimulate inflammation. On the other hand, obesity changes the type of chemicals that fat cells secrete which include several pro-inflammatory mediators, produced by macrophages resident in the adipose tissue. It has been demonstrated that healthy obese subjects have increased circulating levels of pro-inflammatory cytokines such as IL-6, TNF-α and CRP. Weight loss by hypocaloric diets or surgery reduced CRP levels in healthy middle-aged and postmenopausal obese women and obese men.

Chronic diabetic wounds are trapped in a persistent inflammatory state with elevated levels of pro-inflammatory cytokines and proteases together with impaired expression of growth factors. Recent data have demonstrated that the plasma concentration of inflammatory mediators, such as TNF-α and IL-6, are increased in the insulin-resistant states of obesity and type-2 diabetes. The first molecular link between inflammation and insulin resistance was established by observing the insulin resistance in obese mouse can be reduced through neutralization of TNF-α by soluble TNF-α receptors. In the Women’s Health Study, elevated CRP levels were associated with a four-fold increased risk to develop diabetes among healthy middle-aged women after follow up of 4 years. In addition, Dandona et al. demonstrated that insulin has an anti-inflammatory effect that may inhibit atherogenesis in the long term.

Cigarette smoking has been shown to augment the production of pro-inflammatory cytokines such as IL-1, IL-6 and IL-8 and to decrease the levels of anti-inflammatory cytokines such as IL-10. One of the key mechanisms behind smoking-induced inflammation activation is through the NF-kB pathway. In response to environmental stimuli including tobacco exposure, the inactive complex of NF-kB/
intracellular inhibitor (IkB) is activated by phosphorylation of IkB, which leads to the poly-ubiquitination and subsequent degradation of IkB. Degradation of IkB induces transcription of various genes involved in immune regulation and inflammation. The pro-inflammatory impact of smoking on increased level of various inflammatory cytokines was confirmed in several epidemiological studies. The associations between cigarette smoking, years since quitting smoking and inflammatory markers were investigated among 2,920 British men and the result showed that current smokers had higher levels of the acute phase CRP compared to never smokers. Reduced levels of inflammatory markers were found in subjects who quit smoking for 5 years, and the levels of inflammatory markers were reverted to those found in never smokers only in subjects who quit smoking for 20 years or more. Serum levels of the key pro-inflammatory mediator TNF-α were found to be highest among healthy subjects who smoked more than one pack of cigarettes per day, followed by smokers who smoked less than one pack per day and lowest in healthy nonsmokers, demonstrating a positive relationship between cigarette smoke and serum level of TNF-α. Also, significantly higher serum levels of IL-1β was found in healthy active smokers compared with nonsmokers. In a recent multi-ethnic study of atherosclerosis cohort of 6814 adults without prior CDV, a monotonic association was found between higher pack-year quartiles and increasing inflammatory markers including high sensitivity CRP (hsCRP), IL-6 and fibrinogen.

NSAIDs which include aspirin, indomethacin, piroxicam, sulindac, ibuprofen and other COX-2 inhibitors, are a diverse group of similarly acting compounds that are used to treat the signs and symptoms of inflammation by primarily inhibiting the activity of the
COX enzymes and thereby affecting the synthesis of the prostaglandin signaling molecules, which are involved in a wide range of inflammation-related process.\textsuperscript{234} NSAIDs have shown the ability to alter systemic inflammation, reduce tumor recurrence and improve moderate cancer cachexia (a multifactorial syndrome affecting almost 50% of all cancer patients, characterized by skeletal muscle wasting with or without loss of fat mass and is often associated with psychological distress and fatigue).\textsuperscript{235} A large body of evidence supports aspirin’s protective effect of reducing cancer incidence and cancer mortality. The beneficial effects are particularly large and consistent for colorectal, esophageal and gastric cancers, with smaller reductions seen on breast, prostate and lung cancer.\textsuperscript{236} Data from 51 randomized controlled trials (RCTs) showed that aspirin use at doses between 75 and 100 mg/day reduced overall cancer incidence by 12%. This benefit was only noted apparently with a 24% reduction observed after 3 years of follow-up and beneficial effect became larger with increasing follow-up. The benefit was most evident in patients with a scheduled treatment duration of 5 years or longer.\textsuperscript{237} Reductions in cancer incidence were similar in men and women.\textsuperscript{237} Data from multiple RCTs showed that aspirin use can reduce total cancer death by 20% and the protective effect was only observed after 5 years of use. The magnitude of benefit became larger with longer duration of aspirin use, and it had similar benefit in men and women.\textsuperscript{238}

2.4 Risk factors for pancreatic cancer

2.4.1 Selected individual dietary factors

The following selected dietary factors and associated evidence are summarized based on the World Cancer Research Fund/American Institute for Cancer Research 2012 Continuous Update Project (CUP) summary report for pancreatic cancer, which serves as
the most updated authoritative scientific resource generating evidence on food, nutrition and physical activity relating to the prevention of pancreatic cancer. This summary report updates the pancreatic cancer section of the Second Expert Report of Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. Conclusions from the report were made based on the findings of the 2011 systematic literature review and the CUP Expert Panel discussion in June 2012. Evidence of this report was summarized based on literature review restricted to Medline and included only randomized controlled trials, cohort and case-control studies published up to September 2011. Given that there is very little difference between pancreatic cancer incidence and mortality rates due to low survival rate, study results on incidence and mortality have been presented and analyzed together in the current report, unless there is large number of papers reporting pancreatic cancer incidence and mortality separately. I additionally include evidence from literature published after CUP.

2.4.1.1 Red and processed meat intake

High intake of red meat may result in more absorption of heme iron, greater oxidative stress, and potential for DNA damage. It is also associated with the formation of N-nitroso compounds, which shares the same mechanisms for increasing risk with processed meat. Previous studies found inconsistent association for red meat and pancreatic cancer. CUP found three of seven studies on pancreatic cancer incidence that reported an increased risk when comparing the highest red meat intake group to the lowest, two of which were statistically significant. For pancreatic cancer mortality, two of three studies reported an increased risk and only one reached statistical significance. The dose–response meta-analysis showed a non-significant positive
association between red meat intake and pancreatic cancer risk [incidence and mortality combined, relative risk (RR)=1.19, 95% CI=0.98-1.45 per 100g/day with moderate heterogeneity ($I^2 = 52\%$)] and the association was significant in men (RR=1.43, 95% CI=1.10-1.86) but not in women (RR=1.06, 95% CI=0.86-1.30). Results from two later published meta-analysis were similar to the CUP findings, both meta-analysis (one included 11 prospective studies through November 2011 and the other included 10 cohort studies and 11 case-control studies up to the end of 2010) reported a positive relationship. One meta-analysis reported an overall non-significant dose-response relationship (RR=1.13, 95% CI=0.93-1.39) and the association was significant in men although not in women. The other meta-analysis found a significant association in case-control studies (RR=1.48, 95% CI=1.25-1.76) but not in cohort studies (RR=1.14, 95% CI=0.94-1.38). Five individual studies (two case-control studies and three prospective cohort studies) reported on the red meat and pancreatic cancer relationship after the CUP summary report. All five studies reported positive associations between red meat and pancreatic cancer risk, among which three studies reported significant increased risk for the highest compared with the lowest group, one study reported significant association only in men, and one observed a non-significant positive dose-response relationship. A case-control study reported consumption of barbecuing red meat versus no consumption was associated with 67% increased risk of pancreatic cancer risk. Results from the NIH-AARP study showed pancreatic cancer risk significantly increased with intake of high-temperature cooked meat, grilled/barbequed meat, or well/very well done meat, which suggested that meat cooking methods may be important in the association between red meat and risk of developing pancreatic
Similarly, the association between processed meat and pancreatic risk was inconsistent. Overall, the CUP found four of six studies on pancreatic cancer incidence reported an increased risk comparing the highest intake group to the lowest, one of which was statistically significant. For mortality, one of two studies reported a non-significant increased risk and the other reported a non-significant decreased risk. Dose-response meta-analyses which included seven studies (incidence and mortality combined) found a 17% increased risk associated with each 50g increase of processed meat per day, and this was statistically significant (RR=1.17, 95% CI=1.01-1.34) with no heterogeneity ($I^2=0$). When stratified by sex, the effect was significant in men (RR=1.21, 95% CI=1.01-1.45) but not in women (RR=1.09, 95% CI=0.69-1.73). The dose-response finding from CUP was consistent with a recent meta-analysis of prospective cohorts which also reported significantly positive associations. Two recent individual studies examining processed meat and pancreatic cancer risk both showed no associations. Limited evidence for nitrate/nitrite intake from processed meat in association with pancreatic cancer has been published but with inconsistent results. In summary, CUP concluded there was limited and inconsistent but suggestive evidence to implicate red and processed meat in pancreatic cancer etiology.

2.4.1.2 Fat intake

It is well established in animal models that total dietary fat plays a role in pancreatic carcinogenesis: long-term exposure to free fatty acids could result in pancreatic hypertrophy or hyperplasia, which in turn leads to uncontrolled growth of abnormal cells in the pancreas. Large amounts of fat intake may stimulate bile acid
secretion into the pancreatic duct and in turn stimulate the tumor promotor COX-2. In addition, the insulin resistance caused by high fat intake is another mechanism to increase pancreatic cancer risk through metabolic, immunological and hormonal alterations in the body. Several studies examined the association between total fat intake and pancreatic cancer risk with results being inconsistent. In a recent meta-analysis including 6 cohort and 13 case-control studies published up to February 2014 with total of 6,159 pancreatic cancer cases, Shen et al. found a non-significant increased risk for the highest total fat intake group compared to the lowest group (pooled RR=1.04, 95%CI=0.90-1.20, I²=57.3%), with similar effects among case-control and cohort studies. Furthermore, no significant associations were observed when stratifying by fat source. The CUP meta-analysis for total fat intake included 8 studies and showed a marginally significant positive association (RR=1.05, 95%CI=1.00-1.12) for the highest versus the lowest intake group, with no evidence of heterogeneity. In terms of saturated fatty acids, the CUP performed a dose-response meta-analysis including five studies and found an 11% statistically significant increased pancreatic cancer risk for each 10g saturated fatty acids intake per day (RR=1.11, 95% CI=1.01-1.21) with moderate heterogeneity observed. However, the evidence among individual studies is limited and inconsistent, with four of seven studies reporting a non-significant decreased risk and three reporting an increased risk (two of which were significant). In a recently published PLCO study with 411 pancreatic cancer cases, Arem et al. observed an inverse association between saturated fat, total fat intake and pancreatic cancer risk among subjects with less than four years of follow-up, and associations became weaker and nonsignificant after excluding these subjects, whereas intakes of monounsaturated and polyunsaturated fats and fats from animal or plant
sources showed no associations with pancreatic cancer. In another large cohort study (the NIH-AARP), researchers found that higher intake of total fat, saturated fat and monounsaturated fat all significantly increase pancreatic cancer risk, but there was no association with polyunsaturated fat and associations were strongest for saturated fat from animal food sources. The authors also examined individual fatty acids and found increased intake of two types of saturated fatty acids (SFA) (palmitic acid and stearic acid), one monounsaturated fatty acids (MUFA) (palmitoleic acid), one n-6 polyunsaturated fatty acid (PUFA) (arachidonic acid), and two n-3 PUFAs (eicosapentaenoic acid, docosahexaenoic acid) were associated with increased risk of pancreatic cancer. The trans fatty acids and pancreatic cancer relationship was examined in three studies, with two studies yielding non-significant positive associations and one study reporting a non-significant inverse association.

### 2.4.1.3 Vegetable and fruit intake

A large number of antioxidant vitamins and minerals rich in fruits and vegetables have been proposed to have many cancer-protective properties, including reducing oxidative DNA damage/mutations by reducing oxidative stress and inflammation, or stimulating glucose metabolism and/or insulin sensitivity. A recent meta-analysis summarizing available evidence (15 case-control studies, 8 prospective studies, and one pooled analysis) up to January 2015 found a significant reduction of pancreatic cancer risk for the highest versus lowest intake of vegetable and fruit combined (RR=0.73, 95% CI=0.53-1.00), fruit (RR=0.73, 95% CI=0.63-0.84), and vegetable (RR=0.76, 95% CI=0.69-0.83) with significant between-study heterogeneity ($I^2$=70.5%, 55.7%, and 43.0%, respectively). These inverse associations were borderline significant in
prospective studies. In a pooled analysis of 14 prospective cohort studies from North America, Europe, and Australia where primary data from these studies was used by standardizing the definitions of fruit and vegetable intake and covariate categories across studies, Koushik et al. found that for each 100g/day increase in intake of fruits and vegetables during adulthood there was a non-significant increased risk of pancreatic cancer with no statistically significant heterogeneity between studies (pooled multivariable RR=1.01, 95% CI= 0.99-1.03) for total fruits; RR=1.02, 95% CI= 0.99-1.06 for total vegetables). Associations were similar for men and women. This lack of overall association was consistent regardless of whether intake was examined as a continuous measure or in categories based on absolute cut-points or study-specific quartiles. In the analyses of individual foods, statistically significant increased pancreatic cancer risks were observed for each 3-servings/week increment in intake of strawberries, fruit juice, brussels sprouts, green peppers, lettuce/salad, and tomatoes, although most of the positive associations became non-significant after adjustment for total fruit or vegetables. They also found each 100g/ day increment in intake of green leafy vegetables was associated with 17% increased risk with no significant between-study heterogeneity. These non-significant positive associations were not expected a priori and may have been due to chance. Some research has suggested that exposure to pesticides, which may be present on fruits and vegetables, may increase risk. Other research has suggested that indole-3-carbinol, which is found in cruciferous vegetables such as Brussels sprouts, may have some cancer-promoting effects, particularly when administered after carcinogen exposure. In addition, residual confounding from measurement error in the included covariates or uncontrolled covariates as well as
misclassification in estimates of usual consumption due to only one time diet assessment may also contribute to the unexpected results, as suggested by authors of this paper. In the Multiethnic Cohort (MEC) Study with 529 pancreatic cancer cases, no association between total vegetable intake and vegetable subgroup intake and pancreatic risk was observed among the overall population, but an inverse association with total vegetables, light green vegetables, and legumes was observed in overweight/obese subjects. One case-control study looked at nutrient intake from fruits, vegetables, and supplements in association with pancreatic cancer incidence, and found a significant inverse association in a dose-dependent manner for magnesium, potassium, selenium, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin, niacin, total alpha-tocopherol, total vitamin A activity, vitamin B6, and vitamin C.

2.4.1.4 Carbohydrate intake, glycemic load (GL), glycemic index (GI), dietary fructose and sucrose

GI is a value assigned to foods based on how slowly or quickly those foods cause blood glucose levels to increase, while dietary GL, which reflects both the quality and quantity of carbohydrates ingested, is the product of the dietary GI and total dietary carbohydrates. Fructose can increase postprandial plasma glucose levels, and can increase risk of insulin resistance, type-2 diabetes and obesity, which may lead to higher pancreatic cancer risk. Results from a recent cohort study meta-analysis including 10 cohort studies searching up to 2011 September revealed a significant increased risk with fructose intake (RR= 1.22, 95% CI=1.08–1.37, I² = 0% per 25 g/day increase) but did not find an association of pancreatic cancer with dietary GI, GL, total carbohydrates and sucrose. Significantly higher risk of pancreatic cancer was reported to be associated
with higher GL only in a large population-based case-control study conducted in Canada. In the MEC Study, pancreatic cancer risk increased with higher intakes of total sugars, fructose, and sucrose in overweight or obese participants (RR=1.46, 95% CI=0.95–2.25; P for trend =0.04), but the association was not significant in normal-weight participants. CUP conducted a dose-response meta-analyses which included six studies on dietary fructose and pancreatic cancer incidence and results showed a 22% statistically significant increased risk for each 25g increased intake of fructose per day (RR=1.22, 95% CI=1.08-1.37) with no heterogeneity observed and no differences of the association were observed between men and women. The CUP found that there were no clear associations between other related exposures (total carbohydrate, sucrose and soft drinks) and pancreatic cancer risk. Although there was ample consistent evidence, and some evidence for a dose-response relationship, fructose comes from many sources making the evidence difficult to interpret, so CUP concluded that the evidence suggesting that foods and beverages containing fructose are a cause of pancreatic cancer is limited.

Increased carbohydrate intake during adolescence (age 12-13) and midlife could increase pancreatic cancer risk in later life. In a recently published meta-analyses, dietary fiber intake was found to be inversely associated with pancreatic cancer in case-control studies but not in cohort studies.

2.4.1.5 Coffee

There was substantial evidence consistent with low heterogeneity, showing no effect of coffee intake on the risk of pancreatic cancer. The CUP dose-response meta-analysis of 13 cohort studies found an overall non-significant positive association between each one cup of coffee increase per day and pancreatic cancer (incidence and
mortality combined, RR=1.02, 95% CI=0.95-1.09). When stratifying pancreatic cancer outcomes, meta-analysis of three studies on mortality showed no association (RR=0.99, 95% CI=0.76-1.28), and non-significant positive association for incidence (RR=1.03, 95% CI =0.95-1.11). The CUP finding is generally consistent with the other published meta-analyses: the Harvard pooling project of 14 prospective cohort studies revealed a similar pooled RR for each 237g/d of coffee (RR=1.01, 95% CI=0.97-1.04, I²=38);\textsuperscript{272} an updated meta-analysis including 20 cohort studies published up to November 2015 reported the summary RR of pancreatic cancer risk for the highest category of coffee intake compared to lowest category was 1.06 (95% CI= 0.94-1.20, I² = 38.5%) after removing one study which caused largest heterogeneity.\textsuperscript{273} In a large prospective study including the largest number of pancreatic cancer cases to date (NIH-AARP study), no associations between total, caffeinated, or decaffeinated coffee intake and pancreatic cancer risk were observed.\textsuperscript{274}

\textbf{2.4.1.6 Alcohol}

Heavy alcohol consumption might increase pancreatic cancer risk by promoting the effects of other risk factors such as tobacco smoking. Heavy alcohol consumption may also alter metabolic pathways involved in the inflammatory response and carcinogenesis (i.e. increased production of reactive oxygen species resulting in oxidative DNA damage and other independent genetic and epigenetic effects).\textsuperscript{275,276} Furthermore, alcohol use is the single most common cause of pancreatitis (its attributable risk is approximately 40\%).\textsuperscript{277} It is thought that ethanol metabolites, such as acetaldehyde, might be important carcinogens for pancreatic cancer.\textsuperscript{275} The dose-response meta-analyses for total alcoholic drinks and pancreatic cancer (incidence and mortality
combined) conducted by CUP found a nonlinear association with significant risk starting from consuming 17.6 or more drinks per week. When stratifying analysis by sex for incidence and mortality combined, there was no clear linear association in women (RR=1.00, 95% CI: 0.98-1.01), but in men there was a marginally significant increased risk (RR 1.01, 95% CI= 1.00-1.02). When alcohol (as ethanol) was examined alone, CUP dose-response meta-analysis showed a nonlinear association. The risk was significant for those consuming 53.4g ethanol or more a day. Results from a published pooled analyses with a total of 14 cohort studies and a meta-analysis on alcohol (as ethanol) and pancreatic cancer risk consistently showed that daily consumption of 30g of alcohol, or the equivalent of >3 glasses of any alcoholic beverage per day, is associated with a 22% increased risk of pancreatic cancer. A statistically significant increase was only observed among men consuming 45 or more grams of alcohol from liquor per day in the Pancreatic Cancer Cohort Consortium (PanScan). CUP concluded that the increased pancreatic cancer risk was limited to those consuming more than about 3 alcoholic drinks per day.

2.4.2 Dietary patterns

Eleven published studies have investigated the dietary patterns and pancreatic cancer relationship, among them five studies examined a priori dietary patterns (HEI-2005, aMDS, MDS17 and DII38,39), and the other six studies focused on a posteriori dietary patterns. Among the five a priori dietary pattern studies, in general, better dietary quality was associated with lower pancreatic cancer risk. Results were significant for studies examining HEI-2005 and MDS score as well as DII, but not significant when using aMDS282 as the exposure. In the NIH-AARP with 2,383 incident
exocrine pancreatic cancer cases, Arem et al. found the top quintile of HEI-2005 score was associated with a 15% decreased risk of pancreatic cancer compared to the lowest quintile ($HR_{Q5vsQ1}=0.85$, 95% CI=0.74 -0.97, P-trend=0.003) for the overall study population, and the association was significant in men but not in women. In another NIH-AARP investigation which used aMDS as criteria to calculate the dietary score and categorized it to healthy and unhealthy diet, healthy diet was found to be associated with 8% reduction in pancreatic cancer risk compared to unhealthy diet (HR=0.92, 95% CI=0.81-1.05). Based on aggregated primary data from two Italian case-control studies, Bosetti et al. found a significant reduction in risk with increased MDS score ($(hazard ratio (HR) for a unit increase=0.85, 95% CI =0.80–0.91)$) with significant inverse associations observed in each case-control study. Two case-control studies using the DII to examine its association with pancreatic cancer risk found subjects in the highest quintile of DII scores had a 2.48-fold (OR=2.48, 95% CI=1.50-4.10, P trend=0.002) and a 2.54-fold (OR=2.54, 95% CI=1.87-3.46, P trend<0.001) elevated odds of pancreatic cancer compared to those in the first quintile.

The other six a posteriori studies identified food groups/dietary patterns based on dietary data using statistical analysis method which included the RRR and principal component analysis (PCA); factor score was calculated and assigned to each subject for each food item. Nothlings et al. reported in the MEC study that a food group pattern score which was predictive of flavonol intake (quercetin, kaempferol, and myricetin) was associated with lower risk, although the result was not significant ($HR_{Q5vsQ1}=0.88$, 95% CI=0.67-1.15, P-trend=-0.14). Three studies looked at Western dietary patterns and pancreatic cancer relationships, and only one case-control study found a significant
positive association among men only (OR$_{Q5vsQ1}$=2.4, 95% CI=1.3-4.2, P.trend=0.008). This study also found a significant inverse association of a prudent dietary pattern characterized by greater intake of vegetables, fruit, fish, poultry, whole grains, and low-fat dairy and pancreatic cancer.$^{21}$ Results from the other two studies with the Western dietary pattern did not support an association of prudent or Western patterns with pancreatic cancer risk,$^{18,20}$ but a significant positive association for prudent dietary pattern score among men was observed in the Health Professionals Follow-Up Study (HPFS).$^{18}$ A population-based, case-control study conducted in Canada between 1994 and 1997 found “fruit and vegetable” dietary pattern was inversely associated with pancreatic cancer risk for men only (OR$_{Q4vsQ1}$=0.51, 95% CI=0.29–0.90, P-trend<0.01) and “drinker” dietary pattern derived from this study had no association with pancreatic cancer.$^{20}$ In the Iowa Women’s Health Study, Maki Inoue-Choi et al. used PCA method to derive several food patterns (“high vegetable”, “low fat”, Mediterranean, “high fiber” and “high fruit” food patterns) but none of the food patterns was associated with pancreatic cancer risk in the study.$^{15}$ Using the same PCA method, another Italian case-control study found compared to the lowest quartile of score, the highest quartile of “animal product” pattern score and “starch rich” pattern score had 2.03 folds and 1.69 folds increased risk of pancreatic cancer, respectively and an inverse association emerged for the “vitamins and fiber” pattern.$^{16}$

2.4.3 Smoking

Tobacco is the most well-established risk factor for pancreatic cancer, and with alcohol, they are cofactors to increase risk.$^{277}$ Studies have consistently confirmed the relationship between smoking and pancreatic cancer, with smokers having about 2-fold
excess risk compared with nonsmokers. This increased risk is smaller for pancreatic
cancer than for lung cancer, which could be because pancreas has indirect exposure to
tobacco carcinogens, though as in lung cancer, the risk is proportional to the duration and
the intensity of smoking. Predictably, the deleterious effect of smoking on the
pancreas is caused by the release of or formation of carcinogens from tobacco. Several
genes mediate the degradation of tobacco carcinogens but little is known how they
function to affect risk. In a comprehensive meta-analysis of 47 case-control and 35
cohort studies, Iodice et al. concluded that the overall risk of pancreatic cancer for current
and former cigarette smokers was, respectively, 1.74 (95% CI=1.61-1.87) and 1.20 (95%
CI=1.11-1.29) compared to non-smokers. For former cigarette smokers, the risk remains
elevated for a minimum of 10 years after cessation. This study also found a linear
increased trend of pancreatic cancer risk with increasing intensity (cigarette smoked per
day), duration and cumulative dose with 1% increased risk per pack-year. Data from
12 case-control studies within the International Pancreatic Cancer Case-Control
Consortium (PanC4), pooled analysis of 30 cohort studies from the Asia-Pacific
region, a meta-analysis of three case-control and four cohort studies conducted in
Japan and a pooled analysis from the Pancreatic Cohort Consortium confirmed the
positive link, with a summary RR between 1.6 and 2.2 for current cigarette smokers and
between 1.1 and 1.7 for former cigarette smokers, compared to non-smokers. There are
several other forms of tobacco besides cigarette; the PanC4 study found cigar-only users
increased pancreatic cancer risk by 60% (OR=1.6, 95% CI=1.2-2.3) compared with never
tobacco users and had higher risk than cigarette-only smokers, but pipe-smoking and
smokeless tobacco such as chewing tobacco and snuff did not appear to increase the
Some evidence also indicated increased risk with increasing amounts of cigars smoked per day although no association with duration. The recent meta-analysis found that current pipe and/or cigar smokers had 47% elevated pancreatic cancer risk compared to non-smokers, however, the association was not significant for former pipe and/or cigar smokers. Exposure to environmental smoking (passive smoking) during childhood or adulthood at home did not appear to be associated with pancreatic cancer risk.

Mutations in carcinogen-metabolizing genes, such as glutathione-S-transferase, with multiple sequence variants may be genetic modifiers for smoking-related pancreatic cancer. Risk more than 15 years after smoking cessation was similar to that for never smokers. Estimates of excess odds ratio per pack-year declined with increasing intensity, suggesting greater risk for total exposure delivered at lower intensity for longer duration than for higher intensity for shorter duration. This finding and the decline in risk after smoking cessation suggest that smoking has a late-stage effect.

2.4.4 Adult attained height

The number of cell divisions in fetal life and childhood, health and nutrition status in childhood, and age of sexual maturity which will largely determine the adult height play a role in affecting the hormonal microenvironment and circulating levels of growth factors, insulin, and estrogens. Thus, taller adults are more likely to have error during DNA replication, which may result in cancer development. CUP identified 14 studies which examined the adult height and pancreatic cancer association, and the result was generally consistent with eight of 10 studies on incidence showing an increased risk (three of which were statistically significant) and one study on mortality showing a non-significant increased risk when comparing the highest versus lowest groups. The CUP
meta-analysis showed a 7% statistically significant increased risk (incidence and
mortality combined) per 5cm (RR=1.07, 95% CI=1.03-1.12) with considerable
heterogeneity observed, which was consistent with the finding from most recent
published meta-analysis including 12 cohort studies, showing the pooled RR per 5-cm
increase in height was 1.07 (95% CI=1.03-1.12, I² =57%) and the association was
similar among men and women.\textsuperscript{292}

2.4.5 Body fatness/obesity and physical activity

There is an established connection between increasing BMI or body fatness and
insulin resistance, which in turn increase pancreatic cancer risk via hyperinsulinemia.\textsuperscript{293}
Body fat also directly affects levels of a number of hormones and growth factors, such as
insulin, insulin-like growth factor 1 (IGF-1), leptin, and estrogens, creating an
environment that encourages carcinogenesis and discourages apoptosis.\textsuperscript{294} In addition, fat
cell produces pro-inflammatory factors, which may contribute to the development of
several cancers.\textsuperscript{295} Body fat is usually reflected by BMI, measures of abdominal girth
such as waist circumstance and waist to hip ratio (WHR), and weight gain. For both
pancreatic cancer incidence and mortality, CUP found a 10% statistically significant
increased risk per 5 BMI units (RR=1.10, 95% CI=1.07-1.14 for incidence and RR=1.10,
95% CI=1.02-1.19 for mortality) with lower between-study heterogeneity (I²=23%) and
no difference between men and women in the dose-response meta-analysis. There was
evidence of a nonlinear dose-response with an increased risk apparent for BMI of 25
kg/m\textsuperscript{2} or higher. CUP findings on pancreatic cancer incidence are generally consistent
with three large published pooled studies and a recent meta-analysis. The Harvard
pooling project reported a linear increased trend of pancreatic cancer risk for each 5 BMI
units (RR=1.14, 95% CI=1.07–1.21), and reported a positive association for pancreatic cancer with higher BMI in early adulthood, and with greater than 10 kg/m² BMI gain between early adulthood and baseline compared to individuals whose BMI remained stable.\textsuperscript{296} National Cancer Institute’s pooled analysis found that every 5kg/m² increment of BMI was associated with a 1.08-fold increased pancreatic cancer risk for all participants, but the association was only significant for women, and only significant among never and former smokers, but not among current smokers.\textsuperscript{297} The PanScan pooling study reported pancreatic cancer risk increased by 13% for each 5 unit BMI increase (OR=1.13, 95% CI=1.11-1.14).\textsuperscript{298} The recent meta-analysis on BMI and PanC risk found a non-linear association between BMI and pancreatic cancer risk, with the lowest risk among persons with a BMI around 21 kg/m² and with the most pronounced risk among persons with a BMI>35 kg/m², however, among nonsmokers, there was a linearly increased risk.\textsuperscript{299} Data from the NIH-AARP study on lifetime adiposity and pancreatic cancer risk reported a higher risk for those being overweight or obese at ages 18, 35, 50, or >50 years (baseline BMI) compared to normal weight. A longer duration of BMI>25 kg/m² was significantly associated with pancreatic cancer risk, with individuals who reported diabetes having the greatest risk. They also found that a substantial gain in adiposity (>10 kg/m²) after age 50 years old was significantly associated with increased pancreatic cancer risk.\textsuperscript{300} A recently published pooled analysis with data combined from 20 prospective cohort studies which focused on pancreatic cancer mortality showed higher BMI during early adulthood (ages 18-21 years) (HR=1.18, 95% CI=1.11-1.25 per 5 kg/m²) and BMI gain after early adulthood (HR=1.05, 95% CI=1.01–1.10 per 5 kg/m²) was associated with increased mortality.
Five studies included in the CUP all found a non-significant increased pancreatic cancer incidence for highest waist circumference versus lowest category, and meta-analysis using these five studies showed an 11% statistically significant increased risk per 10cm waist circumference increase (RR=1.11, 95% CI=1.05-1.18) with no heterogeneity. In a stratified analysis, the effect was statistically significant in women, but not in men. The CUP findings were consistent with findings from two published pooling studies. Higher waist circumference was also reported to be associated with increased pancreatic cancer mortality in a recent pooled analysis of 20 cohort studies (HR=1.07, 95% CI=1.00–1.14 per 10 cm).

Higher WHR was consistently associated with increased pancreatic cancer incidence and mortality. The CUP reported a 19% statistically significant increased risk of pancreatic cancer for each 0.1 unit increase of the ratio. Others have suggested that overweight and obese individuals develop pancreatic cancer at a younger age than do patients with a normal weight, and that they also have lower survival rate once pancreatic cancer is diagnosed. Given ample and consistent evidence for the positive association between various measures of body fatness and pancreatic cancer incidence and mortality, the CUP concluded that the evidence that greater body fatness, including abdominal fatness and adult weight gain, was a cause of pancreatic cancer is convincing.

Physical activity can play a preventive role in pancreatic cancer development by regulating body weight and reducing insulin resistance, DNA damage, and chronic inflammation. In a recent meta-analysis comprising 30 studies with 10,501 pancreatic...
cancer cases, results from cohort studies were homogeneous and indicated a weak, statistically significant inverse association between high versus low levels of total PA and pancreatic cancer (incidence and mortality combined, RR = 0.93, 95% CI = 0.88–0.98). Sub-analysis in the cohort studies showed that the protective effect appeared to be more pronounced for consistent PA over time (PA maintained for more than 10 years) (RR = 0.86, 95% CI = 0.76–0.97) than for recent past PA (up to 3 years before baseline) or distant past PA (>=3 years prior to baseline). Occupational PA in the cohort studies had statistically significant inverse association with pancreatic cancer risk and appeared to generate a stronger risk reduction than did recreational activity, and that risk reduction was driven mainly by consistent activity over time. Stratified analysis on PA intensity showed null association for vigorous intensity, moderate intensity and low intensity PA in both case-control and cohort studies. The association was not modified by smoking status or BMI. Another meta-analysis examining leisure time PA and pancreatic cancer yielded a summary 11% significant reduction in risk comparing highest to lowest category, but the pooled association was only significant in case-control studies. They also found leisure time PA appeared to have the strongest effect among young populations.

2.4.6 Past medical history

Several medical conditions are associated with pancreatic cancer risk, among them, diabetes has been investigated in the largest number of studies. Diabetes was associated with pancreatic cancer at the onset of symptoms in about 40 to 60% of patients, being a consequence or the cause of the disease, which is not fully known. Five recent pooled analyses have concordant findings, showing that diabetics
had 40% to 90% increased pancreatic cancer risk compared to non-diabetics, and the RR decreased with duration of diabetes, but a significant excess risk was still evident 10 years after diabetes diagnosis. Among diabetics, risk was higher in insulin ever users compared with nonusers, and insulin use of >10 years was associated with a reduced risk of pancreatic cancer (OR=0.5, 95% CI=0.3-0.9, P-trend < 0.001).\(^{40}\) Even in the absence of diabetes mellitus, higher fasting blood sugar and blood glucose or impaired glucose tolerance are associated with higher pancreatic cancer risk.\(^{285,309,310}\)

The lag period between diagnosis of chronic pancreatitis and pancreatic cancer is usually one or two decades, whereas pancreatitis occurring a year or two before the diagnosis of pancreatic cancer is often because of tumor-related ductal obstruction.\(^{311}\) A comprehensive meta-analysis of 22 studies reported a statistically significant increase of pancreatic cancer risk associated with all types of pancreatitis, with summary RRs ranging from 5.1 for unspecified pancreatitis to 100 for tropical pancreatitis.\(^{311,312}\) Results from a pooled analysis of 10 case-control studies revealed ORs ranging from 3.4 (for an interval >25 years) to 21 (for an interval between pancreatitis and pancreatic cancer ≤1 year) which probably reflected a combination of reverse causation and antecedent misdiagnosis of pancreas cancer as pancreatitis. The younger (<65 years) pancreatic cancer cases showed stronger associations with previous (>2 years) pancreatitis than the older (≥65 years) cases.\(^{313}\)

Individuals with a history of gallstones and cholecystectomy were at 70% and 31% increased risk of pancreatic cancer, respectively, reported by a recent metaanalysis.\(^{314}\) The positive associations were observed among both Asian population and Whites.\(^{314}\) Diagnosis of gastric or duodenal ulcer within 2 years before pancreatic cancer
diagnosis increased cancer risk for 2.43 folds, but the significant positive association disappeared when ulcer duration persisted more than 2 years. Similarly, individuals with history of gastrectomy were at elevated pancreatic cancer risk but the excess risk was only limited to a gastrectomy within 2 years before cancer diagnosis. The increased risk for short-term history of ulcer and gastrectomy suggested that such association was due to reverse causality (i.e., underlying diseases) or increased cancer surveillance.\textsuperscript{315,316} No overall association was observed between Helicobacter pylori infection and risk of pancreatic cancer, but cytotoxin-associated gene A (CagA)-negative nonvirulent strains of Helicobacter pylori has been shown to increase pancreatic cancer risk, with findings confirmed in three recent published meta-analyses.\textsuperscript{317-319}

A positive association between periodontal disease (PD) and pancreatic cancer was reported in most studies performed on this topic.\textsuperscript{320} In a recent large cohort study in Taiwan, PD was found to be a risk factor for pancreatic cancer (HR=1.55, 95% CI=1.02-2.33) independent of other comorbidities such as diabetes, and this positive association occurred predominantly among those aged 65 years or older.\textsuperscript{321}

Venous thromboembolic events (VTE) was found to be associated with increased risk of pancreatic cancer in a meta-analysis comprising 12 studies but with significant between-study heterogeneity (RR= 6.1, 95%CI=3.8–9.7, P-heterogeneity<0.001).\textsuperscript{322} Using the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data of 1.2 million cancer cases and 200,000 controls (66-99 years old, 1992-2005), Marks et al. found that VTE has been associated with an increased risk of pancreatic cancer among US elderly adults (OR=1.53, 95% CI=1.43-1.64), with strongest risks observed within 1 year of VTE diagnosis, but risks were still elevated more than 6 years after VTE.\textsuperscript{323} There
was consistent evidence showing that history of allergy, especially allergy to animal or allergy related to atopy and hay fever, reduced pancreatic cancer risk by 20–40%, based on evidence from PanScan pooling analysis\textsuperscript{324} and a meta-analysis.\textsuperscript{325}

Finally, recent meta-analyses summarized the association with hepatitis B virus (HBV) infection.\textsuperscript{326-330} These reviews consistently reported a significant positive association between exposure to HBV infection and pancreatic cancer, but past exposure to HBV with natural immunity (anti-HB surface antibody positive) was not related to pancreatic cancer development, nor was the HBV active replication (hepatitis B e antigen positive status).\textsuperscript{329} Therefore, it is still unclear whether serological pattern of past exposure to HBV with or without natural immunity is associated with an enhanced risk of this malignancy. Results from two meta-analyses suggest a positive association between hepatitis C virus infection and pancreatic cancer risk\textsuperscript{328,329} but the same uncertainty as the HBV serological pattern was present for HCV.

\subsection*{2.4.7 Demographic factors}

As for other cancers, less than 10\% of pancreatic cancer cases occur at age younger than 55 years old, and the median age of onset is 71 years. In all race/ethnicity groups, men have higher incidence rates than women.\textsuperscript{277} Rates of pancreatic cancer are considerably higher in the African American population than in any other racial groups, although little is known about the reasons for the racial disparity.\textsuperscript{331} Males, Jewish descent and black ethnicity are associated with increased risk compared to their counterparts.\textsuperscript{332} No consistent relationship has been confirmed between development of the disease and socioeconomic status or immigration status. Finally, incidence rates of pancreatic cancer are highest in Western and industrialized countries and lowest in
underdeveloped nations.\textsuperscript{332}

2.4.8 Family history and genetic factors

Several hereditary and genetic factors for pancreatic cancer have been identified. PanScan pooled analysis\textsuperscript{333} and a meta-analysis which included seven case-control and two cohort studies\textsuperscript{334} both observed that a family history of pancreatic cancer in a parent, sibling or child was associated with about 80\% increased risk of developing this malignancy. A family history of prostate cancer also was identified to increase pancreatic cancer risk (OR=1.45, 95\% CI=1.12–1.89).\textsuperscript{333} The ABO blood group has recently emerged as an important susceptibility factor for pancreatic cancer. Two recent meta-analyses\textsuperscript{335,336} and a pooled PanScan analysis\textsuperscript{337} reported compared with blood type O, subjects with types A, AB, and B have a 23–53\% increased risk of pancreatic cancer. In addition, compared with OO genotype, subjects with AO, AA, BO, BB genotypes significantly elevated the risk.\textsuperscript{337} Both inherited high-penetrant mutations in \textit{BRCA2}, \textit{ATM}, \textit{PALB2}, \textit{BRCA1}, \textit{STK11}, \textit{CDKN2A} and mismatch repair genes as well as low-penetrant loci were associated with increased risk, and several previous genome-wide association study (GWAS) of pancreatic cancer with large numbers of cases and controls of European or North American populations revealed significant associations with single nucleotide polymorphisms (SNPs) at locations: 9q34.2(\textit{ABO})\textsuperscript{338}, 13q22.1(\textit{KLF5})\textsuperscript{339}, 5p15.33 (\textit{TERT}, \textit{CLPTM1})\textsuperscript{339,340}, 13q12.2 (\textit{PDX1})\textsuperscript{340}, 1q32.1(\textit{NR5A2})\textsuperscript{339}, 7q32.3(\textit{LINC-PINT})\textsuperscript{340}, 16q23.1(\textit{BCAR1})\textsuperscript{340} and 22q12.1 (\textit{ZNRF3})\textsuperscript{340}, 17q25.1 (\textit{LINC00673})\textsuperscript{341}, 7p13 (\textit{SUGCT})\textsuperscript{341}, and 3q29 (\textit{TP63})\textsuperscript{341}, 2p13.3 (\textit{ETAA1})\textsuperscript{341}, with odds ratio from 0.77 to 1.46.

2.4.9 Drugs

Many studies have assessed the effect of common drugs on pancreatic cancer,
such as NSAIDs (with most reports focusing on aspirin), statins and antidiabetic drugs such as metformin. Three most recent meta-analyses reported aspirin use was inversely associated with pancreatic cancer incidence,\textsuperscript{72,342,343} two of them found only high-dose aspirin use was associated with reduced pancreatic cancer,\textsuperscript{72,342} only one study among them\textsuperscript{343} found risk decreased with increasing cumulative year of use of aspirin. Non-aspirin NSAIDs was not associated with pancreatic cancer risk, supported by two meta-analyses.\textsuperscript{72,342} A pooled analysis with eight clinical trials reported the latent period before a protective effect of daily aspirin use on pancreatic cancer death was about 5 years.\textsuperscript{238} Statin use was not found to be associated with pancreatic cancer risk,\textsuperscript{344} while the association between metformin use and pancreatic cancer appeared to be inconsistent\textsuperscript{345-348} among diabetics. With regard to other anti-diabetic medications (ADMs), exogenous insulin use was investigated in many studies, with consistent findings that supported an increased pancreatic cancer risk with insulin use.\textsuperscript{40,346,349,350} Although insulin, itself, can promote carcinogenesis either directly or indirectly by increasing insulin-like growth factor-1 activity, resulting in abnormal stimulation of multiple cellular signaling cascades and affecting cell metabolism,\textsuperscript{351} understanding the complex relationship between ADMs and pancreatic cancer risk is particularly difficult. Under a markedly diabetogenic state (normally found in pancreatic cancer patients), those with previously stable diabetes may experience worsening of their glycemic control and, hence, are more likely to require multiple ADMs, or require aggressive insulin therapy. The reverse causality, wherein the inherent nature of pancreatic cancer may have resulted in overestimation of the apparent carcinogenic effects of insulin, is difficult to measure.\textsuperscript{346} In a recent large prospective randomized trial, use of insulin glargine as compared with standard care was not
associated with an increased incidence of cancer, though pancreatic cancer was not independently evaluated in this study.\textsuperscript{352}

2.5 Summary of dietary factors and pancreatic cancer risk in the PLCO and NIH-AARP Studies

As reported above, several dietary factors have been examined with pancreatic cancer risk in the two prospective cohorts that are utilized in this dissertation (PLCO and NIH-AARP studies). Table 1 below summarizes the main findings with regard to associations between all dietary factors and pancreatic cancer identified from these two cohorts. Some dietary factors such as red meat which contained mostly pro-inflammatory components were associated with increased pancreatic cancer risk in the NIH-AARP,\textsuperscript{248} whereas saturated fat was inversely associated with risk in the PLCO.\textsuperscript{256} Some anti-inflammatory dietary factors such as fruits and vegetables were not associated with pancreatic cancer risk in the pooled cohort which included the PLCO.\textsuperscript{261} The different relationships between inflammation-modulated foods/nutrients and pancreatic cancer provide further justification for examining whole dietary patterns with regard to inflammation and pancreatic cancer risk in these two large, prospective cohort studies.
Table 2.1 Summary table for associations between dietary factors and pancreatic cancer in the PLCO and NIH-AARP

<table>
<thead>
<tr>
<th>Dietary factors</th>
<th>PLCO</th>
<th>NIH-AARP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Citation</td>
<td>Main findings</td>
</tr>
<tr>
<td>Meat and associated products</td>
<td>Pancreatic cancer risk comparing exposure Q5 vs Q1:</td>
<td>Are meat and heme iron intake associated with pancreatic cancer?</td>
</tr>
<tr>
<td></td>
<td>Red meat intake with well to very well doneness level</td>
<td>Results from the NIH-AARP diet and health cohort.</td>
</tr>
<tr>
<td></td>
<td>HR=1.6 (95%CI =1.01-2.54), P-trend=0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Red BBQ meat with well to very well doneness level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR=1.35 (95%CI =1.00-1.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mutagenic Activity Index (MAI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR=1.87 (95%CI=1.16, 3.02), P-trend=0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meat-derived mutagen 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(DiMeIQx)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR=1.81 (95%CI=1.20, 2.74), P-trend=0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meat-derived mutagen 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MelQx)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR=1.75 (95%CI=1.11, 2.76), P-trend=0.08</td>
<td></td>
</tr>
</tbody>
</table>

Pancreatic cancer risk comparing exposure Q5 vs Q1:
- Total meat
  HR = 1.20, 95%CI=1.02-1.42, P-trend = 0.03
- Red meat
  HR=1.22, 95%CI =1.01-1.48, P- trend = 0.02
- High-temperature cooked meat
  HR=1.21, 95%CI=1.00-1.45, P-trend = 0.02
- Grilled/barbequed meat
  HR = 1.24, 95% CI=1.03-1.50, P-trend = 0.007
- Well/very well done meat
  HR=1.32, 95% CI=1.10-1.58, P-trend = 0.005
- Heme iron from red meat (Q4 vs Q1)
  HR=1.21, 95% CI=1.01-1.45, P- trend = 0.04

All these significant associations above were observed among all population and among men only, but not among women.

Meat types: White meat and processed meat were not associated with pancreatic cancer among all, but women had a significant association of white meat and pancreatic cancer
HR=1.33, 95% CI=1.02-1.74, P- trend =0.04

Meat cooking methods: pan-fried meat, oven-broiled meat, sautéed, baked or microwaved meat were not risk factors for pancreatic cancer, but rare/medium done cooked meat was
(BaP) and one hydroxycitric acid [2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)] were not associated with pancreatic cancer risk.

Jiao L et al. (2015) Dietary consumption of advanced glycation end products and pancreatic cancer in the prospective NIH-AARP Diet and Health Study. Am J Clin Nutr

Pancreatic cancer risk comparing exposure Q5 vs Q1:

- **Red meat**
  - Men: HR=1.35, 95%CI=1.07-1.70, P-trend=0.05
  - Red meat cooked at high temperature
  - Men: HR=1.29, 95%CI=1.04-1.59, P-trend=0.005

- **Processed meat**
  - Men: HR=1.15, 95%CI=0.95-1.40, P-trend=0.19
  - N(ϵ)-(carboxymethyl)lysine (CML) Advanced glycation end products (AGEs):
    - Men: HR=1.43, 95%CI=1.06-1.93, P trend = 0.003
    - Women: HR=1.14, 95%CI=0.76-1.72, P-trend = 0.42

Meat consumption was not associated with risk of pancreatic cancer in women.


Pancreatic cancer risk comparing exposure Q5 vs Q1:

- **Total meat**
  - Men: HR=1.41, 95%CI=1.08-1.83, P trend=0.001

- **Red meat**
  - Men: HR=1.42, 95%CI=1.05-1.91, P trend=0.01

- **High-temperature cooked meat**
  - Men: HR=1.52, 95%CI=1.12-2.06, P trend=0.005
| & prevention<sup>153</sup> | Grilled or barbecued meat  
Men: HR=1.46,  
95%CI=1.06-2.00, P  
trend=0.02  
Oven-broiled meat  
Men:HR=1.45 ,95%=1.12-  
1.89, P trend=0.006  
Overall mutagenic activity  
(revertant colonies/1,000 kcal)  
Men: HR=2.32,95%=1.52-  
3.56, P trend=0.001  
Total DiMeIQx among all:  
HR=1.29 ,95%=1.01-1.64, P  
trend=0.006  
White meat and processed meat and other cooking methods and meat doneness were not associated with pancreatic cancer in men. No associations between meat and cooking methods among women were detected. |
|---|---|
| Aschebrook-Kilfoy B et al. (2011)  
Pancreatic cancer and exposure to dietary nitrate and nitrite in the NIH-AARP Diet and Health Study.  
American journal of epidemiology<sup>250</sup> | No association between total nitrate or nitrite intake  
and pancreatic cancer in men or women.  
Processed meat sources of dietary nitrate and nitrite  
Men: HR=1.18, 95% CI= 0.95-1.47, P-trend=0.11  
Women: No association  
Nitrate/nitrite intake from processed meat at ages 12-13 years  
Men: HR= 1.32, 95%CI= 0.99-1.76; P-trend = 0.11  
Women: no association with adult or adolescent nitrate or nitrite intake from processed meats |
| Fat and fatty acids | Arem H et al. (2013). Dietary fat intake and risk of pancreatic cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Annals of epidemiology 256 | Total fat
HR_{Q5VSQ1}=0.64, 95% CI=0.39–1.06, P-trend=0.015 (<4 years);
HR_{Q5VSQ1}=0.76, 95% CI=0.51–1.15, P-trend=0.35 (>=4 years) | Thiebaut AC et al. (2009) Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. J Natl Cancer Inst 257 | Pancreatic cancer risk comparing exposure Q5 vs Q1:
Total fat
HR=1.23, 95% CI=1.03-1.46, P-trend=0.03
Saturated fat
HR=1.36, 95% CI=1.14-1.62, P-trend=0.001
Monoinsaturated fat
HR=1.22, 95% CI=1.02-1.46, P-trend=0.05
Polyunsaturated fat
HR=1.00, 95% CI=0.84-1.18, P-trend=0.68

food sources of fat:
the positive association of total, saturated, and monoinsaturated fat with pancreatic cancer was seen from food sources from animal foods (HR=1.23,1.19,1.22, respectively), especially red meat and dairy products and was not determined by vegetable food sources

Individual fatty acids:
Increased intake of two types of saturated fatty acids (palmitic acid and stearic acid), one MUFA-Palmitoleic acid, one n-6 PUFA-Arachidonic acid, and two n-3 PUFAs (Eicosapentaenoic acid, Docosahexaenoic acid) were associated with increased risk of pancreatic cancer with HR from 1.19 to 1.34.

Total trans fatty acids:
HR=0.99, 95% CI=0.83 to 1.17, P-trend=0.99

| Carbohydrate intake, GL, GI, dietary fructose and sucrose | Meinhold CL et al. (2010) Available carbohydrates , glycemic load, and pancreatic cancer: is | Pancreatic cancer risk comparing exposure 90th versus 10th percentile GL | Jiao L et al. (2009) Glycemic index, carbohydrates , glycemic load, and the risk of | There were no associations between GI, total or available carbohydrates, GL, and pancreatic cancer risk.
In terms of individual available carbohydrate constituents, only fructose |
<table>
<thead>
<tr>
<th>Fruit and vegetable</th>
<th>Koushik A et al. (2012)</th>
<th>Intake of fruits and vegetables and risk of pancreatic cancer in a pooled analysis of 14 cohort studies. American journal of epidemiology 261</th>
<th>Pancreatic cancer risk comparing exposure of each 100g/day increment in intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total fruits and vegetables combined RR=1.01 (95% CI=0.99-1.03) Total vegetables RR=1.02 (95% CI=0.99-1.06) Total fruits RR=1.01 (95% CI=0.99-1.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>there a link?</td>
<td>American journal of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>epidemiology 354</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available carbohydrate</td>
<td>HR=1.47, 95% CI=1.05-2.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>HR=1.08, 95% CI=0.78-1.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>HR=1.37, 95% CI=0.99-1.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI and intakes of starch and fructose were not associated with pancreatic cancer.</td>
<td></td>
<td>Pancreatic cancer in a prospective cohort study. Cancer epidemiology, biomarkers &amp; prevention 355</td>
<td>and glucose were associated with pancreatic cancer risk</td>
</tr>
<tr>
<td>Free fructose</td>
<td>HR_Q5VSQ1=1.29, 95% CI=1.04-1.59, P trend=0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (Q5 VS Q1)</td>
<td>HR_Q5VSQ1=1.35,95% CI=1.10-1.67, P trend=0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Jiao L et al. (2009) Alcohol use and risk of pancreatic cancer: the NIH-AARP Diet and Health Study. American journal of epidemiology</td>
<td>Total alcoholic drinks per day (≥6 drinks/day vs light drinkers who take 0-0.99 drinks/day) RR=1.55, 95% CI=1.13-2.13, P-trend=0.004; Total alcoholic drinks ≥3 drinks/day vs 0-0.99 drinks/day RR=1.45, 95% CI=1.17, 1.80, P-trend = 0.002 Liquor use (≥3 drinks/day vs &gt;0-0.99 drinks/day) RR=1.62, 95% CI=1.24-2.10, P trend=0.001 Significant association between total alcohol and liquor drink was only observed among men not women. Beer or wine use was not associated with the risk.</td>
<td></td>
</tr>
<tr>
<td>Coffee</td>
<td>Guertin KA et al. (2015) A prospective study of coffee intake and pancreatic cancer: results from the NIH-AARP Diet and Health Study. Br J Cancer</td>
<td>No association between total, caffeinated, or decaffeinated coffee intake and pancreatic cancer, and the observed null association was consistent across all examined strata (sex, smoking status and prevalent diabetes)</td>
<td></td>
</tr>
<tr>
<td>Dietary pattern</td>
<td>Arem H et al. (2013) The Healthy Eating Index 2005 and risk for pancreatic cancer in the NIH-AARP study. J Natl Cancer Inst</td>
<td>Pancreatic cancer risk comparing exposure Q5 vs Q1: HEI-2005 Men and women HR=0.85, 95% CI= 0.74-0.97, P-trend=0.003 Men and women had similar HR, but association was not statistically significant among women</td>
<td></td>
</tr>
<tr>
<td>Among men, P interaction by BMI=0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR=1.21, 95% CI=0.88 - 1.67, P-trend=0.23 (normal weight men)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR=0.72, 95% CI = 0.59-0.88, P-trend&lt;0.001 (overweight/obese men)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Jiao L et al. (2009) A combined healthy lifestyle score and risk of pancreatic cancer in a large cohort study. Archives of internal medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health diet quality vs. unhealthy diet quality (5–8 points for aMDS excluding alcohol vs 0–4 points)</td>
</tr>
<tr>
<td>HR=0.92, 95% CI=0.81-1.05</td>
</tr>
</tbody>
</table>
CHAPTER 3

METHODS

3.1 Statement of research aims and hypotheses

The overall aims of the dissertation were to examine the association between the inflammatory potential of diet measured by the DII and pancreatic risk in the PLCO and NIH-AARP cohorts, to assess effect measure modification by sex and inflammation-related lifestyle factors including BMI, cigarette smoking, alcohol drinking, diabetes history and NSAIDs, as well as to investigate the mediated effect of type-2 diabetes in the association of E-DII and pancreatic cancer. Specifically, for Aim 1, we investigated if the inflammatory potential of diet impacted pancreatic cancer in the PLCO, and examined how sex and BMI modified the association. For Aim 2, we examined the association between E-DII and pancreatic cancer risk in the NIH-AARP, and examined effect modification by sex, BMI, smoking status, history of diabetes, alcohol drinking and NSAIDs use. With Aim 3, we conducted a causal mediation analysis to explore the mediated effect of type-2 diabetes in the association between E-DII to pancreatic cancer in the PLCO and NIH-AARP separately and in a pooled analysis after demonstrating that between-study heterogeneity was not significant.

Our hypothesis was that greater inflammatory potential of diet would be associated with higher risk of pancreatic cancer in both studies, inflammation-related lifestyle conditions (overweight or obese individuals, individuals with previous smoking
history, high level of alcohol drinking, those who had presence of diabetes history, or less
NSAIDs use frequency) could act jointly with E-DII to increase pancreatic cancer risk,
and that type-2 diabetes mediated the E-DII and pancreatic cancer association (i.e.,
dietary inflammatory potential has indirect effect on pancreatic cancer through increasing
risk of type-2 diabetes).

3.2 Description of the study population

3.2.1 Participants from PLCO Cancer Screening Trial

PLCO is a large population-based randomized controlled trial with the aim to
assess the effects of prostate, lung, colorectal and ovarian cancer screening tests on
cancer-related mortality and secondary endpoints in men and women aged 55 to 74 years.
A detailed description of the PLCO study design was published elsewhere. Briefly, a
total of 154,897 eligible participants (76,682 men and 78,215 women), aged 55–74, were
enrolled into the trial from 1993 to 2001 from ten screening centers across US and
randomized based on sex and age group into either a control arm where usual care was
received, or an intervention arm where screening exams for prostate, lung, colorectal or
ovarian cancers were received. Participants included in the intervention arm received
screening during their first 6 years in the trial: women had chest x-rays, flexible
sigmoidoscopy, cancer antigen (CA)-125 blood tests, and transvaginal ultrasound and
men received chest x-rays, flexible sigmoidoscopy, prostate-specific antigen (PSA) blood
tests, and digital rectal exams and all the participants in the intervention arm were
subsequently followed up for at least 7 additional years. The screening component of the
trial was completed in 2006. Participants in the control arm were followed for 13 years
after enrollment.
Participants in PLCO were uncompensated volunteers recruited from the general population in the geographic area of each of the screening centers. They were excluded from the study if they met any of the following criteria\textsuperscript{44}: (1) underwent cancer treatment at the time of randomization (excluding basal-cell and squamous-cell skin cancer); (2) had known prior cancer of the colon, rectum, lung, prostate (men only) or ovary (women only), including primary or metastatic PLCO cancers; (3) before October 1996, women with previous surgical removal of both ovaries were excluded from the trial, and beginning in October 1996, these women were not excluded; (4) participated in another cancer screening or cancer primary prevention trial; (5) males who had taken Proscar/Propecia/finasteride in the 6 months before randomization; (6) before April 1, 1999, women were excluded from the trial if they currently took or had taken Tamoxifen or Evista/Raloxifene in the 6 months prior to randomization; after April 1, 1999, women who had been or currently took Tamoxifen or Evista/Raloxifene were not excluded; (7) males who had more than one PSA blood test in the three years prior to randomization; (8) individuals who had a colonoscopy, sigmoidoscopy, or barium enema in the three years prior to randomization; (9) individuals who were unwilling or unable to sign the informed consent form.

In general, a majority of recruited participants were non-Hispanic white, married or living as married, had higher education level than some college, overweight at baseline, and above 85% of female participants were postmenopausal.\textsuperscript{45} A self-administered baseline questionnaire, which included questions on demographic factors, medical history and health-related behaviors was collected from all subjects at the time of randomization. Dietary data were collected with the use of a self-administered FFQ, the
Diet History Questionnaire (DHQ), version 1.0 (National Cancer Institute, 2007), which was introduced to the intervention and control arms between 1998 and 2005. Depending on the time a subject was recruited into study, only a small portion of subjects in the control arm completed DHQ at randomization while most subjects returned back the form at their third to five years after randomization. The DHQ queried frequency and portion size of 124 food items consumption during the past year. A supplemental questionnaire was introduced to all subjects in 2006 to update information that may have changed since completion of baseline questionnaire, which included medication use, demographic factors, and updated healthy history. The study was approved by the Institutional Review Boards of the National Cancer Institute and each of the centers that participated.

3.2.2 Participants from NIH-AARP Diet and Health Study

The NIH-AARP Diet and Health Study is the largest prospective cohort study of diet and health ever conducted in US and it was initiated in 1995 to 1996 when a baseline questionnaire asking information on demographic characteristics, medical history, dietary intake and health behaviors was mailed to 3.5 million AARP members with the goal to examine a number of important diet and cancer relationship hypotheses. The scientific rationale and study design of the cohort was described previously. The initial study population of this cohort was 617,119 females and males who responded to the baseline questionnaire with a response rate of 17.6%. Study exclusion criteria included: (1) responses on the questionnaire were not reliable (i.e., unknown sex, skipped everything, skipped facing page that provided personal information and date when they completed the questionnaire, deceased or proxy respondent, more than 10 recording errors and less
than 10 foods consumed); (2) respondents asked to be dropped from cohort; (3) died or moved before entry; (4) those with duplicate representation of the questionnaire.\textsuperscript{46} Participants in the NIH-AARP were 50 to 71 years old with mean age of 62 years at baseline and lived in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, or Louisiana) or two metropolitan areas (Atlanta, Georgia or Detroit, Michigan).\textsuperscript{46} Participants were predominantly white, have higher education level and lower percentage of current smokers than the general US population.\textsuperscript{46,360} The self-administered NCI-developed DHQ included in the baseline questionnaire assessed participants’ usual frequency of intake and portion size on 124 food items over the past year. It also included 21 additional questions on food choices and cooking practices, and four supplement intake questions.\textsuperscript{361} One year after the baseline questionnaire, a risk factor questionnaire was sent out in 1996 to 1997 to collect information of some common lifestyle or risk factors such as cooking practices in the past year, physical activity, family history of cancer, diet habit during young adulthood and other health behaviors. In 2004, a follow-up questionnaire was sent out to members to record their cancer status and other non-cancer endpoints as well as update medical use and other demographic information.\textsuperscript{359} The study was approved by the National Cancer Institute Special Studies Institutional Review Board.

3.3 Diet assessment

3.3.1 Diet data from PCLO and NIH-AARP

The main exposure variable in this dissertation was the derived E-DII score calculated based on dietary responses from the DHQ in PLCO and NIH-AARP (both studies employed the NCI-developed DHQ but with different templates) with linkage to
the corresponding inflammatory effect score designated in the DII. The DHQ in both studies was used to assess the frequency and portion size of 124 food items during the past year among cohort participants. Participants in both studies were asked to choose from 10 frequency categories ranging from “never” to “>=6 times/d” for beverages, from “never” to “>=2 times/d” for solid foods and three categories of portion sizes. In the PLCO DHQ, from one to seven additional embedded questions are asked about related factors such as seasonal intake, food type (e.g., low fat, fat-free, lean, caffeine free), and/or fat uses or other additions use on 44 out of the 124 foods. Daily nutrient intake was calculated by the DietCalc software, which links responses of food frequency, portion size, and other relevant responses from the DHQ with a nutrient database based on national dietary data (USDA's 1994-96 Continuing Survey of Food Intakes by Individuals and supplemented by the Nutrition Data Systems for Research from the University of Minnesota). Three studies were conducted to evaluate the PLCO DHQ's measurement performance. The first study used a checklist and showed that most of the cognitive improvements incorporated in the PLCO DHQ resulted in better measure of frequency than was 1992 NCI Block questionnaire. The second validation, which compared the DHQ to two widely used FFQs (the 1995 Block FFQ and the Willett FFQ), showed the DHQ performed best overall among the three instruments for estimating absolute intake of most nutrients. However, the third validation study, the Observing Protein and Energy Nutrition (OPEN) study, which compared intake of energy and protein estimated based on the DHQ with unbiased biomarkers, doubly labeled water for energy and urinary nitrogen for protein among 484 healthy adult men and women living in Maryland, suggested significant underreporting by both men and women for protein
and total energy\textsuperscript{366} and measurement error on the DHQ which may lead to severe attenuation in estimated disease relative risks.\textsuperscript{367} We obtained diet data of 35 food parameters out of the 45 food parameters in the DII from PLCO to calculate the E-DII score for each individual, which included alcohol, vitamin B12, vitamin B6, beta-carotene, caffeine, carbohydrate, cholesterol, food energy, total fat, total dietary fiber, folate, iron, magnesium, monounsaturated fatty acids, poly-unsaturated fatty acids, niacin, onions, protein, riboflavin, saturated fatty acids, selenium, thiamin, total trans-fatty acids, vitamin A, vitamin C, vitamin E, vitamin D, zinc, tea, flavan-3-ols, flavones, flavonones, anthocyanidin, isoflavone, and peppers.

The DHQ used in the NIH-AARP allowed for variation in eating patterns in different parts of the country because it contained some regional and ethnic group-specific foods. To assess relative validity and reliability, the baseline DHQ was compared to two nonconsecutive 24-hour dietary recalls (randomly assigned by day of the week with a median of 21 days apart) and a second FFQ among 1,415 participants who responded to baseline DHQ in the NIH-AARP. After adjusting for random within-person error, the energy-adjusted correlation coefficient ranged from 0.40 (vitamin E) to 0.76 (saturated fat) among men, and from 0.36 (vitamin E) to 0.70 (vitamin B6) among women.\textsuperscript{361} NIH-AARP study respondents were found to consume less fat and red meat but more fruits and vegetables than comparably aged general US adults.\textsuperscript{353} Responses from the DHQ were linked to the US Department of Agriculture’s (USDA) Continuing Survey of Food Intakes of Individuals (CSFII) survey databases (1989–91 initially, and 1994–96 as it became available), in order to estimate intake values of nutrients, foods, and food group intakes.\textsuperscript{364} Thirty-four out of the 45 food parameters were available in the
NIH-AARP dataset. These include the following: calories; carbohydrates; protein; total fat; saturated, monounsaturated, and polyunsaturated fat; trans-fat; alcohol; fiber; cholesterol; vitamins B1, B2, B6, B12, A, C, D, and E; niacin; iron; magnesium; zinc; selenium; folic acid; beta-carotene; anthocyanidins; flavan-3-ols; flavones; flavonones; isoflavones; caffeine; green peppers; and tea. To calculate flavonoid classes, DHQ-derived daily fruits and vegetables intake in grams will be linked to the US Department of Agriculture (USDA)'s Database for Flavonoid Content from Selected Foods (Release 3.1, December 2013) by matching foods with the USDA’s 5-digit nutrient database number. Once linked, the content levels of each flavonoid class will be applied to each fruit and vegetable in the DHQ and summed to provide a total value for each flavonoid class.\textsuperscript{34}

3.3.2 E-DII score calculation

The DII is a literature-derived, population-based index used to measure individual’s diet in terms of inflammatory potential. The development\textsuperscript{22} and construct validation\textsuperscript{23,24,26,27,29,30,188} of the DII have been described previously. The goal in developing the DII was to create a score that could assess the overall quality of diet with regard to its inflammatory potential. A total of about 6,500 research articles published through December 2010 on the effect of dietary parameters on six well-established inflammatory markers (CRP, IL-1β, IL-4, IL-6, IL-10, TNF-α) were screened for inclusion in the DII scoring algorithm. CRP, IL-1β, IL-6 and TNF-α are considered pro-inflammatory biomarkers while IL-4 and IL-10 are considered anti-inflammatory cytokines. A total of 1,943 research articles were reviewed and scored based on 45 pro- and anti-inflammatory food parameters identified in the search. One of three possible
values was assigned to each article based on the effect of the food parameter on inflammation: “+1” was assigned if the effects were pro-inflammatory (significantly increased IL-1β, IL-6, TNFα, or CRP or decreased IL-4 or IL-10); “−1” if the effects were anti-inflammatory (significantly decreased IL-1β, IL-6, TNFα, or CRP or increased IL-4 or IL-10) and “0” if the food parameter had no relationship with the inflammatory marker. Sometimes, foods had differential effects in a study (have both anti-inflammatory and pro-inflammatory effects), then this article was scored separately, assigning ‘−1’ for its anti-inflammatory effect and ‘+1’ to the same article for its pro-inflammatory effect.

Articles were first weighted by study design, with clinical trials receiving the highest weight and cell culture studies receiving the lowest weight. Using these weights, the pro- and anti-inflammatory fractions for each food parameter were calculated. The “food parameter-specific overall inflammatory effect score” was then calculated by: 1) dividing the weighted pro- and anti-inflammatory articles by total weighted number of articles and 2) subtracting the anti-inflammatory fraction from the pro-inflammatory fraction. A cut point of 236, the median of the total weighted number of articles across all the food parameters, was chosen to indicate an optimally robust pool of literature. All food parameters with a weighted number of articles ≥236 were assigned the full value of the score which was regarded as the food parameter-specific raw inflammatory effect score. Foods and constituents with a weighted number of articles <236 were adjusted as follows: (1) number of weighted articles was divided by 236; (2) the fraction was then multiplied by the food parameter-specific raw inflammatory effect score. To avoid the arbitrariness as a result of simply using raw intake amounts, having consequence of different units of measurement for various nutrients which could exert large influences on
the overall score, the DII was standardized to a representative range of global dietary intake based on actual human consumption. This was accomplished by constructing a composite database representing a wide range of dietary intake consumed among populations living in countries in different regions in the world. Authors of articles reporting dietary data from nutrition surveys were contacted to request access to complete datasets. A total of 11 such datasets were identified and used in developing the composite worldwide dietary database with the detailed methods described in the reference. Thus, this representative world diet database provided an energy-adjusted mean intake and standard deviation for each food parameter as a reference to standardize the E-DII score. To calculate the overall E-DII score for each participant in a given study, dietary data from each study were first energy adjusted to take into account the difference in total energy intake and linked to the world composite database. By subtracting the standard global energy-adjusted mean from the energy-adjusted intake reported by the individual and dividing this value by its standard deviation, we obtained the multipliers to express an individual's exposure relative to the ‘global mean’ as a Z-score. To minimize the effect of “right skewing,” this value was converted to a percentile score. To achieve a symmetrical distribution with values centered on 0 (null) and bounded between -1 (maximally anti-inflammatory) and 1 (maximally pro-inflammatory), each percentile score was doubled and then 1 was subtracted. The centered-percentile value for each food parameter was then multiplied by its respective food parameter-specific inflammatory effect score to obtain a food parameter-specific E-DII score. Finally, all of the food parameter-specific E-DII scores were summed to create the overall E-DII score for an individual. This approach both ‘anchors’ an individual's exposure to a robust range of
diet habits in a variety of countries and obviates completely the problem of non-comparability of units because the Z-scores and percentiles are independent of the units of measurement (refer to Figure 3.1 for the E-DII score calculation flow chart). More positive scores represent a more pro-inflammatory diet, whereas more negative scores represent a more anti-inflammatory diet. When DII scores were calculated based on the composite global dietary database, the DII score was between +7.98 for maximally pro-inflammatory diet, to −8.87 for the maximally anti-inflammatory diet and the median was +0.23. E-DII scores from food plus supplement were calculated as exposures in each cohort. The DII score, calculated from multiple different dietary assessment instruments, were found to be associated with higher levels of IL-6, TNF-α receptor 2, hsCRP and homocysteine.

3.4 Covariates assessment

Based on the comprehensive literature review about risk factors for pancreatic cancer stated in Chapter 2 and the directed acyclic graph (DAG) (Figure 3.2) which described the relationship among all the considered variables in the association between DII and pancreatic cancer, potential covariates to be included in both PLCO and NIH-AARP studies were age at baseline (continuous), sex (male and female), race/ethnicity (Hispanic, Non-Hispanic Black, Non-Hispanic White, Others, missing), BMI (underweight, normal, overweight, obese, missing), alcohol consumption (continuous, grams/day), screening arm of PLCO (screening arm or control arm), total energy intake (kcal/day, continuous), physical activity (never/rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, or >=5 times per week), past medical disease history including chronic pancreatitis, gallstone, cholecystectomy, gastric or duodenal ulcer, gastrectomy,
periodontal disease, venous thromboembolic events, HBV and HCV infection (yes or no), first-degree family history of pancreatic cancer (yes/no), first-degree family history of prostate cancer (yes/no), cigarette smoking status (never smoker, former smoker, current smoker), pack-years of cigarette smoking (continuous), number of years of smoking cessation among former smokers since stopped smoking (1, 1–5, 5–10, or >10 years before baseline), ever used other tobacco products (yes or no), self-reported history of diabetes (yes or no), and NSAIDs use frequency (none, 1-3 times/month, 1-2 times/week, 3-6 times/week, >=7 times/week). These covariates were all self-reported on baseline questionnaires in PLCO and NIH-AARP except that physical activity over the past year was not assessed at baseline in the PLCO but was assessed on the supplemental questionnaire and NSAIDs use information was collected from the risk factor questionnaire in the NIH-AARP. BMI was calculated as weight (kg)/height(m)^2 and categorized based on the World Health Organization criteria.\(^{368}\)

3.5 Effect measure modifiers assessment

Due to smaller case number in PLCO compared to NIH-AARP, in the NIH-AARP, sex and inflammation-related lifestyle factors were examined as effect modifiers while sex, BMI, diabetes history and smoking status were examined as effect modifiers in the PLCO. As mentioned in section 3.5, these effect modifiers in both studies were all self-reported at baseline or close to baseline (NSAIDs use was assessed in the NIH-AARP at one year after baseline). We categorized alcohol intake into high and low level by using 53.4g as the cut-off point in the interaction test in NIH-AARP given the evidence in the 2012 American Institute for Cancer Research (AICR) CUP report for pancreatic cancer that supported a nonlinear association between alcohol and pancreatic cancer.
cancer risk with increased risk observed among those consuming 53.4g alcohol or more a day.\textsuperscript{239} Based on previous evidence showing time may have a significant interaction with dietary factors in pancreatic cancer etiology using a cutoff of 4 years of follow-up,\textsuperscript{256,354} we also examined time (<4 and \(\geq\)4 years) as effect modifier in both cohorts to be comparable to the two previous studies.

3.6 Outcomes assessment

The outcome of interest for each aim was defined as incident adenocarcinoma of the exocrine pancreas: International Classification of Diseases for Oncology, Third Edition, codes C25.0-C25.3, C25.7- C25.9. In the PLCO, explicit diagnosis date with confirmed cancer status (rather than death) of incident exocrine pancreatic cancer was available, so we used this date as the outcome occurrence date. However, in the NIH-AARP, they did not distinguish between pancreatic cancer death and incidence in the pancreatic cancer diagnosis status variable. Thus, pancreatic cancer date of death was compared to date of diagnosis to determine which subjects died of pancreatic cancer. A sensitivity analysis was conducted where date of pancreatic cancer diagnosis was imputed for those subjects who died from pancreatic cancer. Based on a literature review, the median survival time of exocrine pancreatic cancer after diagnosis is four months,\textsuperscript{369} the value of date of diagnosis is the death date for pancreatic cancer minus four months, since the unit of time we used in the analysis was years, we did not impute the date of diagnosis using statistical method due to the very small values for the time variable. Our case definition in both studies excluded endocrine tumors (histology types 8150–8155, 8240, 8246, and 8502) and some other rare histology types such as islet cell adenoma, carcinoid tumor, sarcoma because these types and exocrine pancreatic cancer may have
different disease mechanisms and etiology. In the PLCO, pancreatic cancer cases were ascertained through a mailed annual questionnaire in which subjects were asked if they had been diagnosed with cancer by a health care provider. They were then asked to provide information on the type of cancer. Additional sources for identification of pancreatic cases included state registries, death certificates, physician reports, and reports from next of kin (for deceased subjects). These cases were then confirmed by abstraction from medical records. We calculated the person-years of follow up for each individual from the date of DHQ to the date of first incident pancreatic cancer diagnosis, to censoring at the date of death, study withdrawal or the end of data collection for the study which was the first of either 13 years after randomization or 12/31/2009, whichever came first.

In the NIH-AARP, participants were followed up yearly by using the National Change of Address database (U.S. Postal Service) and MaxCoA (Anchor Computer Inc.). Approximately 4% of participants were lost to follow-up. Vital status was ascertained by annual linkage to the Social Security Administration Death Master File. Incident pancreatic cancer cases were identified by linkage to 11 state cancer registries (the 8 original states where participants were recruited as well as Arizona, Nevada, and Texas), and mortality cases were identified by linkage to the National Death Index. Similar to PLCO, the person-years of follow up for each individual was calculated from the date of response to baseline questionnaire to the date of first incident exocrine pancreatic cancer diagnosis, or to censoring at the date of death, or move out from the study area, or the end of study which was December 31, 2011, whichever came first.
3.7 Statistical analysis

3.7.1 Statistical methods for specific aim 1 and 2

3.7.1.1 Primary aim analysis: relationship between E-DII and pancreatic cancer risk

Among the eligible study population in each study, we further excluded participants with any cancer history at baseline and with extreme total energy intake and those with implausible BMI. E-DII score was adjusted for total energy intake using the energy density model and categorized to various quantiles (tertiles, quartiles, quintiles, and deciles) first to examine the trend. The decision of which quantile to use in final models was made based on the trend results and distribution of E-DII and case number in each category, as well as the result after examination of the proportional hazards assumption. In both studies, we categorized E-DII into quintiles, and the trend in other quantiles were similar with quintiles of E-DII. In the NIH-AARP, we treated E-DII as both a categorical and a continuous variable. The lowest E-DII category served as the referent group. Potential confounding variables in our analysis include those listed in section 3.5 above. Confounding variables were assessed using two methods: (1) 10% rule method where covariates were added to the crude model individually and ≥10% changes in the risk estimate for the highest compared to lowest E-DII quintile was regarded as confounding; (2) covariates which were both related to E-DII (categorical or continuous) and pancreatic cancer risk were regarded as confounders. Covariates determined to be confounders using either aforementioned method and effect modifiers were retained in the final multivariable-adjusted models. We checked the Spearman rank correlation coefficient between each two continuous variables included in the final model to make sure there was no collinearity indicated by statistically significant large coefficient
Descriptive baseline demographic and lifestyle characteristics of the study population were generated, including means and standard errors (SE) for the continuous variables and frequencies and proportions for the categorical variables. Analysis of variance (ANOVA) was used to test the difference across E-DII quintiles for continuous variables, and Chi-square test was performed to test the difference for categorical variables. To estimate and compare the risk of pancreatic cancer by quintiles of E-DII score, multivariable Cox proportional hazards regression with person-year as the underlying time metric was fitted to estimate the age- and energy-adjusted and multivariable-adjusted hazard ratios HRs and 95% CIs with subjects in the lowest E-DII quintile (the most anti-inflammatory score) as the referent. Proportional hazard (PH) assumption was examined using the Schoenfeld residual test. Stratification or interaction of time and covariate was used for those covariates that did not meet the PH assumption. Linear trend test was performed by using the continuous E-DII variable and in the multivariable-adjusted models. Continuous HR and 95% CIs also were calculated and reported for each one unit of standard deviation increase of E-DII score after the restricted cubic spline test indicated the linear assumption was sufficient in the NIH-AARP. In the NIH-AARP, we presented sex-specific E-DII and pancreatic cancer association given that men and women had different distributions of the E-DII score and other covariates, although the interaction by sex was not statistically significant.

All data analyses were conducted using SAS statistical software (SAS Institute, Cary, NC). All statistical tests were two-sided, and P values less than 0.05 were considered as statistically significant.
3.7.1.2 Secondary aim analyses: effect modification examination

Interaction tests were conducted to examine if the association between E-DII and pancreatic cancer risk was consistent among strata of variables including sex and BMI in the PLCO, and sex and inflammation-related lifestyle factors in the NIH-AARP. An interaction test was performed by including each interaction term (product of quintile E-DII score and categorical effect modifier) one at a time in the final multivariable-adjusted model and conducting -2 log likelihood ratio test. If any interaction was significant (P value from -2 log likelihood ratio test \textless 0.1),\textsuperscript{376} we stratified the effect modifier and reported the E-DII and pancreatic cancer association in each stratum of the effect modifier separately, otherwise, we only reported the combined result.

3.7.1.3 Sensitivity analyses

Several sensitivity analyses to examine the robustness of our results under different scenarios were conducted. In the first sensitivity analysis, we excluded participants with follow-up\textless 5 years to avoid potential subclinical disease which may affect usual diet habit to result in reverse causality. A second sensitivity analysis was conducted to exclude all the participants who self-reported history of diabetes because there was evidence showing diabetes may be a preclinical indicator of pancreatic cancer.\textsuperscript{377} We also restricted the outcome to primary pancreatic cancer only, and in the NIH-AARP, we added pancreatic cancer death cases to both primary pancreatic cancer outcomes and the total incident outcomes using the imputed incidence time. We performed the main analysis and the interaction analyses described in section 3.7.1 in these sensitivity analyses.
3.7.2 Statistical methods for specific aim 3

Based on the analytical cohort of PLCO and NIH-AARP, we further excluded participants who did not have valid supplemental questionnaire in PLCO or follow-up questionnaire in NIH-AARP, which contained follow-up data on diabetes, and those who had baseline diabetes, the remaining subjects constituted the mediation cohort for PLCO and NIH-AARP separately. Causal mediation analysis approach under the counterfactual framework was used to first assess the study-specific mediated effect of type-2 diabetes in the association between E-DII and pancreatic cancer. A SAS macro developed by Valeri and Vanderweele was used to calculate the study-specific mediation parameters: natural direct effect (NDE), natural indirect effect (NIE), and marginal total effect (MTE) of E-DII on pancreatic cancer risk with type-2 diabetes as a mediator. Briefly, mediation parameter estimates were obtained in three steps: 1) type-2 diabetes (mediator variable) was regressed on E-DII using the logistic regression with inclusion of the study-specific set of confounding variables except that diabetes history at baseline was removed; 2) pancreatic cancer was regressed on type-2 diabetes and E-DII with inclusion of the E-DII and type-2 diabetes interaction and the same set of confounders as in 1) using a logistic regression model, if the interaction was not statistically significant, it was then be removed from the model; 3) based on the specified comparison levels of exposure, parameters derived from these two logistic models gave way to essential mediator parameters through a series of mathematical calculations.

The incident follow-up type-2 diabetes data was retrieved from the supplemental questionnaire in the PLCO and from the follow-up questionnaire in the NIH-AARP. Both questionnaires asked participants whether they have been diagnosed with diabetes and the
timing when they were diagnosed (choices were several categories of years of diagnosis or age ranges at diagnosis). Because we excluded participants with baseline diabetes in the mediation analysis, the study-specific responses to the two above-mentioned diabetes questions could be used to identify incident diabetes that occurred during follow-up. The mediator subsequently was coded as a categorical variable with three levels: “yes”, “no” and “missing” using the following method: 1) if subjects answered they were never diagnosed with diabetes on the study-specific follow-up questionnaire, these subjects were assigned “no”; 2) if subjects reported they were ever diagnosed with diabetes, we further compared their ages at first diagnosis of diabetes using the median value of each category of the variable indicating diabetes occurrence time on the study-specific follow-up questionnaires, with their ages at pancreatic cancer diagnosis, and coded mediator as “yes” if diabetes occurred before pancreatic cancer or no pancreatic cancer occurred, “no” if diabetes occurred after pancreatic cancer (because mediator as defined should occur before the occurrence of outcome of interest), or “missing” if no information on age at first diagnosis of diabetes; and 3) if subjects did not report whether they were diagnosed with diabetes, these subjects were assigned “missing” as their mediator level.

In the study-specific mediation analysis, we calculated the NDE, NIE, and MTE of E-DII on pancreatic cancer risk for subjects in each higher E-DII quintile (i.e., quintile 2, quintile 3, quintile 4, quintile 5) compared to those in the lowest quintile with type-2 diabetes as mediator. We also centered each E-DII value to the mean to report the mediation effect of a one-unit increase in centered E-DII on pancreatic cancer with type-2 diabetes as mediator. The Z-score of E-DII was calculated by dividing the centered value by the standard deviation, and used in the mediation model to report the mediation effect
of type-2 diabetes on the association of one standardized unit increment of E-DII with pancreatic cancer risk. For all these mediation analysis, we also calculated the mediation proportion by type-2 diabetes using the equation as follows: proportion of mediation by type-2 diabetes = \( \frac{NDE \times (NIE - 1)}{(NDE \times NIE - 1)} \)

A random effects model was used to pool each study-specific mediation effect (i.e., NDE, NIE, MTE) on pancreatic cancer comparing each higher E-DII quintile to the lowest quintile, and the study-specific mediation effect on pancreatic cancer associated with each one unit increment of centered E-DII value and z-score of E-DII, across two studies. Between-studies heterogeneity was evaluated using the Q statistic\(^{380,381}\) and I\(^2\) statistic.\(^{382}\) If between-study heterogeneity was not significant, we combined primary data from two cohorts into one dataset by harmonizing categories for the categorical covariates which were shared in both studies as potential confounders and performed the mediation analyses as stated above in the pooled mediation cohort of PLCO and NIH-AARP. We reassessed the confounders in the pooled cohort using the two methods as stated in the section 3.7.1.1 and used these confounders in the mediation analysis procedures.

All statistical tests were two-sided and all data analyses were conducted using SAS statistical software (SAS Institute, Cary, NC).
Figure 3.1: Sequence of steps to calculate the energy-adjusted DII score in the PLCO Cancer Screening Trial and NIH-AARP Diet and Health Study. (Adapted from Shivappa, N., Steck SE, Hurley TG, Hussey JR, Hebert JR, Designing and Developing a Literature-derived, Population-based Dietary Inflammatory Index. Public Health Nutr, 2013: p. 1-8.) Abbreviations: DII, dietary inflammatory index; PLCO, the Prostate, Lung, Colorectal and Ovarian; NIH-AARP, the National Institute of Health Association of Retired Persons.
Figure 3.2 DAG that describes the relationships of each covariate with exposure DII and with outcome pancreatic cancer in the PLCO Cancer Screening Trial and NIH-AARP Diet and Health Study. Abbreviations: DAG, directed acyclic graph; DII, dietary inflammatory index; PLCO, the Prostate, Lung, Colorectal and Ovarian; NIH-AARP, the National Institute of Health Association of Retired Persons
CHAPTER 4

INFLAMMATORY POTENTIAL OF DIET AND RISK OF PANCREATIC CANCER IN THE PROSTATE, LUNG, COLORECTAL AND OVARIAN (PCLO) CANCER SCREENING TRIAL

1 Jiali Zheng1,2, Anwar T. Merchant1, Michael D. Wirth1,2,3, Jiajia Zhang1, Samuel O. Antwi4, Azza Shoaibi5, Nitin Shivappa1,2,3, Rachael Z. Stolzenberg-Solomon6, James R. Hebert1,2,3, Susan E Steck1,2

1Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC
2Cancer Prevention and Control Program, University of South Carolina, Columbia, SC
3Connecting Health Innovations, LLC, Columbia, SC
4Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Jacksonville, FL
5Biomedical Informatics Center, Medical University of South Carolina, Charleston, SC
6Division of Cancer Epidemiology and Genetics, Metabolic Epidemiology Branch, National Cancer Institute (NCI/DCEG), Bethesda, MD

Submitted to the International Journal of Cancer

84
4.1 Abstract

**Background:** Inflammation plays a central role in pancreatic cancer etiology and can be modulated by diet. We aimed to examine the association between the inflammatory potential of diet, assessed with the Dietary Inflammatory Index (DII™), and pancreatic cancer risk in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial prospective cohort. **Methods:** Our study included 101,449 participants aged 52 to 78 years at baseline who completed both baseline questionnaire and a diet history questionnaire. Energy-adjusted DII (E-DII) scores were computed based on food and supplement intake. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) with participants in the lowest E-DII quintile (most anti-inflammatory scores) as referent. **Results:** After a median 8.5 years of follow-up, 328 pancreatic cancer cases were identified. E-DII scores were not associated with pancreatic cancer risk in the multivariable model (HR_{Q5 vs Q1} = 0.99; 95% CI=0.69-1.40; P-trend=0.31). Time significantly modified the association (P-interaction=0.02). Among subjects with follow up <4 years, there was an inverse association between E-DII and pancreatic cancer (HR_{Q5 vs Q1} = 0.55; 95% CI=0.32-0.95; P-trend=0.15) while there was a positive trend among those with ≥4 years of follow-up (HR_{Q5 vs Q1} = 1.36; 95% CI=0.85-2.17; P-trend=0.03). Similar results were observed for E-DII from food only. **Conclusion:** Our study does not support an association between inflammatory potential of diet and pancreatic cancer risk; however, heterogeneous results were obtained with different follow-up times. Reverse causality owing to undetected disease may account for the inverse association observed in the first four years of follow-up.
4.2 Introduction

Pancreatic cancer, the majority (~90%) of which is ductal adenocarcinoma of the exocrine pancreas, has the highest case-fatality rate of any major cancer.\textsuperscript{1,383} Despite low incidence, it is the fourth leading cause of cancer death among both men and women in the United States, with a 5-year relative survival rate of only 8% for all stages combined.\textsuperscript{1} Although the etiology of pancreatic cancer is not fully understood, inflammation may play a pivotal role in the pathogenesis of this malignancy, as manifested by the fact that inflammatory states are etiologically linked to well-recognized risk factors for pancreatic cancer, including chronic pancreatitis, cigarette smoking, obesity, and diabetes.\textsuperscript{58,384}

Dietary factors could affect cancer risk through modulation of inflammation,\textsuperscript{385,386} realized mainly by dietary impact on visceral obesity,\textsuperscript{387} oxidative damage\textsuperscript{78} and insulin resistance.\textsuperscript{387} Therefore, understanding the effect of dietary inflammatory potential on the development of pancreatic cancer may guide dietary intervention strategies aimed at the primary prevention of this lethal malignancy. A number of epidemiological studies have reported inconsistent results regarding the relationship between pancreatic cancer risk and inflammation-modulating nutrients or foods, such as fruits and vegetables and associated vitamins,\textsuperscript{388,389} fat and fatty acids,\textsuperscript{390} fiber,\textsuperscript{391} whole grains,\textsuperscript{392} and flavonols.\textsuperscript{393,394}

A typical human diet consists of both pro-inflammatory and anti-inflammatory foods and nutrients. Therefore, a dietary pattern approach, which takes into account the complex interactions among dietary components, has advantages over individual foods or nutrients when being studied for associations with disease risk.\textsuperscript{13} Assessing the overall inflammatory potential of the diet may provide better insight on the effect on pancreatic cancer risk than assessing only a select set of nutrients or individual foods. To date, two
case-control studies have used the DII to assess the association between dietary inflammatory potential and pancreatic cancer risk; both studies reported a significant >2-fold increased risk in the most pro-inflammatory diet group. However, case-control studies are susceptible to recall and selection biases, which may distort the true associations. Therefore, a large prospective cohort study in which exposure information has been collected before the cancer diagnosis is advantageous for examining the role of diet in pancreatic cancer etiology. The objective of this study was to examine the association between inflammatory potential of diet, assessed using the DII, and pancreatic cancer risk with data from the PLCO Cancer Screening Trial prospective cohort.

4.3 Materials and methods

4.3.1 Study design

The PLCO was a multi-center population-based randomized trial designed to assess effects of screening tests for prostate, lung, colorectal and ovarian cancers on mortality and secondary endpoints. Details of this study have been described elsewhere. Briefly, between 1993 and 2001, a total of 154,897 eligible participants (76,682 men and 78,215 women), aged 55–74 years, were enrolled into the trial from ten screening centers across the United States. Participants were randomized by sex and age group into a control arm, where usual medical care was received, or intervention arm where screening exams for PLCO cancers were received. PLCO eligibility criteria excluded a previous personal history of PLCO cancers, ongoing cancer treatment (excluding basal-cell and squamous-cell skin cancer), participation in another cancer screening or cancer primary prevention trial, and a recent screening test for prostate or colorectal cancer.
Participants in the intervention arm received their screening tests during their first six years in the trial and were subsequently followed up for at least seven additional years; participants in the control arm also were followed for 13 years after enrollment.\textsuperscript{44}

\subsection*{4.3.2 Study population}

In our analyses, we further excluded 11,874 participants who had a cancer (except non-melanoma skin cancer) diagnosed before completing the DHQ; 4,920 participants who did not return baseline questionnaires; 36,268 participants who did not have valid DHQ responses (i.e., valid DHQ responses were defined as having DHQ completion date; alive at DHQ completion; \(<8\) missing DHQ responses; and plausible caloric intake defined as within the sex-specific first and last percentiles of total energy); 220 participants who reported unreasonable BMI (i.e., BMI was considered unreasonable if one of the followings occurred: weight\(<60\) pounds; height\(<48\) inches; height\(>78\) inches for females; height\(>84\) inches for males; BMI\(<15\ \text{kg/m}^2\) ) and 166 participants without follow-up data. After these exclusions, the analytical cohort included 101,449 participants (49,347 men and 52,102 women). The study was approved by the institutional review boards of the National Cancer Institute and each of the centers that participated. Informed consent was obtained from each eligible participant in the study.

\subsection*{4.3.3 Dietary assessment}

Diet was assessed by a self-reported FFQ, the DHQ version 1.0 (National Cancer Institute, 2007), which was introduced in 1998 to both control and intervention arms within a median of three years after randomization in the trial.\textsuperscript{396} On the DHQ, participants reported their frequency of intake and portion size of 124 food items and supplement use over the previous year.\textsuperscript{396} Daily nutrient intake was calculated by the
DietCalc software, which links responses of food frequency, portion size, and other relevant responses from the DHQ with a nutrient database based on national dietary data (USDA's 1994-96 Continuing Survey of Food Intakes by Individuals and supplemented by the Nutrition Data Systems for Research from the University of Minnesota). The DHQ has been validated against four 24-hour dietary recalls (one in each season) among 1,640 nationally representative participants in the Eating at America's Table Study where the energy-adjusted correlation coefficients for dietary factors ranged from 0.51 for vitamin E to 0.78 for magnesium among women and from 0.41 for sodium to 0.83 for thiamin among men.

4.3.4 Energy-adjusted DII score calculation

The E-DII score for each participant was calculated based on the reported nutrient and food intake from the DHQ with linkage to the corresponding inflammatory effect scores designated in the DII. The DII is a literature-derived, population-based index designed to estimate the overall inflammatory potential of an individual’s diet. The details of the development of the DII have been published previously. Briefly, 1,943 eligible peer-reviewed primary research articles published through 2010 on the effect of dietary factors on six inflammatory markers (IL-1β, IL-4, IL-6, IL-10, tumor necrosis TNF-α, and CRP) were identified and scored to derive the component-specific inflammatory effect scores for 45 dietary factors (i.e. components of DII), which comprised macronutrients, micronutrients and some foods or bioactive components such as spices and tea.

Ten DII components including ginger, turmeric, garlic, oregano, rosemary, eugenol, saffron, n-3 fatty acids, n-6 fatty acids and flavonols were not available from the
DHQ. Therefore, the remaining 35 components were used for E-DII score calculation in our analysis. The food and nutrient consumption estimated from the DHQ was first adjusted for total energy per 1000 calories to account for the difference in individual energy intake. To avoid the arbitrariness as a result of simply using raw intake amounts, the energy-adjusted dietary intake was subsequently standardized to a composite dietary database representing energy-adjusted dietary intake from 11 populations living in different countries across the world. The energy-adjusted standardized dietary intake was then multiplied by the literature-derived inflammatory effect score for each DII component, and summed across all components to obtain the overall E-DII score. Higher E-DII scores represent more pro-inflammatory diets while lower (i.e., more negative) E-DII scores indicate more anti-inflammatory diets. The DII score has been construct-validated and found to be associated with higher levels of inflammatory biomarkers including IL-6, TNF-α receptor 2, and hsCRP. Because a majority of the participants (79%) in the PLCO consumed supplements, and many dietary factors used in supplements have anti-inflammatory properties, we reported E-DII scores from food plus supplements and E-DII scores from food only as exposures to quantify the association between the inflammatory potential of diet, with and without supplements, in relation to pancreatic cancer risk.

4.3.5 Assessment of other covariates

Baseline characteristics, which included demographic information, personal medical history, family history, and health behaviors, were self-reported through the baseline questionnaire within three months of randomization in the PLCO. BMI was calculated as weight (kg)/height(m)^2 and categorized based on the World Health
Information on physical activity over the past year was not assessed at baseline, but was assessed on the supplemental questionnaire which was introduced at a median of nine years after randomization in the trial.

### 4.3.6 Pancreatic cancer case ascertainment

Incident pancreatic cancer cases were identified through an annual study update questionnaire in which participants reported if they had been diagnosed with any cancer by a healthcare provider, the type of cancer, date of diagnosis, and location of diagnosis. State registries, death certificates, and physician reports also were used as additional sources for identification of pancreatic cancer cases. All reports of pancreatic cancer were followed-up and medical records were abstracted and reviewed for case ascertainment. In this analysis, pancreatic cancer case was defined as primary incident adenocarcinoma of the exocrine pancreas (International Classification of Diseases for Oncology, Third Edition, codes C25.0-C25.3, C25.7- C25.9). Our case definition excluded pancreatic endocrine tumors and other rare histology types of pancreatic cancer (histology type 8150, 8154, 8240,8245, 8246, 8550) as etiology may differ, and we censored these types of pancreatic cancer at the date of diagnosis.

### 4.4 Statistical analysis

The baseline characteristics of the study population were presented by quintiles of E-DII from food plus supplements with cut-off points determined from the distribution of the entire cohort. Means and SE for continuous variables and frequencies and percentages for categorical variables were calculated. Participants were followed up from the date of DHQ completion to the date of diagnosis of pancreatic cancer, death from any cause, study withdrawal, or the end date of study follow-up (the first of either 13 years
after randomization or 12/31/2009), whichever came first. Cox proportional hazards regression, with person-year as the underlying time metric, was used to estimate the HRs and 95% confidence intervals (CIs) for higher E-DII quintiles compared to the lowest E-DII quintile (the most anti-inflammatory score) as referent. To test the linear trend of pancreatic cancer risk across E-DII score, a continuous E-DII variable was used. Variables were considered as confounders if they were associated with both pancreatic risk and E-DII (in either continuous or categorical format), or they changed the crude risk estimate by more than 10% in bivariate analyses. Although BMI did not meet these criteria, we included it as a confounder because BMI is an established risk factor for pancreatic cancer and is also related to diet.²³⁹ In the multivariable models, we adjusted for age at DHQ completion, sex (male or female), BMI (underweight, normal, overweight, obese, missing), pack-years categories within smoking status (never smoker, former smoker with <18 pack-years, former smoker with 18-41 pack-years, former smoker with >41 pack-years, current smoker with <18 pack-years, current smoker with 18-41 pack-years, current smoker with >41 pack-years, missing), history of diabetes (yes, no, missing), and total energy intake (kcal/day). The proportional hazards (PH) assumption was examined using the Schoenfeld residual test.³⁷⁴ There was no evidence that E-DII or any covariate violated the PH assumption.

Effect modifications by sex, BMI, history of diabetes, smoking status were examined by adding the cross-product of each effect modifier with E-DII quintile in the multivariable-adjusted model with P value smaller or equal to 0.10 as an indicator of significant interaction.³⁷⁶ We also examined effect modification by follow-up time in our analysis given the possibility of latent pancreatic cancer affecting recent dietary intake.³⁵⁴
Previous PLCO analyses with diet and pancreatic cancer suggested significant time interaction with dietary fat and available carbohydrate using a cutoff of 4 years of follow-up.\textsuperscript{256,354} Among the effect modifiers of interest, only follow-up time was found to be significant. Therefore, we performed the stratified analyses by two distinct time intervals, with cut-off point at 4 years of follow-up, to be comparable with the other PLCO analyses.\textsuperscript{256,354}

Two sensitivity analyses were performed. First, subjects who self-reported diabetes history at baseline were removed from analyses because diabetes may be a preclinical indicator of pancreatic cancer and diet modification may have occurred after diagnosis of diabetes.\textsuperscript{377,398} Secondly, as we excluded a large number of participants, we compared the demographic characteristics and pancreatic cancer risk factors between our included sample and excluded subjects to examine how results could have been affected by excluding these subjects in our analyses.

Identical analyses, including sensitivity analyses, were performed for E-DII from food only in relation to pancreatic cancer risk. All statistical analyses were conducted using SAS\textsuperscript{®} (version 9.4, Cary, NC). All tests were two-sided, with p values <0.05 considered statistically significant unless otherwise noted.

4.5 Results

After a median of 8.5 years of follow-up, 328 incident pancreatic cancer cases occurred. E-DII scores from food and supplements ranged from -8.43 to 6.38. Compared to participants who had the most anti-inflammatory E-DII scores from food and supplement (i.e., E-DII quintile 1), participants consuming a more pro-inflammatory diet had higher BMI and who smoked more heavily at baseline, were younger at the time of
DHQ completion, consumed more alcohol and total calories, and were more likely to be male, Black non-Hispanic or Hispanic, current smokers, have below-college education level, a family history of pancreatic cancer in a first-degree relative, and have a personal history of diabetes (Table 4.1).

HRs for pancreatic cancer risk across E-DII quintiles from food plus supplement are presented in Table 4.2. After controlling for confounders, there was no significant association between E-DII scores and pancreatic cancer risk (HR_{Q5vsQ1} =0.99, 95% CI=0.69-1.40, P-trend=0.31). After excluding subjects with a history of diabetes at baseline (n=7,319), the multivariable-adjusted HRs changed only slightly.

In stratified analyses by sex, BMI category, history of diabetes, smoking status, and follow-up time (<4 and ≥4 years), only follow-up time had a statistically significant interaction with E-DII scores (P-interaction=0.02). Analyses stratified by follow-up time of <4 years and ≥4 years produced divergent results (Table 4.3). Among 8,977 individuals with <4 years of follow-up, those consuming the most pro-inflammatory diets had a statistically significant 45% lower risk of pancreatic cancer compared with individuals with the most anti-inflammatory diets although the trend was not significant (multivariable HR_{Q5vsQ1} =0.55, 95% CI=0.32-0.95, P-trend=0.15). However, a significant positive trend was seen among individuals with follow-up time of ≥4 years, although the HR comparing two extreme quintiles was not statistically significant (multivariable HR_{Q5vsQ1} =1.36, 95% CI=0.85-2.17, P-trend=0.03). We performed the stratified association by follow-up time <4 years and ≥4 years in the sensitivity analysis (i.e., excluding subjects with diabetes history), and the results did not change (data not shown).
Similar patterns of associations were observed when analyses were performed with E-DII from food only. In the multivariable analyses, E-DII from food only was not associated with pancreatic cancer risk and similar HRs were observed in the sensitivity analyses (Table 4.4). None of the covariates, except follow-up time, significantly modified the observed results (data not shown). A similar but nonsignificant association was observed for E-DII from food only among subjects with less than four years of follow up (HR\textsubscript{Q5vsQ1}=0.60, 95% CI=0.33-1.07, P-trend=0.30) and there was a borderline significant positive trend among those with longer follow-up (HR\textsubscript{Q5vsQ1}=1.28, 95% CI=0.80-2.06, P-trend=0.05) (Table 4.5).

Compared to subjects included in analyses, excluded subjects tended to have less healthy behaviors or characteristics that are likely associated with increased risk of pancreatic cancer, including male, Black or Hispanic, heavier smoking, a more pro-inflammatory diet, older age, diabetes history, lower education attainment (Table 4.6).

4.6 Discussion

This is the first prospective cohort study investigating the association between dietary quality with respect to inflammatory potential and pancreatic cancer risk. Overall, no association was found between inflammatory potential of diet and pancreatic cancer risk. However, there was significant effect modification by follow-up time. In the stratified analysis, we observed a significant increased trend of risk associated with a pro-inflammatory diet among those with follow-up longer than four years, whereas evidence of risk reduction was seen among subjects diagnosed with pancreatic cancer in the first four years of follow-up. These divergent results may indicate the presence of reverse causality in the short-term, where decreases in dietary inflammatory potential may be a
consequence, rather than a cause, of pancreatic cancer or a well-known precursor condition, pancreatitis.\textsuperscript{39} We observed similar results for E-DII from food plus supplements and E-DII from food only. Because supplements may be the preferred choice for people with subclinical disease, this also may reflect issues of appetite control.

Two case-control studies, with one conducted in the U.S.\textsuperscript{39} and the other in Italy,\textsuperscript{38} previously reported positive associations between E-DII scores from food and pancreatic cancer risk. Both studies found an approximate 2.5-fold increased risk of pancreatic cancer in the highest compared to the lowest quintile of the E-DII group (U.S.: OR\textsubscript{Q5 vs Q1} = 2.54, 95% CI=1.87-3.46, P-trend<0.0001;\textsuperscript{39} Italy: OR\textsubscript{Q5 vs Q1} = 2.48, 95% CI=1.50-4.10, P-trend=0.002\textsuperscript{38}). Evidence of effect modification by smoking status and BMI was documented in the Italian case-control study where a significant positive association was observed among never and past smokers but not among current smokers, and among normal and overweight rather than obese subjects, respectively.\textsuperscript{38} In the U.S. case-control study using a joint effect approach, Antwi et al. demonstrated that dietary inflammatory potential may act synergistically with cigarette smoking and diabetes to increase the risk of pancreatic cancer beyond the risk of any of these factors alone.\textsuperscript{39} Compared to these two case-control studies, a significant association was not observed in the PLCO and the magnitude of the association was much weaker, even after excluding the subjects who may have changed diet due to symptoms associated with latent pancreatic cancer in the early follow-up period. There are differences between the prospective cohort design we utilized and a case-control design which are important to note. Differential misclassification of exposure is minimized in a cohort design because exposure is measured before the outcome develops, but after the outcome has occurred in
a case-control design, possibly resulting in differential recall. In addition, there may be biased selection of cases and controls in a case-control study which may induce selection bias and thus biased associations.\textsuperscript{400}

We did not observe evidence of effect modification in our study except for follow-up time which, as noted above, may reflect subclinical disease. Although many pancreatic cancer studies have performed lag time analysis by excluding subjects with short follow-up time in order to alleviate concerns about changes in diet driven by pre-clinical symptoms of pancreatic cancer (or precursor conditions, especially pancreatitis), few studies have examined the time interaction with dietary exposure. Our study finding of significant time interaction with E-DII were consistent with two previous analyses of diet and pancreatic cancer in the PLCO cohort, of which both found time was the only significant effect modifier.\textsuperscript{256,354} In the study by Arem et al, higher total fat and saturated fat intake (both strongly pro-inflammatory) were associated with significant reduced pancreatic cancer risk among subjects with less than four years of follow-up, and associations became weaker and nonsignificant after excluding these subjects.\textsuperscript{256} In the other PLCO study examining dietary glycemic load and available carbohydrates as well as fat (also pro-inflammatory), the positive association of pancreatic cancer with glycemic load and available carbohydrate and inverse association with saturated fat were observed only in the first four years, but not subsequently.\textsuperscript{354} Pancreatic cancer patients may present with severe, though nonspecific symptoms such as impaired glucose control, fatigue, jaundice, abdominal pain, nausea, blunted appetite, and vomiting before actual diagnosis, which is usually at a late stage because there exists no accurate method for early detection.\textsuperscript{401} Thus, assessment of dietary intake in pancreatic cancer studies, which
typically query diet in the past 12 months, may capture disease-related diet changes (or those related to precursor conditions), rather than intake prior to cancer symptoms. In our study, subjects may choose to eat healthier or more anti-inflammatory food or less amount of total food (i.e., fewer calories) due to symptoms associated with latent diseases in the early time period, which resulted in lower E-DII scores. Although prospective studies are less susceptible to reverse causation bias, such bias can occur in prospective studies of pancreatic cancer, given the cancer's unknown latency and the fact that it and its precursor conditions have profound effects on digestion. Differences in associations by follow-up time should be considered in future prospective studies assessing dietary intake and pancreatic cancer. Unlike the previous PLCO studies on fat intake, we observed a significant positive trend among subjects with longer follow up. Differences in results between these investigations may be explained by the different exposure we used that measured the total inflammatory potential from multiple foods and nutrients rather than dietary intake of a single macronutrient.

Five studies investigating a priori dietary patterns other than DII in relation to pancreatic cancer risk have been published, including variants of MDS, the HEI-2005, and dietary total antioxidant capacity score. Results from these studies all suggested better diet quality, was associated with lower pancreatic cancer risk, with effect estimates ranging from 0.44 to 0.92 comparing the highest with the lowest dietary quality group. However, our study suggested a nonsignificant association with total inflammation potential of diet. The different findings may be, to some extent, explained by the differences in dietary patterns under study, the nature of FFQs, study design, study population, sample size, or timing from dietary data collection to diagnosis.
It is well-recognized that pro-inflammatory states foster a cellular environment that supports the development of genetic mutations and the initiation of pancreatic carcinogenesis.\textsuperscript{58} Inflammation associated with diet may contribute to pancreatic malignancy through the increased level of inflammatory cytokines (e.g., TNF-α; IL-6, IL-8 and interferon-γ), reactive oxygen species and mediators in the inflammatory pathway (e.g., NF-κB and cyclooxygenase-2), leading to increased cell cycling, loss of tumor suppressor function, and stimulated oncogene expression, all of which may induce modifications of key cancer-related proteins, and ultimately, tumorigenesis.\textsuperscript{57,58}

Major strengths of our study include its prospective cohort design, which conceptually minimizes the possibility of recall bias. The long follow-up in the PLCO cohort among a large study population allowed for an in-depth evaluation of effect modification by time from the DHQ to cancer diagnosis. Detailed information on a comprehensive list of covariates allowed for careful adjustment in the analyses. The E-DII, a construct-validated tool which takes into account the whole diet instead of single nutrients or foods and is based on the entire literature on inflammation, provided a comprehensive assessment of dietary inflammatory potential. It has major advantages over other \textit{a priori} dietary patterns as it was developed specifically to reflect diet’s effect on inflammation that plays a central role in pancreatic cancer etiology. In addition, the use of a validated FFQ which covered major foods and nutrients consumed by Americans, and application of majority of DII components to calculate the E-DII scores helped to create a large contrast of E-DII scores in this study population. This is the first study to investigate whether dietary inflammatory potential is associated with pancreatic cancer risk in a prospective manner. The significant time interaction identified in our
study and the inverse association between proinflammatory diet and pancreatic cancer within <4 years of follow up, confirmed the previous PLCO findings on diet and pancreatic cancer.

This study also presents several limitations. First, it is likely the case number was not large enough in some stratified analyses so that we lacked statistical power to observe significant associations. Exclusion criteria resulted in exclusion of over 50,000 subjects, and differences were noted between excluded and included participants by various pancreatic cancer risk factors. This may have introduced selection bias and resulted in underestimation of the association. The FFQ is prone to response set bias, including social approval and social desirability, leading to measurement error in FFQ data as another unavoidable limitation, which may have resulted in some misclassification of the E-DII score. Although follow-up data were available on most covariates, the large amount of missing information impeded our ability to use these data. Evaluation of the E-DII at a single time point could result in non-differential misclassification of exposure given diet may change over time. However, we previously found DII scores were relatively stable over a long timeframe in postmenopausal women who were of comparable ages as ours. Another limitation of the study is that data were only available on 37 out of the 45 DII components used to calculate the E-DII scores; however, the range of DII scores may rely more on the amount of foods actually consumed rather than the number of available DII components. While we adjusted for important potential confounders, residual or unmeasured confounding cannot be ruled out.
4.7 Conclusion

In conclusion, this study does not support an association between inflammatory potential of diet and pancreatic cancer risk in the PLCO cohort. However, time significantly modified the association. There was evidence of an inverse association between E-DII and pancreatic cancer in the first four years of follow up, suggesting dietary changes due to undiagnosed disease (or a precursor condition) might affect appetite and food choices to lower the E-DII scores in the early stage, while a positive association was suggested by a significant trend after excluding subjects with follow-up time <4 years. Future prospective cohort studies assessing dietary factors and pancreatic cancer risk should consider differences in associations by follow-up time. Additional cohort studies with large number of cases are warranted to examine effect modification of E-DII and pancreatic cancer by important lifestyle risk factors.
Table 4.1 Baseline characteristics of 101,449 subjects in the PLCO Cancer Screening Trial cohort by quintiles of E-DII from food plus supplement

<table>
<thead>
<tr>
<th></th>
<th>Most anti-inflammatory diet</th>
<th></th>
<th>Most pro-inflammatory diet</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-DII Quintile 1 (-8.43, -5.32)</td>
<td>E-DII Quintile 2 (-5.31, -4.26)</td>
<td>E-DII Quintile 3 (-4.25, -3.03)</td>
<td>E-DII Quintile 4 (-3.02, -1.22)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>20290</td>
<td>20290</td>
<td>20290</td>
<td>20290</td>
</tr>
<tr>
<td><strong>Mean (SE)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at DHQ completion (y)</td>
<td>65.8 (0.04)</td>
<td>65.8 (0.04)</td>
<td>65.6 (0.04)</td>
<td>65.5 (0.04)</td>
</tr>
<tr>
<td>BMI at baseline (kg/m²)</td>
<td>26.4 (0.03)</td>
<td>27.0 (0.03)</td>
<td>27.3 (0.03)</td>
<td>27.7 (0.03)</td>
</tr>
<tr>
<td>Pack-years of cigarette at baseline</td>
<td>13.5 (0.2)</td>
<td>14.8 (0.2)</td>
<td>16.5 (0.2)</td>
<td>19.5 (0.2)</td>
</tr>
<tr>
<td>Alcohol consumption (g/d)</td>
<td>8.2 (0.1)</td>
<td>7.1 (0.1)</td>
<td>7.7 (0.1)</td>
<td>9.9 (0.2)</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6476 (31.9)</td>
<td>7653 (37.7)</td>
<td>9505 (46.9)</td>
<td>11531 (56.8)</td>
</tr>
<tr>
<td>Female</td>
<td>13814 (68.1)</td>
<td>12637 (62.3)</td>
<td>10785 (53.1)</td>
<td>8759 (43.2)</td>
</tr>
<tr>
<td>Trial arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>10361 (51.1)</td>
<td>10253 (50.5)</td>
<td>10302 (50.8)</td>
<td>10460 (51.6)</td>
</tr>
<tr>
<td>Control</td>
<td>9929 (48.9)</td>
<td>10037 (49.5)</td>
<td>9988 (49.2)</td>
<td>9830 (48.4)</td>
</tr>
<tr>
<td>Race/ Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>18124 (89.3)</td>
<td>18413 (90.8)</td>
<td>18615 (91.8)</td>
<td>18655 (91.9)</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>525 (2.6)</td>
<td>618 (3.0)</td>
<td>674 (3.3)</td>
<td>651 (3.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>239 (1.2)</td>
<td>290 (1.4)</td>
<td>278 (1.4)</td>
<td>316 (1.6)</td>
</tr>
<tr>
<td>Others</td>
<td>1402 (6.9)</td>
<td>969 (4.8)</td>
<td>723 (3.5)</td>
<td>668 (3.3)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or below</td>
<td>4291 (21.1)</td>
<td>5328 (26.3)</td>
<td>5736 (28.3)</td>
<td>6471 (31.9)</td>
</tr>
<tr>
<td>Post high school training other than college</td>
<td>2267 (11.2)</td>
<td>2554 (12.6)</td>
<td>2648 (13.1)</td>
<td>2760 (13.6)</td>
</tr>
<tr>
<td>Education</td>
<td>Count (Percentage)</td>
<td>Count (Percentage)</td>
<td>Count (Percentage)</td>
<td>Count (Percentage)</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Some college</td>
<td>4482 (22.1)</td>
<td>4419 (21.8)</td>
<td>4466 (22.0)</td>
<td>4273 (21.0)</td>
</tr>
<tr>
<td>College</td>
<td>4134 (20.4)</td>
<td>3778 (18.6)</td>
<td>3564 (17.6)</td>
<td>3401 (16.8)</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>5077 (25.0)</td>
<td>4154 (20.5)</td>
<td>3850 (19.0)</td>
<td>3349 (16.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>39 (0.2)</td>
<td>57 (0.3)</td>
<td>26 (0.1)</td>
<td>36 (0.2)</td>
</tr>
</tbody>
</table>

**Smoking status at baseline**

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>10396 (51.2)</td>
<td>10357 (51.0)</td>
<td>10175 (50.2)</td>
<td>9357 (46.1)</td>
<td>8116 (40.0)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>8916 (44.0)</td>
<td>8667 (42.7)</td>
<td>8484 (41.8)</td>
<td>8822 (43.5)</td>
<td>8770 (43.2)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>978 (4.8)</td>
<td>1260 (6.2)</td>
<td>1627 (8.0)</td>
<td>2107 (10.4)</td>
<td>3399 (16.8)</td>
</tr>
</tbody>
</table>

**First-degree pancreatic cancer family history**

<table>
<thead>
<tr>
<th>History</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>562 (2.8)</td>
<td>569 (2.8)</td>
<td>496 (2.4)</td>
<td>514 (2.5)</td>
<td>450 (2.2)</td>
</tr>
<tr>
<td>No</td>
<td>19194 (94.6)</td>
<td>19134 (94.3)</td>
<td>19138 (94.3)</td>
<td>19044 (93.9)</td>
<td>18949 (93.4)</td>
</tr>
<tr>
<td>Probable</td>
<td>389 (1.9)</td>
<td>431 (2.1)</td>
<td>516 (2.5)</td>
<td>560 (2.8)</td>
<td>724 (3.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>145 (0.7)</td>
<td>156 (0.8)</td>
<td>140 (0.7)</td>
<td>172 (0.9)</td>
<td>166 (0.8)</td>
</tr>
</tbody>
</table>

**History of diabetes**

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>1160 (5.7)</td>
<td>1313 (6.5)</td>
<td>1481 (7.3)</td>
<td>1532 (7.5)</td>
<td>1299 (6.4)</td>
</tr>
<tr>
<td>No</td>
<td>19025 (93.8)</td>
<td>18869 (93.0)</td>
<td>18711 (92.2)</td>
<td>18631 (91.8)</td>
<td>18894 (93.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>105 (0.5)</td>
<td>108 (0.5)</td>
<td>98 (0.5)</td>
<td>127 (0.6)</td>
<td>96 (0.5)</td>
</tr>
</tbody>
</table>

Abbreviations: SE, standard error

*Sum of percentages may not add up to 100% because of rounding or missing.
Table 4.2 Association between E-DII from food plus supplement and pancreatic cancer risk among 101,449 subjects in the PLCO Cancer Screening Trial cohort

<table>
<thead>
<tr>
<th>E-DII Quintile</th>
<th>Most anti-inflammatory diet</th>
<th>Most pro-inflammatory diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quintile 1 (-8.43, -5.32)</td>
<td>Quintile 5 (-1.21, 6.38)</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>67</td>
<td>75</td>
</tr>
<tr>
<td>Sample size</td>
<td>20290</td>
<td>20289</td>
</tr>
<tr>
<td>Age and energy-adjusted HR (95% CI)</td>
<td>1.00 (0.60-1.22)</td>
<td>1.25 (0.89-1.76)</td>
</tr>
<tr>
<td>Multivariable-adjusted HR (95% CI)</td>
<td>1.00 (0.57-1.17)</td>
<td>0.99 (0.69-1.40)</td>
</tr>
</tbody>
</table>

After excluding subjects with diabetes history at baseline

| Multivariable-adjusted HR (95% CI) | 1.00 (0.56-1.23) | 1.07 (0.73-1.56) |

P-trend\textsuperscript{a}

\textsuperscript{a} Continuous DII score was used to determine $P$ for trend

\textsuperscript{b} Adjusted for age at time of DHQ completion, sex (male and female), body mass index at baseline (underweight, normal, overweight, obesity and missing), history of diabetes (no, yes, missing), packyears within smoking status at baseline (never smoker, former smoker with <18 pack-years, former smoker with 18-41 pack-years, former smoker with $\geq$41 pack-years, current smoker with <18 pack-years, current smoker with 18-41 pack-years, current smoker with $\geq$41 pack-years, missing), total energy intake (kcal/d)

\textsuperscript{c} Model included 94,130 subjects and was adjusted for covariates listed in \textsuperscript{b}. 

---

104
Table 4.3 Stratified analyses of E-DII from food plus supplement and pancreatic cancer risk by follow-up time (i.e. <4 and >=4 years) among 101,449 subjects in the PLCO Cancer Screening Trial cohort

<table>
<thead>
<tr>
<th>E-DII Quintile</th>
<th>Most anti-inflammatory diet</th>
<th>Most pro-inflammatory diet</th>
<th>P-trend</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-DII Quintile 1 (-8.43, -5.32)</td>
<td>E-DII Quintile 2 (-5.31, -4.26)</td>
<td>E-DII Quintile 3 (-4.25, -3.03)</td>
<td>E-DII Quintile 4 (-3.02, -1.22)</td>
</tr>
<tr>
<td>Participants with follow-up time&lt;4 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>34</td>
<td>25</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Sample size</td>
<td>1539</td>
<td>1711</td>
<td>1768</td>
<td>1903</td>
</tr>
<tr>
<td>Age and energy-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>0.66 (0.40-1.11)</td>
<td>0.58 (0.34-0.98)</td>
<td>0.69 (0.42-1.13)</td>
</tr>
<tr>
<td>Multivariable-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>0.65 (0.39-1.09)</td>
<td>0.56 (0.33-0.95)</td>
<td>0.65 (0.39-1.09)</td>
</tr>
<tr>
<td>Participants with follow-up&gt;=4 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>33</td>
<td>31</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>Sample size</td>
<td>18757</td>
<td>18579</td>
<td>18522</td>
<td>18387</td>
</tr>
<tr>
<td>Age and energy-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>0.96 (0.59-1.57)</td>
<td>1.11 (0.69-1.79)</td>
<td>1.33 (0.84-2.10)</td>
</tr>
<tr>
<td>Multivariable-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>0.93 (0.57-1.52)</td>
<td>1.03 (0.64-1.66)</td>
<td>1.17 (0.73-1.87)</td>
</tr>
</tbody>
</table>

\(^a\) Continuous DII score was used to determine \( P \) for trend

\(^b\) P-value for interaction was calculated by adding the cross-product of the E-DII quintiles and binary variable of time (<4 years and >=4 years) in the multivariable-adjusted model

\(^c\) Adjusted for age at time of DHQ completion, sex (male and female), body mass index at baseline (underweight, normal, overweight, obesity and missing), history of diabetes (no, yes), packyears within smoking status at baseline (never smoker, former smoker with<18 pack-years, former smoker with 18-41 pack-years, former smoker with>=41 pack-years, current smoker with<18 pack-years, current smoker with 18-41 pack-years, current smoker with>=41 pack-years, missing), total energy intake (kcal/d)
<table>
<thead>
<tr>
<th>Most anti-inflammatory diet</th>
<th>Most pro-inflammatory diet</th>
<th>( P )-trend(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-DII Q1 (-7.58, -3.82)</td>
<td>E-DII Q5 (0.38, 6.89)</td>
<td></td>
</tr>
<tr>
<td>E-DII Q2 (-3.81, -2.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-DII Q3 (-2.59, -1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-DII Q4 (-1.29, 0.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-DII Q5 (0.38, 6.89)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>64</th>
<th>52</th>
<th>65</th>
<th>78</th>
<th>69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>20291</td>
<td>20289</td>
<td>20290</td>
<td>20289</td>
<td>20290</td>
</tr>
<tr>
<td>Age and energy-adjusted HR (95% CI)</td>
<td>1.00</td>
<td>0.82 (0.57-1.19)</td>
<td>1.06 (0.75-1.49)</td>
<td>1.32 (0.94-1.84)</td>
<td>1.22 (0.86-1.73)</td>
</tr>
<tr>
<td>Multivariable-adjusted HR (95% CI)(^b)</td>
<td>1.00</td>
<td>0.79 (0.55-1.14)</td>
<td>0.97 (0.68-1.37)</td>
<td>1.13 (0.81-1.59)</td>
<td>0.97 (0.67-1.39)</td>
</tr>
</tbody>
</table>

After excluding subjects with diabetes history at baseline

| Multivariable-adjusted HR (95% CI)\(^c\) | 1.00 | 0.70 (0.47-1.06) | 0.90 (0.61-1.32) | 1.21 (0.84-1.73) | 0.97 (0.66-1.43) | 0.17 |

\(^a\) Continuous DII score was used to determine \( P \) for trend

\(^b\) Adjusted for age at time of DHQ completion, sex (male and female), body mass index at baseline (underweight, normal, overweight, obesity and missing), history of diabetes (no, yes, missing), packyears within smoking status at baseline (never smoker, former smoker with\(<\)18 pack-years, former smoker with 18-41 pack-years, former smoker with \(\geq\)41 pack-years, current smoker with\(<\)18 pack-years, current smoker with 18-41 pack-years, current smoker with \(\geq\)41 pack-years, missing), total energy intake (kcal/d)

\(^c\) Model included 94,130 subjects and was adjusted for covariates listed in \(^b\)
Table 4.5 Association between E-DII from food only and pancreatic cancer risk by follow-up time (i.e. <4 and >=4 years) among 101,449 subjects in the PLCO Cancer Screening Trial cohort

<table>
<thead>
<tr>
<th></th>
<th>Most anti-inflammatory diet</th>
<th></th>
<th>Most pro-inflammatory diet</th>
<th></th>
<th>P-trend (^a)</th>
<th>P-interaction (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-DII Q1 ((7.58, -3.82))</td>
<td>E-DII Q2 ((-3.81, -2.60))</td>
<td>E-DII Q3 ((-2.59, -1.30))</td>
<td>E-DII Q4 ((-1.29, 0.37))</td>
<td>E-DII Q5 ((0.38, 6.89))</td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>31</td>
<td>20</td>
<td>35</td>
<td>30</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>1563</td>
<td>1651</td>
<td>1825</td>
<td>1959</td>
<td>1979</td>
<td></td>
</tr>
<tr>
<td>Age and energy-adjusted HR (95% CI)</td>
<td>1.00 (0.36-1.12)</td>
<td>0.98 (0.61-1.60)</td>
<td>0.77 (0.46-1.28)</td>
<td>0.60 (0.34-1.05)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted HR (95% CI)(^c)</td>
<td>1.00 (0.36-1.10)</td>
<td>0.96 (0.58-1.56)</td>
<td>0.76 (0.45-1.28)</td>
<td>0.60 (0.33-1.07)</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

Subjects with follow up <4 years

| Cases (n)            | 33                         | 32                   | 30                          | 48                   | 47                          | 0.01 |
| Sample size          | 18728                      | 18638                | 18465                       | 18330                | 18311                       |
| Age and energy-adjusted HR (95% CI) | 1.00 (0.61-1.60)           | 0.95 (0.58-1.55)     | 1.57 (1.01-2.46)            | 1.61 (1.02-2.54)     | 0.002                       |
| Multivariable-adjusted HR (95% CI)\(^c\) | 1.00 (0.59-1.55)           | 0.88 (0.54-1.45)     | 1.38 (0.87-2.17)            | 1.28 (0.80-2.06)     | 0.05                        |

\(^a\) Continuous DII score was used to determine P for trend
\(^b\) P-value for interaction was calculated by adding the cross-product of the E-DII quintiles and binary variable of time (<4 years and >=4 years) in the multivariable-adjusted model
\(^c\) Adjusted for age at time of DHQ completion, sex (male and female), body mass index at baseline (underweight, normal, overweight, obesity and missing), history of diabetes (no, yes), packyears within smoking status at baseline (never smoker, former smoker with<18 pack-years, former smoker with 18-41 pack-years, former smoker with >=41 pack-years, current smoker with<18 pack-years, current smoker with 18-41 pack-years, current smoker with >=41 pack-years, missing), total energy intake (kcal/d)
Table 4.6 Comparison of important demographic and lifestyle characteristics between study sample and excluded sample in the PLCO Cancer Screening Trial cohort

<table>
<thead>
<tr>
<th></th>
<th>Study population (n=101,449)</th>
<th>Excluded subjects (n=53,448)</th>
<th>P-value $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td></td>
</tr>
<tr>
<td>Age at DHQ (years)</td>
<td>65.5 (0.02)</td>
<td>66.8 (0.04)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pack-years of cigarette at baseline</td>
<td>17.8 (0.08)</td>
<td>21.8 (0.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>E-DII from food and supplement</td>
<td>-3.2 (0.01)</td>
<td>-3.0 (0.02)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>E-DII from food only</td>
<td>-1.7 (0.01)</td>
<td>-1.5 (0.02)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>N (%) $^b$</td>
<td>N (%) $^b$</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male</td>
<td>49347 (48.6)</td>
<td>27335 (51.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52102 (51.4)</td>
<td>26113 (48.9)</td>
<td></td>
</tr>
<tr>
<td>Trial Arm</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Intervention</td>
<td>51666 (50.9)</td>
<td>25778 (48.2)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>49783 (49.1)</td>
<td>27670 (51.8)</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity $^c$</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>92259 (90.9)</td>
<td>40320 (83.2)</td>
<td></td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>3341 (3.3)</td>
<td>4367 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1490 (1.5)</td>
<td>1328 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4359 (4.3)</td>
<td>2477 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Education level $^c$</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>High school or below</td>
<td>29693 (29.3)</td>
<td>15782 (32.7)</td>
<td></td>
</tr>
<tr>
<td>Post high school training other than college</td>
<td>13116 (13.0)</td>
<td>5711 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>21752 (21.5)</td>
<td>10940 (22.6)</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>17799 (17.6)</td>
<td>7545 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>18887 (18.6)</td>
<td>8341 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Smoke status at baseline $^c$</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Never smoked</td>
<td>48401 (47.7)</td>
<td>20871 (43.0)</td>
<td></td>
</tr>
<tr>
<td>Past smoker</td>
<td>43659 (43.0)</td>
<td>20958 (43.2)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>9371 (9.2)</td>
<td>6684 (13.8)</td>
<td></td>
</tr>
<tr>
<td>First-degree pancreatic cancer family history $^c$</td>
<td>2591 (2.6)</td>
<td>1208 (2.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>95459 (94.8)</td>
<td>45308 (94.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2620 (2.6)</td>
<td>1616 (3.4)</td>
<td></td>
</tr>
<tr>
<td>History of diabetes $^c$</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>6785 (6.7)</td>
<td>4744 (9.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>94130 (93.3)</td>
<td>43364 (90.1)</td>
<td></td>
</tr>
</tbody>
</table>

108
\(^a\) P value was calculated from independent t-test for continuous variables and from Chi-Square test for categorical variables.

\(^b\) The sum of percentages for some categorical variables may not add up to 100\% because of rounding.

\(^c\) the proportion was calculated after excluding missing because there were 9\% excluded participants did not return baseline questionnaire which contained these variables
CHAPTER 5
INFLAMMATORY POTENTIAL OF DIET, INFLAMMATION-RELATED LIFESTYLE FACTORS AND RISK OF PANCREATIC CANCER: RESULTS FROM THE NIH-AARP DIET AND HEALTH STUDY

5.1 Abstract

Background: Chronic inflammation is an underlying pathophysiological foundation for many cancers, including pancreatic cancer. Diet is a strong moderator of chronic inflammation. Other inflammation-related lifestyle factors such as smoking and obesity may act synergistically with inflammatory potential of diet, to affect pancreatic cancer risk. We aimed to use data from NIH-AARP Diet and Health Study which includes so far the largest number of pancreatic cancer cases in the US, to prospectively examine the association between dietary inflammatory potential and pancreatic cancer and the association by cancer severity, and also examine the effect modifications by important inflammation-related lifestyle factors including body mass index, cigarette smoking, diabetes history, alcohol drinking and frequency of use of non-steroidal anti-inflammatory drugs. Methods: Our final analytical cohort consisted of 533,286 participants (314,162 men and 219,124 women) aged between 50 to 71 at baseline. Energy-adjusted DII (E-DII) scores were computed based on food and supplement intake.
Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) with participants in the lowest E-DII quintile (most anti-inflammatory scores) as referent. Effect modifications were examined by adding cross-product of each effect modifier as a categorical variable with E-DII quintile in the multivariable-adjusted model. **Results:** After a median 13.4 years of follow-up, a total of 3,338 pancreatic cancer cases occurred. After controlling for confounders, there was no significant association between E-DII scores and pancreatic cancer risk among both men and women. Inflammatory potential of diet was not associated with pancreatic cancer by cancer stage or grade. The E-DII and pancreatic cancer association was not modified by any of the inflammation related lifestyle factors. **Conclusion:** Our study did not support an association between inflammatory potential of diet and pancreatic cancer and no significant effect modifications between diet-associated inflammation and other lifestyles related to inflammation on pancreatic cancer etiology were detected.

5.2 **Introduction**

Inflammation, a critical function of the innate immune system, protects against pathogens and initiates specific immunity. Acute inflammation is not regarded as a risk factor for the development of neoplasia, but frequent acute inflammation results in unresolved wound healing with consequent chronic inflammation. Chronic inflammation has been identified as an underlying pathophysiological foundation for many chronic diseases, including cancers. Chronic inflammation also plays a pivotal role in the development of pancreatic cancer, as exemplified by the fact that both hereditary and sporadic forms of chronic pancreatitis are associated with an increased risk of pancreatic cancer. Due to lack of early detection approaches and limited
effective treatments, pancreatic cancer has the highest case-fatality rate of any major cancer.\textsuperscript{1,370,411} It is the fourth leading cause of cancer death among both men and women in the United States, even with low incidence rates.\textsuperscript{1}

Diet is a strong moderator of chronic inflammation, mainly through its impact on visceral obesity,\textsuperscript{387} oxidative damage,\textsuperscript{78} and insulin resistance.\textsuperscript{387} The DII was developed to assess the inflammatory potential of diet.\textsuperscript{22} The use of a dietary index or patterns approach has advantages over the use of individual inflammation-modulating nutrients or foods, given the complex interaction and correlation among various dietary components.\textsuperscript{412,413} Besides diet, other lifestyle factors are known to be associated with inflammation, such as obesity, diabetes, smoking, alcohol intake, and frequency use of NSAIDs.

To date, two case-control studies have examined the association between the DII and pancreatic cancer risk with both studies reporting a more than 2-fold increased risk among individuals consuming a pro-inflammatory diet. Both studies examined the interaction between DII and some inflammation-related factors but with inconsistent results.\textsuperscript{38,39} However, a cohort study using data from the PLCO Cancer Screening Trial did not find an association between DII and pancreatic cancer, except when stratified by follow-up time where a pro-inflammatory diet was associated with increased risk only in those subjects with >4 years of follow-up (Zheng et al. unpublished data in chapter 4). Therefore, the NIH–AARP Diet and Health Study, one of the largest diet and health prospective cohort studies in the US (approximately 500,000 US adults), provides an invaluable opportunity to examine and verify the relationship between the DII and pancreatic cancer risk with a large number of cases. We also explored if important
inflammation-related lifestyle factors including BMI, cigarette smoking, alcohol drinking, NSAIDs use frequency, and history of diabetes modified the DII and pancreatic cancer association. Additionally, the study examined the association between dietary inflammatory potential and severity of pancreatic cancer (cancer grade and cancer stage).

5.3 Methods

5.3.1 Study population

The NIH-AARP Diet and Health Study is the largest prospective cohort study of diet and health ever conducted in US with the goal to examine a number of important diet and cancer hypotheses. Baseline data collection was initiated between 1995 and 1996 when a baseline questionnaire asking information on demographic characteristics, medical history, dietary intake and health behaviors was mailed to 3.5 million AARP members. The scientific rational and study design of the cohort was described previously. The initial study population of this cohort was 617,119 females and males who responded to the baseline questionnaire with a response rate of 17.6%. Subjects were 50 to 71 years old with mean age of 62 years at baseline and lived in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, or Louisiana) or two metropolitan areas (Atlanta, Georgia or Detroit, Michigan). After excluding respondents whose responses on the baseline questionnaire were not reliable with the following reasons: 1) unknown sex, 2) skipped substantial portions of the questionnaire, 3) skipped facing page that provided personal information and date when they completed the questionnaire, 4) indicated they were not the intended respondent and did not complete the rest of the questionnaire, 5) more than 10 recording errors and less than 10 foods consumed, and respondents who asked to be dropped from cohort, who died or moved
before entry and those with duplicate representation of the questionnaire, there remained 566,398 eligible study participants (339,666 men and 226,732 women). From the eligible participants, we further excluded 15,760 subjects whose baseline questionnaires were filled out by proxy, 8,828 subjects who had any registry-confirmed cancer diagnosis at baseline (except for non-melanoma skin cancer), 4,261 subjects who had extreme daily energy intake [i.e., 2 interquartile ranges (IQRs) below the sex-specific 25th percentile or above the 75th percentile of log-transformed energy intake], 49 subjects who moved out of the study area or died at or before processing of the baseline questionnaire, and 4,214 subjects who had implausible body mass index (BMI) values (2 IQRs below the sex-specific 25th percentile or above the 75th percentile of log-transformed BMI). Our final analytical cohort consisted of 533,286 participants (n=314,162 men and n=219,124 women). The NIH–AARP Diet and Health Study was approved by the National Cancer Institute Special Studies Institutional Review Board, and all participants gave informed consent by virtue of completing and returning the questionnaire.

5.3.2 Dietary assessment and E-DII score calculation

The self-administered NCI-developed FFQ included in the baseline questionnaire assessed participants’ usual frequency of intakes and portion sizes on 124 food items over the past year, using 10 frequency categories ranging from “never” to “>=6 times/d” for beverages and from “never” to “>=2 times/d” for solid foods. Each item has 3 options of portion size. The FFQ also included 21 additional questions on food choices and cooking practices, and four supplement intake questions. In the calibration study, the performance of baseline FFQ was evaluated using two nonconsecutive 24-hour dietary recalls by telephone which were randomly assigned by day of the week with a median of
21 days apart among 1,953 subsample participants who responded to at least a baseline FFQ and one 24-hour recall.\textsuperscript{361} After adjusting for random within-person error, the energy-adjusted correlation coefficient ranged from 0.40 (vitamin E) to 0.76 (saturated fat) among men, and from 0.36 (vitamin E) to 0.70 (vitamin B6) among women.\textsuperscript{361} Responses from the FFQ were linked to the USDA’s CSFII survey databases (1989–91 initially, and 1994–96 as it became available), in order to estimate individuals’ nutrients, foods, and food group intakes.\textsuperscript{364}

The DII is a literature-derived, population-based index designed to assess the overall inflammatory potential of an individual’s diet. The details of the development of the DII have been published previously.\textsuperscript{22} Briefly, 1,943 eligible peer-reviewed primary research articles published up to 2010 on the effect of dietary factors on six inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP) were identified and scored to derive the component-specific inflammatory effect scores for 45 dietary factors (i.e. components of DII), which comprised macronutrients, micronutrients and some bioactive components such as spices and tea.\textsuperscript{22} Thirty-four baseline FFQ-derived food parameters in the NIH-AARP study were used to calculate the E-DII score. These included the following: calories; carbohydrates; protein; total fat; saturated, monounsaturated, and polyunsaturated fat; trans-fat; alcohol; fiber; cholesterol; vitamins B1, B2, B6, B12, A, C, D, and E; niacin; iron; magnesium; zinc; selenium; folic acid; beta-carotene; anthocyanidins; flavan-3-ols; flavones; flavonones; isoflavones; caffeine; green peppers; and tea. To calculate flavonoid classes, daily fruits and vegetables intakes in grams were linked to the USDA’s Database for Flavonoid Content from Selected Foods (Release 3.1, December 2013) by matching foods with the USDA’s 5-digit nutrient database number.
The content levels of each flavonoid class from each fruit and vegetable were calculated and summed to provide amount of consumption for each flavonoid class.\textsuperscript{48}

The food and nutrient consumption estimated from the FFQ was first adjusted for total energy per 1000 calories. The energy-adjusted dietary intake was subsequently standardized to a composite dietary database representing average worldwide energy-adjusted dietary intake from 11 populations in the world, to avoid the arbitrariness of simply using raw intake amounts.\textsuperscript{22} The energy-adjusted standardized dietary intake was then multiplied by the literature-derived inflammatory effect score for each of 34 DII components, and summed across all components to obtain the overall E-DII score.\textsuperscript{22} Higher E-DII scores represent more pro-inflammatory diets while lower (i.e., more negative) E-DII scores indicate more anti-inflammatory diets. The DII score, calculated from multiple different dietary assessment instruments, has been construct validated and found to be associated with higher levels of IL-6,\textsuperscript{24} TNF-\(\alpha\) receptor 2,\textsuperscript{24} hsCRP\textsuperscript{23,27} and homocysteine.\textsuperscript{25}

A majority of the participants (68\%) in the NIH-AARP Study consumed supplements, and most dietary supplements contain components which have anti-inflammatory properties. Thus, we utilized intake data from food and supplements to calculate the E-DII and quantify the association between the inflammatory potential of overall dietary exposures and pancreatic cancer risk.

5.3.3 Assessment of other covariates

Baseline characteristics, which included demographic information, personal medical history, family history, and health behaviors such as smoking, alcohol drinking, and physical activity were self-reported through the baseline questionnaire. BMI was
calculated as weight (kg)/height(m)^2 and categorized based on the World Health Organization criteria. NSAIDs use information was collected from a risk factor questionnaire which was sent to participants in 1996 to 1997.

5.3.4 Cohort follow-up and pancreatic cancer case ascertainment

The NIH-AARP cohort are followed annually for change of address by matching the cohort database to that of the National Change of Address (U.S. Postal Service). Vital status was ascertained by annual linkage of the cohort to the Social Security Administration Death Master File (SSA DMF) on deaths in the U.S., follow-up searches of the National Death Index (NDI) for subjects that match to the SSA DMF, cancer registry linkage, questionnaire responses and responses to other mailings. Incident cases of pancreatic cancer were identified through linkage between the NIH-AARP cohort membership and eight state cancer registry databases which are estimated to be 95% complete within two years of cancer incidents. Uncertain matches underwent a final manual review. A follow-up questionnaire sent out in 2004 to record participants’ cancer status and other non-cancer endpoints was used as an additional resource. Mortality cases were identified by linkage to the NDI. In our analysis, pancreatic cancer case was defined as incident adenocarcinoma of the exocrine pancreas (International Classification of Diseases for Oncology, Third Edition, codes C25.0-C25.3, C25.7- C25.9) and our case definition excluded pancreatic endocrine tumors and other rare histology types (histology type 8150, 8151, 8154, 8155,8160, 8240,8245, 8246, 8430, 8440, 8453, 8470, 8471, 8520, 8550, 8800, 8980) because they may differ etiologically from adenocarcinoma of exocrine pancreas. We treated these cases as censored at the date of diagnosis. Secondary pancreatic cancer cases (i.e., non-primary pancreatic cancer) were excluded.
from outcome in the sensitivity analysis. There were cases who had pancreatic cancer diagnosis at the time of death (diagnosis date=death date), so we imputed their diagnosis date by subtracting 4 months from the death date (4 months is the median survival time for exocrine pancreatic cancer) and we included these people in the outcome in one of the sensitivity analyses.369

5.4 Statistical analysis

The baseline characteristics of the study population by quintiles of E-DII from food plus supplement, with quintile cut-off points determined from the distribution of the entire cohort, was described by calculating means and SE for continuous variables and frequencies and percentages for categorical variables. ANOVA test was used to test the difference across E-DII quintiles for continuous variables, and Chi-square test was performed to test the difference for categorical variables. Participants were followed up from the baseline questionnaire completion to the date of diagnosis of pancreatic cancer, death from any cause, moved out of the study’s ascertainment area, or the end date of study follow-up (12/31/2011), whichever came first. Multivariable Cox proportional hazards regression with person-year as the underlying time metric was fitted to estimate the age- and energy-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) with subjects in the lowest E-DII quintile (the most anti-inflammatory score) as the referent. Proportional hazard (PH) assumption was examined using the Schoenfeld residual test. Only baseline age (continuous format) violated PH assumption, so we fitted a stratified COX model by binary age group using the median age of the cohort. To test the linear trend of pancreatic cancer risk across quintiles of E-DII score, a continuous E-DII variable was used.415 We considered all variables in Table
5.1 as potential confounders during model building and created parsimonious (multivariable-adjusted) models that included variables if they were associated with both pancreatic risk and E-DII (in either continuous or categorical format), or changed the crude risk estimate by more than 10%. In the multivariable-adjusted models, we adjusted for age group at entry (<62 or ≥62 years old), sex (male and female), BMI (underweight; normal; overweight; obese; missing), smoking status (nonsmoker; quit≥10 years, ≤20 cigs/day; quit≥10 years, >20 cigs/day; quit 5-9 years, ≤20 cigs/day; quit 5-9 years, >20 cigs/day; quit 1-4 years, ≤20 cigs/day; quit 1-4 years, >20 cigs/day; quit<1 year or current, ≤20 cigs/day; quit<1 year or current, >20 cigs/day; missing), alcohol intake (g/d), education levels (≤11 years; 12 years or completed high school; post-high school, some college, college or post graduate; unknown), medical history of diabetes (yes; no), and total energy intake (kcal/day). Continuous HR and 95% CIs also were calculated for each one unit of standard deviation increase of E-DII score after the restricted cubic spline test indicated the linear assumption was sufficient. Since men and women had different distributions of the E-DII score and other covariates, we present the associations between E-DII and pancreatic cancer by sex using sex-specific E-DII quintile cut-off points, and among combined men and women.

Effect modifications by inflammation-related lifestyle factors including BMI, smoking status, alcohol drinking, NSAIDs use frequency (i.e., aspirin and ibuprofen products), and diabetes history were examined by adding cross-product of each effect modifier as a categorical variable with E-DII quintile in the multivariable-adjusted model with a P value ≤0.1 as an indicator of significant interaction. HRs and 95% CIs comparing subjects in each higher E-DII group with lowest E-DII were reported for each
stratum of a given effect modifier. According to the American Institute for Cancer Research Continuous Update Project 2012 report for pancreatic cancer, there was evidence of a nonlinear association between alcohol (as ethanol) and pancreatic cancer risk with increased risk observed among those consuming 53.4g alcohol or more a day. Thus, we categorized alcohol intake into high and low level by using 53.4g as the cut-off point in the interaction test. We did not find any difference in the significance of interactions between males and females; thus, we presented the results of interactions without stratifying by sex.

To examine whether associations varied by pancreatic cancer severity, we also performed separate association analysis among cancer cases with different cancer stages and cancer grades.

Multiple sensitivity analyses were performed. First, to alleviate concerns regarding reverse causality (i.e., a biased association attributed to diet or a lifestyle change as a result of latent pancreatic cancer), lag time analysis was performed by excluding study subjects with follow-up <5 years as previously reported. Secondly, subjects who self-reported diabetes history at baseline were removed from analysis as diabetes may be a preclinical indicator of pancreatic cancer, and diet modification may have occurred after diagnosis of diabetes. We also restricted the outcome to primary pancreatic cancer only, and added death cases of pancreatic cancer to both primary pancreatic cancer outcomes and the total incident outcomes using the imputed incidence time.

All statistical analyses were conducted using SAS® (version 9.4, Cary, NC). All tests were two-sided with p values<0.05 considered to be statistically significant if not
otherwise noted.

5.5 Results

After a median 13.4 years of follow up, a total of 3,338 pancreatic cancer cases occurred. E-DII scores ranged from -7.91 to 6.66, which was comparable to other US cohorts. As shown in Table 5.1, compared to participants who had the most anti-inflammatory E-DII scores (i.e. E-DII quintile 1), participants consuming a more pro-inflammatory diet (i.e., higher E-DII scores) were younger at baseline but with larger BMI, consumed more alcohol and energy, and were more likely to be males, current smokers or former smoker who smoked more than 20 cigarettes per day, Black non-Hispanic or Hispanic race/ethnicities, have below-college education level, have history of diabetes, but be less physically active, and report less frequent use of NSAIDs.

HRs for pancreatic cancer risk according to E-DII quintiles and continuous E-DII are presented in Table 5.2. In the age- and energy-adjusted model, significantly increased pancreatic cancer risk with E-DII quintile and continuous E-DII was seen among males and among all subjects combined, but not among females. After controlling for confounders, there was no significant association between E-DII scores and pancreatic cancer risk among men (HR Q5 vs Q1 = 1.03, 95% CI=0.89-1.18, P-trend=0.69), women (HR Q5 vs Q1 = 0.98, 95% CI=0.82-1.17, P-trend=0.98), or all subjects combined (HR Q5 vs Q1 = 0.97, 95% CI=0.87-1.09, P-trend=0.87, P-interaction by sex=0.63) Continuous HRs also were not significant among men or women or all (Table 5.2).

The E-DII and pancreatic cancer association was not modified by any of the inflammation related lifestyle factors which consisted of BMI, smoking status, alcohol drinking, NSAIDs use (i.e. aspirin and ibuprofen products), and diabetes history (Table
Stratified by any effect modifier, no significant association was detected in any of the strata comparing the highest to lowest E-DII group.

Stratified by cancer stage, localized pancreatic cancer made up the least proportion, followed by regional and distant metastasized pancreatic cancers. However, inflammatory potential of diet was not associated with pancreatic cancer in any cancer stage (Table 5.4). Similarly, when stratified by cancer grade, the largest proportion of pancreatic cancer was poorly differentiated or moderately well differentiated. We did not identify any significant association with pancreatic cancer in any cancer grade (Table 5.5).

After excluding subjects with follow-up <5 years, the multivariable HRs did not change materially (Table 5.6). Similar HRs were observed when primary pancreatic cancer was treated as the outcome. After we added pancreatic cancer death cases to outcomes (i.e., total incident pancreatic cancer cases and primary pancreatic cancer cases) by using the imputed incidence time, results did not change (Table 5.7 and 5.8).

5.6 Discussion

The current analyses represent the largest cohort to date to examine the association between dietary inflammatory potential and pancreatic cancer in a prospective manner. No association was observed between the E-DII and pancreatic cancer risk. We also did not observe evidence of effect modification by inflammation-related lifestyle factors including BMI, smoking status, alcohol drinking, NSAIDs use, or history of diabetes. Due to the large sample size, we were able to examine associations by disease severity, but found no evidence of increased risk of pancreatic cancer with a more pro-inflammatory diet among different cancer stages or grades.
Two case-control studies and one cohort study previously investigated the E-DII and pancreatic cancer association. The finding of the present analysis was consistent with our previous work where an overall null association was reported among 101,449 US participants in the PLCO cohort (Zheng et al. unpublished data in Chapter 4). In the two case-control studies from the US and Italy, both reported a more than 2-fold significant increased risk of pancreatic cancer in the highest compared to the lowest quintile of the E-DII group (US: OR \( \text{Q5vsQ1} \) =2.54, 95% CI=1.87-3.46, P trend<0.0001; Italy: OR \( \text{Q5vsQ1} \) =2.48, 95% CI=1.50-4.10, P-trend=0.002). The different results between our analysis and the case-control studies may be explained by the different study designs. The prospective design utilized in the two studies with null associations serves to minimize differential misclassification of exposure which can be present in case-control studies due to recall bias. On the other hand, it is possible that a one-time dietary assessment many years prior to diagnosis in cohort studies is not the most etiologically-relevant timeframe for assessing exposure. Of note, however, our group has reported significant associations between the DII and colorectal cancer, another cancer substantially influenced by inflammation, within the NIH-AARP Study. While there was no evidence of a follow-up time interaction in the current study, previous analyses of the PLCO cohort indicated the association between diet and pancreatic cancer may differ by follow-up time. In that study, decreased risk with a more pro-inflammatory diet was observed with shorter follow-up time, and increased risk was observed for longer follow-up time (Zheng et al. unpublished data in Chapter 4). Thus, the effect of preclinical disease on dietary intake and recall should be further explored in cohort studies.

Previous studies of dietary indices other than the DII using \( a \ priori \) or data-driven
methods for deriving dietary patterns have generally suggested healthier dietary quality characterized by high consumption of fruit, vegetables, whole grains, white meat, fiber, low-fat dairy products was associated with reduced pancreatic risk while patterns characterized by greater intake of animal foods, refined grains, high-fat dairy products, sweets and desserts were associated with increased risk of pancreatic cancer, 16,17,20,21,48,402,403 although the associations were stronger in case-control than cohort studies. 417 The differences in dietary patterns of interest, dietary assessment instruments, study design and study population, number of cases or timing from dietary data collection to diagnosis are important factors that may explain the different results across studies.

No evidence of effect modification by inflammation-related lifestyle factors was identified in the study and no significant association appeared in any stratum of an effect modifier, which was consistent with our findings in the PLCO cohort where BMI, history of diabetes, and smoking status were not effect modifiers. The Italian case-control study reported effect modification by smoking status and BMI where a significant positive association was observed among never smokers (OR Q5 vs Q1 =2.32, 95% CI=1.08-4.99; P-trend=0.01) and past smokers (OR Q5 vs Q1 = 3.37, 95% CI=1.22-9.35; P-trend=0.07), but not among current smokers. Positive associations were observed among normal weight (OR Q5 vs Q1 =2.24, 95% CI=1.03-4.86; P-trend=0.16) and overweight (OR Q5 vs Q1 =2.32, 95% CI=1.03-5.21; P-trend=0.005), but not among obese subjects (P-interactions by BMI and by smoking status were not reported in the study). 38 In the US case-control study, Antwi et al. did not find significant interaction between DII and BMI, diabetes history or cigarette smoking using the statistical test for multiplicative interaction.
However, the quantitative additive and multiplicative interactions calculated by comparing the observed and expected ORs suggested that diet-associated inflammation may act synergistically with cigarette smoking and diabetes to increase the risk of pancreatic cancer beyond the risk of any of these factors alone. This is one of the first cohort studies to examine the association between a dietary index and pancreatic cancer severity. Similar to the overall null association, we did not find a differential association between inflammatory potential of diet and pancreatic cancer in any cancer stage or grade. The only other study to examine DII in relation to pancreatic cancer stage at diagnosis was the case-control study in the US which found a positive association overall. They also did not find differential effects by stage, reporting increased risk for cancers presenting with resectable (OR_{Q5vsQ1} = 2.36, 95% CI = 1.48–3.75), locally advanced (OR_{Q5vsQ1} = 2.21, 95% CI = 1.41–3.46) or metastatic (OR_{Q5vsQ1} = 3.13, 95% CI = 1.85–5.29) tumors. Due to the rapid fatality rates of pancreatic cancer, case-control studies are especially prone to biases with frequent proxy responses used among cases, which in turn may produce more measurement error among cases than controls.

Although no association was found between a pro-inflammatory diet and pancreatic cancer, there is mechanistic support for the hypothesis. It is well accepted that inflammatory states foster a cellular environment that supports the development of genomic mutations and the initiation of pancreatic carcinogenesis. Dietary factors can modify inflammation through multiple mechanisms including regulation of the pro-inflammatory cytokines, NF-κB pathway activation, changes in DNA methylation, and influence on the antioxidant defense. Pro-inflammatory diets can increase insulin
resistance, increase reactive oxygen species and mediators in the inflammatory pathway (e.g., NF-kB and COX-2), leading to increased cell cycling, loss of tumor suppressor function, and stimulated oncogene expression, genetic alterations and modifications of key cancer-related proteins and ultimately cause malignancy.\textsuperscript{57,58,418,419} Anti-inflammatory diets can have strong antioxidant and carcinogenesis-inhibition properties, owing to healthy fatty acid profiles, large fiber content, high antioxidants and phytochemicals from vegetables and fruits which help to reduce insulin resistance, oxidative stress and damage, and inhibit tumor initiation and promotion.\textsuperscript{182,420}

This study has several strengths. The NIH-AARP Diet and Health Study is a large well-established prospective cohort study with diet and lifestyle factors assessed before cancer diagnosis, which minimized the recall bias and selection bias that may be found in a typical case-control study. A large number of pancreatic cancer cases has provided sufficient statistical power to detect the main association and interaction by several important inflammation-related lifestyle factors. Detailed information on a comprehensive list of covariates allowed for careful adjustment in the analyses. This is the first cohort study to examine whether inflammatory potential of diet could act synergistically with other inflammation-related lifestyle factors to influence pancreatic cancer risk. It is also the first cohort study to examine the association between a dietary index and pancreatic cancer severity. The use of the DII, a construct-validated measurement tool which takes into account the whole diet to assess dietary inflammatory potential has major advantage over other \textit{a priori} dietary patterns as it was developed specifically for inflammation mechanism,\textsuperscript{22} which plays a central role in the pancreatic cancer carcinogenesis.\textsuperscript{58,59}
Despite these strengths, study limitations also are noted. The number of cases in certain cancer stage (localized pancreatic cancer) and grade (well-differentiated pancreatic cancer and undifferentiated/anaplastic pancreatic cancer) categories and some other stratified analyses was not large enough to infer valid associations. Measurement error in FFQ data and other covariates is another unavoidable limitation, and a measure of social desirability was not obtained in this study.\(^{421, 422}\) Although follow-up data on covariates were available in the risk factor or follow-up questionnaires, the large missing percentage impeded the possibility to use these data. Diet was only assessed at baseline, therefore, any changes in diet over follow up were not captured, which could result in non-differential misclassification of exposure. However, we previously found DII scores were relatively stable over a long timeframe in postmenopausal women where the study participants were of comparable age as the NIH-AARP study.\(^{405}\) Another possible limitation in our study was that only data on 34 components of the DII were available to calculate the E-DII scores. However, the range of DII scores may rely more on the amount of foods actually consumed rather than on the number of available DII components.\(^{406}\) Although important potential confounders were adjusted for in our analyses, residual or unmeasured confounding may still be a possibility.

5.7 Conclusion

In conclusion, there was no association between dietary inflammatory potential and pancreatic cancer risk in this large cohort among both men and women. Inflammation-related lifestyle factors including BMI, smoking status, alcohol drinking, NSAIDs use, and history of diabetes did not modify the association. Dietary inflammatory potential was not associated with pancreatic cancer risk by cancer stage or
grade. Future large cohort studies are warranted to test the effect modification of E-DII and cancer by inflammation-related lifestyle factors and test the association between E-DII and severity of pancreatic cancer to confirm our findings. Future cohort studies should also examine the difference in associations by follow-up time.
Table 5.1 Baseline characteristics of 533,286 subjects in the NIH-AARP Diet and Health Study by quintiles of E-DII

<table>
<thead>
<tr>
<th>E-DII Q1 (-7.91,-5.61)</th>
<th>E-DII Q2 (-5.60,-4.51)</th>
<th>E-DII Q3 (-4.50,-3.29)</th>
<th>E-DII Q4 (-3.28,-1.51)</th>
<th>E-DII Q5 (-1.50,6.66)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>106658</td>
<td>106657</td>
<td>106657</td>
<td>106655</td>
<td>106659</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td></td>
</tr>
<tr>
<td>Age at baseline (y)</td>
<td>62.0 (0.02)</td>
<td>61.9 (0.02)</td>
<td>61.8 (0.02)</td>
<td>61.6 (0.02)</td>
<td>61.1 (0.02)</td>
</tr>
<tr>
<td>Total energy intake (kcal/d)</td>
<td>1564.7 (1.8)</td>
<td>1722.9 (2.2)</td>
<td>1817.2 (2.4)</td>
<td>1937.7 (2.6)</td>
<td>2180.1 (3.1)</td>
</tr>
<tr>
<td>BMI at baseline (kg/m²)</td>
<td>26.3 (0.01)</td>
<td>26.8 (0.01)</td>
<td>27.1 (0.01)</td>
<td>27.4 (0.01)</td>
<td>27.6 (0.01)</td>
</tr>
<tr>
<td>Alcohol consumption (g/d)</td>
<td>8.9 (0.05)</td>
<td>9.1 (0.06)</td>
<td>10.1 (0.07)</td>
<td>12.5 (0.1)</td>
<td>22.7 (0.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male</td>
<td>48772 (45.7)</td>
<td>56695 (53.2)</td>
<td>62315 (58.4)</td>
<td>69005 (64.7)</td>
<td>77375 (72.5)</td>
</tr>
<tr>
<td>Female</td>
<td>57886 (54.3)</td>
<td>49962 (46.8)</td>
<td>44342 (41.6)</td>
<td>37650 (35.3)</td>
<td>29284 (27.5)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>98311 (92.2)</td>
<td>97681 (91.6)</td>
<td>97094 (91.0)</td>
<td>97170 (91.1)</td>
<td>97249 (91.2)</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>3249 (3.1)</td>
<td>3915 (3.7)</td>
<td>4359 (4.1)</td>
<td>4319 (4.1)</td>
<td>4532 (4.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1675 (1.6)</td>
<td>1901 (1.8)</td>
<td>2114 (2.0)</td>
<td>2195 (2.1)</td>
<td>2015 (1.9)</td>
</tr>
<tr>
<td>Other races</td>
<td>2170 (2.0)</td>
<td>1873 (1.8)</td>
<td>1709 (1.6)</td>
<td>1457 (1.4)</td>
<td>1353 (1.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1253 (1.2)</td>
<td>1287 (1.2)</td>
<td>1381 (1.3)</td>
<td>1514 (1.4)</td>
<td>1510 (1.4)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>less than or equal to 11 years</td>
<td>3689 (3.5)</td>
<td>5050 (4.7)</td>
<td>6106 (5.7)</td>
<td>7429 (7.0)</td>
<td>9593 (9.0)</td>
</tr>
<tr>
<td>High school completion</td>
<td>16655 (15.6)</td>
<td>19182 (18.0)</td>
<td>20309 (19.0)</td>
<td>22155 (20.8)</td>
<td>25819 (24.2)</td>
</tr>
<tr>
<td>Education Level</td>
<td>Never</td>
<td>Rarely</td>
<td>1-3 time per month</td>
<td>1-2 times per week</td>
<td>3-4 times per week</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Post high school training other than college</td>
<td>9548 (9.0)</td>
<td>10032 (9.4)</td>
<td>10336 (9.7)</td>
<td>10810 (10.1)</td>
<td>11630 (10.9)</td>
</tr>
<tr>
<td>Some college</td>
<td>25274 (23.7)</td>
<td>25051 (23.5)</td>
<td>24514 (23.0)</td>
<td>24577 (23.0)</td>
<td>24331 (22.8)</td>
</tr>
<tr>
<td>College and postgraduate</td>
<td>48561 (45.5)</td>
<td>44210 (41.5)</td>
<td>42193 (39.6)</td>
<td>38555 (36.2)</td>
<td>32090 (30.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>2931 (2.8)</td>
<td>3132 (2.9)</td>
<td>3199 (3.0)</td>
<td>3129 (2.9)</td>
<td>3196 (3.0)</td>
</tr>
</tbody>
</table>

### Smoking status and dose combined

<table>
<thead>
<tr>
<th>Status</th>
<th>Never smoked</th>
<th>Quit, &lt;=20 cigs/d</th>
<th>Quit, &gt;20 cigs/d</th>
<th>Current smoker, &lt;=20 cigs/d</th>
<th>Current smoker, &gt;20 cigs/d</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>41415 (38.8)</td>
<td>33914 (31.8)</td>
<td>20853 (19.6)</td>
<td>5219 (4.9)</td>
<td>1443 (1.4)</td>
<td>3814 (3.6)</td>
</tr>
<tr>
<td>Rarely</td>
<td>40371 (37.9)</td>
<td>31148 (29.2)</td>
<td>21904 (20.5)</td>
<td>6790 (6.4)</td>
<td>2615 (2.5)</td>
<td>3829 (3.6)</td>
</tr>
<tr>
<td>1-3 time per month</td>
<td>38425 (36.0)</td>
<td>29957 (28.1)</td>
<td>22738 (21.3)</td>
<td>7870 (7.4)</td>
<td>3621 (3.4)</td>
<td>4046 (3.8)</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>35937 (33.7)</td>
<td>28543 (26.8)</td>
<td>23947 (22.5)</td>
<td>9070 (8.5)</td>
<td>5182 (4.9)</td>
<td>3976 (3.7)</td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>29965 (28.1)</td>
<td>24776 (23.2)</td>
<td>25782 (24.2)</td>
<td>12256 (11.5)</td>
<td>9571 (9.0)</td>
<td>4309 (4.0)</td>
</tr>
<tr>
<td>5 or more times per week</td>
<td>24331 (22.8)</td>
<td>24776 (23.2)</td>
<td>25782 (24.2)</td>
<td>12256 (11.5)</td>
<td>9571 (9.0)</td>
<td>4309 (4.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3196 (3.0)</td>
<td>3196 (3.0)</td>
<td>3196 (3.0)</td>
<td>3196 (3.0)</td>
<td>3196 (3.0)</td>
<td>3196 (3.0)</td>
</tr>
</tbody>
</table>

### Physical activity frequency in the past year

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Never</th>
<th>Rarely</th>
<th>1-3 time per month</th>
<th>1-2 times per week</th>
<th>3-4 times per week</th>
<th>5 or more times per week</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>2379 (2.2)</td>
<td>3493 (3.3)</td>
<td>4402 (4.1)</td>
<td>5529 (5.2)</td>
<td>8127 (7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>9316 (8.7)</td>
<td>12124 (11.4)</td>
<td>13962 (13.1)</td>
<td>16348 (15.3)</td>
<td>20676 (19.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 time per month</td>
<td>11280 (10.6)</td>
<td>13170 (12.4)</td>
<td>14412 (13.5)</td>
<td>15631 (14.7)</td>
<td>17353 (16.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>21867 (20.5)</td>
<td>23070 (21.6)</td>
<td>23192 (21.7)</td>
<td>23503 (22.0)</td>
<td>22817 (21.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4 times per week</td>
<td>34950 (32.8)</td>
<td>31369 (29.4)</td>
<td>28947 (27.1)</td>
<td>26253 (24.6)</td>
<td>21085 (19.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 or more times per week</td>
<td>25974 (24.4)</td>
<td>22408 (21.0)</td>
<td>20555 (19.3)</td>
<td>18184 (17.1)</td>
<td>15213 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>892 (0.8)</td>
<td>1020 (1.0)</td>
<td>1187 (1.1)</td>
<td>1207 (1.1)</td>
<td>1388 (1.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### History of diabetes

<.0001

<.0001
<table>
<thead>
<tr>
<th></th>
<th>Aspirin products use frequency</th>
<th></th>
<th>Ibuprofen products use frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No use</td>
<td>1-3 times/month</td>
<td>No use</td>
</tr>
<tr>
<td></td>
<td>17070 (16.0)</td>
<td>19527 (18.3)</td>
<td>26408 (24.8)</td>
</tr>
<tr>
<td></td>
<td>(15.6)</td>
<td>(17.9)</td>
<td>(25.0)</td>
</tr>
<tr>
<td></td>
<td>16650 (15.9)</td>
<td>19139 (15.9)</td>
<td>26659 (25.0)</td>
</tr>
<tr>
<td></td>
<td>(15.9)</td>
<td>(18.1)</td>
<td>(25.7)</td>
</tr>
<tr>
<td></td>
<td>16996 (15.9)</td>
<td>19267 (18.3)</td>
<td>27366 (25.7)</td>
</tr>
<tr>
<td></td>
<td>(15.9)</td>
<td>(18.1)</td>
<td>(20.0)</td>
</tr>
<tr>
<td></td>
<td>16914 (15.9)</td>
<td>19542 (18.3)</td>
<td>27690 (26.0)</td>
</tr>
<tr>
<td></td>
<td>(15.8)</td>
<td>(18.9)</td>
<td>(26.2)</td>
</tr>
<tr>
<td></td>
<td>1-6 times/week</td>
<td>&gt;=1 time/day</td>
<td>No use</td>
</tr>
<tr>
<td></td>
<td>11384 (10.7)</td>
<td>17982 (16.9)</td>
<td>26408 (24.8)</td>
</tr>
<tr>
<td></td>
<td>(10.6)</td>
<td>(16.9)</td>
<td>(25.0)</td>
</tr>
<tr>
<td></td>
<td>11272 (10.6)</td>
<td>17057 (16.0)</td>
<td>27366 (25.0)</td>
</tr>
<tr>
<td></td>
<td>(10.6)</td>
<td>(15.3)</td>
<td>(27.6)</td>
</tr>
<tr>
<td></td>
<td>10466 (9.8)</td>
<td>16267 (15.3)</td>
<td>27690 (26.0)</td>
</tr>
<tr>
<td></td>
<td>(9.8)</td>
<td>(19.3)</td>
<td>(26.2)</td>
</tr>
<tr>
<td></td>
<td>10226 (9.6)</td>
<td>14956 (14.0)</td>
<td>27911 (26.2)</td>
</tr>
<tr>
<td></td>
<td>(9.6)</td>
<td>(12.0)</td>
<td>(26.2)</td>
</tr>
<tr>
<td></td>
<td>9259 (8.7)</td>
<td>12750 (12.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(8.7)</td>
<td>(12.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1-3 times/month</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>40695 (38.1)</td>
<td>22739 (21.3)</td>
<td>40195 (38.4)</td>
</tr>
<tr>
<td></td>
<td>(38.1)</td>
<td>(21.3)</td>
<td>(40.1)</td>
</tr>
<tr>
<td></td>
<td>42539 (39.9)</td>
<td>21333 (20.0)</td>
<td>42733 (40.1)</td>
</tr>
<tr>
<td></td>
<td>(39.9)</td>
<td>(20.0)</td>
<td>(41.1)</td>
</tr>
<tr>
<td></td>
<td>43661 (40.9)</td>
<td>20563 (19.3)</td>
<td>43870 (41.1)</td>
</tr>
<tr>
<td></td>
<td>(40.9)</td>
<td>(19.3)</td>
<td>(41.1)</td>
</tr>
<tr>
<td></td>
<td>45017 (42.2)</td>
<td>19646 (18.4)</td>
<td>45268 (42.4)</td>
</tr>
<tr>
<td></td>
<td>(42.2)</td>
<td>(17.3)</td>
<td>(44.9)</td>
</tr>
<tr>
<td></td>
<td>47684 (44.7)</td>
<td>18403 (17.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(44.7)</td>
<td>(17.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SE, standard error

* Statistical analyses were performed by ANOVA test for continuous variables and by Chi-Square test for categorical variables.

* Sum of percentages may not add up to 100% because of rounding or missing.
Table 5.2 Hazard ratios of pancreatic cancer by quintiles of E-DII score among 533,286 subjects in the NIH-AARP Diet and Health Study

<table>
<thead>
<tr>
<th>E-DII</th>
<th>Total subjects</th>
<th>E-DII</th>
<th>Total sample</th>
<th>Number of cases</th>
<th>Age and energy-adjusted model HR (95% CI)</th>
<th>Multivariable-adjusted model HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Total sample</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q5</td>
<td>Continuous HR and 95% CI</td>
</tr>
<tr>
<td></td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>666</td>
<td>618</td>
<td>683</td>
<td>660</td>
<td>711</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.94</td>
<td>1.05</td>
<td>1.03</td>
<td>1.14</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(0.84-1.05)</td>
<td>(0.95-1.17)</td>
<td>(0.92-1.15)</td>
<td>(1.02-1.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>Total sample</td>
<td>62833</td>
<td>62833</td>
<td>62833</td>
<td>62830</td>
<td>62833</td>
</tr>
<tr>
<td></td>
<td>422</td>
<td>413</td>
<td>435</td>
<td>407</td>
<td>448</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.07</td>
<td>1.01</td>
<td>1.15</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(0.87-1.14)</td>
<td>(0.93-1.22)</td>
<td>(0.88-1.16)</td>
<td>(1.01-1.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>Total sample</td>
<td>43826</td>
<td>43822</td>
<td>43827</td>
<td>43824</td>
<td>43825</td>
</tr>
<tr>
<td></td>
<td>254</td>
<td>237</td>
<td>211</td>
<td>253</td>
<td>258</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.94</td>
<td>0.85</td>
<td>1.04</td>
<td>1.09</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>(0.79-1.13)</td>
<td>(0.71-1.02)</td>
<td>(0.87-1.23)</td>
<td>(0.92-1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.93</td>
<td>0.82</td>
<td>0.98</td>
<td>0.98</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>(0.78-1.11)</td>
<td>(0.68-0.98)</td>
<td>(0.82-1.17)</td>
<td>(0.82-1.17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-trend was calculated using the continuous E-DII score in the model.
b The continuous HR and associated 95% CI for one standard deviation increase of E-DII score

c P-interaction was calculated with the cross-product of sex and E-DII quintile in the multivariable adjusted

COX model

d Model was adjusted for age group (<62 and >=62 years old), sex (male or female), body mass index
category (underweight, normal, overweight, obese, missing), smoking, quit and dose combined
(nonsmoker, quit>=10 years, <=20 cigs/day, quit>=10 years, >20 cigs/day, quit 5-9 years, <=20 cigs/day,
quit 5-9 years, >20 cigs/day, quit 1-4 years, <=20 cigs/day, quit 1-4 years, >20 cigs/day, quit<1 year or
current, <=20 cigs/day, quit<1 year or current, >20 cigs/day, missing), total energy (kcal/day), alcohol from
alcoholic drinks (g/d), diabetes history (yes/no), education level (=11 years, 12 years or completed high
school, post-high school, some college, college and post graduate, unknown).
Table 5.3 Hazard ratios* of pancreatic cancer by quintiles of E-DII score among 533,286 subjects in the NIH-AARP Diet and Health study, stratified by inflammation-related lifestyle factors

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-trend&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P-interaction&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>1.00 (0.46-5.53)</td>
<td>1.60 (0.59-6.43)</td>
<td>1.95 (0.91-1.31)</td>
<td>0.41 (0.07-2.29)</td>
<td>0.84 (0.21-3.36)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.00 (0.76-1.10)</td>
<td>0.91 (0.86-1.19)</td>
<td>1.09 (0.80-1.12)</td>
<td>0.86 (0.71-1.05)</td>
<td>0.94 (0.77-1.15)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.00 (0.75-1.05)</td>
<td>0.89 (0.86-1.19)</td>
<td>1.01 (0.80-1.12)</td>
<td>0.95 (0.80-1.12)</td>
<td>1.01 (0.85-1.19)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1.00 (0.67-1.09)</td>
<td>0.86 (0.59-0.97)</td>
<td>0.75 (0.70-1.12)</td>
<td>0.88 (0.70-1.12)</td>
<td>0.86 (0.67-1.09)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>1.00 (0.68-0.98)</td>
<td>0.81 (0.70-1.01)</td>
<td>0.84 (0.71-1.04)</td>
<td>0.86 (0.71-1.04)</td>
<td>0.88 (0.72-1.07)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>1.00 (0.82-1.12)</td>
<td>0.96 (0.89-1.22)</td>
<td>1.04 (0.88-1.21)</td>
<td>1.03 (0.88-1.21)</td>
<td>1.05 (0.89-1.24)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>1.00 (0.67-1.34)</td>
<td>0.95 (0.85-1.63)</td>
<td>1.18 (0.63-1.23)</td>
<td>0.88 (0.63-1.23)</td>
<td>1.09 (0.80-1.49)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Alcohol level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00 (0.81-1.01)</td>
<td>0.90 (0.88-1.09)</td>
<td>0.98 (0.83-1.04)</td>
<td>0.93 (0.83-1.04)</td>
<td>0.96 (0.86-1.08)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.00 (0.50-1.77)</td>
<td>0.95 (0.68-2.19)</td>
<td>1.22 (0.62-1.95)</td>
<td>1.10 (0.62-1.95)</td>
<td>1.14 (0.66-1.96)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Frequency of use of aspirin products</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>1.00 (0.59-1.03)</td>
<td>0.78 (0.73-1.23)</td>
<td>0.95 (0.66-1.14)</td>
<td>0.87 (0.66-1.14)</td>
<td>0.99 (0.76-1.31)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Monthly use</td>
<td>1.00 (0.64-1.11)</td>
<td>0.84 (0.90-1.49)</td>
<td>1.15 (0.75-1.27)</td>
<td>0.97 (0.75-1.27)</td>
<td>0.89 (0.68-1.17)</td>
<td>0.42</td>
<td></td>
</tr>
</tbody>
</table>
The model was adjusted for age group, sex, body mass index category, smoking status with quit and dose combined, total energy(kcal/day), alcohol intake (g/d), diabetes history, education level while adding the cross-product term of the quintile E-DII and each effect modifier in the model.

a. $P$-trend was calculated using the continuous E-DII score in the model.

b. $P$-interaction was calculated with the cross-product of the effect modifier and E-DII quintile in the multivariable-adjusted COX model.

<table>
<thead>
<tr>
<th>Frequency of use of ibuprofen products</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No use</td>
<td>1.00</td>
<td>0.97</td>
<td>1.15</td>
<td>0.98</td>
<td>1.09</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>(0.78-1.20)</td>
<td>(0.93-1.41)</td>
<td>(0.79-1.21)</td>
<td>(0.88-1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly use</td>
<td>1.00</td>
<td>0.88</td>
<td>1.03</td>
<td>0.93</td>
<td>1.07</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>(0.69-1.13)</td>
<td>(0.81-1.31)</td>
<td>(0.72-1.19)</td>
<td>(0.82-1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly and daily use</td>
<td>1.00</td>
<td>0.90</td>
<td>0.87</td>
<td>0.86</td>
<td>0.94</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>(0.68-1.20)</td>
<td>(0.65-1.17)</td>
<td>(0.63-1.16)</td>
<td>(0.68-1.29)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Self-reported diabetes history</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.00</td>
<td>0.92</td>
<td>1.02</td>
<td>0.93</td>
<td>0.99</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>(0.82-1.04)</td>
<td>(0.91-1.14)</td>
<td>(0.83-1.05)</td>
<td>(0.88-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.00</td>
<td>0.79</td>
<td>0.79</td>
<td>0.93</td>
<td>0.86</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>(0.57-1.09)</td>
<td>(0.58-1.09)</td>
<td>(0.68-1.26)</td>
<td>(0.62-1.21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The model was adjusted for age group, sex, body mass index category, smoking status with quit and dose combined, total energy(kcal/day), alcohol intake (g/d), diabetes history, education level while adding the cross-product term of the quintile E-DII and each effect modifier in the model.

a. $P$-trend was calculated using the continuous E-DII score in the model.
b. $P$-interaction was calculated with the cross-product of the effect modifier and E-DII quintile in the multivariable-adjusted COX model.
Table 5.4 The association between E-DII quintiles and risk of pancreatic cancer by cancer stage in the NIH-AARP Diet and Health Study

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-trend&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized pancreatic cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>106658</td>
<td>106657</td>
<td>106657</td>
<td>106655</td>
<td>106659</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>25</td>
<td>33</td>
<td>31</td>
<td>22</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Age and energy adjusted model HR (95% CI)</td>
<td>1.00 (0.80-2.27)</td>
<td>1.29 (0.76-2.20)</td>
<td>0.94 (0.53-1.67)</td>
<td>1.66 (0.98-2.79)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 (0.78-2.21)</td>
<td>1.23 (0.72-2.09)</td>
<td>0.87 (0.49-1.57)</td>
<td>1.48 (0.86-2.53)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td><strong>Regional pancreatic cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>137</td>
<td>126</td>
<td>136</td>
<td>123</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>Age and calorie adjusted model HR (95% CI)</td>
<td>1.00 (0.73-1.19)</td>
<td>1.02 (0.81-1.30)</td>
<td>0.94 (0.73-1.20)</td>
<td>1.10 (0.86-1.40)</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 (0.71-1.16)</td>
<td>0.97 (0.76-1.23)</td>
<td>0.87 (0.68-1.11)</td>
<td>0.96 (0.75-1.24)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td><strong>Distant metastasized pancreatic cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>214</td>
<td>180</td>
<td>200</td>
<td>215</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>Age and energy adjusted model HR (95% CI)</td>
<td>1.00 (0.70-1.03)</td>
<td>0.95 (0.79-1.16)</td>
<td>1.03 (0.85-1.25)</td>
<td>1.12 (0.92-1.36)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 (0.66-0.99)</td>
<td>0.87 (0.72-1.06)</td>
<td>0.91 (0.75-1.10)</td>
<td>0.90 (0.74-1.10)</td>
<td>0.82</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> P-trend was calculated using the continuous E-DII score in the model

<sup>b</sup> Model was adjusted for age group(<62 and >=62 years old), sex (male or female), body mass index category (underweight, normal, overweight, obese, missing), smoking, quit and dose combined (nonsmoker, quit>=10 years,<=20 cigs/day, quit<10 years,>=20 cigs/day, quit<1 year or current,<=20 cigs/day, quit<1 year or current,>20 cigs/day, missing), total energy(kcal/day), alcohol from alcoholic drinks(g/d), diabetes history(yes/no), education level (<=11 years, 12 years or completed high school, post-high school, some college, college and post graduate, unknown).
Table 5.5 The association between E-DII quintiles and risk of pancreatic cancer by cancer grade in the NIH-AARP Diet and Health Study

<table>
<thead>
<tr>
<th>Grade I or well-differentiated pancreatic cancer</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-trend&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>106658</td>
<td>106658</td>
<td>106657</td>
<td>106655</td>
<td>106659</td>
<td>0.69</td>
</tr>
<tr>
<td>Number of cases</td>
<td>35</td>
<td>31</td>
<td>29</td>
<td>37</td>
<td>24</td>
<td>0.25</td>
</tr>
<tr>
<td>Age and energy-adjusted model HR (95% CI)</td>
<td>1.00</td>
<td>0.91 (0.56-1.48)</td>
<td>0.87 (0.53-1.43)</td>
<td>1.13 (0.71-1.81)</td>
<td>0.77 (0.45-1.32)</td>
<td>0.69</td>
</tr>
<tr>
<td>Multivariable-adjusted model HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00</td>
<td>0.86 (0.53-1.40)</td>
<td>0.79 (0.48-1.31)</td>
<td>0.99 (0.62-1.59)</td>
<td>0.64 (0.37-1.10)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

| Grade II or moderately well differentiated pancreatic cancer | | | | |
| Number of cases | 105 | 94 | 106 | 93 | 112 | 0.26 |
| Age and energy-adjusted model HR (95% CI) | 1.00 | 0.91 (0.69-1.20) | 1.04 (0.80-1.37) | 0.93 (0.70-1.23) | 1.16 (0.88-1.52) | 0.26 |
| Multivariable-adjusted model HR (95% CI)<sup>b</sup> | 1.00 | 0.89 (0.67-1.17) | 0.99 (0.76-1.31) | 0.86 (0.65-1.14) | 1.00 (0.75-1.33) | 0.99 |

| Grade III or poorly differentiated pancreatic cancer | | | | |
| Number of cases | 121 | 103 | 110 | 123 | 123 | 0.08 |
| Age and energy-adjusted model HR (95% CI) | 1.00 | 0.86 (0.66-1.12) | 0.94 (0.72-1.21) | 1.06 (0.82-1.36) | 1.09 (0.85-1.42) | 0.08 |
| Multivariable-adjusted model HR (95% CI)<sup>b</sup> | 1.00 | 0.83 (0.64-1.08) | 0.88 (0.68-1.14) | 0.97 (0.75-1.25) | 0.94 (0.72-1.23) | 0.60 |

| Grade IV or undifferentiated/anaplastic pancreatic cancer | | | | |
| Number of cases | 9 | 6 | 7 | 10 | 9 | 0.79 |
| Age and energy-adjusted model HR (95% CI) | 1.00 | 0.67 (0.24-1.90) | 0.79 (0.29-2.14) | 1.14 (0.46-2.85) | 1.06 (0.41-2.74) | 0.79 |
| Multivariable-adjusted model HR (95% CI)<sup>b</sup> | 1.00 | 0.64 (0.23-1.79) | 0.72 (0.27-1.95) | 0.99 (0.39-2.51) | 0.86 (0.32-2.32) | 0.87 |

<sup>a</sup> P-trend was calculated using the continuous E-DII score in the model

<sup>b</sup> Model was adjusted for age group (<62 and >=62 years old), sex (male or female), body mass index category (underweight, normal, overweight, obese, missing), smoking, quit and dose combined (nonsmoker, quit>=10 years,<20 cigs/day, quit=10 years,>=20 cigs/day, quit 5-9 years,<20 cigs/day, quit 5-9 years,>=20 cigs/day, quit 1-4 years,<20 cigs/day, quit 1-4 years,>=20 cigs/day, quit<1 year or current,<20 cigs/day, quit<1 year or current,>=20 cigs/day, missing), total energy(kcal/day), alcohol from alcoholic drinks(g/d), diabetes history(yes/no), education level (<=11 years, 12 years or completed high school, post-high school, some college, college and post graduate, unknown).
Table 5.6. Multivariable-adjusted HRs of lag time analysis of DII and pancreatic cancer risk after excluding subjects with follow-up<5 years

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-trend&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects with follow-up &gt;=5 years (N=489,744)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>99008</td>
<td>98407</td>
<td>97799</td>
<td>97694</td>
<td>96836</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>515</td>
<td>489</td>
<td>514</td>
<td>495</td>
<td>539</td>
<td></td>
</tr>
<tr>
<td>Multivariable-</td>
<td>1.00</td>
<td>0.94</td>
<td>0.98</td>
<td>0.93 (0.82- 0.98 (0.86- 0.86- 0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted model</td>
<td>(0.83-</td>
<td>(0.86-</td>
<td>(1.05)</td>
<td>0.98 (0.86- 1.05)</td>
<td>0.75)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.06</td>
<td>1.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>P-trend was calculated using the continuous E-DII score in the model

<sup>b</sup>The model was adjusted for age group, sex, body mass index category, smoking status with quit and dose combined, total energy(kcal/day), alcohol from alcoholic drinks(g/d), diabetes history, education level
Table 5.7 Multivariable-adjusted HRs of sensitivity analysis of adding pancreatic cancer death cases with imputed incident time to the first incident pancreatic cancer

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-trend&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Continuous HR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-interaction by sex&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>803</td>
<td>759</td>
<td>804</td>
<td>791</td>
<td>843</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.00</td>
<td>0.92</td>
<td>0.97</td>
<td>0.93</td>
<td>0.96</td>
<td>0.84</td>
<td>1.00 (0.96-1.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.84-1.02)</td>
<td>(0.87-1.07)</td>
<td>(0.84-1.03)</td>
<td>(0.86-1.06)</td>
<td>(0.84-1.03)</td>
<td>(0.86-1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>62833</td>
<td>62833</td>
<td>62833</td>
<td>62830</td>
<td>62833</td>
<td></td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>533</td>
<td>502</td>
<td>513</td>
<td>489</td>
<td>535</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.00</td>
<td>0.94</td>
<td>0.95</td>
<td>0.90</td>
<td>0.97</td>
<td>0.72</td>
<td>0.99 (0.95-1.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.83-1.06)</td>
<td>(0.84-1.08)</td>
<td>(0.79-1.02)</td>
<td>(0.85-1.10)</td>
<td>(0.84-1.06)</td>
<td>(0.85-1.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>43826</td>
<td>43822</td>
<td>43827</td>
<td>43824</td>
<td>43825</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>289</td>
<td>289</td>
<td>253</td>
<td>295</td>
<td>302</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.00</td>
<td>1.00</td>
<td>0.87</td>
<td>1.02</td>
<td>1.03</td>
<td>0.84</td>
<td>1.01 (0.95-1.06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.85-1.18)</td>
<td>(0.73-1.03)</td>
<td>(0.87-1.21)</td>
<td>(0.87-1.21)</td>
<td>(0.87-1.21)</td>
<td>(0.87-1.21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>P-trend was calculated using the continuous E-DII score in the model

<sup>b</sup>The continuous HR and associated 95% CI for one standard deviation increase of E-DII score

<sup>c</sup>P-interaction was calculated with the cross-product of sex and E-DII quintile in the multivariable adjusted COX model

<sup>d</sup>Model was adjusted for age group, sex, body mass index category, smoking, quit and dose combined, total energy(kcal/day), alcohol from alcoholic drinks(g/d), diabetes history, education level
Table 5.8 Multivariable-adjusted HRs of sensitivity analysis of adding pancreatic cancer death cases with imputed incident time to incident primary pancreatic cancer

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td><strong>Total subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td>10665</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Multivariable - adjusted model(^d)</td>
<td>1.00</td>
<td>0.92</td>
<td>0.98</td>
<td>0.94</td>
<td>0.98</td>
<td>0.70 (0.97-1.05)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>62833</td>
<td>62833</td>
<td>62833</td>
<td>62830</td>
<td>62833</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>410</td>
<td>385</td>
<td>412</td>
<td>375</td>
<td>416</td>
<td></td>
</tr>
<tr>
<td>Multivariable - adjusted model(^d)</td>
<td>1.00</td>
<td>0.94</td>
<td>1.00</td>
<td>0.90</td>
<td>0.99</td>
<td>0.92 (0.96-1.05)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>43826</td>
<td>43822</td>
<td>43827</td>
<td>43824</td>
<td>43825</td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>237</td>
<td>240</td>
<td>205</td>
<td>244</td>
<td>257</td>
<td></td>
</tr>
<tr>
<td>Multivariable - adjusted model(^d)</td>
<td>1.00</td>
<td>1.01</td>
<td>0.86</td>
<td>1.02</td>
<td>1.05</td>
<td>0.55 (0.96-1.08)</td>
</tr>
</tbody>
</table>

\(^a\) P-trend was calculated using the continuous E-DII score in the model

\(^b\) The continuous HR and associated 95% CI for one standard deviation increase of E-DII score

\(^c\) P-interaction was calculated with the cross-product of sex and E-DII quintile in the multivariable adjusted COX model

\(^d\) Model was adjusted for age group, sex, body mass index category, smoking, quit and dose combined, total energy(kcal/day), alcohol from alcoholic drinks(g/d), diabetes history, education level
CHAPTER 6
MEDIATION EFFECT OF TYPE-2 DIABETES IN THE ASSOCIATION BETWEEN DIETARY INFLAMMATORY POTENTIAL AND PANCREATIC CANCER RISK: A POOLED ANALYSIS OF THE PLCO CANCER SCREENING TRIAL AND NIH-AARP DIET AND HEALTH STUDY

6.1 Abstract

**Background**: inflammation plays an important role in pancreatic cancer pathogenesis and can be modulated by diet. Two case-control studies have reported a significant positive association between dietary inflammatory index and pancreatic cancer risk. However, little is known about the mechanism underlying the pathway from dietary inflammatory potential to pancreatic cancer development. Given type-2 diabetes is an inflammatory disease and a large amount of biological and epidemiological evidence have suggested a strong positive association between type-2 diabetes and pancreatic cancer, we aimed to investigate whether type-2 diabetes mediated the association between dietary inflammatory potential and pancreatic cancer risk in a pooled cohort of two similar large prospective cohorts in the US (PLCO Cancer Screening Trial and NIH-AARP Diet and Health Study). **Methods**: A total of 74,826 participants from the PLCO and 194,815 subjects from the NIH-AARP with age range from 50 to 74 years
at baseline comprised the pooled mediation cohort which included a total of 269,641 subjects (144,999 men and 124,642 women). E-DII scores from food plus supplement were calculated based on study-specific baseline diet questionnaire. Information on incident diabetes occurrence status (i.e., mediator) during follow-up and the age/year of first diagnosis was obtained through the follow-up questionnaires of both studies. Study-specific primary incident adenocarcinoma of the exocrine pancreas was regarded as the outcome of interest. Causal mediation approach under the counterfactual concept, was used to calculate the study-specific natural direct effect (NDE), natural indirect effect (NIE), and marginal total effect (MTE) on pancreatic cancer risk with type-2 diabetes as a mediator by quintile E-DII while treating the lowest quintile as the reference. Mediation effects of type-2 diabetes also were calculated for pancreatic cancer associated with each unit increment of centered E-DII value and z-score of E-DII. Random effects model was used to pool each mediation effect together, and since there was no significant between-study heterogeneity, we further calculated and reported the pooled mediation results using same approach. Results: In the pooled cohort, incident type-2 diabetes significantly mediated associations between both categorical and continuous E-DII and pancreatic cancer although the mediated effect was small. The overall effect of E-DII on pancreatic cancer, averaged over direct and indirect effect with type-2 diabetes as a mediator was not statistically significant. Conclusion: Incident type-2 diabetes may play a mediator role in the association between dietary inflammatory potential and pancreatic cancer development.

6.2 Introduction

Pancreatic cancer, the majority (~90%) of which is ductal adenocarcinoma of the
exocrine pancreas, is one of the most rapidly fatal malignancies with the highest case fatality rate among any major cancers. Despite its low incidence rate, pancreatic cancer is the fourth leading cause of cancer mortality in the United States among both men and women. Inflammation plays a critical role in the pathogenesis of this malignancy, as manifested by the fact that inflammatory states are etiologically linked to well-recognized risk factors for pancreatic cancer, including chronic pancreatitis, cigarette smoking, obesity, and diabetes. Diet, an important modifiable lifestyle factor, can modulate inflammation through its effect on visceral obesity, oxidative damage, and insulin resistance. The DII™ was developed to assess the inflammatory potential of an individual’s diet, which has the advantage over individual foods or nutrients when being studied for associations with disease risk as it takes into account the complex interactions among dietary components.

To date, the association between the inflammatory potential of diet and pancreatic cancer risk has been investigated and reported in two case-control studies and two cohort studies. Both case-control studies identified a significant more than 2-fold increased risk among individuals consuming a pro-inflammatory diet. As described in this dissertation, no associations were observed overall in the two cohort studies (Zheng et al., unpublished data). Little is known about the mechanism underlying the pathway from dietary inflammatory potential to pancreatic cancer development. Enhancing knowledge about potentials in the pathway could provide scientific evidence for identifying intermediate biomarkers to screen high risk populations for pancreatic cancer. It also helps with the design and guidance of an effective dietary intervention to reduce risk of pancreatic cancer. Given the large amount of biological and epidemiological evidence
that suggests a strong positive association between type-2 diabetes and pancreatic cancer and the inflammatory nature of diabetes, we hypothesized that type-2 diabetes may play a role as a mediator linking dietary inflammatory potential to increased pancreatic cancer risk.

Causal mediation analysis, under the counterfactual concept, could discover the causal role of a mediator underlying the relation between an exposure and outcome by quantifying the extent to which this relationship is mediated by the mediator. The conventional mediation analysis approach proposed by Baron and Kenny could give rise to biased estimates if there is any uncontrolled mediator-outcome confounding or if an interaction between exposure and mediator exists, and could not be used to obtain causal inference of the mediated effect. In contrast, causal mediation analysis, with the clear no-unmeasured-confounding assumption, is able to be used to obtain unbiased casual inference of direct and indirect effects under the counterfactual framework.

Therefore, we aimed to investigate whether the associations between dietary inflammatory potential and pancreatic cancer are mediated by incident type-2 diabetes by using the causal mediation approach, in the pooled analysis of two large, well-established cohorts in the U.S., the PLCO Cancer Screening Trial and NIH-AARP Diet and Health Study.

6.3 Methods

6.3.1 Study population

The PLCO is a population-based randomized trial aimed to assess the effects of screening tests for prostate, lung, colorectal, and ovarian cancers on mortality and secondary endpoints. A total of 154,897 eligible participants (76,682 men and 78,215
women) with age range from 55 to 74 years, were enrolled into the trial at baseline between 1993 to 2001 from different centers spanning across the United States.\textsuperscript{43} Participants were randomized into either a control arm, where usual medical care was received, or intervention arm where PLCO cancers screening tests were received. The whole PLCO cohort was followed up for 13 years after enrollment, and participants in the intervention arm received their screening tests during their first six years in the trial.\textsuperscript{44}

The NIH-AARP Diet and Health Study is the largest prospective cohort study of diet and health ever conducted in the US with the goal to examine a number of important diet and cancer hypotheses. The details of the study design were described previously.\textsuperscript{46} Briefly, 566,398 eligible AARP members living across the country (339,666 men and 226,732 women) with age of 50 to 71 years old, who responded to the baseline questionnaire, were enrolled between 1995 and 1996. NIH-AARP participants were followed until the end of 2011 for the current analysis. In general, although the NIH-AARP had approximately 3.6 times more participants and slightly longer follow-up than PLCO, these two cohorts share substantial similarities in terms of the characteristics of study population, with similar age ranges at enrollment and similar proportions of racial/ethnic groups and other health behavior factors. In addition, the two studies were initiated during similar time periods and utilized similar diet questionnaires which included similar lists of food items (diet questionnaires in both studies were developed based on the NCI-developed DHQ but with different templates and a few different questions),\textsuperscript{396,361} and included comprehensive information on covariates and cancer outcomes.

Study-specific exclusions included 1) cancer (except non-melanoma skin cancer) diagnosed before dietary measurement; 2) participants did not return diet questionnaire or
did not have valid responses; 3) participants reported unreasonable BMI (in the PLCO, BMI was considered unreasonable if one of the followings occurred: weight<60 pounds; height<48 inches; height>78 inches for females; height>84 inches for males; BMI<15 kg/m²; in the NIH-AARP, implausible BMI was defined as 2 IQRs below the sex-specific 25th percentile or above the 75th percentile of log-transformed BMI) or calorie intake (unreasonable calorie intake was defined as sex-specific first and last percentiles of total energy in the PCLO and 2 IQRs below the sex-specific 25th percentile or above the 75th percentile of log-transformed energy intake in the NIH-AARP); or 4) no follow-up data. After exclusions, the analytical cohort of the PLCO included 101,449 participants (49,347 men and 52,102 women) and the NIH-AARP had a final sample size of 533,256 (314,139 men and 219,117 women). Therefore, the pooled analytical cohort of PLCO and NIH-AARP has a total of 634,705 participants (363,486 men and 271,219 women).

In the analytical cohort of 101,449 PLCO participants, we further excluded participants who did not have valid supplemental questionnaire, which contained follow-up data on diabetes and was introduced at a median of nine years after randomization into the trial (n=22,046), and those who had baseline diabetes (n=4,577), leaving a total of 74,826 participants involved in the PLCO mediation analysis cohort. Similarly, after excluding 321,377 participants who did not have follow-up questionnaire or the questionnaire was filled out by proxy, and 17,064 people who had baseline diabetes, 194,815 subjects remained in the mediation analysis cohort of NIH-AARP. In the pooled mediation cohort of PLCO and NIH-AARP, there were a total of 269,641 participants (144,999 men and 124,642 women).

The PLCO was approved by the institutional review boards of the National
Cancer Institute and each of the centers that participated, and the NIH-AARP was approved by the National Cancer Institute Special Studies Institutional Review Board. All participants from the two studies gave informed consent.

### 6.3.2 Dietary assessment and E-DII score calculation

Both PLCO and NIH-AARP used self-administered NCI-developed DHQ to assess participants’ usual frequency of intakes and portion sizes on 124 food items over the previous year, using multiple frequency categories ranging from “never” to “>=6 times/d” for beverages and from “never” to “>=2 times/d” for solid foods, and each item has 3 options of portion size. Supplement intake questions also were included in FFQs from both studies. In the PLCO, the DHQ was introduced to trial participants within a median of three years after randomization, while the DHQ was completed at baseline in the NIH-AARP. Responses from the DHQ were linked to the USDA’s CSFII survey databases in both studies, in order to estimate individuals’ nutrients, foods, and food group intakes. Results from comparisons with multiple 24 hour recalls in both cohorts suggested moderate energy-adjusted correlation coefficients for important dietary factors such as fat, total energy, fiber and micronutrients, which generally exceeded 0.4.

The DII, a literature-derived index designed to assess the overall inflammatory potential of an individual’s diet, was used in each study to calculate the overall E-DII score for each participant. The details of the development of the DII have been published previously. Briefly, 1,943 eligible peer-reviewed primary research articles published through 2010 on the effect of dietary factors on six inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP) were identified and scored to derive the component-
specific inflammatory effect scores for 45 dietary factors (i.e. components of DII), which comprised macronutrients, micronutrients and some bioactive components such as spices and tea.\textsuperscript{22} Thirty-five FFQ-derived dietary factors in the PLCO were used to calculate the E-DII, and 34 components were used for E-DII score calculation in the NIH-AARP (refer to table 6.1 footnote for details of the dietary components in each cohort for E-DII calculation).

To calculate individual’s E-DII score in each study, the FFQ-derived food and nutrient intake values were first adjusted for total energy intake and expressed per 1000 calories. The energy-adjusted dietary intake was subsequently standardized to a global composite dietary database representing average energy-adjusted dietary intake from 11 populations living in different countries across the world, to avoid the arbitrariness of simply using raw intake amounts.\textsuperscript{22,201} The energy-adjusted standardized dietary intake was then multiplied by the literature-derived inflammatory effect score for each DII component, and summed across all components to obtain the overall E-DII score. Higher E-DII scores represent more pro-inflammatory diets and lower (i.e., more negative) E-DII scores indicate more anti-inflammatory diets. The DII score has been construct validated and found to be positively associated with several inflammatory biomarkers such as IL-6,\textsuperscript{24} TNF-\(\alpha\) receptor 2,\textsuperscript{24} high-sensitivity CRP\textsuperscript{23,27} and homocysteine.\textsuperscript{25}

In both the PLCO and NIH-AARP, a majority of the participants consumed supplements. Given that most dietary supplements contain anti-inflammatory components, we calculated the E-DII from food plus supplement as the exposure in all analyses to quantify the association between the inflammatory potential of overall dietary exposures and pancreatic cancer risk with type-2 diabetes as the mediator.
6.3.3 Mediator assessment

Information on incident diabetes occurrence during follow up was obtained through the follow-up questionnaires of both studies. In the PLCO, participants were asked on supplemental questionnaire whether or not they were ever diagnosed with diabetes (yes, no, or missing), and at what age they were first diagnosed with diabetes. Participants could choose their age of first-diagnosed diabetes at "< 50", "50-59", "60-69", "older than 70" or can leave it blank. Participants in the NIH-AARP reported whether they were ever diagnosed with diabetes (yes, no, unknown) and year of first diagnosis of diabetes (no, before 1985, 1985-1994, 1995-1999, 2000 to present, unknown) on follow up questionnaire. Because we excluded participants with baseline diabetes in the mediation analysis, the study-specific responses to the two above-mentioned diabetes questions on the follow-up questionnaires can be used to identify incident diabetes that occurred during follow-up. The mediator was coded as a categorical variable with three levels: “yes”, “no” and “missing” using the following method: 1) if subjects answered they were never diagnosed with diabetes on the study-specific follow-up questionnaire, these subjects were assigned “no”; 2) if subjects reported they were ever diagnosed with diabetes, we further compared their ages at first diagnosis of diabetes using the median value of each category of the variable indicating diabetes occurrence time on the study-specific follow-up questionnaires, with their ages at primary pancreatic cancer diagnosis, and coded mediator as “yes” if diabetes occurred before primary pancreatic cancer or no primary pancreatic cancer occurred, “no” if diabetes occurred after primary pancreatic cancer (because mediator as defined should occur before the occurrence of outcome of interest), or “missing” if no information on
age at first diagnosis of diabetes; and 3) if subjects did not report whether they were
diagnosed with diabetes, these subjects were assigned “missing” as their mediator level.
Figure 6.1 illustrates this method used to code the mediator. We assume the incident
diabetes in our study is type-2 diabetes as type-2 diabetes accounts for 90%-95% of those
with diabetes, while the majority of type-1 diabetes which results from a cellular-
mediated autoimmune destruction of the β-cells of the pancreas, is typically a juvenile-
onset disease.425

6.3.4 Covariates assessment

Data on covariates were retrieved from study-specific self-reported baseline
questionnaires, which included demographic information, personal medical history,
family history, and health behaviors such as smoking and alcohol drinking. BMI was
calculated as weight (kg)/height(m)^2 and categorized based on the World Health
Organization criteria.368 In PLCO, information on physical activity over the past year was
not assessed at baseline, but was assessed on supplemental questionnaire, while physical
activity was assessed in the baseline questionnaire in the NIH-AARP. We did not use
follow-up data of covariates in analyses because of the large missing proportion and
inconsistent assessment time.

6.3.5 Harmonization of potential confounders across two studies

In the aggregated analysis where data from two cohorts were combined into one
dataset, we created harmonized categories for the shared potential confounding variables
of the E-DII and pancreatic cancer association across two studies. Because the physical
activity variable was measured from essentially different questions and using different
units in the two studies (physical activity in NIH-AARP was measured as frequency but
in PLCO it was measured using Met-hours), we excluded this variable as a potential confounder in the aggregated analysis. Family history of pancreatic cancer also was excluded because this variable was not available in the NIH-AARP. The other potential confounders shared between the two studies were created with harmonized categories for categorical variables, including age at baseline (continuous), sex (male or female), total energy intake (kcal/day), race (White non-Hispanic; Black non-Hispanic; Hispanic; Asian, Pacific Islander or American Indian/Alaskan Native; or unknown), BMI (underweight, normal, overweight, obese, or missing), alcohol intake (g/day), diabetes history at baseline (yes, no, or missing), combination of smoking status and years since quitting smoking (never smoked, stopped 10 or more years ago, stopped 5-9 years ago, stopped 1-4 years ago, stopped within last year, currently smoking, or missing), and education levels (≤11 years, high school completion, post high school training other than college, some college, college and postgraduate, or missing).

6.3.6 Pancreatic cancer case ascertainment

Incident pancreatic cancer cases in the PLCO were identified through an annual study update questionnaire in which participants reported if they had been diagnosed with any cancer, the type of cancer, and date of diagnosis. State registries, death certificates, and physician reports were used as additional sources for identification of pancreatic cancer cases. In the NIH-AARP, incident cases of pancreatic cancer were identified through linkage between the NIH-AARP cohort membership and eight state cancer registry databases. Uncertain matches underwent a final manual review. The follow-up questionnaire used to record participants’ cancer status and other non-cancer endpoints in the NIH-AARP was used as an additional resource. In the present analysis, pancreatic
cancer case was defined as primary incident adenocarcinoma of the exocrine pancreas (International Classification of Diseases for Oncology, Third Edition, codes C25.0-C25.3, C25.7- C25.9). Our case definition excluded pancreatic endocrine tumors and other rare histology types of pancreatic cancer in each study, as etiology may differ,\textsuperscript{248,370} and we censored these types of pancreatic cancer at the date of diagnosis.

6.4 Statistical analysis

The baseline characteristics of the study population in the pooled mediation analysis cohort combining PLCO and NIH-AARP (n=269,641) were presented by quintiles of E-DII with cut-off points determined from the distribution of the entire pooled cohort. Means and SE for continuous variables and frequencies and percentages for categorical variables were calculated. ANOVA was used to test the difference across E-DII quintiles for continuous variables, and Chi-square test was performed to test the difference for categorical variables. Because we excluded a substantial amount of individuals in the pooled mediation cohort, we assessed the difference of important baseline characteristics between study population in the pooled mediation cohort and those in the combined PLCO and NIH-AARP cohorts.

We first assessed the study-specific total, direct, and indirect effects of E-DII on pancreatic cancer risk with type-2 diabetes as a mediator by using the causal mediation approach in a counterfactual framework.\textsuperscript{378,423,426} In this approach, total effect can be decomposed into direct effect (not mediated by type-2 diabetes) and indirect effect (mediated by type-2 diabetes). A SAS macro developed by Valeri and Vanderweele\textsuperscript{379} was used to calculate the study-specific mediation parameters: natural direct effect (NDE), natural indirect effect (NIE), and marginal total effect (MTE) of E-DII on
pancreatic cancer risk with type-2 diabetes as a mediator. Briefly, mediation parameter estimates were obtained using the causal mediation approach in three steps: 1) type-2 diabetes was regressed on E-DII using the logistic regression with inclusion of the set of confounding variables which were the same as those we reported in the association between E-DII and pancreatic cancer in each cohort except that diabetes history at baseline was removed (Zheng et al. unpublished data in chapter 4 and 5); 2) pancreatic cancer was regressed on type-2 diabetes and E-DII with inclusion of the E-DII and type-2 diabetes interaction and the same set of confounders as in 1) using a logistic regression model; since the interaction was not statistically significant, we removed it from the model; 3) based on the specified comparison levels of exposure, parameters derived from these two logistic models gave way to essential mediator parameters through a series of mathematical calculations. In the study-specific mediation analysis, we calculated and reported the NDE, NIE, and MTE of E-DII on pancreatic cancer risk for subjects in each higher E-DII quintile (i.e., quintile 2, quintile 3, quintile 4, quintile 5) compared to those in the lowest quintile with type-2 diabetes as mediator, by using ordinal E-DII variable in the model (compare 2,3,4,5 with 1, respectively). We also centered each E-DII value to the mean to report the effect of a one-unit increase in centered E-DII on pancreatic cancer with type-2 diabetes as mediator (1 and 0 were specified as two exposure levels of comparison). The Z-score of E-DII was calculated by dividing the centered value by the standard deviation, and used in the mediation model to demonstrate the mediation effect of type-2 diabetes on the association of increment of one standardized unit of E-DII with pancreatic cancer risk (1 to 0 were specified as two exposure levels of comparison). For all these mediation analysis, we also calculated the mediation proportion by type-2
diabetes using the equation as follows: Proportion of mediation by type-2 diabetes = 
\[
\frac{\text{NDE} \times (\text{NIE} - 1)}{(\text{NDE} \times \text{NIE} - 1)}
\]

The following four assumptions suffice to identify valid NDE and NIE from the data: 1) there is no unmeasured exposure-outcome confounding given measured covariates, 2) there is no unmeasured mediator-outcome confounding given measured covariates and exposure, 3) there is no unmeasured exposure-mediator confounding given measured covariates, and 4) there is no effect of the exposure that confounds the mediator-outcome relationship. Under such assumptions, the NDE and NIE can be conceptually evaluated as follows: NDE is the contrast between the counterfactual outcome if all subjects were exposed at a higher E-DII quintile and the counterfactual outcome if the same subjects were exposed at the lowest E-DII quintile, with probability of having type-2 diabetes assuming the value at when E-DII quintile was at the lowest level. The NIE is the contrast, having set the E-DII at each higher quintile, between the counterfactual outcome if probability of developing type-2 diabetes assumed whatever value it would have taken at a value of the higher E-DII quintile and the counterfactual outcome if probability of developing type-2 diabetes assumed whatever value it would have taken at the lowest E-DII quintile. The MTE was the average of the NDE and NIE estimated at the population level. 426,427

Each study-specific mediation effect (i.e., NDE, NIE, MTE) for pancreatic cancer comparing each higher E-DII quintile to the lowest quintile, weighted by the inverse of the sum of their variance and the estimated between-studies variance component, was pooled using a random effects model. The study-specific NDE, NIE and MTE for pancreatic cancer associated with each one unit increment of centered E-DII value and z-
score of E-DII with type-2 diabetes as the mediation factor, also were pooled using the same method.\textsuperscript{428} Between-studies heterogeneity was evaluated using the Q statistics\textsuperscript{380,381} and I$^2$ statistics.\textsuperscript{382}

There was no significant between-study heterogeneity on the mediation parameter estimates as assessed using the random effects models, and diet and other covariates were measured using comparable ways across two studies. Thus, we further combined primary data from two cohorts to take advantage of differences in the distributions of the exposure variable across studies and to increase number of pancreatic cancer cases to increase power.\textsuperscript{429} In addition, we can directly calculate the mediation parameter estimates in the pooled cohort instead of combining the results from separate studies with larger statistical errors. In this aggregated dataset, we considered all variables listed in the section of “Harmonization of potential confounders across two studies” as potential confounders during model building and selected and added those as confounders in the model if they were associated with both pancreatic risk and E-DII (in either continuous or categorical format), or changed the crude risk estimate by more than 10%. We finally adjusted for age at baseline, sex, total energy intake, BMI, education levels, alcohol intake, and the combined variable of smoking status and years since quitting smoking in the mediation analysis with aggregated data from PLCO and NIH-AARP mediation cohorts. The same mediation analyses as performed in each study as stated above were conducted in this pooled cohort.

We also conducted analysis of association between E-DII and pancreatic cancer among the participants in the pooled mediation cohort since this subset of people may be
different from the full cohort because they were survivors and chose to complete the follow-up questionnaire of both studies.

All statistical analyses were conducted using SAS® (version 9.4, Cary, NC) except that the assessment of between-studies heterogeneity was conducted in STATA (release 14, College Station, TX). All tests were two-sided with p values <0.05 considered to be statistically significant if not otherwise noted.

6.5 Results

As shown in Table 6.1, the range of the E-DII in the pooled mediation cohort of 269,641 participants from the PLCO and NIH-AARP was from -8.43 to 6.66. Compared to participants who had the most anti-inflammatory E-DII scores (i.e., E-DII quintile 1), participants consuming a more pro-inflammatory diet (i.e., higher E-DII scores) were younger at baseline but consumed more alcohol and energy, were more likely to develop incident type-2 diabetes during follow-up, and more likely to be males, Black non-Hispanic or Hispanic race/ethnicities, overweight or obese, current smokers or former smoker who stopped smoking within last 9 years, and have below-college education level, but there was no difference in developing pancreatic cancer comparing high to low dietary inflammatory potential.

Table 6.2 presents the study-specific NDE, NIE and MTE of E-DII on pancreatic cancer risk comparing subjects in each higher E-DII quintile to those in the lowest quintile with type-2 diabetes as the mediator, using the ordinal E-DII variable. In each study, when comparing risk of pancreatic cancer for subjects in each higher E-DII quintile to the lowest group, we observed a similar NDE, NIE, MTE and mediation proportion with type-2 diabetes as a mediator, and identified a similar P value of each
effect across different comparisons. The mediated effect of type-2 diabetes was
significant in both studies although the effect was small (slightly over 1). The overall
mediation proportion by type-2 diabetes was larger in the NIH-AARP than in the PLCO.
The total effect of E-DII on pancreatic cancer averaged over NDE and NIE was not
significant for each higher level of E-DII quintile compared to the lowest quintile. In both
studies, the association between E-DII and pancreatic cancer was fully mediated by
incident type-2 diabetes. The NDE, which was the E-DII and pancreatic cancer
association that was not mediated through type-2 diabetes, was not significant. When
pooling the mediation effect estimates from two studies using random effects model,
significant between-study heterogeneity for NDE, NIE and MTE was not observed in any
comparison group ($P_{\text{heterogeneity}} > 0.5$). The pooled results generally provide the same
information as suggested by the study-specific results. There was a significant although
small mediated effect of type-2 diabetes and the E-DII and pancreatic cancer association
was fully mediated through type-2 diabetes. No significant overall effect of E-DII on
pancreatic cancer was identified (Table 6.3).

Study-specific NDE, NIE, and MTE of one-unit increase in centered E-DII and E-
DII z-score on pancreatic cancer risk with type-2 diabetes as mediator are presented in
Table 6.4 along with the pooled results from two studies using the random effects model.
Similar to the categorical E-DII results, in both studies and pooled results, NDE, NIE and
MTE effects of continuous E-DII on pancreatic cancer still presented the significant
mediated effect of type-2 diabetes which was in a small magnitude. The continuous
association between E-DII and pancreatic cancer also was fully mediated through type-2
diabetes. But overall there was no significant total effect of centered E-DII value or a
standard unit of E-DII (z score) averaged over NDE and NIE on pancreatic cancer risk. Between-study heterogeneity on three mediation effects of these two continuous E-DII variables was not observed. The mediation proportion by type-2 diabetes was larger when using the continuous E-DII format than the categorical comparisons in the PLCO.

When we combined the primary data into a single dataset, we still identified the significant though small mediated effect of type-2 diabetes (i.e., NIE was significant), whether it was in the association for categorical E-DII or in the continuous association by using the centered E-DII value or z-score of E-DII (Tables 6.5 and 6.6). However, compared to the study-specific results and pooled analysis results using random effects model, the aggregated analysis presented the attenuated MTE averaged over NDE and NIE of E-DII on pancreatic cancer with point estimates less than 1 in both categorical and continuous associations, but the association was not significant. In the aggregated analysis, the NDE attenuated too with point estimate below 1, thus it was in an opposite direction with NIE in both the categorical and continuous associations between E-DII and pancreatic cancer, which impeded us from obtaining an interpretable mediation proportion.

Compared to subjects included in the pooled mediation analyses, excluded subjects tended to be younger at baseline and had baseline characteristics that were more likely to be associated with higher risk of health outcome, including male, Black or Hispanic, recent smoking, a more pro-inflammatory diet, more calories intake, more alcohol consumption, lower education attainment. Excluded participants also had higher pancreatic cancer incidence (Table 6.7).

In the pooled mediation cohort, we did not find an association between E-DII
from food plus supplement and pancreatic cancer risk after adjusting for confounders (OR \textsubscript{Q5 vs Q1} = 1.04, 95% CI = 0.82-1.33; P-trend = 0.86), which was consistent with the null association we identified in the separate cohort of PLCO and NIH-AARP (Table 6.8).

6.6 Discussion

The present study is the first to use the causal mediation approach to evaluate the mediation role of type-2 diabetes incidence in the relation between dietary inflammatory potential and pancreatic cancer risk in two large well-established nationally representative cohorts in the U.S. In the pooled mediation cohort of the PLCO and NIH-AARP, incident type-2 diabetes significantly mediated both categorical and continuous associations between E-DII and pancreatic cancer, although the mediated effect was small. The E-DII and pancreatic cancer association was fully mediated by type-2 diabetes with the aggregated data from two cohorts. We did not observe a statistically significant association of E-DII on pancreatic cancer, averaged over direct and indirect effect with type-2 diabetes as a mediator. In both studies and pooled analyses, we identified a null MTE of E-DII on pancreatic cancer, which was consistent with the findings of the E-DII and pancreatic cancer association we observed in each study (Zheng et al. unpublished data in Chapters 4 and 5) and with similar point estimate of effect.

In our analyses, we found the E-DII and pancreatic cancer association was fully mediated through incident type-2 diabetes. There was strong biologic and epidemiological evidence of the positive link between inflammation and diabetes. The leading hypothesized mechanisms to explain insulin resistance in type-2 diabetics suggests oxidative stress, endoplasmic reticulum stress, amyloid deposition in the pancreas, ectopic lipid deposition in the muscle, liver and pancreas, and lipotoxicity and
glucotoxicity are each thought to either induce inflammation or to be exacerbated by or associated with inflammation.\textsuperscript{42,430,431} Prospective studies have also found that elevated levels of IL-1β, IL-6, IL-1 receptor antagonist (IL-1Ra) and CRP are associated with type-2 diabetes.\textsuperscript{226,432,433} Although only one study to date has reported an association between the DII and fasting glucose, postload glucose or insulin resistance,\textsuperscript{434} there is a substantial amount of research reporting a positive association between DII scores and insulin-resistance-related conditions such as metabolic syndrome and various types of cancers,\textsuperscript{189,435,26,203} supporting our observed link between type 2 diabetes and the DII. The strong and positive association of type 2 diabetes with pancreatic cancer risk has been verified in a large number of studies. Recent data from five pooled analyses\textsuperscript{40,41,306-308} have concordant findings, showing that diabetics have 40\% to 90\% increased pancreatic cancer risk compared to non-diabetics, and the relative risk decreases with duration of diabetes, though a significant excess risk was still evident 10 years after diabetes diagnosis. Even in the absence of diabetes mellitus, higher fasting blood sugar and blood glucose or impaired glucose tolerance are associated with higher pancreatic cancer risk.\textsuperscript{285,309,310} However, it is still controversial whether type-2 diabetes is a consequence or a cause of the pancreatic cancer.\textsuperscript{305,436,437}

The significant mediated effect of type-2 diabetes in the E-DII and pancreatic cancer association is well-supported by the biologic mechanism stated as consecutive steps as follows: 1) Pro-inflammatory diets can increase insulin resistance through multiple mechanisms including regulation of pro-inflammatory cytokines, NF-κB pathway activation, changes in DNA methylation, increase in oxidative stress, and influences on antioxidant defense;\textsuperscript{79,73} 2) Defective response of body tissues to insulin,
i.e., reduced insulin sensitivity, increases demand on pancreatic islets to secrete higher quantities of insulin, leading to hyperinsulinemia and subsequent type-2 diabetes development,\textsuperscript{438,439} and 3) Locally elevated insulin supply coming from the endocrine islets of pancreas, which acts as a potential growth factor in the promotion of cell proliferation and angiogenesis,\textsuperscript{440} lead to increased loss of tumor suppressor function, and stimulated oncogene expression which altogether form a malignant transformation of pancreatic cells, predominantly the ductal epithelial cells of the exocrine pancreas, and ultimately cause malignancy.\textsuperscript{58,419}

Our study has some major strengths. First, the PLCO and NIH-AARP were very similar in the measurement of diet and important covariates and in the characteristics of their study populations related to many key risk factors for pancreatic cancer such as age, BMI, education level, smoking behavior. Additionally, the two studies were initiated at similar times and follow-up diabetes was measured at a similar length of follow-up (about 9 years into each study) These similarities enabled us to combine primary data from the two cohorts to increase the number of pancreatic cancer cases and incident type-2 diabetes cases, as well as take advantage of differences in the distributions of the exposure variable across studies. Second, there are several advantages of using PLCO and NIH-AARP: the prospective cohort design of both studies minimizes the possibility of recall bias and selection bias; the long follow-up in both cohorts among a large study population accumulated a large number of pancreatic cancer cases, especially in the NIH-AARP; and detailed information on a comprehensive list of covariates which were assessed in a similar way in two cohorts allowed for harmonization with less misclassification bias in the pooling analysis and also allowed for careful adjustment in
the analyses. Third, the E-DII was a strength, as it was designed specifically related to the biologic mechanism of inflammation which links the DII-diabetes-pancreatic cancer pathway and it provided a comprehensive assessment of dietary inflammatory potential. Fourth, the null MTE of E-DII on pancreatic cancer in each study and in the pooled cohort further confirmed the lack of association in each study separately as reported previously (Zheng et al. unpublished data). Finally, in all the mediation analyses of this paper (no matter in study-specific mediation analysis or in pooled cohort, and whether we conducted categorical or continuous mediation analyses), we consistently observed the significant mediated effect of type-2 diabetes, which suggested type-2 diabetes played a role as a mediator in the DII and pancreatic cancer association.

Despite these advantages, limitations of this study are also noted. When we created the mediator variable, we compared the age at first diagnosis of diabetes and age at incident primary pancreatic cancer if the subject had both diseases occur in the follow-up, using the median value of each category of the follow-up diabetes occurrence time variable. As we cannot obtain the precise age at diabetes occurrence, it may cause non-differential misclassification of mediator variable, but the measurement error as a result of using mean value of range was estimated to be small, because in PLCO only 21 subjects and in NIH-AARP only 86 subjects undergone the comparison of diagnosis times at two diseases. Although the two studies we combined were very similar in many aspects and there was no significant between-study heterogeneity, there was still the possibility that the assumption of pooling the primary data may not be fully met in that differences in the measurement and distribution of covariates (i.e., different questions to obtain data, different categories of a covariate, different units) and in the number of
available DII components used to calculate the E-DII score were present; however, there was no method to test the assumptions. The follow-up data on many covariates were available in each study but the large missing percentage impeded our ability to use these data. Diet was only assessed at baseline, therefore, any changes in diet over follow up were not captured, which could result in non-differential misclassification of exposure. However, we previously found DII scores were relatively stable over a long timeframe in postmenopausal women where the study participants were of comparable age as our study. Although important potential confounders were adjusted for in our analyses, residual or unmeasured confounding may still be a possibility. In addition, we can only calculate the mediation proportion when the NDE and NIE were in the same direction, so in some situations in this paper we cannot derive an interpretable mediation proportion.

6.7 Conclusion

In conclusion, in the pooled cohort of PLCO and NIH-AARP, we identified a significant though small mediated effect of incident type-2 diabetes in the association between dietary inflammatory potential and pancreatic cancer with the use of causal mediation approach. The association of inflammatory potential of diet with pancreatic cancer was fully mediated through incident diabetes. No significant overall effect of E-DII on pancreatic cancer, averaged over direct and indirect effect with type-2 diabetes as a mediator, was observed. Future large cohort studies are warranted to test other possible mediators in the pathway from dietary inflammatory potential to pancreatic cancer risk.
Table 6.1 Baseline characteristics of 269,641 subjects by quintiles of E-DII in the pooled mediation cohort of PLCO Cancer Screening Trial and NIH-AARP Diet and Health Study

<table>
<thead>
<tr>
<th></th>
<th>Most anti-inflammatory diet</th>
<th>Most pro-inflammatory diet</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-DII Q1</td>
<td>E-DII Q2</td>
<td>E-DII Q3</td>
</tr>
<tr>
<td></td>
<td>(-8.43, -5.57)</td>
<td>(-5.56, -4.47)</td>
<td>(-4.46, -3.24)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>53929</td>
<td>53927</td>
<td>53928</td>
</tr>
<tr>
<td><strong>Mean (SE)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at baseline (y)</td>
<td>62.7 (0.02)</td>
<td>62.8 (0.02)</td>
<td>62.6 (0.02)</td>
</tr>
<tr>
<td>Total energy intake (kcal/d)</td>
<td>1553.7 (2.4)</td>
<td>1675.1 (2.8)</td>
<td>1756.9 (3.0)</td>
</tr>
<tr>
<td>Alcohol consumption (g/d)</td>
<td>9.3 (0.06)</td>
<td>9.0 (0.08)</td>
<td>9.7 (0.09)</td>
</tr>
<tr>
<td>n (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3198 (5.9)</td>
<td>3835 (7.1)</td>
<td>4205 (7.8)</td>
</tr>
<tr>
<td>No</td>
<td>45950 (85.2)</td>
<td>45368 (84.1)</td>
<td>45087 (83.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>4781 (8.9)</td>
<td>4724 (8.8)</td>
<td>4636 (8.6)</td>
</tr>
<tr>
<td>Primary pancreatic cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>153 (0.3)</td>
<td>146 (0.3)</td>
<td>159 (0.3)</td>
</tr>
<tr>
<td>No</td>
<td>53776 (99.7)</td>
<td>53781 (99.7)</td>
<td>53769 (99.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21886 (40.6)</td>
<td>25020 (46.4)</td>
<td>28048 (52.0)</td>
</tr>
<tr>
<td>Female</td>
<td>32043 (59.4)</td>
<td>28907 (53.6)</td>
<td>25880 (48.0)</td>
</tr>
<tr>
<td>Race/ Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>50323 (93.3)</td>
<td>50406 (93.5)</td>
<td>50402 (93.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>1173 (2.2)</td>
<td>1274 (2.4)</td>
<td>1388 (2.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>645 (1.2)</td>
<td>722 (1.3)</td>
<td>765 (1.4)</td>
</tr>
<tr>
<td>Asian, Pacific Islander or American Indian/Alaskan Native</td>
<td>1434 (2.7)</td>
<td>1189 (2.2)</td>
<td>1023 (1.9)</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Unknown</td>
<td>354 (0.7)</td>
<td>336 (0.6)</td>
<td>350 (0.7)</td>
</tr>
</tbody>
</table>

**BMI**

| Underweight | 453 (0.8) | 392 (0.7) | 402 (0.8) | 370 (0.7) | 347 (0.6) |
| Normal | 24510 | 21778 | 20006 | 18086 | 15700 |
| (45.5) | (40.4) | (37.1) | (33.5) | (29.1) | |
| Overweight | 20701 | 21840 | 22711 | 23495 | 24196 |
| (38.4) | (40.5) | (42.1) | (43.6) | (44.9) | |
| Obese | 7441 (13.8) | 9135 | 10028 | 11167 | 12781 |
| (16.9) | (18.6) | (20.7) | (23.7) | | |
| Missing | 824 (1.5) | 782 (1.5) | 781 (1.5) | 811 (1.5) | 904 (1.7) |

**BMI** under <.0001

**Education level**

| less than or equal to 11 years | 1197 (2.2) | 1644 (3.1) | 1869 (3.5) | 2435 (4.5) | 3382 (6.3) |
| High school completion | 7668 (14.2) | 8990 | 9586 | 10608 | 12611 |
| (16.7) | (17.8) | (20.0) | (23.4) | |
| Post high school training other than college | 4801 (8.9) | 5348 (9.9) | 5585 | 5659 | 6459 |
| (10.4) | (10.5) | (12.0) | | |
| Some college | 12108 | 12166 | 11980 | 11943 | 11973 |
| (22.5) | (22.6) | (22.2) | (22.2) | (22.2) |
| College and postgraduate | 27311 | 24929 | 24101 | 22499 | 18717 |
| (50.6) | (46.2) | (44.7) | (41.7) | (34.7) |
| Missing | 844 (1.6) | 850 (1.6) | 807 (1.5) | 785 (1.5) | 786 (1.5) |

**Education level** under <.0001

**Smoking status and years of quit combined**

| Never smoked | 23526 | 23834 | 23425 | 22293 | 19297 |
| Stopped 10 or more years ago | 21166 | 19919 | 19546 | 19154 | 18299 |
| (39.3) | (36.9) | (36.2) | (35.5) | (33.9) | |
| Stopped 5-9 years ago | 3125 (5.8) | 3050 (5.7) | 3018 (5.6) | 3162 (5.9) | 3320 (6.2) |
| Stopped 1-4 years ago | 1529 (2.8) | 1623 (3.0) | 1619 (3.0) | 1779 (3.3) | 2072 (3.8) |
| Stopped within last year | 723 (1.3) | 825 (1.5) | 882 (1.6) | 960 (1.8) | 1202 (2.2) |
| Currently smoking | 2571 (4.8) | 3527 (6.5) | 4277 (7.9) | 5453 | 8533 |
| (10.1) | (15.8) | | | |
| Missing | 1289 (2.4) | 1149 (2.1) | 1161 (2.2) | 1128 (2.1) | 1205 (2.2) |

**Smoking status and years of quit combined** under <.0001

Abbreviations: SE, standard error

\( ^{a} \) Statistical analyses were performed by ANOVA test for continuous variables and by Chi-Square test for categorical variables.

\( ^{b} \) Sum of percentages may not add up to 100% because of rounding or missing.
Table 6.2 Study-specific natural direct effect, natural indirect effect and marginal total effect\(^a\) of E-DII\(^b\) on pancreatic cancer risk with incident type-2 diabetes as mediator

<table>
<thead>
<tr>
<th></th>
<th>Natural direct effect</th>
<th>Natural indirect effect</th>
<th>Marginal total effect</th>
<th>Mediation Proportion(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate with 95% (CI)</td>
<td>P value</td>
<td>Estimate with 95% (CI)</td>
<td>P value</td>
</tr>
<tr>
<td>PLCO Cancer Screening Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q5 vs Q1</td>
<td>1.14 (0.59-2.17)</td>
<td>0.70</td>
<td>1.02 (1.002-1.03)</td>
<td>0.03</td>
</tr>
<tr>
<td>Q4 vs Q1</td>
<td>1.10 (0.68-1.79)</td>
<td>0.70</td>
<td>1.01 (1.00-1.03)</td>
<td>0.03</td>
</tr>
<tr>
<td>Q3 vs Q1</td>
<td>1.07 (0.77-1.47)</td>
<td>0.70</td>
<td>1.01 (1.00-1.02)</td>
<td>0.03</td>
</tr>
<tr>
<td>Q2 vs Q1</td>
<td>1.03 (0.88-1.21)</td>
<td>0.70</td>
<td>1.004 (1.00-1.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>NIH-AARP Diet and Health Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q5 vs Q1</td>
<td>1.01 (0.79-1.30)</td>
<td>0.93</td>
<td>1.009 (1.004-1.015)</td>
<td>0.001</td>
</tr>
<tr>
<td>Q4 vs Q1</td>
<td>1.01 (0.84-1.22)</td>
<td>0.93</td>
<td>1.007 (1.003-1.01)</td>
<td>0.001</td>
</tr>
<tr>
<td>Q3 vs Q1</td>
<td>1.01 (0.89-1.14)</td>
<td>0.93</td>
<td>1.004 (1.002-1.007)</td>
<td>0.001</td>
</tr>
<tr>
<td>Q2 vs Q1</td>
<td>1.00 (0.94-1.07)</td>
<td>0.93</td>
<td>1.002 (1.00-1.003)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

a. Logistic models involved in the causal mediation approach to derive the mediation parameter estimates were adjusted for study-specific confounders.

b. Ordinal E-DII format was used in the model to compare risk of pancreatic cancer for subjects in each higher E-DII quintile to subjects in the lowest quintile with type-2 diabetes as mediator. E-DII score was derived in the PLCO based on 35 dietary components: alcohol, vitamin B12, vitamin B6, betacarotene, caffeine, carbohydrate, cholesterol, food energy, total fat, total dietary fiber, folate, iron, magnesium, monounsaturated fatty acids, poly-unsaturated fatty acids, niacin, onions, protein, riboflavin, saturated fatty acids, selenium, thiamin, total trans-fatty acids, Vitamin A, Vitamin C, Vitamin E, Vitamin D, zinc, tea, Flavan-3-ols, flavones, flavonones, anthocyanidin, isoflavone, and peppers. E-DII score was derived in the NIH-AARP based on 34 dietary components: data on onions were not included and the others are same as those in PLCO.

c. Mediation proportion of type-2 diabetes was calculated using the equation NDE x (NIE – 1)/ (NDE x NIE – 1)
Table 6.3 Pooled PLCO and NIH-AARP natural direct effect, natural indirect effect and marginal total effect\textsuperscript{a} of categorized E-DII\textsuperscript{b} on pancreatic cancer risk with incident type-2 diabetes as mediator, using random effect model

<table>
<thead>
<tr>
<th></th>
<th>Natural direct effect</th>
<th>Natural indirect effect</th>
<th>Marginal total effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate with 95% (CI)</td>
<td>P value</td>
<td>$I^2$</td>
</tr>
<tr>
<td>Q5 vs Q1</td>
<td>1.03 (0.81-1.29)</td>
<td>0.83</td>
<td>0%</td>
</tr>
<tr>
<td>Q4 vs Q1</td>
<td>1.02 (0.86-1.22)</td>
<td>0.81</td>
<td>0%</td>
</tr>
<tr>
<td>Q3 vs Q1</td>
<td>1.02 (0.91-1.14)</td>
<td>0.77</td>
<td>0%</td>
</tr>
<tr>
<td>Q2 vs Q1</td>
<td>1.00 (0.95-1.07)</td>
<td>0.89</td>
<td>0%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Pooled mediation estimates from PLCO and NIH-AARP mediation analyses were obtained using the random effects model.

\textsuperscript{b} DII was treated as an ordinal variable in the study-specific mediation model to compare risk of pancreatic cancer for subjects in each higher E-DII quintile to subjects in the lowest quintile with type-2 diabetes as mediator.

\textsuperscript{c} $I^2$ statistic describes the percentage of total variation that is due to heterogeneity rather than chance; 0% represents no heterogeneity.

\textsuperscript{d} $P_{het}$ was calculated from test for between-studies heterogeneity using the random effect model.
Table 6.4 Study-specific and random-effect model pooled natural direct effect, natural indirect effect and marginal total effect\(^a\) of one-unit increase in centered E-DII and E-DII z-score on pancreatic cancer risk with type-2 diabetes as mediator

<table>
<thead>
<tr>
<th></th>
<th>Natural direct effect</th>
<th>Natural indirect effect</th>
<th>Marginal total effect</th>
<th>Mediation proportion(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate with 95% (CI)</td>
<td>P value (P^b)</td>
<td>(P_{\text{he}}^e)</td>
<td>Estimate with 95% (CI)</td>
</tr>
<tr>
<td><strong>PLCO Cancer Screening Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one unit increase in centered E-DII value</td>
<td>1.00 (0.91-1.10)</td>
<td>0.96</td>
<td>N/A</td>
<td>1.002 (1.00-1.004)</td>
</tr>
<tr>
<td>one unit increase in E-DII z-score</td>
<td>1.01 (0.8-1.26)</td>
<td>0.96</td>
<td>N/A</td>
<td>1.006 (1.00-1.01)</td>
</tr>
<tr>
<td><strong>NIH-AARP Diet and Health Study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one unit increase in centered E-DII value</td>
<td>1.00 (0.96-1.04)</td>
<td>0.97</td>
<td>N/A</td>
<td>1.002 (1.00-1.003)</td>
</tr>
<tr>
<td>one unit increase in E-DII z-score</td>
<td>1.00 (0.91-1.09)</td>
<td>0.97</td>
<td>N/A</td>
<td>1.004 (1.001-1.005)</td>
</tr>
<tr>
<td><strong>Pooled estimates from PLCO and NIH-AARP using random effect model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>one unit increase in centered E-DII value</td>
<td>1.00 (0.96-1.04)</td>
<td>0.99</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\(^a\)One-unit increase in centered E-DII and E-DII z-score on pancreatic cancer risk with type-2 diabetes as mediator. 
\(^b\)P value. 
\(^c\)Pooled estimate. 
\(^d\)Mediation proportion. 
\(^e\)Not interpretable.
<table>
<thead>
<tr>
<th>E-DII value</th>
<th>one unit increase in E-DII z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>(0.92-1.09)</td>
</tr>
<tr>
<td>0.9</td>
<td>0%</td>
</tr>
<tr>
<td>0.9</td>
<td>4%</td>
</tr>
<tr>
<td>1.004</td>
<td>(1.002-1.006)</td>
</tr>
<tr>
<td>&lt;0.0</td>
<td>0%</td>
</tr>
<tr>
<td>0.4</td>
<td>7%</td>
</tr>
<tr>
<td>1.00</td>
<td>(0.92-1.09)</td>
</tr>
<tr>
<td>0.9</td>
<td>0%</td>
</tr>
<tr>
<td>0.9</td>
<td>4%</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available

a. Logistic models involved in the causal mediation approach to derive the mediation parameter estimates were adjusted for study-specific confounders.

b. I² statistic describes the percentage of total variation that is due to heterogeneity rather than chance; 0% represents no heterogeneity.

c. P heterogeneity was calculated from test for between-studies heterogeneity using the random effect model.

d. Mediation proportion of type-2 diabetes was calculated using the equation \[ \frac{NDE \times (NIE - 1)}{(NDE \times NIE - 1)} \]

e. Because the direction of NDE and NIE is different, the mediation proportion is not interpretable
Table 6.5 Natural direct effect, natural indirect effect and the marginal total effect\(^a\) of the categorized E-DI\(^b\) on pancreatic cancer mediated by type-2 diabetes using primary data of 269,641 subjects from the PLCO and NIH-AARP

<table>
<thead>
<tr>
<th></th>
<th>Natural direct effect</th>
<th>Natural indirect effect</th>
<th>Marginal total effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate with 95% (CI)</td>
<td>P value</td>
<td>Estimate with 95% (CI)</td>
</tr>
<tr>
<td>Q5 vs Q1</td>
<td>0.91 (0.72-1.15)</td>
<td>0.45</td>
<td>1.009 (1.004-1.013)</td>
</tr>
<tr>
<td>Q4 vs Q1</td>
<td>0.93 (0.78-1.11)</td>
<td>0.45</td>
<td>1.006 (1.003-1.01)</td>
</tr>
<tr>
<td>Q3 vs Q1</td>
<td>0.96 (0.85-1.07)</td>
<td>0.45</td>
<td>1.004 (1.002-1.006)</td>
</tr>
<tr>
<td>Q2 vs Q1</td>
<td>0.98 (0.92-1.04)</td>
<td>0.45</td>
<td>1.002 (1.001-1.003)</td>
</tr>
</tbody>
</table>

a. Logistic models involved in causal mediation approach to derive the mediation parameter estimates were adjusted for age at baseline (continuous), sex (male and female), total energy intake (kcal/day), BMI (underweight, normal, overweight, obese, missing), alcohol intake (g/day), combination of smoking status and years since quitting smoking (never smoked, stopped 10 or more years ago, stopped 5-9 years ago, stopped 1-4 years ago, stopped within last year, currently smoking, missing), education levels (\(<=11\) years, high school completion, post high school training other than college, some college, college and postgraduate, missing).

b. Ordinal E-DII format was used in the model to compare risk of pancreatic cancer for subjects in each higher E-DII quintile to subjects in the lowest quintile with type-2 diabetes as mediator.
Table 6.6 Natural direct effect, natural indirect effect and marginal total effect\(^a\) of one-unit increase in centered E-DII and E-DII z-score on pancreatic cancer risk with type-2 diabetes as mediator using primary data of 269,641 subjects from the PLCO and NIH-AARP

<table>
<thead>
<tr>
<th></th>
<th>Natural direct effect</th>
<th></th>
<th>Natural indirect effect</th>
<th></th>
<th>Marginal total effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate with 95% (CI)</td>
<td>P value</td>
<td>Estimate with 95% (CI)</td>
<td>P value</td>
<td>Estimate with 95% (CI)</td>
</tr>
<tr>
<td>One unit increment of centered E-DII value</td>
<td>0.98 (0.95-1.02)</td>
<td>0.28</td>
<td>1.001 (1.00-1.002)</td>
<td>0.0001</td>
<td>0.98 (0.95-1.02)</td>
</tr>
<tr>
<td>One unit increase of z-score of E-DII</td>
<td>0.95 (0.88-1.04)</td>
<td>0.28</td>
<td>1.003 (1.002-1.005)</td>
<td>0.0001</td>
<td>0.96 (0.88-1.04)</td>
</tr>
</tbody>
</table>

\(a.\) Logistic models involved in causal mediation approach to derive the mediation parameter estimates were adjusted for age at baseline (continuous), sex (male and female), total energy intake (kcal/day), BMI (underweight, normal, overweight, obese, missing), alcohol intake (g/day), combination of smoking status and years since quitting smoking (never smoked, stopped 10 or more years ago, stopped 5-9 years ago, stopped 1-4 years ago, stopped within last year, currently smoking, missing), education levels (<=11 years, high school completion, post high school training other than college, some college, college and postgraduate, missing).
### Table 6.7 Comparison of important demographic and lifestyle characteristics between study sample and excluded sample in the pooled PLCO Cancer Screening Trial and NIH-AARP

<table>
<thead>
<tr>
<th></th>
<th>Study population (n=269,641)</th>
<th>Excluded subjects (n=365,064)</th>
<th>P-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
<td></td>
</tr>
<tr>
<td>Age at DHQ (years)</td>
<td>62.6 (0.01)</td>
<td>62.1 (0.01)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total energy intake (kcal/d)</td>
<td>1793.4 (1.5)</td>
<td>1852.9 (1.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Alcohol consumption (g/d)</td>
<td>11.9 (0.06)</td>
<td>12.4 (0.06)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>E-DII from food and supplement</td>
<td>-3.6 (0.004)</td>
<td>-3.3 (0.003)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>N (%)$^b$</td>
<td>N (%)$^b$</td>
<td></td>
</tr>
<tr>
<td>Primary pancreatic cancer</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>755 (0.3)</td>
<td>2397 (0.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>268886 (99.7)</td>
<td>362667 (99.3)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Male</td>
<td>144999 (53.8)</td>
<td>218487 (59.9)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>124642 (46.2)</td>
<td>146577 (40.1)</td>
<td></td>
</tr>
<tr>
<td>Race/ Ethnicity</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>251856 (93.4)</td>
<td>327882 (89.8)</td>
<td></td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>6925 (2.6)</td>
<td>16789 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3728 (1.4)</td>
<td>7662 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Asian, Pacific Islander or American Indian/Alaskan Native</td>
<td>5376 (2.0)</td>
<td>7508 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1756 (0.7)</td>
<td>5223 (1.4)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Underweight</td>
<td>1964 (0.7)</td>
<td>2836 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>100080 (37.1)</td>
<td>113802 (31.2)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>112943 (41.9)</td>
<td>152290 (41.7)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>50552 (18.8)</td>
<td>86200 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4102 (1.5)</td>
<td>9936 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>less than or equal to 11 years</td>
<td>10527 (3.9)</td>
<td>27456 (7.5)</td>
<td></td>
</tr>
<tr>
<td>High school completion</td>
<td>49463 (18.3)</td>
<td>78227 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Post high school training other than college</td>
<td>27852 (10.3)</td>
<td>37619 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>60170 (22.3)</td>
<td>85316 (23.4)</td>
<td></td>
</tr>
<tr>
<td>College and postgraduate</td>
<td>117557 (43.6)</td>
<td>124730 (34.2)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4072 (1.5)</td>
<td>11716 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Smoking status and years of quit combined</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Never smoked</td>
<td>112375 (41.7)</td>
<td>122133 (33.5)</td>
<td></td>
</tr>
<tr>
<td>Stopped 10 or more years ago</td>
<td>98084 (36.4)</td>
<td>130113 (35.6)</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Stopped 5-9 years ago</td>
<td>15675 (5.8)</td>
<td>26715 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Stopped 1-4 years ago</td>
<td>8622 (3.2)</td>
<td>15881 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Stopped within last year</td>
<td>4592 (1.7)</td>
<td>7523 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Currently smoking</td>
<td>24361 (9.0)</td>
<td>48641 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>5932 (2.2)</td>
<td>14058 (3.9)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) P value was calculated from independent t-test for continuous variables and from Chi-Square test for categorical variables.

\(^b\) The sum of percentages for some categorical variables may not add up to 100% because of rounding.
Table 6.8 Hazard ratios of pancreatic cancer by quintiles of E-DII score from food and supplement in the pooled mediation cohort of 269,641 subjects

<table>
<thead>
<tr>
<th></th>
<th>Most anti-inflammatory diet</th>
<th>Most pro-inflammatory diet</th>
<th>Continuous HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-DII Q1</td>
<td>E-DII Q2</td>
<td>E-DII Q3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>153</td>
<td>146</td>
<td>159</td>
</tr>
<tr>
<td>Sample size</td>
<td>53929</td>
<td>53927</td>
<td>53928</td>
</tr>
<tr>
<td>Age and energy-adjusted HR (95% CI)</td>
<td>1.00 (0.81-1.28)</td>
<td>1.14 (0.91-1.42)</td>
<td>1.08 (0.86-1.35)</td>
</tr>
<tr>
<td>Multivariable-adjusted HR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.00 (0.80-1.26)</td>
<td>1.11 (0.89-1.39)</td>
<td>1.03 (0.82-1.30)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Continuous DII score was used to determine $P$ for trend

<sup>b</sup> The continuous HR and associated 95% CI for one standard deviation increase of E-DII score

<sup>c</sup> Adjusted for age at baseline (continuous), sex (male and female), body mass index at baseline (underweight, normal, overweight, obesity and missing), years of quit and smoking status combined (never smoked, stopped 10 or more years ago, stopped 5-9 years ago, stopped 1-4 years ago, stopped within last year, currently smoking, unknown), total energy intake (kcal/d), education level (<=11 years, 12 years or completed high school, post-high school, some college, college and post graduate, unknown), alcohol intake (g/day)
Figure 6.1 Coding of mediator of type-2 diabetes on the association between E-DII and pancreatic cancer risk in the pooled analysis of the PLCO and NIH-AARP. Abbreviations: PanC, primary pancreatic cancer; D, mediator variable indicating incident type-2 diabetes occurrence during follow-up; P, primary pancreatic cancer.
CHAPTER 7
DIETARY INFLAMMATORY POTENTIAL AND PANCREATIC CANCER RISK: DISCUSSION OF STUDY RESULTS OF INTERACTION AND MEDIATION ANALYSES IN TWO PROSPECTIVE COHORTS

7.1 Summary of results

This dissertation aimed to investigate the association between inflammatory potential of diet and pancreatic cancer in the PLCO Cancer Screening Trial and the NIH-AARP Diet and Health Study, and examine important inflammation-related lifestyle effect modifiers in the association. In the pooled analysis with combined data from the PLCO and NIH-AARP, we aimed to examine whether incident type-2 diabetes mediated the association between inflammatory potential of diet and pancreatic cancer using the causal mediation approach. Generally, we did not observe a significant association between E-DII and pancreatic cancer after adjusting for confounders in both PLCO and NIH-AARP cohorts. However, in the PLCO specifically, time (<4 and >=4 years) was found to be the only significant effect modifier (P-interaction=0.02). Among subjects with follow up <4 years, there was an inverse association between E-DII and pancreatic cancer (HR_{Q5vsQ1}=0.55; 95% CI=0.32-0.95; P-trend=0.15), while there was a positive trend among those with ≥4 years of follow-up (HR_{Q5vsQ1} =1.36; 95% CI=0.85-2.17; P-
trend=0.03). Similar results were observed for E-DII from food only. In the NIH-AARP, inflammation-related lifestyle factors including BMI, smoking status, alcohol drinking, NSAIDs use, and history of diabetes did not modify the E-DII and pancreatic cancer association. Dietary inflammatory potential was not associated with pancreatic cancer risk by cancer stage or grade. Both study-specific and pooled mediation analysis using combined data from both the PLCO and NIH-AARP confirmed the significant though small mediated effect of incident type-2 diabetes on the association between E-DII and pancreatic cancer. However, the overall effect of E-DII on pancreatic cancer averaged over direct and indirect effects with type-2 diabetes as a mediator was not significant.

7.2 Comparisons of dissertation findings with findings from two case-control studies

Findings from our dissertation did not confirm the significant positive associations of the E-DII and pancreatic cancer reported in the two previously published case-control studies.\textsuperscript{38,39} In both case-control studies, an approximate 2.5-fold increased risk of pancreatic cancer in the highest compared to the lowest quintile of the E-DII group was observed (U.S.: \( \text{OR}_{Q5\text{vs}Q1} = 2.54, 95\% \text{ CI}=1.87-3.46, \text{P-trend}<0.0001; \textsuperscript{39} \) Italy: \( \text{OR}_{Q5\text{vs}Q1} = 2.48, 95\% \text{ CI}=1.50-4.10, \text{P-trend}=0.002\textsuperscript{38} \)). In addition to the primary association results, both studies also identified evidence of effect modification by a few inflammation-related factors including smoking, BMI, and diabetes history. The Italy case-control study documented evidence of effect modification by smoking status and BMI where a significant positive association was observed among never and past smokers but not among current smokers, and among normal and overweight rather than obese subjects, respectively.\textsuperscript{38} In the U.S. case-control study, using a joint effect
approach, Antwi et al. demonstrated that dietary inflammatory potential may act synergistically with cigarette smoking and diabetes to increase the risk of pancreatic cancer beyond the risk of any of these factors alone.\textsuperscript{39} However, this dissertation using data from two large well-established prospective cohorts in the US consistently demonstrated the null overall E-DII and pancreatic cancer association and no significant effect modification by inflammation-related factors, although a significant positive trend was detected in the PLCO among participants with follow up $\geq$4 years. The major reasons for the inconsistent results may be owing to the strengths and limitations of the different study designs utilized. Differential misclassification of exposure is minimized in a cohort design but is inextricable in a case-control design as a result of recall bias and selection bias. In addition, due to the high fatality of pancreatic cancer, case-control study of pancreatic cancer is susceptible to measurement error induced by using proxy’s responses, which also could distort the association. However, as observed in Aim 1 analyses, although prospective studies measured exposure before outcome occurrence which may minimize reverse causality bias, such bias can occur in prospective studies given the unknown latency of pancreatic cancer. In addition, its precursor conditions have profound effects on digestion, implying that dietary changes may be made at the early stage of cancer development.

7.3 Potential mechanisms of action

Chronic inflammation has been identified as an underlying pathophysiological foundation for many chronic diseases, including cancers.\textsuperscript{407,408} Uncontrolled pro-inflammatory responses could create a chronic inflammatory state, promoting a tumor-favorable microenvironment that supports the development of genomic mutations and
potentially triggers immune overactivation and initiation of pancreatic cancer.\textsuperscript{58,441} The process for pro-inflammatory cytokines (e.g., tumor necrosis factor, IL-6, IL-11 or IL-22) to trigger signaling cascades that activate key transcription factors directly or indirectly which control cell-cycle, cell death, dedifferentiation, stemness, motility, and migration have gone astray in chronic inflammation.\textsuperscript{442} In addition, inflammatory states are etiologically linked to well-recognized risk factors for pancreatic cancer, including chronic pancreatitis, cigarette smoking, obesity, and diabetes.\textsuperscript{58,384}

Dietary factors could affect cancer risk through modulation of inflammation,\textsuperscript{385,386} mainly realized through their impact on visceral obesity,\textsuperscript{387} oxidative damage,\textsuperscript{78} and insulin resistance.\textsuperscript{387} Multiple mechanisms are involved in this process, including regulation of the pro-inflammatory cytokines, NF-κB pathway activation, changes in DNA methylation and influence on the antioxidant defense.\textsuperscript{79,73} Dietary patterns, which take into account the complex interaction between foods or nutrients, such as Western type diet and the Mediterranean diet, have been found to affect inflammatory biomarkers.\textsuperscript{6,443-445}

Pro-inflammatory diets can increase insulin resistance, increase reactive oxygen species, and influence mediators in the inflammatory pathway (e.g., NF-kB and COX-2), leading to increased cell cycling, loss of tumor suppressor function, stimulated oncogene expression, genetic alterations, and modifications of key cancer-related proteins, ultimately causing malignancy.\textsuperscript{57,58,418,419} Diets high in red and processed meat may contain high amount of nitrosamine and nitrate which may cause DNA damage.\textsuperscript{243} A recent investigation also found a chemical contributed primarily from red meat consumption (dietary $N^\omega$-(carboxymethyl) lysine (CML) glycation end products) had a
pancreatic cancer promoting effect. An anti-inflammatory diet has strong antioxidant and carcinogenesis inhibition properties, which could help to reduce insulin resistance, oxidative stress and damage, and inhibit pancreatic tumor development.

There are other lifestyle factors known to be associated with inflammation besides diet and that may have an effect on pancreatic cancer development. Obesity and diabetes are inflammatory conditions, and recent data have demonstrated that the plasma concentration of inflammatory mediators, such as TNF-α and IL-6, are increased in the insulin-resistant states of obesity and type-2 diabetes. Cigarette smoking has been shown to augment the production of pro-inflammatory cytokines and decrease the levels of anti-inflammatory biomarkers. Chronic alcohol exposure promotes pro-inflammatory immune responses, and also impairs anti-inflammatory cytokines. The pro-inflammatory effects of high-level alcohol drinking also play a major role in the pathogenesis of pancreatitis. Non-steroidal anti-inflammatory drugs (NSAIDs), which include aspirin, piroxicam, ibuprofen and other COX-2 inhibitors, have shown the ability to alter systemic inflammation, reduce tumor recurrence and improve moderate cancer cachexia.

7.4 Strengths and limitations

This dissertation has several major strengths. The use of two large, well-characterized prospective cohorts with long follow-up and adequate numbers of pancreatic cancer cases and incident type-2 diabetes cases provided us with ample power to test our hypotheses in three aims. In the pooled analyses (Aim 3), the similarities between the PLCO and NIH-AARP cohorts provided us a strong justification to combine primary data from these two cohorts to increase outcome and mediator numbers as well
as take advantage of differences in the distributions of the exposure variable across studies, in order to better test the mediated effect of incident type-2 diabetes. With diet and lifestyle factors assessed before cancer diagnosis, recall bias and selection bias that are inevitable in a typical case-control study were minimized in our research. To the best of our knowledge, we are among the first to test the dietary inflammatory potential and pancreatic cancer association in a prospective manner and examine whether inflammatory potential of diet acted synergistically with other inflammation-related lifestyle factors to influence pancreatic cancer risk. Using the NIH-AARP, this also is the first prospective investigation to examine the association between a dietary index and pancreatic cancer severity. The other strengths included detailed information on a comprehensive list of covariates which allowed for careful adjustment in the analyses, the use of a construct-validated dietary index which was designed specifically on the inflammation mechanism and provided a comprehensive assessment of inflammatory potential of an individual’s entire diet, and the application of majority of DII components to calculate the E-DII scores which created a large contrast of exposure. We obtained consistent results from three aims to support the lack of overall association of E-DII and pancreatic cancer. In all the mediation analyses of Aim 3, we consistently observed the significant mediated effect of type-2 diabetes, which suggested type-2 diabetes may play a role as a mediator in the DII and pancreatic cancer association.

Several limitations should be considered in the interpretation of the results. In each study, we excluded a substantial number of participants based on exclusion criteria, but differences of some pancreatic cancer risk factors may exist between excluded and included participants which may have introduced selection bias and resulted in
underestimation of the association. The FFQ and other questionnaires used in each study were prone to measurement error as another unavoidable limitation, which may have resulted in some misclassification of the E-DII score and covariates. Although follow-up data were available on most covariates, the large amount of missing information impeded our ability to use these data. Evaluation of the E-DII at a single time point could result in non-differential misclassification of exposure given diet may change over time. However, we previously found DII scores were relatively stable over time in postmenopausal women who were of comparable ages as our study populations.405 Another limitation of the study was that not all of the 45 DII components were available in both the PLCO and NIH-AARP to calculate the E-DII scores. However, the range of DII scores may rely more on the amount of foods actually consumed rather than the number of available DII components,406 and a previous study found a significant association between the DII and colorectal cancer using data from the NIH-AARP,34 suggesting that the smaller number of DII components would not limit the ability to detect an effect. While we adjusted for important potential confounders, residual or unmeasured confounding cannot be ruled out. In the mediation analysis specifically (Aim 3), we cannot rule out the possibility that the assumption of pooling the primary data may not be fully met in that differences in the measurement and distribution of covariates (i.e., different questions to obtain data, different categories of a covariate, different units) and in the number of available DII components used to calculate the E-DII score were present; however, there was no method to test the assumptions.429 We also were unable to report some of the mediation proportion as the NDE and NIE were not in the same direction.
7.5 Public health implications

Pancreatic cancer has a high case-fatality rate, and due to lack of reliable screening method for early detection, it is usually diagnosed at an advanced stage with a very low survival rate. Therefore, identifying modifiable factors, including diet, can help reduce the burden of this malignancy. Findings from this dissertation had scientific, clinical, and public health significance.

The null association identified from the PLCO and NIH-AARP between the DII and pancreatic cancer suggested that the total dietary inflammatory potential may not be a major contributor to pancreatic cancer risk, which implies that maybe other mechanisms, other dietary factors, or only a portion of the DII components are associated with pancreatic cancer. These possible explanations warrant future studies to test and confirm. Since our studies obtained a null association conclusion with several limitations, future studies that can overcome these limitations are needed to confirm our results. Nevertheless, striving toward a more anti-inflammatory diet may have other potential health benefits beyond pancreatic cancer prevention.

Providing evidence of inflammation-related effect modifiers on the dietary inflammatory potential and pancreatic cancer relationship is informative to evaluate total risk of pancreatic cancer while taking into account other common lifestyle factors, especially for people who have a pro-inflammatory diet such as Western type diet. However, we did not observe any significant effect modification in the association, which could be due to the small numbers in some strata or because we only conducted multiplicative interaction test in the COX model but did not use the joint effect approach to test the multiplicative and additive interactions. Therefore, our results laid the
groundwork for future studies without these limitations to confirm our findings. Even if there is a lack of significant results from statistical tests, that does not actually mean no biologic interactive effects.

The finding of the significant mediated effect of type-2 diabetes in the association between dietary inflammatory potential and pancreatic cancer not only elucidated a mechanism through which dietary inflammatory potential could lead to development of pancreatic cancer, it also provides clinical evidence and guidance to identify possible intermediate biomarkers related to type-2 diabetes mechanism such as insulin resistance in order to indirectly identify high risk population for developing pancreatic cancer, especially for those who consume a more pro-inflammatory diet. In addition, our findings could help with the design and guidance of an effective dietary intervention to reduce risk of pancreatic cancer through intervening on type-2 diabetes.

7.6 Implications for future research

Given the conclusion from the PLCO that time was a significant effect modifier of the E-DII and pancreatic cancer association, future prospective cohort studies assessing dietary factors and pancreatic cancer risk should consider differences in associations by follow-up time. It is possible for future studies to investigate how diet has been changed in the early period of pancreatic cancer diagnosis. Future large cohort studies with repeated diet measurements are warranted to confirm our findings in this dissertation. Studies that have follow-up data missing at a small percentage are also needed to test our hypotheses and confirm the results. Large cohort studies are needed to test the effect modification of E-DII and pancreatic cancer by important inflammation-related lifestyle factors and the association between E-DII and severity of pancreatic
cancer to confirm our findings in the NIH-AARP. Since age at diagnosis of diabetes during the follow-up was not measured in a precise way in both the PLCO and NIH-AARP, future prospective cohort studies with follow-up type-2 diabetes measured in more details are needed to test and confirm our mediation analysis findings. Other possible mediators in the pathway from dietary inflammatory potential to pancreatic cancer risk may exist. Therefore, future studies could test other possible mediators in the association and further investigate the relationship between multiple mediators in the DII and pancreatic cancer association. Given the significant mediator role of type-2 diabetes in the association between DII and pancreatic cancer, the inclusion of diabetes as a covariate in future analysis of DII and pancreatic cancer is not recommended.

7.7 Conclusion

Both the PLCO and NIH-AARP did not support a significant association between inflammatory potential of diet and pancreatic cancer risk. However, in the PLCO cohort, time significantly modified the E-DII and pancreatic cancer association. An inverse association between E-DII and pancreatic cancer in the first four years of follow up was observed, suggesting dietary changes due to undiagnosed disease might have affected appetite or food choices to lower the E-DII scores in the early stages. A positive association, as hypothesized, was suggested by a significant trend after excluding subjects with follow-up time <4 years. In the NIH-AARP, inflammation-related lifestyle factors including BMI, smoking status, alcohol drinking, NSAIDs use, and history of diabetes did not modify the association. Dietary inflammatory potential was not associated with pancreatic cancer risk by cancer stage or grade.

In the pooled analysis of the PLCO and NIH-AARP, we identified a significant
though small mediated effect of incident type-2 diabetes in the associations between both
categorical and continuous DII and pancreatic cancer. The association of inflammatory
potential of diet with pancreatic cancer was fully mediated through incident type-2
diabetes. However, the overall effect of E-DII on pancreatic cancer, averaged over direct
and indirect effect with type-2 diabetes as a mediator, was not significant.

7.8 Acknowledgements

Research reported in this discussion was supported by a Support to Promote
Advancement of Research and Creativity (SPARC) grant by the University of South
Carolina Office of the Vice President for Research, to Jiali Zheng. Dr. Michael D. Wirth
was supported by grant number R44 DK103377 from the National Institute of Diabetes
and Digestive and Kidney Diseases. The PLCO Cancer Screening Trial (Aim1) was
approved and supported by contracts from the Division of Cancer Prevention, National
Cancer Institute, National Institutes of Health, DHHS. We express our genuine gratitude
to the PLCO Cancer Screening Trial investigators and staff, and thank Mr. Jerome Mabie
and Alan Bangura from Information Management Services, Inc. for data preparation and
delivery, and analysis suggestions. Most important, we acknowledge the PLCO
participants for their significant contributions to making this study possible. The NIH-
AARP Diet and Health Study was supported by the Intramural Research Program of the
National Cancer Institute, NIH. We are indebted to the participants in the NIH-AARP
Diet and Health Study for their outstanding cooperation. We express our genuine
gratitude to those institutions or departments that helped to collect cancer incidence data
in the study or took responsibility for any analyses, interpretations or conclusions. We
gratefully acknowledge the contributions of Leslie Carroll and David Campbell at
Information Management Services and Tawanda Roy at the Nutritional Epidemiology Branch for research assistance.
REFERENCES

30. Houdek JM. Validity of a dietary inflammatory index in predicting serum inflammatory markers C-reactive protein, interleukin-6, and tumor necrosis factor-alpha in two separate patient samples, RUSH UNIVERSITY; 2015.


208


