Flavonoid Intake and Breast Cancer Incidence and Survival

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology, School of Public Health

Chapel Hill
2006

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ABSTRACT

Brian N. Fink: Flavonoid Intake and Breast Cancer Incidence and Survival
(Under the direction of Marilie D. Gammon)

Background: Flavonoids are phytochemicals found in a variety of foods that have demonstrated anti-carcinogenic properties in experimental studies. Two epidemiologic studies conducted in the Mediterranean have observed an inverse association between dietary intake of certain flavonoid classes and breast cancer incidence. However, it is unknown whether a similar association is evident among American women. Further, whether flavonoids affect breast cancer survival is unknown. We investigated whether dietary flavonoid intake influences breast cancer incidence and survival among a population-based cohort of American women. ***Methods:*** A population-based, case-control study was conducted among women ages 20-98 years who resided in Nassau and Suffolk counties in Long Island, New York. Cases were newly diagnosed with a first invasive breast cancer between August 1, 1996 and July 31, 1997; controls were identified using random digit dialing and Health Care Finance Administration rosters. Trained interviewers administered an in-person questionnaire to participants on known and suspected breast cancer risk factors. Participants also completed a self-administered food frequency questionnaire regarding their average frequency of food and beverage consumption in the prior 12 months. For those with known menopausal status, 1,434 breast cancer cases and 1,440 controls provided adequate dietary responses. Case medical records were obtained to assess tumor characteristics and initial course of treatment. Cases were followed-up through 2002. All-cause mortality (n =

173) and breast cancer-specific mortality (n = 113) were determined through the National Death Index. ***Results:*** Increasing intake of flavonols, flavones, flavan-3-ols, and lignans, as reported at the case-control interview, was associated with a reduced risk of incident post-menopausal breast cancer among Long Island women. All-cause mortality among post-menopausal women was reduced for intake of flavones and isoflavones and similar results were observed for breast cancer-specific mortality. ***Conclusion:*** Findings provide evidence for a beneficial effect of flavones, flavonols and lignans on breast cancer incidence among post-menopausal women. Results from the follow-up study indicate that mortality among post-menopausal breast cancer patients is reduced in association with high intake of flavones and isoflavones near the time of diagnosis. These findings suggest American women can consume sufficient levels of flavonoid-rich foods to benefit from their potential chemopreventive effects.

DEDICATION

To Dave Larabee; the man who inspired me to be a teacher and to teach with the passion, excitement, and dedication that he gave to his classes and his students each and every day of his life. I will do everything possible to carry on your legacy of excellence and I will always keep you in my memory. Thank you for being my teacher and my friend.

To my mother, father, and sister; thank you for all your love and support throughout my life. My life has been shaped by your guidance and this work is the product of your love and wisdom that you have shared with me. I will continue to make you all proud.

TABLE OF CONTENTS

Page

LIST OF TABLES xv

LIST OF FIGURES xviii

LIST OF ABBREVIATIONS xix

CHAPTER I: BACKGROUND AND INTRODUCTION 1

Overview of Study Background, Specific Aims, and Hypotheses 1

Specific Aims and Hypotheses 4

Epidemiology of Breast Cancer Incidence 4

Introduction 4

Reproductive Risk Factors 8

Pregnancy 9

Oral Contraceptive Use 10

Hormone Replacement Therapy (HRT) 11

Breastfeeding 13

Early Age at Menarche 14

Late Age at Menopause 15

Late Age at First Birth 15

Demographic Risk Factors 16

Increasing Age 16

Socioeconomic Status (SES) and Race....17
Medical Risk Factors....17
Family History of Breast Cancer....17
Endogenous Estrogen Levels....18
Estrogen Receptor (ER) and Progesterone Receptor (PR) Status....19
Benign Breast Disease (BBD)....20
Environmental and Lifestyle Risk Factors....22
Post-menopausal Obesity and Weight Gain....22
Alcohol Consumption....23
Physical Inactivity....24
Ionizing Radiation....26
Cigarette Smoking....27
Fat Consumption....28
Non-steroidal Anti-inflammatory Drug (NSAID) Use....28
Fruit and Vegetable Consumption....29
Flavonoids....31
Breast Cancer and Flavonoids....34
Epidemiology of Breast Cancer Survival....36
Clinical and Non-Clinical Prognostic Factors....37
Tamoxifen....37
Radiation and Chemotherapy Treatment....38
Tumor Size at Diagnosis....39
Stage at Diagnosis....39

Node Involvement/Status 40
Tumor Estrogen Receptor (ER) / Progesterone Receptor (PR) Status 41
Obesity at Diagnosis 42
Socioeconomic Status (SES), Race, and Age 44
Potential Prognostic Factors 45
Physical Activity 45
Cigarette Smoking 45
Dietary Fat and Energy Intake 46
Alcohol Consumption 46
Oral Contraceptive Use 47
Reproductive Patterns 47
Fruit and Vegetables 48
Flavonoids and Background Summary 50
Tables and Figures 52
CHAPTER II: RESEARCH METHODS AND DESIGN 56
Overview of Study Methods 56
Exposure Assessment 56
Modified Block FFQ (LIBCSP Food Questionnaire) 56
USDA Database for the Flavonoid Content of Selected Foods 58
USDA - Iowa State University Database on the Isoflavone Content of Selected Foods 59
Additional Isoflavone and Lignan Values Obtained from the Literature 60
Classification of items using the Modified Block FFQ and USDA Database for the Flavonoid Content of Selected Foods 61

Overview of the Long Island Breast Cancer Study Project (LIBCSP) 62

Case-Control Study Population Identification 63

Subject Recruitment in the Case-Control Study 64

Case-Control Subject Participation 65

Case-Control Study Interview 66

Demographics and Risk Factor Description of the Case-Control Population 67

Results of Established Risk Factors for Breast Cancer in the Case-Control Population 68

Potential Biases and Effects of Study Participation in the Case-Control Study 68

Overview of the LIBCSP Follow-Up Study 69

Subject Recruitment for the Follow-up Study 70

Data Collection at Follow-up 71

Case Interviews: Exposure Ascertainment 71

Retrieval and Abstraction of Medical Records 72

Potential Biases and Effects of Study Participation in the Follow-up Study 73

Case Outcome Ascertainment (Death) 73

Flavonoid Database Construction for Analysis 75

Weighting Foods from the Modified Block FFQ 75

USDA Database for the Flavonoid Content of Selected Foods Adjustments: Repeated Food and Beverage Items 77

New Variable Creation in Excel from the Modified Block FFQ Foods and Beverages 77

New Variable Creation in SAS 78

USDA Database for the Flavonoid Content of Selected Foods Adjustments: Foods and Beverages Omitted 79

Specific Variable Definitions and Confounders 80
Socioeconomic Status (SES) 81
Hormone Replacement Therapy (HRT) 82
Family History and Benign Breast Disease (BBD) 83
Physical Activity 84
BMI, Obesity, Weight, and Weight Gain 85
Alcohol Consumption 85
Specific Variable Definitions of Other Risk Factors 87
Menopausal Status 87
Age at Menarche 87
Age at First Birth and Parity 88
Oral Contraceptive Use 88
Race 89
Passive/Active Cigarette Smoking 89
Fruit and Vegetable Consumption 90
Statistical Methods and Data Analysis 90
Aim 1 Analysis and Results 91
Flavonoid Intake 91
Aim 2 Analysis and Results 93
Description of Exposures 93
Crude Results 93
Fruit and Vegetable-adjusted Results 94
ER/PR Stratified Results 94

Aim 3 Analysis and Results....96
Description of Exposures....96
Crude Results....97
Fruit and Vegetable-adjusted Results....98
ER/PR Stratified Results....98
Study Size and Power....98
Study Strengths....99
Study Limitations....100
Summary....102
Tables....105
Chapter III: DIETARY FLAVONOID INTAKE AND BREAST CANCER RISK AMONG WOMEN IN THE LONG ISLAND BREAST CANCER STUDY PROJECT....110
Abstract....110
Introduction....111
Methods and Materials....112
Participants....112
Exposure Assessment....112
Dietary Flavonoid Intake Assessment....113
Statistical Analysis....114
Results....115
Discussion....116
Tables....121

CHAPTER IV: DIETARY FLAVONOID INTAKE AND BREAST CANCER SURVIVAL AMONG WOMEN IN THE LONG ISLAND BREAST CANCER STUDY PROJECT 126

Abstract 126

Introduction 127

Materials and Methods 128

Overview 128

Study Subjects 128

Exposure Assessment 128

Baseline, Case-Control Interview 129

Dietary Flavonoid Intake Assessment at Baseline 129

Treatment Data 130

Case-control Interview 130

Follow-up Interview 130

Study Outcome 131

Statistical Analysis 131

Results 133

Discussion 135

Tables 139

Chapter V: DISCUSSION 145

Summary 145

Study Strengths 145

Biologic Plausibility of the Hypothesis 145

Novelty of the Hypothesis 147

Flavonoid Database....147
Sample Size and Source of Population....148
Interview and Dietary Data....148
Measurement of All-Cause and Breast Cancer-Specific Mortality....149
All-Cause Mortality....149
Breast Cancer-Specific Mortality....149
Study Limitations....150
Exposure Misclassification....150
Dietary Recall in the Case-Control Study....150
Dietary Recall Error....151
Time Period of Dietary Assessment for the Case-Control Study....152
Time Period of Dietary Assessment for the Follow-Up Study....152
Omission of Flavonoid-Rich Foods and Beverages on the Block FFQ....153
Other Nutrients....153
Serum Flavonoid Levels....154
Classification of Flavonoids....155
Covariate Misclassification....155
Treatment Information....155
Co-morbidities....156
Lifestyle Factors....156
Social Support and Health Care Factors....157
Outcome Misclassification....158
Sample Size Considerations....158

Future Directions 158

APPENDIX I: Additional Tables and Figures.....161

APPENDIX II: Construction of a flavonoid database for assessing intake in a population-based sample of women on Long Island, New York.....206

REFERENCES 224

LIST OF TABLES

Table 1.1. Known and potential risk factors for breast cancer incidence 52

Table 1.2. Known and potential prognostic factors for breast cancer survival 53

Table 2.1. Classes and Dietary Sources of Flavonoids 105

Table 2.2. Classification of FFQ Food and Beverage Contribution of Flavonoid Table 106

Table 2.3. Example of Flavonoid Data in Excel Spreadsheet 107

Table 2.4. Minimum Detectable Odds Ratios in the Proposed Case-Control Study of the LIBCSP Population, Alpha = 0.05 108

Table 2.5. Power calculations (expressed as %) assuming different true hazard ratios of breast cancer mortality for certain variables of interest 109

Table 3.1. Distribution of flavonoid intake (mg/d) for cases and controls of the Long Island Breast Cancer Study Project 121

Table 3.2. Age and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between menopausal-specific flavonoid intake in relation to breast cancer incidence 122

Table 3.3. Age and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between flavonoid intake in relation to breast cancer incidence among post-menopausal women, stratified by ER/PR status 124

Table 4.1 Demographic characteristics of invasive cases in the LIBCSP 139

Table 4.2. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996-1997 141

Table 4.3. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to breast cancer-specific mortality 143

Table A.1. Primary cause of death for invasive cases according to NDI records 162

Table A.2. Distribution of flavonoid intake (mg/d) for cases and controls of the Long Island Breast Cancer Study Project. 163

Table A.3. Distribution of geometric means of flavonoid intake for cases and controls of the LIBCSP 164

Table A.4. Foods and beverages included in each flavonoid class, listed according to flavonoid content (highest to lowest) 165

Table A.5. Cases total flavonoid intake and class intake per day (in mg) by ER/PR status 168

Table A.6. Controls total flavonoid intake and class intake per day (in mg) by ER/PR status 169

Table A.7. Case and control distribution for each quintiled flavonoid exposure stratified by menopausal status 170

Table A.8. A summary of the preliminary evaluation of confounding and effect modification of flavonoids and breast cancer incidence by selected covariates 172

Table A.9. Age and energy-adjusted ORs and 95% CIs for the association between menopausal-specific flavonoid intake in relation to breast cancer incidence 173

Table A.10. Age and energy-adjusted ORs and 95% CI for the association between flavonoid intake and breast cancer incidence among post-menopausal women, stratified by ER/PR status 175

Table A.11. Age, fruit, fruit juice, vegetable, antioxidant, and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to breast cancer incidence 177

Table A.12. Age and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) stratified by ER/PR status for the association between flavonoid intake and breast cancer incidence among post-menopausal women 179

Table A.13. Age and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between flavonoid intake and breast cancer incidence among post-menopausal women, stratified by ER/PR 181

Table A.14. Number and percentage of eligible invasive breast cancer cases for each categorical characteristic included in the LIBCSP follow-up study 183

Table A.15. Number and percentage of invasive breast cancer cases for each

categorical characteristic included in the LIBCSP follow-up study.....184

Table A.16. Invasive case distribution for each quintile of flavonoid exposure stratified by menopausal status.....185

Table A.17. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996-1997.....187

Table A.18. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to breast cancer-specific mortality.....189

Table A.19. A summary of the preliminary evaluation of confounding and effect modification of flavonoids and breast cancer survival by selected covariates.....191

Table A.20. Age, fruit, fruit juice, vegetable, antioxidant, and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality.....192

Table A.21. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by ER/PR status for the association between flavonoid intake in relation to all-cause mortality.....194

Table A.22. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by ER/PR status for the association between flavonoid intake in relation to breast cancer-specific mortality.....196

Table A.23. Age, fiber, and energy-adjusted ORs and 95% CIs for the association between menopausal-specific flavonoid intake in relation to breast cancer incidence.....198

Table A.24. Age, fiber, and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996-1997.....200

Table A.25. Age, co-morbidity, and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996-1997.....202

LIST OF FIGURES

Figure 1.1. Reproductive risk factors proposed mechanism behind breast cancer 54

Figure 2.1. Proposed DAG of potential confounders to the association between flavonoid intake and breast cancer incidence 55

Figure A.1. Flavonoids ability to reduce breast cancer through the estrogen pathway 204

Figure A.2. Flavonoids ability to reduce breast cancer through the oxidative stress pathway 205

LIST OF ABBREVIATIONS

ABCFS	Australian Breast Cancer Family Study
ACS	American Cancer Society
ADH	alcohol dehydrogenase
ALSWH	Australian Longitudinal Study on Women's Health
ARS	Agricultural Research Service
BBD	benign breast disease
BCT	breast conservation therapy
BHNRC	Beltsville Human Nutrition Research Center
BMI	body mass index
BRCA1	breast cancer 1
BRCA2	breast cancer 2
CFR	case-fatality rate
CGHFBC	Collaborative Group on Hormonal Factors in Breast Cancer
CI	confidence interval
COX	cyclooxygenase
CPS	Cancer Prevention Study
CSFII	Continuing Survey of Food Intakes by Individuals
CTS	California Teachers Study
DFS	disease-free survival
DNA	deoxyribonucleic acid
EC	epicatechin
ECG	epicatechin gallate

EGC	epigallocatechin
EGCG	epigallocatechin gallate
EPIC	European Investigation into Cancer and Nutrition
ER	estrogen receptor
FCL	Food Composition Laboratory
FDA	Food and Drug Administration
FFQ	food frequency questionnaire
FSH	follicular stimulating hormone
G	grams
HCFA	Health Care Finance Administration
HDCT	high-dose chemotherapy
HPLC	high-performance liquid chromatography
HR	hazard ratio
HRT	hormone replacement therapy
ID	identification
INOS	inducible nitric oxide synthase
Kg	kilograms
LH	luteinizing hormone
LIBCSP	Long Island Breast Cancer Study Project
LRT	likelihood ratio test
M	meters
N	sample size
NBSS	National Breast Screening Study

NCHS	National Center for Health Statistics
NDI	National Death Index
NDL	Nutrient Data Laboratory
NHANES II	Second National Health and Nutrition Examination Survey
NSAID	non-steroidal anti-inflammatory drug
OC	oral contraceptives
OR	odds ratio
OS	overall survival
PAH	polycyclic aromatic hydrocarbon
PBI	Pension Benefit Information Company
PCB	polychlorinated biphenyls
PR	progesterone receptor
RDD	random digit dialing
RIA	radioimmunoassay
ROS	reactive oxygen species
RR	risk ratio
SAS	Statistical Analysis Software
SEER	Surveillance, Epidemiology, and End Results Program
SES	socio-economic status
SHBG	steroid hormone binding globulin
SSA	Social Security Administration
US	United States
USDA	United States Department of Agriculture

VEGF	vascular endothelial growth factor
WHR	waist-to-hip ratio
XO	xanthine oxidase

CHAPTER I: BACKGROUND AND INTRODUCTION

Overview of Study Background, Specific Aims, and Hypotheses

In 2005, an estimated 211,240 new cases of invasive breast cancer were diagnosed and 40,110 deaths among American women were attributable to breast cancer (1). Migration studies and variation of international incidence and mortality rates suggest breast cancer is affected by lifestyle and environmental factors (2).

Analytic epidemiology studies have identified many reproductive and lifestyle factors that modestly influence breast cancer risk, and may influence survival. The generally accepted reproductive risk factors for breast cancer development, such as the timing of menarche, age at first birth, and menopause, strongly implicate ovarian hormones, particularly the estrogens, in breast cancer development (3).

In terms of breast cancer survival, many of the related clinical and non-clinical factors may also work through an estrogen pathway. Poor prognosis is associated with large tumor size, axillary node involvement, stage at diagnosis, and estrogen receptor negative and progesterone receptor negative tumors (4-9). Also influential on the time between diagnosis and mortality are the treatment undergone, including surgery, radiation, chemotherapy, and hormone therapy (9).

Of the non-clinical factors, obesity at the time of breast cancer diagnosis has been the most frequently recognized determinant of breast cancer survival among both pre-menopausal and post-menopausal women (10-30). If obesity affects prognosis, so may other non-clinical factors. Some follow-up studies have suggested that increased consumption of fruits and

vegetables may enhance breast cancer prognosis (31-33), and thus estrogen and oxidative stress pathways may be involved.

The effects of dietary practices on breast cancer have garnered a great deal of focus, particularly fruit and vegetable consumption. While fruits and vegetables appear to reduce the risk of breast cancer incidence, the exact components driving this effect are unknown (34-36). A common counterargument to their potential benefit is that people who eat plenty of fruits and vegetables tend to eat healthier overall diets and are less likely to smoke cigarettes, consume alcohol, and live a sedentary lifestyle (37). Yet, certain components of fruits and vegetables are suspected to prevent various types of cancer (34, 36). Fruits and vegetables are known to contain antioxidants and phytoestrogens, both of which have demonstrated effects on the estrogen pathway (38-42) and oxidative stress pathway (43-47). A previous analysis of case-control data from the Long Island Breast Cancer Study Project (LIBCSP) found that increased intake of fruits and vegetables was associated with a decreased risk of breast cancer (48). This association remained even after adjustment for several, conventionally-evaluated antioxidants under study as well as supplement use, suggesting there may be additional chemopreventive agents involved, such as flavonoids (48). Flavonoids are polyphenolic compounds that occur naturally in foods and beverages of plant origin including fruits, vegetables, chocolate, tea, and wine, and are hypothesized to be associated with a lower risk of breast cancer and improved prognosis (49).

It is suspected that flavonoids may operate through an estrogen pathway and oxidative stress pathway, the same pathways that many risk factors for breast cancer operate (38-47). For example, some flavonoids have demonstrated an ability to inhibit aromatase, a cytochrome p450 enzyme that synthesizes endogenous estradiol (50-53). Flavonoids may

therefore reduce estradiol's growth stimulatory effects in breast cancer cells (49). Additionally, some flavonoids have demonstrated the ability to inhibit tumor cell proliferation through enzyme inhibition (54, 55). This may reduce the amount of reactive oxygen species (ROS), which are also believed to be catalysts of tumor promotion and progression of cancer (56-58). Thus, there is a sound biologic rationale for studying flavonoids in relation to breast cancer risk and survival.

Using the USDA Database for the Flavonoid Content of Selected Foods and the modified Block food frequency questionnaire (FFQ) from the LIBCSP, the proposed study will be the first to examine whether flavonoids affect survival, and among the first to look at flavonoids in relation to breast cancer incidence. In the two recently published studies using this database (59, 60), researchers assessed breast cancer incidence in a Greek population (59) and an Italian population (60), both with a high and wide range of intake of fruits and vegetables that provided enough heterogeneity to determine if there were beneficial effects. A decreased risk of breast cancer was found with increased intake of flavones, a class of flavonoids, in both populations (59, 60). In the Italian study, a decreased risk of breast cancer was also found for flavonols (60). However, there have been no published studies using this database on American populations.

The overall aim of the proposal was to evaluate the relationship between dietary intake of flavonoids and breast cancer risk and survival. This project attempted to shed light on this area by examining specific dietary factors, in particular, flavonoids, assessed at breast cancer diagnosis and their associations with breast cancer incidence and survival. To test this hypothesis, data from the case-control (N = 1,508 cases and 1,556 controls) and follow-up study (N = 1,273 invasive cases) of the LIBCSP were utilized.

This study improved upon previous research by assessing intakes of flavonoids in a U.S. population and their association with breast cancer. With the use of the USDA Database for the Flavonoid Content of Selected Foods and the USDA - Iowa State University Isoflavones Database, primarily, we can study all foods contained in the database which are also included in the modified Block FFQ used in the LIBCSP. Flavonoid intake for seven classes of flavonoids that comprise a total of 30 individual flavonoids were estimated.

Specific Aims and Hypotheses

The specific aims of the proposed research are as follows.

Aim 1. To estimate intake of seven classes of flavonoids and total flavonoid intake among breast cancer cases and controls using the USDA Database for the Flavonoid Content of Selected Foods, the USDA - Iowa State University Isoflavones Database, additional literature sources, and the LIBCSP dietary data.

Aim 2. To examine the association among dietary intake of flavonoids and risk of breast cancer. This will test the hypothesis that there is an inverse association between flavonoid intake and risk of breast cancer.

Aim 3. To examine the association among dietary intake of flavonoids and survival with breast cancer. This will test the hypothesis of an inverse association between flavonoid intake and mortality following diagnosis with breast cancer.

Epidemiology of Breast Cancer Incidence

Introduction

Breast cancer is the most common incident cancer among women except for non-melanoma skin cancers (61). It is the second leading cause of cancer death in women, exceeded only by lung cancer (61). Currently, there are over 2 million women living in the United States who have been diagnosed and treated for breast cancer (61). Death rates from breast cancer among American women are declining due to earlier detection and improved treatment while incidence rates have begun to plateau in women age 50 and older (61).

In rural Asian areas, this disease is relatively uncommon (62). Some researchers, based on data from previous ecologic studies, have attributed this international heterogeneity in risk to the higher consumption of fruits, vegetables, and soy products in Asian countries (63). Migration studies and variation of international incidence rates suggest breast cancer is affected by lifestyle and environmental factors (64).

Breast cancer incidence rates have historically been 4 to 7 times higher in the U.S. than in China or Japan, but the reasons for this are not entirely clear (65). In 1980, the breast cancer incidence rate for white women in the U.S. was 2.5 to 4 times that of women living in China, Japan, or the Phillipines (66). The variation in risk is not due to underlying genetic differences because the rates of breast cancer in Asian-American women shift substantially toward those of white U.S. women within a few generations after migration (67).

A case-control study of breast cancer by Ziegler and colleagues (65) among women of Chinese, Japanese, and Filipino ethnicities, aged 20-55 years, was conducted in parts of California and Hawaii. A six-fold gradient in breast cancer risk by migration patterns was observed. Asian-American women born in the West had a breast cancer risk 60% higher than Asian-American women born in the East (65). Migrants who had lived in the West for a decade or longer had a risk 80% higher than more recent migrants (65). Furthermore, the

age-standardized incidence rates of breast cancer for Asian-Americans living in the U.S. (53.7 per 100,000 person-years in Chinese women, 69.0 per 100,000 person-years in Japanese women) were intermediate to the incidence rates of Asians (27.5 per 100,000 person-years in China; 28.9 per 100,000 person-years in Japan; and 45.7 per 100,000 person-years in Phillipines) and U.S. whites in California and Hawaii (91.8 per 100,000 person-years) (65).

Similarly, using Surveillance, Epidemiology, and End Results (SEER) data, Stanford and colleagues studied breast cancer incidence in Asian residents of three U.S. geographic areas (68). The rates in Asian-American women born in China or Japan and in their U.S.-born counterparts were approximately 50% and 75% (73 per 100,000 person-years in Asian born women; 117 per 100,000 person-years in U.S. born Asians) that of U.S.-born whites (159 per 100,000 person-years), respectively (68). This difference in rates between U.S. and Asia-born women was present at all ages (68). Compared with Chinese women living in the mainland, Singapore, and Hong Kong, Asian-born Chinese women living in the U.S. had a higher annual rate of breast cancer (47 per 100,000 person-years compared to 20-30 per 100,000 person-years) and U.S.-born Chinese women had an even higher rate than this (59 per 100,000 person-years) (68). These results may help to explain those of Pineda and colleagues (69) who, also using SEER data, found that Japanese women had better overall survival (24.8% deaths from all causes) and better survival after breast cancer diagnosis (14.8% deaths from breast cancer) than all other races, including Chinese, Filipino, U.S.-born Asian Americans, and Caucasians (39.1% deaths from all causes and 20.1% deaths from breast cancer) (69).

Additional studies of Asians and Asian migrants have had comparable findings with regard to breast cancer risk. Chie and colleagues (70) calculated and compared age-specific and age-adjusted incidence rates and mortality rates of breast cancer patients from Taiwan to other cities and states in Asia and the U.S. The lowest incidence rates of breast cancer among Chinese women were found in Taipei, Tianjin, and Shanghai while the highest rates were found in Los Angeles and Hawaii (70). They concluded that lifestyle characteristics, especially the Westernization of dietary patterns may be the most important factors (70).

A study by Wu and colleagues (71) assessed breast cancer risks in relation to reproductive and menstrual histories in migrant and U.S.-born Asian Americans. Using the same population as Ziegler (65), it was found that there were differences between each group (71). U.S.-born Asian Americans had an average age at menarche of 12.2 years, 1.4 years earlier than Asian women who migrated to the U.S. (71). A slightly higher proportion of Asian American women breastfed compared with U.S. whites and the duration was longer in Asian migrants compared to U.S. whites (71). However, the effects of these reproductive and menstrual factors were small and the ORs for migration variables changed only slightly after adjustment for these factors, suggesting the lower rates of breast cancer in Asians are primarily a result of environmental and lifestyle factors (71).

This wealth of research emphasizes the disparities between Asian, Asian-American, and American women with respect to reproductive, lifestyle, and environmental factors and subsequent breast cancer risk. Since Americans tend to consume less flavonoid-rich fruits, vegetables, and soy products compared to Asians and Asian-Americans (72), it is possible that compounds in these products which have known biologic activity may decrease breast cancer risk and improve survival after diagnosis. The lifestyle and environmental disparities

support the study of factors that may contribute to these differences, including dietary flavonoid intake.

Despite all of the previous research, only a few modifiable risk factors have been identified with which to make public health recommendations to reduce the risk of breast cancer. Well-established risk factors include few or no pregnancies, oral contraceptive use, hormone replacement therapy (HRT), little or no breastfeeding, early age at menarche, late onset of menopause, late age at first birth, age, family history of a first-degree relative, high endogenous estrogen levels in serum, history of benign breast disease (BBD), lack of physical activity, high body mass index (BMI) in post-menopausal women, high socioeconomic status (SES), ionizing radiation, and alcohol consumption (64, 73) (Table 1.1).

Possible relationships have been found with cigarette smoking, fat consumption, use of non-steroidal anti-inflammatory drugs (NSAIDs), and fruit and vegetable consumption (73). Elucidating the pathways in which potential protective compounds reduce breast cancer risk may clarify prior conflicting or weak study results.

The following pages address the epidemiologic rationale and biologic basis of the aforementioned risk factors for breast cancer incidence. Consideration of whether flavonoids affect breast cancer risk and survival would be strengthened if it is consistent with our current understanding of the descriptive and analytic epidemiology of breast cancer (Figure 1.1).

Reproductive Risk Factors

The reproductive risk factors have long been implicated in breast cancer incidence. These factors appear to act through their effects on endogenous estrogen levels. Because of flavonoids' reported effects on the estrogen pathway, which will be described in more detail later, the impact of these risk factors must be assessed in the proposed analysis.

Pregnancy

Pregnancy has been found to induce transient and permanent structural changes in breast tissue in laboratory animals (74). Transiently, the hormonal influence of pregnancy may enhance the progression of cells that may have already started to undergo malignant transformation, and in the long term, it may cause stem cells to differentiate and become less susceptible to carcinogenesis (74). The increased estrogen levels that occur in each full-term pregnancy may promote the growth of cells that have already undergone malignant transformation, resulting in an initial increase in breast cancer risk (75).

There is evidence of a transient increase in breast cancer risk after giving birth: some investigators have found an association between shorter interval since last birth and a higher risk of breast cancer (76, 77); others have found that uniparous women were at higher risk than nulliparous women in the period immediately after delivery (78, 79). However, this risk dissipates and eventually reduces the lifetime risk of breast cancer because of the differentiation of additional breast cells with each pregnancy (75). Liu and colleagues (80) investigated time-points when the elevated postpartum maternal breast cancer risk peaks. After conducting a nested case-control study within the Swedish Fertility Register, the researchers discovered that uniparous women had an increased risk of breast cancer compared to nulliparous women and that this risk peaked five years following delivery (OR =

1.49, 95% CI: 1.01-2.20) (80). The biparous women had lower levels of estrogens in their second pregnancy compared to their first pregnancies (80). The differentiation of mammary cells induced by the first delivery may have lowered the short-term adverse effects of the second childbirth (80).

Over a lifetime, nulliparous women are at an increased risk for breast cancer in comparison with parous women (81). In studies of white women, higher parity confers a reduced risk of breast cancer for women ages 35 and older (81). In a study comparing the risk in U.S. women at all ages (82), the odds ratio (OR) for breast cancer in white women ages 35 to 49 ranged from 0.75 to 0.30 for number of full-term pregnancies ranging from 1 to 5+ (82).

Number of pregnancies have also been recognized as reducing the risk of breast cancer (81). A case-control study of Caucasian and African-American women found that both races of women had a decreased risk of breast cancer per full-term pregnancy (13% among women ages 35-49 years and 10% in women ages 50-64 years in Caucasians, 10% among women ages 35-49 years and 6% in women ages 50-64 years in African-Americans) (82). Compared with women who had never had a full-term pregnancy, women who had experienced at least one pregnancy had an estimated 20-24% reduction in breast cancer risk (82).

Oral Contraceptive Use

Oral contraceptives (OCs) were first introduced in 1960 and have since been used by an estimated 200 million women (83). In 1992, the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) was formed to reanalyze available worldwide studies. They conducted a meta-analysis of 54 studies and found that current OC users were at an increased

risk of breast cancer compared to never users (RR = 1.24, p-value = 0.00001) (84). The risk estimate was only slightly attenuated for women who had stopped using OCs one to four years before diagnosis (RR = 1.16, p-value = 0.0001) (84). Overall, there was a small increase in risk up to ten years from cessation of use (84).

The Women's Lifestyle and Health Cohort Study, conducted in Norway and Sweden, also examined this association (85). 103,027 women provided information on contraceptive use and 1,008 primary breast cancers were diagnosed through 1999 (85). An increased risk of breast cancer was observed among current/recent OC users RR = 1.6 (95% CI: 1.2, 2.1) (85). This result was similar for current/recent users of combined OCs (RR = 1.6 (95% CI: 1.0, 2.0) and progestin-only pills (RR = 1.6 (95% CI: 1.0, 2.4) (85).

The theorized mechanism ("Estrogen Augmented by Progestogen Hypothesis") behind combined OC use and breast cancer risk is that the combination of hormones induces more cell divisions than estrogen alone (86). If there are adverse effects of OCs, these may appear in younger women whose risk may increase soon after exposure to exogenous hormones containing estrogen and progestin (87). Concurrent with this information is a finding that OC use before age 30 was associated with increased post-menopausal breast cancer among women with the NAD(P)H Quinone Oxoreductase (NQ01) genotype, suggesting that the association may include products of estradiol and estrone metabolism (88). This hypothesis predicts that estrogen replacement therapy will increase breast cancer risk, and that the addition of a progestogen will increase risk further (86).

Hormone Replacement Therapy (HRT)

For HRT, the most prominent concern on the part of health professionals and post-menopausal women remains the possibility that HRT, especially if used for a long period of time, may contribute to the development of breast cancer (89). Epidemiologic studies have reported an increased risk of breast cancer with HRT use for many years, with conjugated estrogens (90, 91) or estradiol compounds (92, 93) whereas others have failed to show any alteration of risk (94, 95).

Current use of HRT is associated with an increased risk of breast cancer according to three meta-analyses (RRs range from 1.21 to 1.40) (96-98). This risk increased with longer duration of use (96-98). These findings were confirmed by results from the Women's Health Initiative, a randomized clinical trial that indicated the overall health risks of using estrogen and progestin for an average of 5.2 years (HR = 1.26, 95% CI: 1.00, 1.89) (99). In fact, this trial was stopped because the test statistics indicated the risks, mainly for cardiovascular disease, were too great compared to the benefits of the hormone use (99).

Along this line of evidence, a 1997 meta-analysis of 51 studies found that breast cancer risk increases by 2.3% with each additional year of HRT use (100). Since 1997, several case-control studies (101-105) and cohort studies (106-108) have assessed estrogen plus progestin regimens and all but one study (105) suggested an increased risk of breast cancer.

Estrogens strongly influence the growth of breast tissue (86, 109). Estrogen receptors (ER) in breast tissue, which are well-known as prognostic indicators, provide further reasons to suspect the effects of using exogenous estrogens such as HRT (109). The estrogen augmented by progestogen hypothesis predicts that HRT will increase breast cancer risk and that the addition of a progestogen will increase risk further (86). Breast cancer incidence increases about 2.1% per year of age in the post-menopausal period (86). This rise can be

attributed solely to endogenous estrogens (110, 111), so the breast cancer risk associated with HRT can be predicted by serum estrogen levels to the serum estrogen levels achieved during HRT (86).

Breastfeeding

In a review by Willett and colleagues of 32 published studies (112), 16 of the studies showed a statistically significant reduction in risk with longer duration of breast feeding. Meta-analyses such as the one from the Collaborative Group on Hormonal Factors in Breast Cancer (100) support the reduction in breast cancer risk by breastfeeding, 4.3% with every 12 months of having breastfed. A study by Ursin and colleagues (82) noted a 5% reduction for every 12 months of having breastfed. Another meta-analysis (113) indicated the risk of breast cancer was decreased for ever-breastfeeding women compared to never-breastfeeding women (OR = 0.90, 95% CI 0.86-0.94). The decrease in risk continued as duration of breastfeeding increased, as the risk for those having breastfed at least 12 months was OR = 0.75 (95% CI: 0.71-0.81) (113). Similarly, a recent study of breastfeeding and breast cancer was conducted in Connecticut with women ages 30 to 80 years (114). Parous women who reported ever lactation had a slightly reduced risk of breast cancer (OR = 0.83, 95% CI: 0.63-1.09) (114). For women who breastfed more than three children compared to those who never lactated, their OR = 0.53 (95% CI: 0.27-1.04) (114). Women who breastfed their child for more than 13 months had an OR of 0.47 (95% CI: 0.23-0.94) (114).

While the mechanisms associated with the beneficial effects of lactation have not been completely elucidated, several have been proposed (82, 114). Lactation may protect against breast cancer by postponing the resumption of ovulatory menstrual cycles after a pregnancy

and thus reducing exposure to cyclic hormones (82), by increasing the differentiation of breast tissue (115), by altering estrogen levels in the breast (116), or by allowing excretion of carcinogenic agents such as organochlorines from the breast ductal tissue (114, 117).

Early Age at Menarche

Age at menarche is presumably a risk factor because it marks the beginning of ovarian menstruation and the cyclic flow of reproductive hormones (3). Researchers have found that the risk of breast cancer decreases by 5 to 20% for each year the onset of menarche is delayed (81), (79). A study by Brinton (118) and colleagues found that women with onset of menstruation at or after age 15 years had a 23% lower risk than those with an age at menarche of 12 years or younger. In addition, because recall of age at menarche can be difficult, especially for older women, the strength of the association may be even stronger than reported (81).

The earlier the age at menarche, the earlier a young women experiences increased steroid hormone levels, which presumably means more exposure over a long period of time and this may increase a woman's risk of breast cancer (112). A series of reports on the hormonal patterns of a cohort of Finnish girls followed through puberty and into adulthood indicated that early menarche (before age 12) was associated with significantly higher estradiol levels in the adolescent period and with higher follicular phase estradiol levels in women aged 20-31 years (119, 120).

Related studies have found differences in cycle lengths between breast cancer patients and control patients (121, 122). Women in countries with different breast cancer risk were consistent with menstrual cycle length modulating breast cancer risk (122). A study by

Kumar and colleagues (40) supports the hypothesis that soy consumption may alter circulating ovarian steroid hormone concentrations in pre-menopausal women and increase menstrual cycle length. The average menstrual cycle length of women in Western populations is 26 to 29 days whereas it is longer for Asian populations (123-125).

Late Age at Menopause

The later a woman's age at menopause, the higher her risk of breast cancer (81, 112). For every five-year difference in age at menopause, the risk of breast cancer changes by about 17% (79). On average, risk increases by about 3% per year that menopause is delayed (81). Moolgavkar and colleagues (126) found that menopause at 52 years of age carried a two-fold increased risk of breast cancer over menopause at 42 years of age. This corresponds to a 7% increase in risk per year increase of age at menopause (126). Among post-menopausal women, the increased risk associated with late age at menopause is generally not seen until after age 65, suggesting that the effect of age at menopause is not seen for 10 to 20 years after menopause (127).

Similar to many of the other risk factors, including early age at menarche, it is suggested that the longer the exposure to sex hormones during the reproductive years, the higher the risk of breast cancer (128). Thus, the reduction in risk associated with an earlier menopause is likely due to the cessation of ovarian function and the resultant reduction in circulating hormone levels (112).

Late Age at First Birth

Late first full-term pregnancy is generally accepted as a major breast cancer risk factor (86). MacMahon and colleagues (129), in their international case-control study, found that women who had their first full-term pregnancy under age 20 had approximately one-half the risk of breast cancer as nulliparous women. However, nulliparous women did not have as a high a risk as women with a first full-term pregnancy after age 35 (129). This is concurrent with findings from other studies indicating women who give birth to their first child after age 30 have a higher risk of breast cancer compared to nulliparous women (130-132).

When the first birth occurs at an early age, fewer cells are likely to have been initiated and the period of protection, afforded by terminal differentiation of the breast glandular epithelium, covers a longer period of the woman's remaining lifetime (112). Further explanation for the increased risk includes a full-term pregnancy at an early age may reduce the likelihood of tumor initiation while a full-term pregnancy at a later age may promote the growth of existing tumor cells (129).

Demographic Risk Factors

Increasing Age

Breast cancer incidence continues to increase with age, however, there is a distinct slowing of the rate of increase around age 50, which is approximately the average age at menopause (86). Incidence continues to climb after age 50, but the slope is less steep (86). However, comparing older women to younger women, breast cancer incidence rates are considerably higher for older women (133). For example, the incidence rate for breast cancer calculated from SEER data for 1987 to 1991 was 25.6 cases per 100,000 person-years for women ages

30-34 years (133). However, for women ages 70 to 74 years, the incidence rate was 450.3 cases per 100,000 person-years (133).

Socioeconomic Status (SES) and Race

Breast cancer incidence rates generally have been found to increase as SES increases (134, 135). A cross-sectional study using breast cancer information for 37,921 cases diagnosed in New York City from 1986-1995 was conducted by Merkin and colleagues (136) to assess the association between a residential area's SES, race, and advanced stage breast cancer. After adjusting for age and year at diagnosis, living in areas with lower levels of education and income increased the odds of presenting with advanced stage breast cancer by 50% for African-American women and 75% for white women (136). This is corroborated by findings from Schwartz and colleagues (137) that African-Americans are more likely than Caucasians to be diagnosed at an advanced stage of breast cancer. This difference has been attributed to underutilization of screening services (138, 139) as well as living in socioeconomically disadvantaged neighborhoods (140-142).

Other risk factors such as nulliparity, late age at first birth, and late age at menopause (143-148) may be partially responsible for any increase in breast cancer risk because these characteristics are more prevalent among women of higher SES. According to Gordon (149), SES factors have been associated with additional risk factors for breast cancer such as diet, lifestyle factors, physical characteristics, and tumor characteristics.

Medical Risk Factors

Family History of Breast Cancer

In general, a family history of breast cancer in a first-degree relative has been associated with a two- to three-fold increase in risk of invasive breast cancer (150). A relative risk of 1.5 to 3.0 has generally been found when women whose mother or sister had breast cancer are compared to those whose first-degree female relatives did not have breast cancer (151). A meta-analysis found that individuals with a positive family history of breast cancer incidence had a RR of 2.1 (95% CI: 2.0-2.2) for breast cancer incidence (152, 153). The prevalence of a family history of breast cancer has been estimated to range from 5% to 22% (154-157) but much of the variation is due to methodology and the study population. Some studies included distant relatives whereas others used first-degree relatives in defining positive family history (153).

It is estimated that 5% to 10% of all breast cancers can be attributed to highly penetrant germline mutations (158). The well-known BRCA1 and BRCA2 genes were identified in the 1990s and have since been discovered to be responsible for 2% to 5% of all breast cancers (112). These mutations, while rare in the general population, may be responsible for the early onset of breast cancer for high-risk breast cancer families (159, 160). Up to age 40, women with BRCA1 are estimated to have a 20-fold greater risk of breast cancer compared to the general population and to have a lifetime risk of breast cancer of 60% to 85% (161).

Endogenous Estrogen Levels

There is substantial experimental, epidemiologic, and clinical evidence that breast cancer risk is influenced by endogenous hormones (3). According to Key (162), the evidence of ovarian hormones playing a role in breast cancer development is strong. Estrogens modulate gene expression in breast cells through interaction with nuclear proteins (receptors) (163).

Estrogen and progesterone aid in maintaining breast cancer growths through paracrine and autocrine signaling (163).

After menopause, adipose tissue is the major source of estrogen production (112), (164, 165). This is a suspected reason why obese, post-menopausal women have both higher levels of estrogen and a higher risk of breast cancer than do non-obese, post-menopausal women (112). Estradiol, which is considered to be the most biologically active endogenous estrogen, circulates free in the blood or bound to sex hormone-binding globulin (SHBG) or albumin (112). Free estradiol is thought to be available to breast tissue and possibly more related to breast cancer risk than total estradiol (112). Post-menopausally, estrone is the most abundant circulating estrogen (3, 166). Estrone and estrone sulfate may be sources of intracellular estradiol (3, 112). In post-menopausal women, there is a positive association between total estradiol and breast cancer risk (112).

In a meta-analysis of six prospective studies, breast cancer cases had mean estradiol levels 15% higher than those of healthy controls (167). Additional studies published since this meta-analysis found a positive association between plasma estradiol and the risk of cancer when comparing the top to bottom quartile (RR = 1.9) (168). Among women with no prior use of post-menopausal hormone therapy, the association was even stronger (RR = 3.8) (168). Endogenous estrogen levels are affected by both genetic and lifestyle factors (169).

Estrogen Receptor (ER) / Progesterone Receptor (PR) Status

Whereas ER and PR have a well-established role in assessing the prognosis of breast cancer (as discussed below), their role in breast cancer etiology remains unclear (170-173). There is evidence that several risk factors related to hormones, including age at menarche,

parity, BMI, waist-hip ratio, and age at first live birth have been associated with ER+PR+ breast cancer, but not ER+PR- or ER-PR- breast cancers (172). Giuffrida and colleagues (174) reported that breast cancer patients with a higher BMI, compared to those with a lower BMI, were more likely to have ER+PR+ tumors. Similar to this, dietary fat intake has been positively associated with ER+PR+ breast cancer (173).

The only established risk factor known to be consistently associated with hormone receptor type is age (175). For example, Yasui and colleagues (171) estimated age-specific incidence rates stratified by ER/PR status and found that all four receptor types (ER+PR+, ER+PR-, ER-PR+, ER-PR-) showed increasing risk with age, but only ER+ tumors were the only subtype to increase with age among Western women.

Benign Breast Disease (BBD)

Benign breast disease (BBD) comprises a wide-spectrum of conditions whose pathology ranges from minor deviations of normal features to gross atypia falling short of malignancy (176). A number of benign breast conditions have been evaluated in terms of their influence on subsequent breast cancer risk (177). Results have been inconsistent and part of this problem may be due to an inconsistent definition of benign disease and the failure to consider different types of conditions as separate entities, given that not all confer an increased risk of breast cancer (178). Recent studies have indicated that BBD increases the risk of breast cancer (179-182) but this risk varies by histopathological types (183).

Minami and colleagues (183) used a retrospective cohort design to investigate the risk of breast cancer development in Japanese women who were participants in a breast cancer screening program. An elevated risk of breast cancer was observed in all women with BBD (RR = 3.26, 95% CI: 1.08-9.93) (183). Women with proliferative BBD were at high risk for

breast cancer (RR = 8.48, 95% CI: 2.99-24.10), but no risk was observed for women with non-proliferative BBD (RR = 0.93, 95% CI: 0.11-7.66) (183). It should be noted, however, that only 11 of the 1,876 women developed breast cancer during the follow-up period and this small number may be a key reason for such imprecise confidence intervals. According to the authors, however, the results are consistent with those in high-risk countries for breast cancer (183).

Another study of histologic type of BBD and breast cancer was conducted among 2,731 women in the San Francisco Bay Area (184). The women were followed for an average of 16 years after their first occurrence of biopsy-proven BBD between 1948 and 1973 (184). The cohort's age-adjusted rate of breast cancer was 1.8 times that of the general population (RR = 1.8, 95% CI: 1.6-2.2) (184). Among the different histologic types of BBD, rates were greatest for intraductal papilloma (RR = 3.9, 95% CI: 2.0-7.4) and adenosis (RR = 2.5, 95% CI: 1.2-4.9) (184). Rates were also elevated for fibrocystic BBD (RR = 1.5, 95% CI: 1.1-1.9) (184).

The most common types of cancer chiefly occur within an organism's most rapidly growing and least-differentiated tissues (185, 186), presumably because DNA is most vulnerable to initiation during periods of mitotic growth (186, 187). In the breast, the rate of DNA synthesis is greatest in the epithelial cells that line the terminal ducts; the rate is intermediate in the larger ducts and is lowest in the alveoli (188-191). Additionally, over 90% of breast carcinomas are thought to arise within the terminal ducts (192, 193). In the study by Krieger and colleagues (184), the greatest risk of breast cancer was detected among types of BBD that chiefly involved ductal epithelial tissue.

Environmental and Lifestyle Risk Factors

Post-menopausal Obesity and Weight Gain

A recent meta-analysis estimated a 3% increase in post-menopausal breast cancer risk per 1 kg/m^2 increase in BMI (194). Additionally, the meta-analysis conducted by the Breast Cancer Collaborative Group, which included eight cohort studies of post-menopausal women, concurred with previous research indicating an increase in breast cancer risk with increasing BMI (195).

The association between body mass and breast cancer is modified by menopausal status, with higher weight or BMI at diagnosis associated with a decreased risk in pre-menopausal women and an increased risk in post-menopausal women (196). The European Investigation into Cancer and Nutrition (EPIC) Study was designed to assess relationships between nutrition and cancer. When studying body size and breast caner risk, post-menopausal women not taking exogenous hormones had a higher risk of breast cancer due to obesity (RR = 1.36, 95% CI: 1.06-1.75 for BMI $\geq$ 28.8 kg/m^2) (196). The relative risk and corresponding confidence intervals were nearly identical for women with a BMI in the 23.6 to 25.6 kg/m^2 range (RR = 1.35, 95% CI: 1.06-1.73) and the 25.7 to 28.7 kg/m^2 range (RR = 1.38, 95% CI: 1.08-1.76) (196). Among pre-menopausal women, however, BMI was inversely associated with breast cancer risk (RR = 0.82, 95% CI: 0.59-1.14) (196). The authors concluded that general obesity had a much stronger association with post-menopausal breast cancer risk than waist circumference or waist-to-hip ratio (WHR) (196).

Weiderpass and colleagues (197) used data from the aforementioned Women's Lifestyle and Health Cohort and found that being overweight and obese (BMI > 25kg/m^2) at enrollment was associated with a decreased risk of breast cancer in pre-menopausal women

(RR = 0.66, 95% CI: 0.40-1.07). In post-menopausal women, as stated previously, circulating estrogens are mainly derived from extraglandular aromatization of plasma androstendione to estrone in adipose tissue (198). Thus, estrogen production is correlated with body weight and obesity is associated with proportions of estrogens in circulation (198). Additionally, being overweight decreases women's levels of SHBG and increases bioavailable estrogen, which increases the risk of breast cancer (112).

Some studies which have examined both adult weight gain and adult BMI in the same study population have found weight gain to be an equivalent (199, 200) or stronger predictor (164, 201-203) of post-menopausal breast cancer risk than BMI (198). Total adult weight gain has strongly predicted breast cancer risk among former and never users of HRT (198). In the Cancer Prevention Study (CPS) II Nutrition Cohort, total adult weight gain was associated with breast cancer incidence in post-menopausal women who were not taking HRT, as a weight gain of 21-30 pounds had a rate ratio (RR) = 1.4 (95% CI: 1.1-1.8) (198). After accounting for weight gain, neither recent BMI or BMI at age 18 years predicted breast cancer risk (198).

Alcohol Consumption

Although all studies do not report an association between alcohol consumption and breast cancer risk (204), there is accumulated evidence for a positive association from both cohort and cross-sectional studies (205-208). The 1994 meta-analysis by Longnecker and colleagues (206) noted that overall, women who consumed two drinks per day experienced a 20% increase in risk compared to non-drinkers and those consuming more than two drinks per day had a 40% increase in risk. The Smith-Warner pooled analysis of cohort studies

(207) found the relative risk for each 10-gram increase in alcohol intake, compared to non-use, was 1.09; women who consumed 30-60 grams per day had a 41% higher risk of invasive breast cancer.

Alcohol is proposed to be involved through its ability to increase circulating hormone levels in pre- and post-menopausal women, a direct carcinogenic effect of alcohol metabolites such as acetaldehyde and an antagonistic effect on folate absorption and metabolism (112, 209-211). Moderate alcohol consumption increases some biomarkers of oxidative stress in post-menopausal women. Alcohol also influences breast cancer by altering absorption and metabolism of protective antioxidants and increasing oxidative stress (212).

Hartman's work with the Women's Alcohol Study in post-menopausal women involved evaluating moderate alcohol consumption on potential risk factors for breast cancer and alcohol's effect on antioxidants and other indicators of oxidative stress (212). When post-menopausal women consumed 30 grams per day during an 8-week period, there was a 5% increase in plasma isoprostane and a 4.6% decrease in plasma α-tocopherol concentration (212). This suggests that chronic consumption of moderate alcohol amounts by post-menopausal women may lead to significant changes in oxidative stress biomarkers (212).

Physical Inactivity

Physical inactivity may be one of the main risk factors for breast cancer that can be modified through lifestyle/behavior change (213). A 2002 review of the literature found that 32 of the 44 studies conducted observed a reduction in breast cancer risk in women who were most physically active (213). On average, this reduction in risk was 30% to 40% (213).

Coogan and colleagues (214) conducted a case-control study to evaluate the effect of occupational physical activity on breast cancer risk and found that women with heavy-activity occupations had a lower risk than women with sedentary jobs (OR = 0.82, 95% CI: 0.63-1.08). This reduced risk was also found in women with jobs requiring medium activity (OR = 0.86, 95% CI: 0.77-0.97) and light activity (OR = 0.92, 95% CI: 0.84-1.01) (214).

Similarly, a case-control study of a Swedish population assessed leisure-time and occupational physical activity and breast cancer risk (215). After adjustment for potential confounders, women in sedentary occupations during their reproductive years (25-44 years of age) had a 50% higher risk for post-menopausal breast cancer (OR = 1.5, 95% CI 1.0-2.2), compared to those with the most physically-demanding jobs (215). Women with a combination of a sedentary job and lack of leisure-time exercise had a three-fold higher risk of breast cancer, compared to the most physically active both inside and outside the workplace (215).

A 2003 publication from John and colleagues (216) described a case-control study of breast cancer in Latinas, African-Americans, and whites ages 35-79 years to assess the association with lifetime histories of moderate and vigorous physical activity, including recreational activity, walking, bicycling, chores, and occupation. Summing these activities over each woman's lifetime, a reduced risk of breast cancer was found in both pre- and post-menopausal women with the highest versus lowest tertile of average lifetime activity (OR = 0.74, 95% CI: 0.52-1.05) (216).

Physical activity in girls can delay both menarche and the onset of regular menstrual cycles (112). These effects reduce the number of ovulatory cycles a woman has in her life, which is an important determinant of breast cancer risk (128). In women, strenuous activity,

such as running, can alter circulating hormone levels and increase the frequency of anovulation (112). Physical activity may also reduce breast cancer risk by preventing weight gain or reducing body fat, which, as stated previously, is the primary source of estrogen production in post-menopausal women (216).

Ionizing Radiation

Ionizing radiation is an established cause of breast cancer in both animals and humans (217, 218). An increased risk has been consistently reported for radiation exposure from various sources, including the atomic bomb explosions in Japan (219, 220). The effect of radiation on breast cancer is greatly dependent on age at exposure (221). Among women under the age of 40 at exposure, a linear increase in breast cancer risk with increasing radiation dose has been consistently reported (221, 222). Relative risks are small for radiation exposure after age 40 years and increase with decreasing age at exposure, with the highest risk for exposure before age 20 years (221-223).

The Life Span Study of a defined population of survivors of the atomic bombing of Hiroshima and Nagasaki demonstrated that radiation dose response corresponds to a linear model and the risk of breast cancer is closely associated with estimated breast tissue dose (224). The age-adjusted excessive relative risk of developing breast cancer per Sv (Sievert, a weighted sum of doses used for different types of radiation such as the mixed gamma and neutron radiation from the atomic bombings (222)) was 1.56 (90% CI: 1.91-1.99) (223). The incidence of breast cancer is 25% lower in Nagasaki than Hiroshima, the former being the city of lower radiation exposure (225).

Cigarette Smoking

Cigarette smoking has been inconsistently associated with breast cancer risk (226, 227). Case-control studies have been more likely to report a positive association while cohort studies have reported little or no relationship between smoking and breast cancer incidence (228, 229). A recent analysis of 53 studies showed no risk of smoking in relation to breast cancer (230). However, inconsistencies may be due to heterogeneity in risk according to timing of exposure, age at diagnosis, or genetic susceptibilities (231, 232), as well as poor recall (233). Additionally, passive smoking was often not accounted for and since it may also be related to breast cancer risk, failing to account for it would dilute risk estimates for active smoking (232).

Reynolds and colleagues (232) examined breast cancer risk and active and passive smoking in the California Teachers Study (CTS) cohort and found that breast cancer incidence was higher in current smokers compared to never smokers (HR = 1.32, 95% CI: 1.10-1.57) and passive smokers (HR = 1.25, 95% CI: 1.02-1.53). This passive smoking finding is consistent with a meta-analysis result of RR = 1.43 (95% CI: 1.10-1.85) (234). Data from the LIBCSP, however, indicate a non-significant effect of passive smoking, active smoking, or joint exposure (OR = 1.15, 95% CI: 0.90-1.48) (233).

Smoking cigarettes generates free radicals, increases lipid peroxidation levels, and is associated with lower blood levels of antioxidants after controlling for dietary intake (212). Free radical derivatives of molecular oxygen (superoxide, hydrogen peroxide, and hydroxyl radical) are generated during normal metabolism and increased following cigarette smoking (235). Cigarette smoking may increase the risk of breast cancer through exposure to known carcinogens, such as benzo[a]pyrene, which is present in tobacco products (112). However,

smoking may decrease the risk of breast cancer through an anti-estrogenic effect by altering hormone metabolism or lowering the age by which women reach menopause (112).

Fat Consumption

Overall, a relationship between fat intake and breast cancer is inconsistent, at best (236). For example, results from a cohort study conducted amongst women in the Nurses Health Study provided no evidence that lower intake of total fat or specific types of fat were associated with a decreased risk of breast cancer (237). A total of 2,956 women were diagnosed with breast cancer over the 14-year follow-up period (237). Women obtaining 30.1% to 35% of their energy from fat, compared to those obtaining 20% or less of their energy from fat, had a RR for breast cancer of 1.15 (95% CI: 0.73-1.80) (237).

The studies which point towards a positive correlation tend to be migration studies comparing Asian populations to Asian-American and American populations (238, 239). Migrants from low-risk countries generally increase their risk after immigrating to higher-risk countries (240), coinciding with data suggesting that these migrants have higher dietary fat patterns (241, 242). International correlation studies conducted with incidence and mortality data from several countries support an association between dietary fat and breast cancer, with correlation coefficients between 0.7 and 0.9 (243-248).

Non-steroidal Anti-inflammatory Drug (NSAID) Use

Use of aspirin and other NSAIDs has been shown to reduce risk of breast cancer in some epidemiologic studies (249-255). Results from cohort studies have been inconsistent as some have found a reduced risk while others have found no association (256). In the Cancer

Prevention Study II Nutrition Cohort, Jacobs and colleagues found that neither current total NSAID use nor current aspirin use were associated with breast cancer incidence, RR = 1.07 (95% CI: 0.96-1.21) for ≥ 60 NSAID pills per month compared with no reported use of NSAIDs. Conversely, data collected from the LIBCSP (249) indicated that ever use of aspirin or other NSAIDs at least once per week for 6 months was associated with a reduced risk of breast cancer, OR = 0.80 (95% CI: 0.66-0.97). It is thought that aspirin may suppress aromatase activity through its inhibition of cyclooxygenase (COX)-derived prostaglandins (249). Thus, frequent use may reduce the amount of circulating estrogen and therefore reduce the risk of breast cancer (249).

Fruit and Vegetable Consumption

Diets rich in fruits and vegetables are frequently recommended for the prevention of cancer. Yet, similar to dietary fat, the relationship of consumption of fruits and vegetables and breast cancer remains unclear (48). A review of 19 case-control studies and 3 cohort studies concluded that elevated fruit and vegetable consumption likely reduces the risk of breast cancer (257). However, a 2001 meta-analysis of eight cohort studies found weak, non-significant associations for total fruits (RR = 0.93, 95% CI: 0.86-1.00), total vegetables (RR = 0.96, 95% CI: 0.89-1.04), and total fruits and vegetables (RR = 0.93, 95% CI: 0.86, 1.00) with breast cancer risk (258). It should be noted that these cohort studies were conducted in Western societies where the intake level of fruits and vegetables is relatively homogeneous, making it difficult to detect an effect (259).

Fruits and vegetables have a wide variety of compounds that have demonstrated potential anticarcinogenic effects in vivo (260). These include carotenes, dithiolthiones, flavoids,

indoles, isothiocyanates, phenols, folic acid, and vitamins C and E (261). The suspected cancer-preventive mechanisms of these compounds include antioxidant effects, carcinogen detoxification, alteration of estrogen metabolism, effects on DNA, and antiproliferative effects (261, 262). Vegetarians or Asian women have higher 2-hydroxyestrone (2HE) / 16-hydroxyestrone (16HE) levels in their urine in response to their low-fat, high-fiber diet (263). A high ratio of 2HE to 16HE may be associated with a decreased risk of breast cancer (263, 264), though not all studies observe an association (265, 266). Low values of this ratio in urine may be an endocrine biomarker for greater breast cancer risk (263).

Malin and colleagues (259) conducted a case-control study of women from the Shanghai Breast Cancer Study and found that the intake of many fruits and vegetables was associated with a decreased risk of breast cancer. Of note in Shanghai, women eat lots of fruits and vegetables but do not use vitamin supplements much, if at all (259). The researchers found no inverse association of carotene and breast cancer risk and concluded it was possible that other phytochemicals may explain the inverse association (259). In fact, a wide variety of flavonoids in citrus fruits may act as antioxidants (43, 44).

Zhang and colleagues examined dietary carotenoid and vitamin intake for incident cases of breast cancer from the Nurses Health Study participants (45). Strong inverse associations were found with alpha and beta carotene, vitamin C, vitamin A, and lutein among pre-menopausal women with a family history of breast cancer (45). Also, pre-menopausal women consuming 5 or more servings of fruits and vegetables per day had a decreased risk of breast cancer (RR = 0.77; 95% CI: 0.58-1.02) (45). They suspected this result may be due to the fact that carotenoids and vitamin C can metabolize reactive oxygen species (ROS) and may decrease DNA damage and genetic mutations. However, they also concluded that fruits

and vegetables contain many other phytochemicals, which include flavonoids, that are protective against cancer in in vitro models. Thus, other constituents in fruits and vegetables may account for the inverse association.

Recently, a case-control study of women from the LIBCSP examined fruit and vegetable consumption in relation to breast cancer risk (48). Among post-menopausal women, vegetable intake (OR = 0.63; 95% CI: 0.46-0.86) and leafy vegetable intake (OR = 0.66; 95% CI: 0.48-0.90) were inversely associated with breast cancer risk, adjusting for age and energy intake (48). Risk was particularly decreased among post-menopausal women with estrogen receptor positive (ER+) breast cancer and progesterone receptor positive (PR+) breast cancer. The proportion of estrogen receptor positive (ER+) breast tumors is reportedly higher among Caucasian than Asian women (112). Breast cancer risk increases when there is over-expression of estrogen receptor in surrounding, normal epithelium (267).

In the LIBCSP, adjusted odds ratios were also uniformly decreased in relation to high intakes of carotenoids, alpha and beta carotene, lutein, and lycopene (48). The inverse association between fruits and vegetables and breast cancer remained after adjustment for the antioxidants and supplement use (48). This, like previous studies' conclusions, this suggests that other constituents in fruits and vegetables may be involved in the prevention of breast cancer incidence.

Flavonoids

Flavonoids are one of the principal groups of phytoestrogens (72). Phytoestrogens are plant-derived, organic, non-steroidal molecules possessing a weak estrogenic or anti-estrogenic activity (72, 268). These have demonstrated inhibitory effects on hormone-related

cancers (49, 63). Flavonoids are a group of more than 4,000 polyphenolic compounds that occur naturally in foods of plant origin (49). Evidence from laboratory studies and epidemiological investigations implicate flavonoids as chemopreventive agents (49, 51-58, 269-277).

Flavonoids appear to act through two distinct pathways, the estrogen pathway (Figure A.1) and the oxidative stress pathway (Figure A.2). The estrogenic activity of various flavonoids has led to many proposed mechanisms by which they may modify breast cancer risk. Because they are similar to estrogen in both structure and function, they modulate steroid hormones (40). Some flavonoids, such as lignans (53, 278), have demonstrated an ability to reduce circulating hormone levels in the body through aromatase inhibition (41, 51, 52). This research has led to the hypothesis that flavonoids compete with estradiol for binding to estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) and thus inhibit cell proliferation and tumorigenesis via gene transcription (269).

Isoflavonoids have been shown to increase serum levels of SHBG, which decreases the amount of bioavailable estrogen by decreasing levels of free estradiol (42), (39, 279-282). The weak estrogenic effect of phytoestrogens can stimulate SHBG production, like tamoxifen can, in the liver (39). Again, this increase in SHBG helps to decrease the ovarian steroid levels in the body. This may be a cancer-preventive mechanism in that flavonoids could potentially counteract negative effects of oral contraceptive use. SHBG and albumin determine the bioavailability of sex steroids to most tissue and the metabolic clearance of the steroids (279-283). Phytoestrogens can convert endogenous estrogens to protective 2-hydroxylated estrogens in women and thus may play a role in decreasing levels of 17α-hyroxyestrone, which is a stimulant of breast proliferation (284-288).

Isoflavones in soy protein, particularly genistein and daidzein, have demonstrated effects similar to that of breastfeeding through an ability to increase the length of the follicular phase and delay menstruation (289, 290). They achieve this by suppressing luteinizing hormone (LH) and follicular stimulating hormone (FSH), which may decrease breast cancer risk (284, 289, 290). A change in menstrual cycle length alters the duration of mammary epithelial cells in the luteal phase of the cycle where breast cells are more proliferative (40) (291).

Some flavonoids have demonstrated an ability to reduce the number of ovulatory cycles and delay menstruation, potentially reducing the risk of breast cancer (40, 289-291). Kumar and colleagues (40) observed an increase in cycle length and follicular cycle length in those who consumed soy supplements and concluded this may shorten the exposure of the breast epithelia to progesterone in the luteal phase. If this occurs over a period of time with consistent soy consumption, then the relative time during which breast epithelia is stimulated to proliferate may be decreased (40). After 12 weeks, SHBG levels had increased while levels of free estradiol and estrone decreased in many who consumed the soy supplements (40 mg of soy isoflavonoids per day) (40). The theory is that the number of menstrual cycles in a woman's lifetime can be reduced as well as her breasts' exposure to estrogen.

According to Kris-Etherton and colleagues (277), flavonoids may act in a variety of ways to interfere with carcinogenesis, such as protecting DNA from oxidative damage, deactivating carcinogens, and inhibiting the expression of mutated genes and the activity of enzymes that promote carcinogenesis, and promoting detoxification of xenobiotics. For instance, chocolate, a rich source of catechins, has demonstrated the ability to inhibit COX activity, hydrogen peroxide, and superoxide anion production (277). As described earlier, anthocyanidins, which are present in fruits, vegetables, and red wine, have demonstrated

free-radical scavenging abilities as well as inhibition of xanthine oxidase (XO) in animal models (292, 293). For example, apigenin, genistein, and kaempferol, which are rich in berries, soy, and citrus products respectively, have demonstrated the ability to inhibit pro-oxidant enzymes such as COX-2 and inducible nitric oxide synthase (iNOS) (294).

Flavonoids contain a number of phenolic hydroxyl groups attached to ring structures, conferring their antioxidant activity (46). They can act as reducing agents, hydrogen donating antioxidants, and singlet oxygen quenchers (46). Numerous flavonoids, such as lignans (295) and flavan-3-ols (47), have demonstrated abilities to inhibit tumor cell proliferation through various antioxidant mechanisms . The principal flavan-3-ols, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) (47), act as antioxidants in vitro by scavenging ROS and nitrogen species, and chelating redox active metal ions (47). They may also function as antioxidants through inhibition of redox-sensitive transcription factors, nuclear factor-kB and activator-protein-1; inhibition of pro-oxidant enzymes such as iNOS, lipoxygenases, COX, and XO; and induction of phase II and antioxidant enzymes such as glutathione-S-transferases and superoxide dismutases (47).

The flavonoids involved in antioxidant activities and the estrogen pathway can be measured by the modified Block FFQ, the USDA databases; and scientific literature and these issues will be described in more detail in the Methods section.

Breast Cancer and Flavonoids

High intake of flavonoid-rich foods and beverages may reduce breast cancer risk and thus play an important role in the primary prevention of breast cancer, though this has scarcely

been researched. Epidemiologic studies have indicated an inverse association between dietary flavonoid intake and the risk of cancer, including the breast (72, 295-297). Most epidemiological studies have investigated whole foods rich in flavonoids while most in vitro studies have focused on individual flavonoids present within them. A major concern of previous studies is the validity of the dietary measurement tool in assessing usual flavonoid intake. Although many ecological and experimental studies have suggested a potential role of flavonoids in breast cancer prevention, results have been inconsistent in part due to the difficulty in measuring intake (72).

However, most human studies have only been able to quantitate intake of a small portion of flavonoids, or quantitate intake of a small portion of foods containing flavonoids, because of the lack of a flavonoid database. A recent exception (59) examined the relationship among a Greek population with high fruit and vegetable intake utilizing the USDA Flavonoid Database for Selected Foods and discovered a reduction in breast cancer risk with flavone intake (OR = 0.87, 95% CI 0.77-0.97). Bosetti and colleagues investigated this relationship in 2,569 women from a case-control study conducted in Italy (60). A reduced risk of breast cancer was found for increasing intake of flavones (OR = 0.81, 95% CI 0.66-0.98 for the highest versus lowest quintile) and flavonols (OR = 0.80, 95% CI 0.66-0.98 for the highest versus lowest quintile) (60). A recent analysis of the LIBCSP data (48) confirmed a reduced risk of breast cancer in relation to fruit (OR = 0.78, 95% CI 0.58,1.03) and vegetable (OR = 0.63, 95% CI 0.46-0.86) intake. However, no specific nutrient or antioxidant was strongly inversely related to breast cancer. This analysis demonstrated that the study population consumed a diverse and rich amount of fruits and vegetables to address our hypotheses but suggested that constituents other than antioxidants may be driving the inverse link between

fruits and vegetables and breast cancer. For example, lignans, a type of flavonoid, are found in many fruits and vegetables, as well as tea, coffee, seeds, and whole grains and have been associated with a reduced risk of pre-menopausal breast cancer (OR = 0.66, 95% CI 0.44-0.98) (295).

Although soy and soy products are the richest source of certain phytoestrogens (mainly isoflavonoids), other flavonoid food sources may be more common in the United States, such as fruits and vegetables (e.g. apples and onions), and beverages (e.g. tea and wine) (295, 298). Daily human consumption of all flavonoids is estimated to be a few hundred milligrams to one gram (62, 270). Conducting studies of flavonoid intake and cancer risk in the United States requires a database that captures these common American food sources. Thus, the USDA Database for the Flavonoid Content of Selected Foods is a logical choice. With the creation of this database, we now have a more comprehensive tool to assess dietary intake of flavonoids and their associations with breast cancer.

Epidemiology of Breast Cancer Survival

The most important predictors of survival are characteristics of the tumor and treatment undergone and age (27, 299-301). SES and race may also affect disease prognosis as lower SES and African-American race are associated with greater risk of death (149, 302). The only other non-clinical parameter that is known to affect disease prognosis is obesity at diagnosis, which is known to adversely affect survival (10-30). Other than avoiding weight gain prior to diagnosis, other modifiable factors that may potentially improve survival include improved diet and increasing exercise (37, 246, 303-306). Use of oral contraceptives and reproductive history prior to diagnosis may also affect prognosis (300, 307-309).

However, little research to date has focused on these other modifiable factors. Researchers have recently turned to examining whether factors that influence the development of breast cancer also influence disease progression. As mentioned earlier, results from previous studies have indicated that fruits and vegetables may reduce the risk of developing breast cancer (48). Thus, it is plausible to consider whether fruit and vegetable intake influences survival, and to explore what components in these products may be involved in the biological pathways related to breast cancer development and progression.

Numerous studies, as recently reviewed by Page (5), have shown that the time between breast cancer diagnosis and recurrence, and subsequent death, is significantly decreased among women with tumors greater than 1 centimeter (cm) or 2 cm; with an increasing number of axillary node involvement and with increasing stage at diagnosis; and ER- tumors (6-9). First, tamoxifen will be described because it is the predominant hormonal drug treatment following breast cancer diagnosis and surgery (310), followed by radiation and chemotherapy treatment. The clinical and non-clinical prognostic factors will then be described (Table 1.2).

Clinical and Non-Clinical Prognostic Factors

Tamoxifen

Tamoxifen, a type I anti-estrogen which has mixed estrogenic and anti-estrogenic actions, has become the predominant drug treatment following breast cancer diagnosis and surgery (310). The therapeutic effect of tamoxifen on ER+ breast cancer patients is more beneficial than on ER- breast cancer patients (311). Patient with ER+ breast cancer have an increased reduction in death rate with longer duration of tamoxifen treatment, whereas patients who are

ER- do not benefit from tamoxifen, regardless of therapy duration (311). Tamoxifen has been shown to increase the survival of patients with breast cancer and in 1994, the FDA approved the claim that tamoxifen prolonged the overall survival of the patient with breast cancer (312).

Tamoxifen seems to form a receptor complex that is converted incompletely to the fully activated form (313). As a result of the imperfect changes, the ER complex is then only partially active in initiating the series of events necessary to orchestrate gene activation (314). Studies demonstrate that high concentrations of anti-estrogens like tamoxifen can inhibit the replication of breast cancer cells (315). Tamoxifen exhibits estrogen-like effects in the post-menopausal patient causing a partial decrease in LH and FSH and an increase in SHBG (316, 317).

Radiation and Chemotherapy Treatment

Following breast cancer diagnosis, treatment with mastectomy or lumpectomy, followed by radiation and/or chemotherapy generally ensues (318-322). Prospective, randomized trials confirmed that the combination of breast conservation surgery with whole breast radiotherapy (breast conservation therapy (BCT)) produces effective local control and equivalent survival when compared to radical or modified radical mastectomy (323-325). Additionally, thousands of women worldwide underwent high-dose chemotherapy (HDCT) with autologous hematopoetic stem cell support during the 1990s because it represented a standard of care for patients with high-risk primary or metastatic breast cancer (321). These common treatments are undergone in attempt to minimize the chance of recurrence and improve prognosis.

A randomized trial of locoregional radiation therapy compared with no further treatment after mastectomy among axillary lymph node-positive, pre-menopausal patients with breast cancer treated with adjuvant intravenous chemotherapy (326), indicated an improvement in overall survival with the radiation therapy (RR = 0.73, 95% CI: 0.55-0.98). This finding corresponds to post-menopausal patients in the Danish Breast Cancer Cooperative Group where increased survival was found with a combination of radiation therapy and chemotherapy or hormonal therapy (327).

Tumor Size at Diagnosis

In a study by Schairer and colleagues (301), probabilities of death from breast cancer and other causes were calculated according to stage, race, and age at diagnosis using SEER data of women diagnosed with breast cancer between 1973 and 2000. Among white women with tumors 2 cm or less in diameter, the probability of death from breast cancer at the end of the follow-up period was 0.04 to 0.07 for patients with ER+ tumors and 0.09 to 0.10 for those with ER- tumors, depending on age (301). For white women with tumors greater than 2 cm in diameter, the respective probabilities of death were 0.13 to 0.15 for ER+ tumors and 0.16 to 0.23 for ER- tumors, depending on age (301). These findings are consistent with those of Zhang and colleagues (306), that women with a tumor size ≥ 2 cm in diameter had a case-fatality rate (CFR) of 5.2 deaths per 100 person-years, compared to a CFR of 1.7 deaths per 100 person-years for women with a tumor < 2 cm in diameter.

Stage at Diagnosis

Survival after breast cancer is strongly related to stage at diagnosis (300, 328). In the Schairer study (301), the probability of death from breast cancer increased with advancing stage; from 0.03 to 0.10 for patients with *in situ* disease to 0.70 to 0.85 for patients with distant disease, depending on age and race. A case-only study including over 1,200 women diagnosed with breast cancer was conducted in London (300) and accordingly, the most important predictors of survival were clinical stage and nodal status (300). As stage at diagnosis increased, the respective RR of death increased; RR = 1.52 (95% CI: 1.26-1.83) for Stage II, RR = 2.84 (95% CI: 2.31-3.48) for Stage III, and RR = 7.70 (95% CI: 4.47-13.25) for Stage IV (300). Similar results were found in another case-only study of women in the Malmo Mammographic Screening Trial (329). The respective mortality rates were the following, 443 cases per 100,000 person-years in women with Stage 0-I tumors, 2,225 cases per 100,000 person-years in women with Stage II tumors, 11,374 cases per 100,000 person-years in women with Stage III tumors, and 32,927 cases per 100,000 person-years in women with Stage IV tumors (329).

Node Involvement/Status

Nodal involvement is a key prognostic factor in breast cancer survival (27, 299-301, 330). In a retrospective analysis of 813 patients with locoregional or distant recurrence of primary breast cancer (331), the estimated median survival times were quite different depending on nodal involvement. The median survival time after relapse in node-negative women was 42 months (95% CI: 31-52 months), 20 months (95% CI: 16-24 months) in patients with 1-3 axillary lymph node metastases, and only 13 months (95% CI: 12-15 months) in women with at least 4 axillary lymph node metastases (331). In the Reeves study (300), the RR of dying

was much higher among women with node-positive disease than among those with node-negative disease or with unknown status. Those with node-negative disease (no nodal involvement) had a RR of dying = 0.48 (95% CI: 0.40-0.57) (301). These results corroborate with the conclusion of Voordeckers and colleagues (332) that the percentage of positive lymph nodes in an axillary lymph node dissection is an important prognostic factor for breast cancer survival.

Tumor Estrogen Receptor (ER) / Progesterone Receptor (PR) Status

ER and PR status of breast tissue are established clinical parameters in predicting prognosis of breast cancer (333). Survival time differs by ER/PR status with ER-/PR- women having worse survival compared to ER+/PR+ women (333). Estrogen binds to the ER, phosphorylation occurs, and the ER becomes transcriptionally active (310). The Schairer study (301) indicated that the probability of death from breast cancer was higher in women with ER- tumors compared to those with ER+ tumors. This is corroborated by findings from the Iowa Women's Health Study that reported a CFR of 6.2 deaths per 100 person-years for ER- women compared to a CFR of 2.5 for ER+ women (306). Both of these studies corroborate with data collected from 4,473 breast cancer cases diagnosed in 1990-1992 in Estonia, France, Italy, Spain, the Netherlands, and the United Kingdom (334). The 5-year relative survival of ER- women was 77% (95% CI: 73-81%), compared to 90% (95% CI: 88-92%) for ER+ women (334). The 5-year relative survival of PR- women was 79% (95% CI: 75-83%) compared to 90% (95% CI: 88-92%) for PR+ women (334). These findings persisted after adjustment for age and stage at diagnosis (334). Similarly, women

who had given birth within 2 years of their breast cancer diagnosis were more likely to have tumors that were ER- (335).

All of these findings concur with the deductions of Putti (336, 337) and Maynard (337) that better-differentiated tumors are likely to be ER+ and that ER+ tumors have relatively better prognosis. Conversely, ER- tumors are more likely to be of higher histological grade and the patients tend to have a decreased overall survival depending on age and nodal status (338).

Obesity at Diagnosis

Obesity or overweight at diagnosis is associated with poorer prognosis in the majority of studies examining these factors and breast cancer (29, 306, 339). A meta-analysis by Goodwin and colleagues (27) found that increasing body weight exerted a negative prognostic effect. Nine of the 13 cohort studies reported statistically significant associations between a measure of body size at diagnosis and prognosis; that the greater the body size at diagnosis, the poorer the prognosis (27). The RR or OR estimates of death for those with a large body size ranged from 1.12 to 4.17, with most estimates in the range of 1.5 to 2.0 (27). When these analyses were adjusted for other clinical risk factors such as tumor size, nodal status, and stage at diagnosis, body size remained an adverse prognostic factor (27).

A more recent meta-analysis (340) found that 17 of 26 studies detected a high BMI or body weight at diagnosis as a significant risk factor for breast cancer recurrence, death, or both. In those studies which found the positive association between overweight and poor breast cancer prognosis, women categorized in the higher (versus lower) levels of obesity exhibited a 30% to 540% increased risk of death (29, 340). A study (306) included in the

review by Rock and Demark-Wahnefried (29), analyzed breast cancer mortality rates in a cohort of 698 post-menopausal patients with unilateral breast cancer. After adjustment for age, women in the highest tertile of BMI had a 1.9-fold (95% CI: 1.0-3.7) higher risk of dying than those in the lowest tertile (306). This association remained after adjusting for stage and tumor size (RR = 1.5, 95% CI: 0.7-2.9). Also included in the review was a study by Jain and colleagues (339), which among 676 incident cases of invasive breast cancer from the National Breast Screening Study (NBSS) in Canada, found that the only nutritional factors affecting breast cancer prognosis were total energy intake and obesity (RR = 1.64, 95% CI: 0.99-2.73).

To examine the impact of BMI at diagnosis on breast cancer prognosis, Barclaz and colleagues (341) studied 6,792 patients in trials of the International Breast Cancer Study Group (IBCSG). They found that patients with "ideal" BMI ($\leq$ 24.9 kg/m^2) had significantly longer overall survival (OS) and disease-free survival (DFS) than patients with intermediate (25-29.9 kg/m^2) or obese BMI ($\geq$ 30 kg/m^2) (341). The HR for obese DFS = 1.17 (95%: CI: 1.07-1.28) while that for obese OS = 1.25 (95% CI: 1.13-1.38) (341). Again, this association remained after adjustment for other factors which included treatment, tumor size, nodal status, ER status, menopausal status, hormone use, and chemotherapy (HR = 1.11, 95% CI: 1.10-1.20 for obese OS) (341).

According to Zhang and colleagues (306), there are a few explanations for poor prognosis after breast cancer diagnosis among those women who are overweight. First, obesity may make breast cancer more difficult to detect and therefore it is more advanced at diagnosis. Second, the increased endogenous estrogen level of obese women may accelerate tumor

spread. And, finally, obesity is a marker of potentially adverse dietary contributors, such as excess fat intake (306).

Socioeconomic Status (SES), Race, and Age

SES is a significant predictor of both disease-free and overall survival (149). Differences in survival risk factors for black and white women have been observed, but the differences are not uniform among all studies (149). Some studies indicate that white patients, who tend to have higher survival rates than black patients (342), have, on average, a higher SES (343-346). In the review by Gordon and colleagues (149), women with lower social class indices were more likely to have ER- tumors (High School Education: OR = 1.98, 95% CI: 1.43-2.73; Living below the poverty line: OR = 1.76, 95% CI: 1.28-2.42). SES continued to be a marker of lower survival even after adjustment for ER status (149).

The effects of patient and tumor characteristics on breast cancer survival were examined with SEER data from 1973 to 1998 (302). Larger tumor size and higher tumor grade were found to have large negative effects on survival, as did African-American race (HR = 1.47, 95% CI: 1.39-1.58) (302). Accordingly, the effect of race is most likely due to a combination of other biological and social factors that are not recorded in the SEER database (302).

Breast cancer in adolescence and early adulthood is a rare condition (347). However, invasive ductal carcinoma occurring in young women has a more aggressive biological behavior and a worse prognosis than breast cancer in older, pre-menopausal women (348). Studies and reports have indicated that women younger than 35 years of age have more advanced disease at diagnosis and a poorer 5-year survival than older, pre-menopausal women (349-353). Similarly, a study of breast cancer cases in France (354) indicated that in

women age 40-54 years, therapeutic treatment strategies may have been more selective compared to women under age 40 years, leading to a better prognosis. Relative survival figures indicated that poor prognosis in women over 75 years was essentially due to natural mortality (354). It is hypothesized that breast cancer may be better diagnosed in women age 40-54 years because they and their doctors may pay more attention to any modifications of the breast at this time of life (354).

Potential Prognostic Factors

Physical Activity

Physical activity has been associated with weight loss and weight maintenance among healthy individuals (355, 356), and a few recent studies have suggested a favorable effect of exercise on body weight among breast cancer survivors (357, 358). In a study of energy balance during the first year after breast cancer diagnosis, Demark-Wahnefried and colleagues (359) found that physical activity throughout the year was low and that weight gain during chemotherapy was associated with an increase in fat mass. They concluded that reduced physical activity is the primary cause of this weight gain (359). It is hypothesized that physical activity aids in weight maintenance and loss, as well as decreasing adiposity, thus reducing the amount of bioavailable estrogen produced endogenously (360).

Cigarette Smoking

A study that followed women diagnosed with breast cancer for twelve years indicated that the risk of death from breast cancer in cigarette smokers (RR = 1.44, 95% CI: 1.01, 2.06) and ex-smokers (RR = 1.13, 95% CI: 0.66,1.94) was greater than that for non-smokers (329).

This relationship remained statistically significant after adjustment for age and stage at diagnosis (RR = 2.14, 95% CI 1.47, 3.10). Smokers may have a less favorable prognosis than non-smokers because smoking may promote the development of more aggressive ER- tumors (329).

Dietary Fat and Energy Intake

Several studies have associated decreased survival with pre-diagnosis fat intake (31, 33, 361), whereas others have failed to detect any association (304, 362). Saxe and colleagues (30) followed women who had been diagnosed with primary breast cancer for five years and found that both total energy intake (HR = 1.58, 95% CI: 1.05-2.38) and saturated fat intake (HR = 1.19, 95% CI: 1.05-3.04) were associated with an increased risk of breast cancer recurrence. Both saturated and polyunsaturated fats were also associated with an increased risk of death for each additional 10 grams per day in the diet (HR = 1.84, 95% CI: 1.09-3.13 for polyunsaturated fat) (30). Energy intake is highly correlated with fat intake and in this study, energy intake was found to be an important independent risk factor for both recurrence and death (30).

Alcohol Consumption

The known and potential prognostic risk factors of breast cancer may all have influences on estrogen and insulin resistance and hyperinsulinemia (363). Pre-morbid alcohol consumption of at least one drink per week was associated with a 2.7 fold increase in risk of death in a study by McDonald et al. (364). Alcohol consumption may be a surrogate for decreased fruit and vegetable consumption (364), indicating decreased flavonoid intake.

Alcohol effects estrogen concentration and metabolism as well as alcohol dehydrogenase (ADH) and ROS (364). Other studies have demonstrated at least a slight increase in risk of mortality from breast cancer due to alcohol consumption (362, 365). Post-menopausal women may decrease their risk by avoiding or minimizing their consumption (365).

Oral Contraceptive Use

The literature on oral contraceptive use and breast cancer survival remains inconclusive as most studies are based on small and heterogeneous patient populations (308). Studies since that time have improved, including one by Reeves and colleagues (300) that examined the relationship between all-cause mortality and various hormonal and other factors in 1,208 women with breast cancer. Oral contraceptives were found to influence survival in women with breast cancer, even after adjustment for stage and nodal status, though the results were not statistically significant (HR = 0.88, 95% CI: 0.63-1.22 for 10+ years since last OC use, compared to never use) (300).

Reproductive Patterns

In a study of childbirth and breast cancer survival conducted among breast cancer cases from the Australian Breast Cancer Family Study (ABCFS) (335), researchers found that those who had given birth within two years before their breast cancer diagnosis were more likely to have tumors that involved axillary lymph nodes. This finding is supported by Olson and colleagues (366), who found an adjusted relative risk of 3.1 (95% CI: 1.8-5.4) comparing women who had given birth within two years before breast cancer diagnosis and nulliparous women. These women have been found to have more axillary nodes involved as well as ER-

/PR- tumors of a high grade (335, 366). Age at menarche, age at menopause, and oral contraceptive use were not associated with survival in a study of women under age 71 with stage I, II, or III breast cancer (367). The most obvious host factor potentially mediating the adverse prognostic effect of recent childbirth is the hormonal milieu of pregnancy, which may result in increased estrogen and progesterone levels stimulating pre-existing breast cancer clones (335).

Fruit and Vegetables

Some studies have indicated that fruits and vegetables, as well as micronutrients such as Vitamin C and carotenoids, may enhance breast cancer survival (30-33, 37). In those studies that found an inverse relationship with survival and intake of fruits, vegetables, and related nutrients, the estimates ranged from a 20% to 90% reduction in risk of death (31-33, 37). However, variability in these findings and in the vegetable-related dietary factors have been examined in these studies and these data do not provide conclusive evidence for a beneficial effect (31-33, 37).

The study by Jain and colleagues (33), which was described earlier, found a decreased risk of dying from breast cancer in the highest quartiles of beta-carotene intake (HR = 0.48, 95% CI: 0.23-0.99) and Vitamin C intake (HR = 0.43, 95% CI: 0.21-0.86). The authors also mentioned that diets high in saturated fat, which were associated with an increased risk of death (HR = 1.44, 95% CI: 1.16-1.78), may be lower in fruit and vegetable intake and therefore lower in carotenes and Vitamin C, which may implicate excess fat intake and inadequate fruit and vegetable intake as playing roles in decreased survival after breast cancer diagnosis (33). Similarly, the study by Rohan and colleagues (31) found a decreased

risk of death with increasing intake of beta-carotene (HR = 0.68, 95% CI: 0.36-1.27) and Vitamin C (HR = 0.74, 95% CI: 0.42-1.30) among cases from the South Australian Central Cancer Registry (SACCR), but confidence intervals were wide. The association for beta-carotene consumption and Vitamin C consumption was strong and there was found to be improvement in tumor differentiation with increasing consumption of these nutrients (32).

Additional studies have also assessed fruits and vegetables and their potential associations with breast cancer survival. A study of 149 patients diagnosed with primary breast cancer between 1989 and 1991 were followed up for 5 or more years from the University of Michigan Medical Center (30). Fruit (HR = 1.06, 95% CI: 0.69-1.63) and green and yellow vegetables (HR = 0.97, 95% CI: 0.70-1.35) did not appear to reduce the risk of breast cancer recurrence and death (30). However, when stratified by menopausal status, fruit appeared to enhance survival among pre-menopausal women (HR = 0.17, 95% CI: 0.01-1.86) and decrease survival for post-menopausal women (HR = 1.23, 95% CI: 0.79-1.91) (30), though, again, neither was precisely estimated. Green and yellow vegetables had no appreciable association for pre-menopausal (HR = 0.96) or post-menopausal women (HR = 0.95) (30).

Hebert and colleagues (368) studied the effect of diet and body weight on recurrence and death in 472 women with early stage breast cancer and noticed the dietary effects were found in post-menopausal women only. A decreased risk of death was found for each increase of 100 mg in Vitamin C intake (RR = 0.48, p = 0.14) and for each serving of vegetables consumed (RR = 0.31, p = 0.08) (368). These results are similar to those from a study of female registered nurses from the Nurses Health Study who had been diagnosed with breast cancer (369). Increased intake of vegetables was associated with a decreased risk of death in the third (HR = 0.80, 95% CI: 0.59-1.08) and fourth quintile (HR = 0.81, 95% CI: 0.59-1.11),

though neither estimate was statistically significant (369). Similar to the conclusions of Jain and colleagues (33), these authors felt the inverse associations could reflect part of an overall healthy diet rather than just vegetable intake alone (369).

To improve upon this prior research, it would be useful to add flavonoids to the list of components to be measured. If flavonoids' effects are stronger than those of fruits, vegetables, and antioxidants such as vitamins C and E, then there would be evidence indicating flavonoid intake may be beneficial with regard to survival following breast cancer diagnosis. These thoughts have been echoed by other researchers who feel that examination of various constituent phytochemicals would be useful (29, 368, 370).

Flavonoids and Background Summary

Flavonoids are hypothesized to be associated with a lower risk of developing breast cancer and in decreasing the probability of death (49). In particular, the proposed study was the first to examine whether flavonoids affect survival, and among the first to look at flavonoids in relation to breast cancer incidence. As stated earlier, there have been no published studies conducted on American populations using the USDA Flavonoid Database for Selected Foods. In the two published studies using this database (59), researchers assessed breast cancer incidence in a Greek population (59) and an Italian population (60), both with high and wide ranges of fruit and vegetable intake, providing enough heterogeneity to determine if there were beneficial effects; which there were. The large sample size of the LIBCSP study population has this same variability and consumption pattern, making it possible to determine if flavonoids may reduce breast cancer risk among American women and enhance survival after diagnosis.

Improved understanding of carcinogenesis and cancer progression, and uniform results, can lead to consistent public health messages that will help women enhance their survival following the diagnosis of breast cancer. Since these messages are currently unknown and thus, lacking, now is a perfect time to conduct research that start to answer these important questions.

Tables and Figures

Table 1.1. Known and potential risk factors for breast cancer incidence.

Known and Potential Risk Factors for Breast Cancer Incidence	
Reproductive Risk Factors	**Demographic Risk Factors**
Pregnancy	Increasing age
Oral contraceptive use	Race
Hormone replacement therapy (HRT)	Socioeconomic status (SES)
Little or no breastfeeding	
Early age at menarche	**Potential Risk Factors**
Late age at menopause	Cigarette smoking
Late age at first birth	Fat consumption
	Non-steroidal anti-inflammatory drug (NSAIDs) use
Medical Risk Factors	Fruit and vegetable consumption
Family history of breast cancer in sister or mother	
Endogenous estrogen levels	
Benign breast disease (BBD)	
Environmental/Lifestyle Risk Factors	
Post-menopausal obesity and weight gain	
Alcohol consumption	
Physical inactivity	

Adapted from Adami (112) and Kelsey (64).

Table 1.2. Known and potential prognostic factors for breast cancer survival.

Known and Potential Prognostic Factors for Breast Cancer Survival	
Known Prognostic Factors	**Potential Prognostic Factors**
Tamoxifen	Physical activity
Age	Cigarette smoking
Radiation and chemotherapy treatment	Dietary fat and energy intake
Tumor size at diagnosis	Alcohol consumption
Stage at diagnosis	Oral contraceptive use
Node involvement/status	Reproductive patterns
Tumor estrogen receptor (ER) / progesterone receptor (PR) status	Fruits and vegetables
Obesity at diagnosis	Flavonoids
Socioeconomic status (SES) and race	

Adapted from Jain (299), Schairer (301), Reeves (300), Rosen (6-8), and Fisher (9).

Figure 1.1. Reproductive risk factors proposed mechanism behind breast cancer.

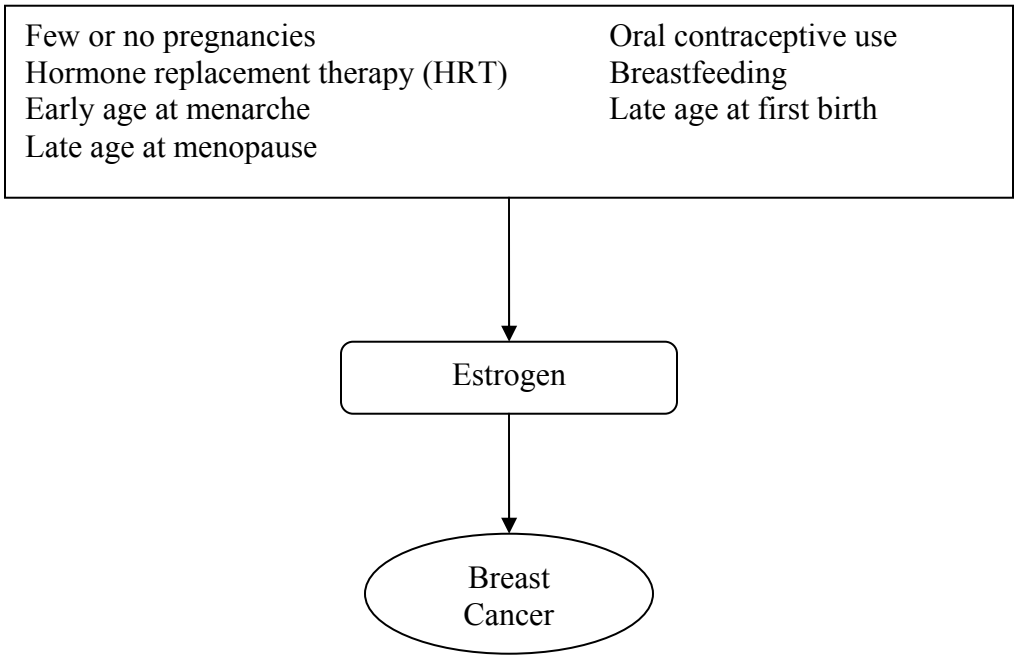
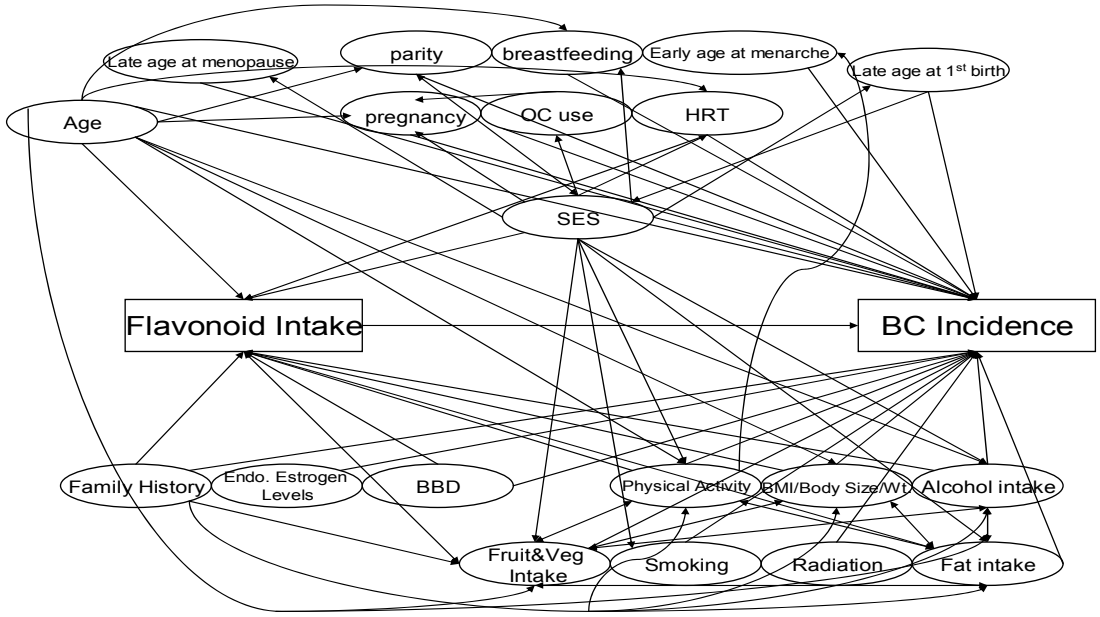


Figure 2.1. Proposed DAG of potential confounders to the association between flavonoid intake and breast cancer incidence.



CHAPTER II: RESEARCH METHODS AND DESIGN

Overview of Study Methods

To study the associations of flavonoid intake with breast cancer risk and survival, existing data collected as part of the LIBCSP was used. The LIBCSP is a population-based study of women of Nassau and Suffolk counties in Long Island, New York; the case-control component was conducted in 1996-1998 and the follow-up was conducted in 2002-2004. Dietary intake in the year prior to the case-control interview was collected utilizing a modified version of the 100-item Block food frequency questionnaire (FFQ). 98.2% (N = 1,481) of the cases and 97.6% (N = 1,508) of the controls self-completed the FFQ in an average of 36 minutes immediately after the main questionnaire had been completed (371). The dietary intake of respondents (which was collected as part of the case-control study) was coupled with the USDA Database for the Flavonoid Content of Selected Foods, the USDA – Iowa State University Database on the Isoflavone Content of Selected Foods, and Statistical Analysis Software (SAS) to obtain a measure of flavonoid intake. For the two lignans that are precursors to enterolactone and enterodiol, matairesinol and secoisolariciresiol (372), respectively, intake were estimated from dietary phytoestrogen concentrations of food (373). Unconditional logistic regression was used to study risk, and proportional hazards modeling and survival analysis techniques was used to study survival.

Exposure Assessment

Modified Block FFQ (LIBCSP Food Questionnaire)

The original Block FFQ was developed using dietary data from 11,658 adult respondents to the Second National Health and Nutrition Examination Survey (NHANES II) (374). Food items were selected on the basis of their contribution to the total population intake of energy and each of 17 nutrients in the NHANES II data, and represent over 90% of each of those nutrients (374). Associated nutrient composition values were determined from the NHANES II database using frequency of consumption data in that survey (374).

The Block FFQ included a food list to ensure adequate assessment of dietary fiber intake, intake of cruciferous vegetables, foods and beverages with suspected health benefits (e.g., tea), and foods important in geographic and ethnic subgroups (e.g., chili peppers) (374). Some fruits were separated into "fresh, in season" and "canned/frozen" because respondents had difficulty with a combined item (374). Additionally, the questionnaire has an open-ended question where the respondent can indicate other frequently eaten foods, permitting the capture of foods important to a particular individual or demographic group (374). Questions on special diets and vitamin supplements were also included (374).

The Block FFQ was modified by Potischman and colleagues (375) to include questions differentiating low and high fat dairy items, low and high caffeine beverages with and without artificial sweeteners, separation of items that differed in fat or fiber content, as well as sections for foods relevant to their study population and an open-ended section to include foods consumed more than once per week that were missing from the food list.

For the LIBCSP, the Block FFQ was further modified; the portion size question for each food (with an average serving size as a guide), was followed by three possible choices for the respondent's serving size; less, average, or more. Additional food items that contain phytoestrogens were also added to this FFQ (376). A private research firm, Intercontinental

Marketing Services (IMS), located in Bethesda, Maryland, derived estimates for each serving size choice for each food and beverage in grams and milliliters, respectively.

USDA Database for the Flavonoid Content of Selected Foods

The recent interest in the potential anticarcinogenic and antioxidative properties of flavonoids by the scientific community led to the development of the USDA Database for the Flavonoid Content of Selected Foods (377). The Nutrient Data Laboratory (NDL) and the Food Compostion Laboratory (FCL) of the Beltsville Human Nutrition Research Center (BHNRC) of the Agricultural Research Service (ARS) and U.S. Department of Agriculture (USDA), along with epidemiology and nutrition groups from universities, institutes, and corporations collaborated on the two-phase project (377). The first phase consisted of an extensive survey of the literature for articles containing data on the flavonoid content of food. Data from analytical studies which used only acceptable procedures defined as those which lead to good separation of flavonoid compounds, such as column chromatography or high-performance liquid chromatography (HPLC), were used (377). Papers that contained data generated by thin layer or paper chromatography, radioimmunoassay (RIA), pH differential methods, or only spectrophotometric quantitation were not retained because of the lack of specificity of these methods (377). This database was created through great attention to detail to produce the most comprehensive tool available to study the potential link between flavonoids and human health. It is the new standard for flavonoid research and was used to help answer the questions posed and be a building block for future flavonoid databases.

The USDA Database for the Flavonoid Content of Selected Foods contains values for five classes of flavonoids: flavanols, flavones, flavanones, flavan-3-ols, and anthocyanidins.

Twenty-six individual flavonoids comprise these classes and they are measured in 225 foods and beverages. Values are reported as mg/100g of fresh weight of edible portion of food and values of beverages were adjusted by their respective gravities and are reported as served. Values of tea are given as mg/100ml (100g weight) of tea infusions (as consumed). This database was linked to the dietary data from the modified Block FFQ used in the LIBCSP to estimate individual and total flavonoid intake in these women. In addition to identifying which group (cases or non-cases) consumes, on average, more total flavonoids and classes of flavonoids, it was determined whether greater total and individual flavonoid intakes are inversely associated with breast cancer risk and mortality. Table 2.1 displays the five classes of flavonoids assessed in the USDA Database for the Flavonoid Content of Selected Foods, the individual flavonoids which make up these classes, and the main dietary sources of these flavonoid classes.

USDA - Iowa State University Database on the Isoflavone Content of Selected Foods

Prior to the creation of the USDA Database for the Flavonoid Content of Selected Foods, a database for isoflavones, another class of flavonoids, was developed and introduced in 1999. The USDA - Iowa State University Database on the Isoflavone Content of Selected Foods was a collaborative effort between the FCL and NDL of the ARS/USDA and the Department of Food Science and Human Nutrition of the Iowa State University (378). The main dietary sources of isoflavones are soybeans and soyfoods. Some other food legumes contain very small amounts of isoflavones (378). Data for isoflavone contents of foods were collected from scientific articles published in refereed journals and by extensive sampling of soy-containing foods and subsequent analyses at the Iowa State University (378).

Data for the isoflavones, genistein and daidzein, have been added to the database to measure flavonoid intake from tofu, beans, and peas. Tofu is a flavonoid-rich food that is listed on the FFQ but not the USDA Flavonoid Database, hence its addition. The USDA - Iowa State University Database on the Isoflavone Content of Selected Foods was used to add this data because it contains genistein and daizein content of 14 different kinds of tofu. The modified Block FFQ used in the LIBCSP inquired about tofu consumption but it was labeled only as 'Tofu'. Thus, the values of genistein and daidzein (in mg per 100 g) added to the flavonoid database for analysis were derived by taking the average content of these isoflavones in the 14 kinds of tofu.

Additional Isoflavone and Lignan Values Obtained from the Literature

Since isoflavones and lignans, two additional classes of flavonoids, also occur in various fruits, vegetables, beverages, nuts, and grain products (379-382) (though in respectively smaller amounts compared to soy), additional data were obtained (379-382). This supplementation of the two USDA databases ensured inclusion of as many flavonoid-containing products as possible in the database to be used for analysis. The manuscript that describes the creation of this enhanced database is in Appendix 2. These sources are the result of previous analyses and compilations of the literature (382), including chemical analyses of foods and beverages in laboratories (379-381). De Kleijn and colleagues (382) located published laboratory analysis data by searching the medical (Medline) and agricultural (Agricola) scientific literature and through contact with several experts in the field of phytoestrogens. Values for lignans for some foods were also obtained via an isotope dilution gas chromatography/mass spectrometry method in the laboratory (382).

In the laboratory analyses of Liggins and colleagues (379-381), foods were obtained from supermarkets, freeze-dried, milled, dessicated, and eventually assayed to obtain their contents of daidzein and genistein. The values obtained from two of these laboratory investigations (379, 380) were recently used by Bosetti and colleagues (60) in their study assessing flavonoids and breast cancer risk in Italy.

Classification of items using the Modified Block FFQ and USDA Database for the Flavonoid Content of Selected Foods

Descriptive analysis of the dietary data from the LIBCSP was conducted to determine the mean intake of each food and beverage item that was assessed in the study. Table 2.2 displays categories of foods and beverages which were listed on the modified Block FFQ. Foods and beverages consumed in 'high' quantities in the LIBCSP were considered to be those with a mean consumption of at least 15 g per day. Foods and beverages consumed in 'small' quantities therefore had a daily mean consumption of less than 15 g. 'Large' contributors of flavonoids were considered to be foods and beverages which contained at least one flavonoid at 5 mg or greater per 100 g of the respective food or beverage. 'Small' contributors of flavonoids therefore did not contain at least one flavonoid at 5 mg or greater per 100 g.

This table demonstrates the ability of the modified version of the Block FFQ used in the LIBCSP to reflect consumption of many flavonoid-rich foods and beverages, which represented the bulk of the content of the newly-constructed flavonoid database. It was difficult to quantify flavonoid content for mixed dishes, which were assumed to include spaghetti; hamburgers, beef burritos, and meatloaf; pizza; and vegetable soup. However, they are all relatively small contributors of flavonoid content (377) and thus any

misclassification should have a negligible effect on estimation. The handling of 'large' and 'small' contributors of flavonoids that were not listed on the modified Block FFQ, but are listed on the USDA Database for the Flavonoid Content of Selected Foods, are described in more detail later.

The contribution of herbs and spices, such as basil and oregano, were not considered when assessing flavonoid content. This is because standard containers of basil and oregano contain 1 oz. (28 g) and 1.2 oz. (34 g), respectively. Since flavonoid content for all items on the USDA Database for the Flavonoid Content of Selected Foods are reported in mg per 100 g, it was unnecessary to estimate a trivial amount of these products in mixed dishes because it would take approximately 3 containers to have 100 g of basil or oregano.

Overview of the Long Island Breast Cancer Study Project (LIBCSP)

The LIBCSP was a group of projects funded by the National Cancer Institute and National Institute of Environmental Health Sciences in response to federal legislation (Public Law 103-43, June 10, 1993), which mandated that an epidemiologic study be conducted to assess environmental and other potential risk factors contributing to the incidence of breast cancer in the Long Island counties of Nassau and Suffolk in New York (371). The primary study of the LIBCSP was a population-based case-control study undertaken to determine whether the risk of breast cancer among women residing on Long Island was associated with polycyclic aromatic hydrocarbons (PAHs) and organochlorine compounds, such as DDT and polychlorinated biphenyls (PCBs) (371). To assess these primary exposures of interest, the study involved a comprehensive in-person questionnaire, biologic sample collection of blood and urine, and collection of environmental home samples of dust, water, and soil at the time

of the personal interview (371). The following description of the is derived from Gammon and colleagues (371).

Case-Control Study Population Identification

For the case-control study, cases were women with newly diagnosed, primary in-situ or invasive breast cancer between August 1, 1996 and July 31, 1997, confirmed by the physician and medical record, who were residents of either Nassau or Suffolk counties in Long Island, New York (371). All cases were over the age of 20 years and English-speaking. Cases were ascertained using a rapid reporting network developed with 33 hospitals and 450 physicians known to treat or diagnose breast cancer for the women of Long Island (371). To facilitate collection of blood samples from cases prior to chemotherapy, a "super-rapid" identification network was established to ascertain potentially eligible case women with newly diagnosed breast cancer (371). Study personnel contacted the pathology departments of all 28 hospitals on Long Island, as well as three large tertiary care hospitals in New York City, at least two to three times per week. Seven institutions in the Long Island – New York City area with the largest numbers of newly diagnosed breast cancer cases among Long Island women were contacted daily (371).

Physicians of the potentially eligible case women were then contacted to confirm the subject's diagnosis, the date of her diagnosis, and for permission to contact the subject. To promote physician cooperation prior to initiating subject identification, over 400 physicians who as general practitioners, internists, surgeons, or oncologists on Long Island, who had the potential to diagnose or treat women with breast cancer, were mailed a packet describing the study which allowed them to indicate their willingness to participate in the study in writing.

No physician refused to participate. A total of 2,271 women were initially identified and considered as potentially eligible cases. Of these, 2,030 were determined likely to be eligible by the physician and physician consent was obtained for 1,837 (90.5%). Physician refusal for contact was generally based on a subjects' poor health status, which was often due to age-related co-morbidity.

Control women were a sample of current residents of Nassau and Suffolk counties who spoke English, did not have a personal history of breast cancer, and who were frequency-matched to the expected distribution of the case women by 5-year age group (371). Controls were identified using random digit dialing (RDD) for women under the age of 65 years and Health Care Finance Administration rosters for women 65 years or older (371). HCFA selection occurred twice during the 12-month identification period that coincided with the 12 months of case ascertainment. RDD selection began July 1, 1996 and continued in eight waves over the following 12 months. The response rate to the RDD telephone screener was 77.9% (371).

Subject Recruitment in the Case-Control Study

Potentially eligible controls and cases with physician consent were first contacted by the study team via an overnight letter. Due to concerns about the overnight service in some potential control women who were 65 years of age or older, subsequent older potential controls were contacted by a regularly mailed letter. A recruitment letter explained the purpose of the study, the various components of the study interview, and that participation in the study was completely voluntary. They could choose to participate in any or all of the components for which they were selected. Along with this letter, in the packet of

information sent to potential participants, was a flyer that answered commonly asked questions about the study and a form letter signed by the Long Island Breast Cancer Network members, a community-based organization, explaining that the LIBCSP case-control study was a direct result of the community's activism and it urged women to consider participating. Study recruiters contacted the study subjects to answer questions and arrange for an interview. For most of the women, the recruiters contacted potential respondents by telephone. For some control women who were difficult to contact by telephone, they were approached by recruiters in person. Written, signed informed consent was obtained from participants prior to conducting any component of the interview.

Case-Control Subject Participation

The main questionnaire was completed by 1,508 (82.1%) of the eligible case women (N = 235 with *in situ* and 1,273 with invasive breast cancer) and 1,556 (62.7%) of the eligible control women (371). The reasons for non-response to the interview among cases and controls included subject refusal (218 (12.4%) and 573 (21.6%)); too ill, cognitively impaired, or deceased (76 (4.1%) and 193 (7.8%)), and unlocatable, moved out of the area, or other (26 (1.4%) and 195 (7.9%)) (371). Study subjects ranged in age from 20 to 98 years and response to the interview varied with the age of the respondents, with 88.9% of the cases and 76.1% of the controls under age 65 years participating versus 71.6% and 43.3%, respectively, among those age 65 years and older (371). The average length of time between the referent date (date of diagnosis for cases and date of identification for controls) and interview date was 96 days for cases and 167 days for controls (371).

For case women, final study eligibility was based upon thorough review of the medical record, which could only be obtained with a signed medical record consent form (371). This form was signed by the cases themselves and it allowed study personnel to, in addition to determining final eligibility, determine the clinical characteristics of the breast cancer diagnosis (e.g., stage of disease and hormone receptor status). Signed medical record release forms were obtained for 1,473 (97.7%) case respondents and records were successfully located and abstracted for 1,402 (95.2%). Due to the fact that a goal of this study was to collect blood samples prior to chemotherapy, most case women were interviewed prior to the completion of their course of treatment. Thus, complete treatment information is not available on the majority of case subjects at the time of the case-control interview.

The final eligibility of controls was obtained through direct contact with the subject (371). It is therefore possible that the interview response rates may be underestimates as they include in the denominator 25 potentially eligible case women and 193 potentially eligible control women for whom study subject eligibility could not be determined because they were never located or had moved out of the area (371).

Case-Control Study Interview

The interview consisted of five components, which were administered in the following order: (1) signed informed consent; (2) the interview-administered main questionnaire; (3) collection of biologic samples (blood and urine) and administration of a specimen checklist; (4) administration of a modified Block FFQ; and (5) among a sub-sample of long-term residents, collection of environmental home samples (soil, dust, and water). The first four components required between two to three hours to complete. For those subjects who

completed the fifth component, an additional 30 to 60 minutes was required. Completion of all components of the interview was done in the respondent's home. Interviewers, who were certified to collect blood samples in the state of New York, received a one-week, standardized, intensive training course in all aspects of interview administration.

The interviewer explained the contents of the written informed consent form to each eligible subject, and if the participant wished to continue, she was asked to read and sign the form. Upon receiving physician and participant consent, cases and controls were administered an in-home interview with a trained nurse (371). The main case-control questionnaire, which took approximately 100 minutes to administer, was administered focusing on known and suspected risk factors for breast cancer such as reproductive history, residence, physical activity, hormone use, and environmental exposures. Subjects were also administered a modified version of the Block FFQ to assess dietary intake (371). Most of the modifications were validated against six 24-hour recalls over a twelve month period (375, 383). A total of 1,508 (82.1%) eligible cases and 1,556 (62.7%) eligible controls completed the main questionnaire. Of the women who completed the main case-control questionnaire, 98.2% of cases and 97.6% of controls completed the FFQ. This instrument was completed in an average of 36 minutes immediately following the completion of the main questionnaire. Response for the FFQ did not vary with age of the respondent.

Demographic and Risk Factor Description of the Case-Control Population

There was no age limit for participation in the LIBCSP and this allowed for a wide age range of women to be included for study. 519 cases (34.4%) and 440 controls (28.3%) were at least 65 years of age or older. 2,840 (1,411 cases and 1,429 controls) (92.7%) of the 3,064

combined cases and controls reported themselves as Caucasian, 154 (5.0%) as African-American, 67 (2.2%) as 'Other', and 3 women had missing racial status. The education level of the population ranged from less than high school to post-graduate status. More than one-fourth of both cases and controls (28.0% and 29.7%, respectively) were college graduates or current or former post-graduate students. Likewise, income level spanned a wide array as it ranged from less than $15,000 in 8.9% and 6.4% of the cases and controls, respectively, to greater than $90,000 in 13.1% and 21.5% of the cases and controls, respectively.

Results of Established Risk Factors for Breast Cancer in the Case-Control Population

Many established risk factors for breast cancer that have been identified in previous studies (384), including parity (OR = 0.63, 95% CI 0.48-0.82 for 4+ children versus none), breastfeeding (OR = 0.70, 95% CI 0.53-0.89 for 14 months versus none), age at first birth (OR = 1.36, 95% CI 1.10-1.69 for 28+ versus < 22 years), and family history of breast cancer in a mother or sister (OR = 1.66, 95% CI 1.36-2.02 for family history versus no family history) , were confirmed to affect risk among women of all ages on Long Island (371).

Potential Biases and Effects of Study Participation in the Case-Control Study

Response rates were lower among controls than in cases, which was driven by poor participation among elderly control women (371). Co-morbidity among the elderly and the protective efforts of the subjects' families prevented full study participation among these older women (371). If the older respondents differed systematically from older non-respondents, results based on this segment of the study population may be biased and

therefore should be interpreted cautiously as they may not be generalizable to all older women (371).

Additionally, a low screener rate obtained during RDD contributed to the lower participation rate of the controls and it affected results based on women under the age of 65 years (371). RDD has been an effective and common technique to identify a pool of potential eligible population-based controls since the technique was introduced by Waksberg (385). However, with the increasing use of telephone answering machines and caller ID, particularly in high-income areas such as Long Island where residents were subjected to extensive telephone marketing, the RDD technique may be less effective (371).

As stated previously, there was a difference between cases and controls in the time lag between the reference date and the interview date, with cases interviewed on average within about 3 months of diagnosis and the controls within about 5.5 months of identification (371). This is a common feature of case-control studies when cases are deliberately recruited more quickly than controls, to enhance accurate recall of events prior to diagnosis (371). This strategy was also employed to facilitate collecting blood samples before the initiation of chemotherapy treatment among case women. For most factors in this study, cases and controls were asked to recall lifetime or historical exposures that occurred prior to the reference date, which was the date of diagnosis for cases and date of identification for controls (371). The modified Block FFQ required cases and controls to recall their dietary practices in the year prior to the interview date when the FFQ was administered.

Overview of the LIBCSP Follow-Up Study

The LIBCSP follow-up study was conducted among the breast cancer cases who participated in the LIBCSP case-control study who had given study personnel permission to re-contact them (n = 1,414) (371). Because case women were rapidly identified for the case-control study, many women were still receiving treatment at the time of the case-control interview. Often care was not at the institution where a case obtained her diagnosis and thus study personnel were unable to identify from which hospital to obtain the necessary treatment information. Thus, five years after the initial diagnosis, subjects were re-contacted to obtain the necessary data on treatment for their initial breast cancer. The proposal was to follow-up the population-based case participants from the original case-control study in order to assess their overall survival 5 years after diagnosis of their first primary breast cancer. The analyses reported here are restricted to women diagnosed with a first primary breast cancer at the time of the case-control study (n = 1,273).

Subject Recruitment for the Follow-up Study

There were a total of 1,508 case women interviewed as part of the case only study. Potentially eligible subjects for the follow-up study were those who indicated at the case-control interview that it was permissible to contact them in the future (n = 1,414). The eligible case participants or their next of kin were re-contacted first by mail approximately 5 years after the initial diagnosis, and then by telephone, and invited to participate in a 60-minute telephone interview. Informed consent was obtained verbally by telephone. Extensive efforts were made to contact and interview the next of kin because a large proportion of non-response could have been due to mortality. Sixty of the 1,414 case women replied to the first mail contact and indicated refusal to participate, leaving 1,354 case women

(1,273 invasive case women and 81 *in situ* case women) available to be contacted by telephone. Reasons for non-response included refusal to participate when contacted by telephone (n = 65), refusal to participate due to illness (n = 18), lost-to-follow up (n = 55), multiple contacts yet unable to complete the interview (n = 22), and deceased with no proxy to contact (n = 96). Thus, 1,098 total interviews (93 with proxies) via telephone (1,066 complete and 32 partial) were conducted.

Data Collection at Follow-up

At the 5-year follow-up, two sources were used to determine treatment and outcome data of the initial breast cancer diagnosis: (1) subject interviews and (2) medical record abstraction. Cases were interviewed via telephone, by a trained interviewer, to assess two types of information: (1) treatment modalities undergone for the initial breast cancer diagnosis with the aim of obtaining the name(s) and location(s) of the treating physician(s) and institution(s), and dates of the treatment(s); and (2) outcomes and treatments for the outcomes since the initial breast cancer diagnosis date, with the aim of obtaining the name(s) and location(s) of the diagnosis and treatment physician(s) and location(s). For case women (or their proxy) who provided a signed medical record release form (n = 598), all relevant medical records with regard to the initial breast cancer diagnosis and outcomes were requested; those successfully retrieved were systematically abstracted by trained abstractors.

Case Interviews: Exposure Ascertainment

The cases were asked to recall the names of the hospitals, any other institutions, and treating physicians associated with all treatments undergone since the diagnosis date of their

initial breast cancer. Although the case-control interview attempted to ascertain this information, most women had not yet finished their treatment regimen. In the follow-up interview, more detailed information could now be obtained because the first course of treatment was now complete. In order to facilitate recall, subjects were systematically queried about procedures they may have undergone including: surgery (needle biopsies, tumor biopsies, modified mastectomy, radical mastectomy, node removal); radiation; chemotherapy (specific combinations undergone, if possible); and hormone treatments (tamoxifen, etc.). For each type of procedure, the subjects were asked to recall the number of times the procedure was performed, the frequency, the date(s), the treating physician(s), and the location of the institution, office, or free-standing facility where each procedure was performed. The subject was also asked to complete another medical record release form giving the study staff permission to access their records.

From information collected in the case-control interview, treatment and co-morbidity data exists for the entire sample of cases (n = 1,508). During the follow-up interview, detailed information on treatment and co-morbidity was obtained from most of these cases (n = 1,098). This information was then collected a third time through medical record abstraction, to confirm the interview data, and is available for women who signed a medical record release form (n = 598).

Retrieval and Abstraction of Medical Records

Additional medical record release forms were obtained from the follow-up subjects by mail. During the follow-up interview, subjects were asked to recall any relevant information regarding: (1) treatment they may have undergone for the initial breast cancer; and (2) study outcomes of interest and any treatment undergone for those outcomes. For the proxy

interviews and self-respondents, relevant medical records regarding treatment (surgery, radiation, chemotherapy, hormone therapy, etc.) and outcomes (death) were retrieved from the appropriate hospitals. Using a standardized form, trained abstractors reviewed and abstracted all medical records to determine each subject's treatment regimen for their initial breast cancer and to determine relevant outcome information.

Potential Biases and Effects of Study Participation in the Follow-up Study

The next-of-kin (proxy) questionnaire was identical to the instrument used to interview a breast cancer case other than the wording was modified to reflect that the questions referred to the case and not the proxy. However, the ability of a proxy to recall treatment and outcome data of the initial breast cancer diagnosis for the case may not be as accurate as a self-report from the case herself. This could result in more thorough and complete data collection from cases which may bias results of subsequent analyses. Correspondingly, a review on the use of proxy respondents noted that some exposures are measured with less misclassification than others and that, in general, the misclassification is due to underreporting of the exposure by the proxy as compared with directly-reported responses (386).

Case Outcome Ascertainment (Death)

The NDI, a central computerized index of death record information on file in the State vital statistics offices (387), was established by the National Center for Health Statistics (NCHS) to aid epidemiologists and other health and medical investigators with their mortality ascertainment activities. The NDI contains state-mandated death records from 1979 to present, as it is updated 12 months after the end of each year (388). Data which

included participant identification number, first and last name, city, state, date of birth, Social Security number, last contact, gender, reference date, race, and marital status, obtained from the telephone interview, were combined into a spreadsheet and converted into an ASCII file for NDI (389). This list of information was matched with the NDI search, which includes matching algorithms on first and last names, middle initial, father's surname, Social Security number, birth date, and gender (388), to provide a list of names of the invasive cases that did not match any death records or a list that could be considered a match.

The NDI is currently considered the "gold standard" of mortality ascertainment (389). The ability of the NDI to ascertain deaths of study participants was tested with information regarding 197 participants whose deaths had been reported and 1,997 participants who were known to be alive, all from the Nurses' Health Study (388). Information was sent to the NDI and a newly-developed service, the Equifax Nationwide Data Search. The sensitivity of the NDI to accurately report deaths was 98.0% compared to just 79.2% for the Equifax service (388), making the NDI a preferred method to search for deaths in prospective cohort studies (388).

More recently, in a study of 31,223 subjects with unconfirmed vital status in an ongoing occupational cohort mortality study, information was submitted to the Health Care Finance Administration (HCFA), Social Security Administration (SSA), and Pension Benefit Information Company (PBI) to obtain death certificate numbers (390). The NDI provided exact matches for 92-96% of deaths identified by each of the three services (390). The effectiveness of the NDI has also been tested by identifying participants in the oldest cohort of the Australian Longitudinal Study on Women's Health (ALSWH) who had died between

1996 and 1998 (391). The sensitivity of the NDI for identifying known deaths was 95% (391).

In the LIBCSP Follow-up, the all-cause mortality rate was 13.0% (196 deaths amongst 1,508 cases). Of the 196 cases that died, 123 died from breast cancer (breast cancer-specific mortality rate of 62.7%). Therefore, there are two possible methods for assessing the outcome of death, all-cause mortality or breast cancer (disease-specific) mortality. Of the 1,273 invasive cases, 188 (14.8%) died during the follow-up period. Table A.1 provides a list of the number of deaths and causes of death for the 1,273 invasive cases. 121 of the invasive cases (64.4%) died from breast cancer. Among older women, the increasing probability of developing other debilitating conditions or diseases is an issue. However, for the 32.4% (n = 387) pre-menopausal invasive cases, co-morbidity is less likely to have an effect on death from breast cancer.

Flavonoid Database Construction for Analysis

The traditional construction of a database for analysis involves linking subject responses to the FFQ, specifically frequency and portion size, with an existing database for the components being studied. This was the first study using both the USDA Database for the Flavonoid Content of Selected Foods and USDA – Iowa State University Database on the Isoflavone Content of Selected Foods to assess flavonoid intake with an American population.

Weighting Foods from the Modified Block FFQ

The first step in constructing the database for analysis was to weight foods and beverages listed on the USDA Database for the Flavonoid Content of Selected Foods. This procedure was necessary because some food items on the modified Block FFQ include multiple foods or beverages rather than single foods (e.g., 'Cauliflower or brussel sprouts'). Weights (percentages) were assigned to the respective USDA Database items (e.g., give equal weight to both foods by assigning 0.50 to 'Cauliflower, raw' and 0.50 to 'Brussel sprouts, raw'). These weights were then linked with the modified Block FFQ food item, 'Cauliflower or brussel sprouts', providing the flavonoid contribution of that FFQ item. These weights are estimates of the proportion of each food or beverage consumed by the LIBCSP per item listed in the modified Block FFQ. In order to assign these weights, the Foods Commonly Eaten in the United States: Quantities Consumed Per Eating Occasion and in a Day, 1994-1996 was used (392). This report was authored by Helen-Smiciklas-Wright, Diane Mitchell, Sharon Mickle, Annetta Cook, and Joseph Goldman. The report contains estimates of food intakes by individuals residing in households in the entire United States (392). The estimates were based on information from 14,262 non-breast fed individuals ages 2 and above for whom 2 days of dietary intake information was obtained in the 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII 1994-96), which was conducted by the United States Department of Agriculture (USDA) (392). Food intake data were collected by in-person interviews from 1994 through 1996.

The CSFII 1994-96 has two tables of information (392), one which provides quantities consumed per eating occasion in grams (Table Set 1) and another which provides estimates for the quantities of 96 foods and food groups eaten per individual per day (Table Set 2). Since the LIBCSP participants consist of females ages 20 and older, only information

pertaining to females in the following age categories listed on the tables was used: Age 20-39, Age 40-59, and Age 60 and older. The quantities consumed by users in Table Set 2 are reported in terms of gram weights. Both table sets were used in this weighting process.

USDA Database for the Flavonoid Content of Selected Foods Adjustments: Repeated Food and Beverage Items

Some foods and beverages from the modified Block FFQ used in the LIBCSP were listed on the USDA Database for the Flavonoid Content of Selected Foods multiple times yet in different forms. For example, 'Apples, Applesauce, and Pears' is listed on the FFQ, but six items on the USDA Flavonoid Database contain at least one of these products (e.g., 'Apples, raw, with skin'; 'Apples, raw, without skin'; 'Pears, with skin, raw'; 'Pears, without skin, raw'; 'Pears, without skin, cooked'; and 'Applesauce, canned, unsweetened, without added ascorbic acid'). For these occurrences, the CSFII 1994-96 (392) was used to provide estimates of the proportion consumed (weights) of each USDA Database item.

New Variable Creation in Excel from the Modified Block FFQ Foods and Beverages

The data from the USDA Database for the Flavonoid Content of Selected Foods was placed into an Excel spreadsheet for ease of formula and variable creation. New variables were created for each of the items on the modified Block FFQ. For example, the 'Apples, Applesauce, and Pears' item on the FFQ was created into one variable called 'FFQapple'. Next, seven columns (Total Flavonoid Intake / Day, Total Flavonols / Day, Total Flavones / Day, Total Flavanones / Day, Total Flavan-3-ols / Day, Total Anthocyanidins / Day, and Total Isoflavones / Day) were added to the right of each of these new variables. An additional column for Total Lignans / Day was added to those foods and beverages which are shown to contain lignans from the phytoestrogen concentrations of food items (382).

Formulas were created in Excel to calculate the totals for each new variable. Next, these new variables' respective total flavonoid and flavonoid class values were entered into a new Excel spreadsheet.

The Excel spreadsheet contains a column for the identification number (ID) of each LIBCSP participant. Each Excel spreadsheet had this same column of information to facilitate merging of data into one SAS dataset. To the right of each ID number were the total flavonoid and total flavonoid class per day variables (e.g. appletotalday and appleflavone) and their respective values. The values for each variable were identical for each participant in order to estimate flavonoid intake based on their actual intake of the food or beverage (Table 2.3).

When assessed separately, the total lignan intake per day variable was multiplied by 1000 so that all values were in micrograms (μg) per day. This was done because the levels of lignan intake are typically estimated to be in μg per day (393, 394). The Excel spreadsheets were imported into SAS and merged by ID with an existing dataset which includes the gram per day variables and values for the modified Block FFQ items, as well as the data obtained from the other LIBCSP Case-Control and Follow-Up Study exposure assessment tools.

New Variable Creation in SAS

The USDA Flavonoid Database for the Flavonoid Content of Selected Foods and the USDA – Iowa State University Database on the Isoflavone Content of Selected Foods report flavonoids in mg per 100 g of food or beverage. Thus, within the Program Editor of SAS, the gram per day variables created from the modified Block FFQ data were to be divided by 100, creating new variables which represent the number of 100 g servings of each item on the

FFQ. Next, these new variables were multiplied by the total flavonoid per day intake variable and total flavonoid class intake variables, respectively, to obtain estimates which represented the actual intake (in mg per day) of total flavonoids and each flavonoid class per day by the women in the LIBCSP.

Next, new variables were created which represent the grand total of flavonoid intake and flavonoid class intake. This was accomplished by taking each of the variables created in the previous step and summing them together (within their own class: e.g. the anthocyanidins, flavones, etc.) to create new variables that represent the grand total (in mg per day) of flavonoids (total flavonoids and each flavonoid class) consumed for all the women in the LIBCSP.

USDA Database for the Flavonoid Content of Selected Foods Adjustments: Foods and Beverages Omitted

The USDA Database for the Flavonoid Content of Selected Foods contains many foods and beverages which are not commonly consumed in the American diet and are small contributors to American consumption of flavonoids (377, 392). These products are not inquired about on the modified FFQ used in the LIBCSP and include the following, apple cider (European); avocados; bee pollen; bilberries; bilberry soup; black currant juice; blood orange juice; bog whortle berries; buckwheat flour, groats; capers; celeriac; celery hearts; chicory greens; chicory roots; chokeberries; cloudberries; corn poppy leaves; cowberries; cress, garden, raw; crowberries, juice; crown daisy leaves; currants; dock leaves; elderberries; endive; gooseberries; gourd; Greek greens pie; Hartwort leaves; Horseradish root, whole; kohlrabi; leeks; lemon balm leaves; lemons; licorice root; lingonberries, juice; lovage leaves; mangos, raw; marrowfat pea; olives; parsnips; peppermint; perilla leaves;

pummelo juice; purslane; Queen Anne's lace; radishes; raisins; rhubarb; rowanberries; rutabagas; saw thistle, leaves; sour orange juice; sweet potato leaves; tangelo juice; tangerine juice; tangor juice; vinegar (cider, wine, red, white); water spinach; and water cress. Because these foods are rarely consumed in the American diet (392), it would be difficult for them to contribute to the daily intake of flavonoids in the LIBCSP. Therefore, an assumption was made that the effect of misclassification of flavonoid exposure related to intake of these foods and beverages was trivial and thus would not have an impact on study results.

Specific Variable Definitions and Confounders

Many of the risk factors for breast cancer incidence that were described in the Background section may also affect flavonoid intake, thus confounding the association between flavonoid intake and breast cancer incidence. These confounders may act on flavonoid intake directly or indirectly through another risk factor, such as SES. In the literature, these confounders are generally described in relation to diet, which typically are fruit and vegetable intake and fat intake. The main studies of flavonoids have been conducted on soy-derived isoflavones (e.g. daidzein and genistein) (395, 396) whereas the information about the other classes of flavonoids found in the principal aliments of the Western diet is still scarce (397). Therefore, in the following discussion of these confounders, they will often be referred to through their effects on diet and these products, which will serve as proxies for flavonoids. These confounders were assessed in the main questionnaire of the LIBCSP and subsequent variables have been derived from this information and used in the proposed study of flavonoid intake and breast cancer.

Socioeconomic Status (SES)

As stated previously, many of the potential confounders of the association between flavonoid intake and breast cancer incidence may work through a pathway involving SES. Surveys describing social differences in dietary habits indicate that subjects of lower SES are more likely to eat less healthily (398, 399). For example, a review of surveys conducted between 1985 and 1999 in 15 European countries, higher SES was associated with greater consumption of both fruit and vegetables (400, 401). The pooled estimate of the difference in intake of fruit was 33.6 grams/day (95% CI: 22.5-44.8) and vegetables was 13.4 grams/day (95% CI: 7.1-19.7) for women (400). Likewise, other studies have shown that groups with high SES adopt healthier dietary behavior than lower SES groups (402-404).

Additionally, living in a disadvantaged community may affect BMI and obesity in at least two ways (405). First, poorer communities may lack the resources necessary to support a healthy diet and sufficient physical activity (405). Disadvantaged communities also present fewer opportunities and more constraints to eat healthy foods (405). Wealthy and predominantly white neighborhoods have over four times the number of large supermarkets, which tend to have low food prices and an abundant selection of healthy foods such as fresh fruits and vegetables, compared to poor and predominantly black neighborhoods (406).

Assessment of income was derived from the LIBCSP Main Questionnaire, where subjects were asked to indicate the range of their total household income before taxes for the last calendar year. This income included that provided by a spouse or partner, as well as any other person living in the household. This variable, like those that will soon be described, was used in the assessment of its effects on the association between flavonoid intake and breast cancer risk.

Hormone Replacement Therapy (HRT)

Similar to pregnancy, HRT use may affect flavonoid intake indirectly through SES (407). Additionally, HRT use may affect flavonoid intake because of its potential correlation with physical activity (408-410). In a cross-sectional study of women ages 60 to 79 years from the British Women's Heart and Health Study (411), the association between SES and HRT use was assessed. Indicators of a low SES; measured by income, education, and job status; were associated with reduced odds of using HRT (411). All indicators of low childhood SES were also associated with reduced odds of ever using HRT (OR = 0.72, 95% CI: 0.58-0.89) (411). Likewise, a cross-sectional survey of women ages 50 to 79 years in Vermont (412) indicated that those with a moderate to high income were three times more likely to use HRT than those with a low income. This corroborates with results of another U.S. survey of post-menopausal women (413) which indicated that both income level and education were associated with an increased likelihood of HRT counseling being obtained, comparing women earning at least $50,000 per year to women earning less than $30,000 per year (OR = 2.9, 95% CI: 1.7-4.8) (413).

American prospective cohort studies have found that before they started to do so, women who used HRT were better educated, had a lower BMI, and were more physically active than women never using HRT (408-410). Other American studies have found that women who use HRT are healthier or report better health than non-users, indicating that women with a better health prognosis are selected for HRT (414, 415).

Subjects were asked to report their hormone medication history in the main questionnaire. They were initially asked if they had ever used any of the medications listed on a card

provided to them during the interview. If they responded 'yes' to any of the medications, they were prompted to provide further information regarding the hormone use such as the name of the hormone, when it was first used, how often it was used, and when it was no longer used. This data was converted to a dichotomous variable which indicated if HRT was ever or never used.

Family History and Benign Breast Disease (BBD)

The literature on family history of breast cancer and diet is scarce. However, it is reasonable to infer that if a first-degree relative of a woman has or had breast cancer, then the woman may tailor her lifestyle in a healthful manner. In fact, general anxiety and depression were clear predictors of consuming a low-fat diet in a study of affect and health behaviors in 1,366 U.S. women ages 18 to 74 years (416). Negative affect has been shown to be a determinant of eating behavior for women (417). A study of first-degree relatives of breast cancer patients with high perceived risk were more likely to engage in leisure physical activity (418). Both a family history (154-157) of breast cancer and having BBD (179-182) increase a woman's risk of developing breast cancer. Thus, if a woman knows she is at an increased risk of developing breast cancer, she may modify her dietary intake and amount of physical activity.

During administration of the main case-control questionnaire, the subjects completed a section devoted to family history. They were asked about their immediate blood relatives (parents, grandparents, siblings, and children) and their respective cancer histories. This information included the type of cancer and when it was diagnosed. If breast cancer was reported, they were asked if one breast or both breasts were involved. A variable was created

from this reported information that indicated whether or not the subject had a mother, sister, or daughter with breast cancer. Information regarding BBD was abstracted from a section of the main questionnaire which inquired about the subject's medical history. Similar to family history, a dichotomous variable was created to indicate whether or not a subject had a history of BBD.

Physical Activity

Women who exercise may follow different diets than non-exercisers (419). Furthermore, physical activity may be associated with other healthy behaviors besides dietary intake; including alcohol intake, weight maintenance, and not smoking (213). Similarly, low levels of physical activity are often associated with other unhealthy lifestyle factors such as smoking and alcohol consumption (420, 421). In a study of the EPIC population in Spain (36), vegetable intake increased with education and physical activity. These findings make sense with what most people would assume, that women who are more physically active, on average, consume healthier diets which include fruits and vegetables. As stated by Gerber and colleagues (422), the better-informed and increasingly health-conscious population of the present day are seeking to identify and eliminate the putative carcinogenic risk factors and to exploit the preventive effects attributed to certain dietary components.

Subjects were asked to report their physical activity history in a section of the main case-control questionnaire. Information on the type of activity, when the activity began and ceased, as well as the frequency of activity were collected. Additionally, the date of the subject's first menstrual period and the reference date were abstracted from the questionnaire

to create a variable which provided the average hours per week of physical activity from menarche to the reference date.

BMI, Obesity, Weight, and Weight Gain

These body size risk factors are affected by dietary intake and visa versa. In a study documenting BMI and knowledge regarding obesity as a risk factor for breast cancer (423), the authors noted of the African, Caribbean, and European-American women that their dietary habits and those of the population at large put them at risk of becoming overweight. Excess body weight is one of the most readily preventable risk factors (424, 425) for breast cancer and estimates suggest it can directly explain at least 10% of female cancers (194). In characterizing obesity as a risk factor for breast cancer, other contributory effects should be considered (422). Some women not only consume poor diets, but are also less physically active, from a lower SES class, and have other detrimental habits such as smoking (426-430). Thus, for obese people, diet and lifestyle modification is widely considered the primary means to control weight (431).

In the section of the questionnaire which inquired about body size and physical activity, subjects were asked how tall they were (in feet and inches) and how much they weighed (in pounds) at age 20 and at their reference date. These data were converted to meters squared (m^2) and kilograms (kg) so BMI could be calculated in kg/m^2.

Alcohol Consumption

Alcohol consumption is an important constituent of the American diet (432). In addition, dietary and lifestyle characteristics may differ for consumers of specific alcoholic beverages

and non-consumers which may have important implications for studies of alcohol and disease (433). For example, a cross-sectional study of data from the Malmo Diet and Cancer Study (434) indicated that intakes of alcoholic beverages were positively associated with fat intake in women. This held true for beer, wine, and spirits but the majority of the alcohol came from beer (434). Fruit and vegetable intake was also lower among the high-fat consumers (434). Thus, high fat intake and low fruit and vegetable intake were markedly pronounced in the high alcohol consumers (434).

Similarly, a series of case-control studies (433) of alcohol use and different types of cancer, including breast, in western New York indicated that wine drinkers had higher education and household incomes, lower prevalence of current smoking, lower total fat intakes, and higher intakes of fruits and vegetables than consumers of other beverages. Conversely, beer and liquor drinkers tended to have lower education and household incomes, higher rates of current smoking, higher fat intakes, and lower intakes of fruits and vegetables (433). Thus, alcoholic beverage preference may encompass other health-related behaviors such as diet and SES (433).

Information on subjects' alcohol intake was collected from a section in the main case-control questionnaire. Subjects were asked to report the frequency of consumption (e.g. times per day) and amount consumed (such as 12 ounces (oz.) of beer) of beer, wine, and liquor. To facilitate subject recall, these questions were divided into six age groups ranging from 'Under 20 years old' to 'Age 60 or older'. The frequencies and amounts of each alcoholic beverage consumed (12 oz. beer, 4 oz. wine, and 1.5 oz. shots of liquor) were averaged over the decades to obtain the grams of intake per day.

Specific Variable Definitions of Other Risk Factors

These well-known or potential risk factors of breast cancer incidence were assessed in the LIBCSP. This section describes how these risk factors were assessed and how variables were created from the information provided to allow for subsequent data analysis.

Menopausal Status

According to Gammon and colleagues (371), menopausal status was defined using information provided by the subject during the case-control interview on her date of last menstrual period, prior surgical information on hysterectomy or oophorectomies, her smoking status, and use of hormone replacement. A subject was defined as post-menopausal if her last menstrual period was more than 6 months before the reference date or if she had both ovaries removed prior to reference date (371). If a subject was taking hormone replacement therapy or had a hysterectomy without removal of both ovaries, her menopausal status was initially classified as unknown (11.81% of subjects). To reduce the number of subjects with unknown menopausal status, information was utilized about the subject's reference age (371). That is, any smoker with unknown menopausal status was categorized as post-menopausal if her age at reference was $\geq$ 54.8 years (90% percentile for natural menopause among smoking controls), and any non-smoker with unknown menopausal status was categorized as post-menopausal if her age at reference was $\geq$ 55.4 years (90% percentile for natural menopause among non-smoking controls) (371). Subjects whose final classification of menopausal status was missing was 3.04% (371).

Age at Menarche

In the main case-control questionnaire, subjects were asked about their menstruation and menopause history. The first question of this section asked for the month and year (or age) of their first menstrual period. Because of the proposed link of hormones to breast cancer, this variable was useful in determining lifetime exposure to reproductive hormones.

Age at First Birth and Parity

Subjects completed a section in the main case-control questionnaire which inquired about their pregnancy history. Information was collected by questions regarding the type of pregnancy (live birth, stillbirth, miscarriage, abortion, or ectopic pregnancy), gender of the newborn, length of the pregnancy, and what date the pregnancy ended upon. Any pregnancy which lasted at least 6 months was considered to be a full-term pregnancy. From this information, age at first birth and parity (number of full-term live births) could be determined.

Age at first birth was derived from the date of the first full-term pregnancy's endpoint and the date of birth of the mother. This was initially a continuous variable in the dataset but was then centered for ease of use in data analysis. The youngest age of a subject at first birth was the amount of years subtracted from all ages at first birth, thus making the youngest age at first birth equal to zero. Parity was derived by adding the number of full-term live births together.

Oral Contraceptive Use

In the main case-control questionnaire, subjects were asked about their contraceptive history. The first question in this section asked if they had ever used pills, shots, or implants

as methods of birth control. The remainder of the section inquired about the type of birth control method used and the start and stop dates of use for each. The variable that was created to assess oral contraceptive use came from the first question, a dichotomized assessment of ever or never use of oral contraceptives.

Race

The main case-control questionnaire contained a Background section which asked subjects the category that best described them; White, Black/African American, Asian/Pacific Islander, American Indian/Aleut/Eskimo, or Other (Specify). The majority of the LIBCSP population reported themselves as White (94%).

Passive/Active Cigarette Smoking

Subjects were inquired about their cigarette smoking behavior in a section of the main case-control questionnaire. Subjects were first asked to indicate if they had ever smoked cigarettes, age when they started to smoke, age they stopped smoking (if ever), as well as amount and frequency of cigarettes smoked. A current active smoker was defined as smoking within the 12 months prior to the reference date (date of diagnosis for the invasive cases) (233). A former active smoker was defined as a smoker who reported quitting more than 12 months prior to the reference date (233). Passive smoking data was defined as exposure to cigarette smoke in the household (which included caregivers). A passive smoker was defined as either a current or former smoker or non-smoker who reported ever living with an active smoker; and a never smoker was defined as a non-smoker who also did not report living with an active smoker (233). The relationship to the subject of the cigarette

smoker was inquired, in addition to the subject's first age of exposure to this household member's smoke, the age of last exposure to this smoke (if ever), and how many years the subject was exposed to the smoke. From this data, two variables was created; one to assess their current active smoking status and one to assess their current passive smoking status as, both as current, past/former, or never.

Fruit and Vegetable Consumption

As described by Gaudet and colleagues (48), individual fruits and vegetables were categorized into nine food groups: any fruits, fruit juices, and vegetables; any fruits; fruit juices; citrus fruits; any vegetables; leafy vegetables; yellow vegetables; and cruciferous vegetables. The food groups were based on published literature from Potischman (435) and Frudenheim (44).

Statistical Methods and Data Analysis

Preliminary descriptive statistics of the study population were generated, including means, medians, standard errors and t-tests (comparing cases and controls) for continuous variables such as flavonoid intake, fat intake, alcohol intake, age, BMI, age at menarche and age at menopause; and frequencies and Chi-square tests (comparing cases and controls) for categorical variables such as stage at diagnosis, race, socioeconomic status (SES), education, parity, hormone replacement therapy use, and family history of breast cancer. The average intakes of dietary variables included total energy, fat, fruits, vegetables, and fiber for cases and controls. This is common in breast cancer nutrition papers and allows for facilitated comparison of each group's dietary practices.

Aim 1: To estimate intake of seven classes of flavonoids and total flavonoid intake among breast cancer cases and controls using the USDA Flavonoid Database for the Flavonoid Content of Selected Foods and LIBCSP dietary data.

To address this aim, univariate and frequency procedures were conducted to calculate the mean, median, minimum, maximum, and standard deviation of each of the classes of flavonoid intake, as well as total flavonoid intake, among cases and controls. Flavonoid intake was quintiled to better assess the actual distribution of intake in the cases and controls. The individual flavonoids which make up each class were summed together to total class values. Additionally, total flavonoid intake was estimated through summation of all the individual flavonoids for cases and controls, respectively. The final database was designed to estimate all of these measures, making Aim 1 fairly easy to achieve.

Aim 1 Analysis and Results

Flavonoid Intake

The distribution of flavonoid intake among the breast cancer cases and controls is presented in Tables 3.1 and A.2. Overall, cases consumed a lower amount of total flavonoids per day than controls among both post-menopausal (mean = 220.74 mg/d and 242.66 mg/d, respectively) and pre-menopausal women (mean = 211.12 mg/d and 212.19 mg/d, respectively), though the differences were more pronounced among post-menopausal women. Flavan-3-ols were the largest contributor to total intake and were most disparate between post-menopausal cases (mean = 163.29 mg/d) and post-menopausal controls (mean = 182.68 mg/d). Geometric means of flavonoid intake for pre- and post-menopausal cases and controls are presented in Table A.3.

A list of the foods and beverages containing each class of flavonoids is presented in Table A.4. Flavonols and lignans are the most prevalent classes of flavonoids in the items. Tables A.5 and A.6 present the intakes of each class of flavonoids for cases and controls by ER/PR status. Women who were ER-PR+ consumed the greatest daily intake of flavonoids per day, though this was the smallest hormone receptor group (n = 48). The distribution summary of cases and controls within each quintile of flavonoid intake, stratified by menopausal status, is presented in Table A.7.

Aim 2: To examine the association between each class of flavonoid intake and total dietary intake of flavonoids and risk of breast cancer. This tested the hypothesis that there is an inverse association between flavonoid intake and risk of breast cancer.

To address this aim, data from the case-control study was used and unconditional logistic regression was used to calculate ORs and 95% confidence intervals (CI) of breast cancer in relation to quintiles of flavonoid intake. All ORs and CIs assessed the association between flavonoids and risk of breast cancer. Each class of flavonoid intake and total flavonoid intake was also assessed. Age-adjusted ORs and corresponding 95% CIs were calculated, as well as ORs adjusting for potential confounders to examine the main effects of flavonoid intake on breast cancer risk (436). In building regression models, backward elimination processes was used to determine effect measure modifiers and confounders to be included in the models. Effect measure modification, for example, by BMI, which is a risk factor for post-menopausal breast cancer and may be related to flavonoid intake, was assessed with interaction terms and the Likelihood Ratio Test (LRT) comparing a full model which included the interaction term and a reduced model which excluded the interaction term.

Other potential effect measure modifiers included physical activity, family history of breast cancer in a mother or sister, and menopausal status. Potential confounders (age, family history of breast cancer in a mother or sister, BBD, physical activity, BMI, SES, HRT, and alcohol consumption, fruits, vegetables, and micronutrients) were evaluated by crude ORs and adjusted ORs which are adjusted by the potential confounder. A 10% change or greater between these two effect measures resulted in retaining the potential confounder in the model (436).

Aim 2 Analysis and Results

Description of Exposures

This study found a decreased risk of breast cancer for post-menopausal women and women with high parity (≥ 3 births). An increased risk was observed for those with a family history of breast cancer and those with a history of BBD. No association was observed for BMI, education, alcohol, cigarette smoking, oral contraceptive use, income, physical activity, age at menarche, race, religion, marital status, and HRT use. As demonstrated in the summary of this preliminary analysis, detailed in Table A.8, only age and menopausal status showed evidence of effect modification between flavonoid intake and breast cancer incidence. None of the evaluated factors showed evidence of confounding the flavonoid-breast cancer association (Table A.8).

Crude Results

Among post-menopausal women, breast cancer risk was decreased in relation to intake of all flavonoids except for flavanones and isoflavones (Tables 3.2 and A.9). ORs (95% CIs) were reduced by 25% among post-menopausal women in the highest fifth of intake of total

flavonoids (OR = 0.75, 95% CI = 0.56-1.01), by nearly 40% for flavones (OR = 0.61, 95% CI = 0.45-0.83), by nearly 50% for flavonols (OR = 0.54, 95% CI = 0.40-0.73), and by 30% for lignans (OR = 0.69, 95% CI 0.51-0.94). In contrast, among pre-menopausal women, there was no evidence for a decreased risk of breast cancer for any class of flavonoids.

When stratified by ER/PR status, there was little or no heterogeneity in breast cancer risk in relation to flavonoid intake for post-menopausal women (Tables 3.3 and A.10). A consistent trend towards a reduced risk was found for all hormonal receptor types in relation to flavonols, flavones, and total flavonoids.

Fruit and Vegetable-adjusted Results

Table A.11 presents the associations between each class of flavonoid intake and breast cancer risk, adjusted by age, energy, fruits, vegetables, and micronutrients. The results are similar to the age and energy-adjusted results in Tables 3.2 and A.10.

ER/PR Stratified Results

Table A.12 presents the odds ratios and 95% confidence intervals for post-menopausal women by each of the four hormone receptor types. Table A.13 presents these results among post-menopausal women in a slightly different form, by comparing those who are ER+PR+, ER-PR-, or ER-PR+, to those who are ER-PR-. Neither table provided useful information for the formal analysis. Stratification by each hormone receptor type caused small numbers in the ER+PR- and ER-PR+ groups and therefore results were imprecise.

Aim 3: To examine the association between each class of flavonoid intake and total dietary intake of flavonoids and survival with breast cancer. This tested the hypothesis of an inverse association between flavonoid intake and mortality following diagnosis with breast cancer.

To address this aim, dietary intake assessed at the time of the original case-control study interview, which reflectd intake in the year prior to the reference date, was examined as the primary exposure.

The endpoint was time to death, which was considered to be all-cause mortality or breast cancer mortality. Kaplan-Meier survival curves were constructed to give actuarial estimates of the 5-year cumulative incidences for the endpoint of interest (437). Cox regression models were used with exact handling of ties to assess the associations of each death with the covariates under study (437). Differences between the cumulative incidence curves for the different exposure categories were assessed with a log-rank test. If there was a greater than 10% difference, subsequent analyses were performed using stratified Cox models. To assess the proportional hazards assumption of the Cox model, graphical and formal tests were performed.

Log-minus-log survival curves were examined for different stratifying variables created from the covariates of interest. If the resulting curves showed substantial non-parallelism, then the assumption of proportional hazards was assumed to be violated. All models were specified with a time-varying "proportional" hazards constant to reflect the change in magnitude of relative risks in the two strata with follow-up time. Further tests of the proportional hazards assumption could also have been conducted by adding a time-dependent covariate representing the interaction of an original covariate and time.

The covariates of interest were determined by evaluation of potential confounders and effect measure modifiers. Data for these covariates were generated from the main case-control questionnaire but the data regarding treatment history was also generated from the follow-up interview and medical record abstraction. Effect measure modification, for

example, by obesity, a poor prognostic factor for post-menopausal breast cancer survival which may be related to flavonoid intake, was assessed with interaction terms and the Likelihood Ratio Test (LRT) comparing a full model which included the interaction term and a reduced model which excluded the interaction term. Other potential effect measure modifiers included age, radiation therapy, chemotherapy, family history of breast cancer in a mother or sister, tumor ER/PR status, cigarette smoking, SES, and physical activity. Potential confounders (age, family history of breast cancer in a mother or sister, menopausal status, physical activity, BMI, SES, parity, alcohol consumption, radiation therapy, chemotherapy, and fruits, vegetables, and micronutrients) were evaluated by crude HRs and HRs adjusted by the potential confounder. A 10% change or greater between these two effect measures resulted in retaining the potential confounder in the model (436).

Aim 3 Analysis and Results

Description of Exposures

Tables A.14 and A.15 display a comparison of characteristics for all invasive cases (n = 1,273) and the sub-sample of case women with dietary data available for the survival analysis reporte here (n = 1,210). Based on crude, unadjusted analyses, post-college education, HRT use, and income ≥ $70,000 was associated with a decreased risk of mortality, and black race was associated with an increased risk of mortality. The distribution of these 1,210 invasive cases by quintile of flavonoid intake is presented in Table A.16. The majority of invasive cases were white, post-menopausal, married, and non-smokers. Approximately 20% had a family history of breast cancer in a first degree relative.

Crude Results

Among post-menopausal women, risk of all-cause mortality was decreased in relation to flavones (HR = 0.59, 95% CI: 0.35-0.99) and isoflavones (HR = 0.44, 95% CI = 0.24-0.81), comparing the highest quintile of intake to the lowest quintile (Tables 4.2 and A.17). Total flavonoids (HR = 0.78, 95% CI = 0.49-1.25) and anthocyanidins (HR = 0.66, 95% CI = 0.40-1.08) were also associated with a modest reduction in mortality. Flavones (HR = 0.64, 95% CI = 0.42-0.98) and anthocyanidins (HR = 0.62, 95% CI = 0.40-0.94) also reduced the risk of mortality when both pre- and post-menopausal women were analyzed together.

Among pre-menopausal women, similar reductions in all-cause mortality were observed for flavones (HR = 0.69, 95% CI = 0.32-1.47), isoflavones (HR = 0.71, 95% CI = 0.34-1.48), and anthocyanidins (HR = 0.62, 95% CI = 0.27-1.40). Total flavonoids (HR = 1.77, 95% CI = 0.91-3.46), flavonols, flavan-3-ols, and lignans were positively associated with mortality; however, estimates were imprecise and no clear dose-response trends were evident.

As shown in Tables 4.3 and A.18, results for breast cancer-specific mortality were similar to those for all-cause mortality, including an inverse association with mortality for flavones among post-menopausal women (HR = 0.49, 95% CI: 0.24-0.99) and all women (HR = 0.50, 95% CI = 0.29-0.87), comparing the highest quintile of intake to the lowest quintile. Total flavonoids (HR = 0.62, 95% CI = 0.33-1.16), anthocyanidins (HR = 0.62, 95% CI = 0.33-1.18), and isoflavones (HR = 0.79, 95% CI = 0.43-1.44) were also associated with a modest reduction in breast cancer mortality.

Similar reductions in breast cancer mortality were observed among pre-menopausal women for flavones (HR = 0.45, 95% CI = 0.17-1.19) and anthocyanidins (HR = 0.81, 95% CI = 0.35-1.89). Total flavonoids (HR = 1.75, 95% CI = 0.82-3.72), flavanols, flavan-3-ols,

and lignans were positively associated with mortality, though no dose-response relationship existed.

Table A.19 lists the preliminary analysis of confounding and effect measure modification for the survival study. Again, only age and menopausal status showed evidence of effect measure modification. No factors confounded the association between flavonoids and survival.

Fruit and Vegetable-adjusted Results

Table A.20 presents the associations between each class of flavonoid intake and breast cancer survival, adjusted by age, energy, fruits, vegetables, and micronutrients. The results are similar, yet more modest compared to those in Table 4.1.

ER/PR Stratified Results

Table A.21 presents the hazard ratios and 95% confidence intervals for invasive cases by each of the four hormone receptor types. Table A.22 provides the same measures for breast cancer-specific mortality. Stratification by each hormone receptor type caused small numbers in the ER+PR- and ER-PR+ groups and therefore results were imprecise.

Study Size and Power

Since flavonoid intake was categorized, power calculations for the second specific aim were based on the assumption of quintile distribution. For the second specific aim, power was calculated with NQuery software. For the third specific aim, a web-based program from Johns Hopkins University (438) was used. For this study, each quintile was assumed to have approximately 300 women for cases and controls, respectively. Hypothesized odds ratios and proportions of cases and controls comparing the lowest quintile of intake to the highest

quintile of intake were explored for the study's 1,481 cases and 1,508 controls, using an estimate of 600 total subjects per quintile. A two-sided alpha value of 0.05 was presumed for these estimates. The sample size of our study had adequate power (> 80%) to detect an odds ratio of 0.70 (Table 2.4).

For the survival analysis, the sample size of the study had relatively adequate power (75%) (Table 2.5) to detect a hazard ratio of 0.50 (439, 440). Of the 1,273 invasive cases, 186 (14.6%) died during the follow-up period. The primary aim of the survival analysis was to examine the association between each class of flavonoid intake and total dietary intake of flavonoids and survival with breast cancer.

Study Strengths

At the time the women were diagnosed, between August 1, 1996 and July 30, 1997, the U.S. retail of soy-based foods was approximately $1.4 billion (441). As of 2002, the U.S. retail had nearly tripled at $3.7 billion (441). Soy isoflavone consumption has been estimated to range from 25-45 mg/day in Asian populations compared to < 5 mg/day in Western populations (442). Fruit and vegetable intake has remained significantly higher as the mean frequency of daily consumption was 3.66 servings per day of fruits and vegetables in women in 1996 (443). This number has stayed relatively constant over the years at approximately 3.6 (443). The LIBCSP population consumed a diverse amount of fruits and vegetables (48), 3.94 ½ cup servings per day, which made it possible to determine if flavonoids may reduce breast cancer risk and enhance survival after diagnosis. Thus, while the FFQ is not perfect, the major sources of flavonoids in the LIBCSP population diet were able to be measured.

The study design, sample size, and comprehensive interview data for the LIBCSP Case-Control Study and Follow-Up Study provided us with an efficient opportunity to examine important yet unresolved questions in breast cancer research. In addition, the flavonoid intake and survival question had yet to be addressed in published research. Thus, a new area of breast cancer survival research was studied.

The Block FFQ is a validated and reliable dietary assessment tool for estimating usual food group intake and ranking individuals into categories of intake (374, 375, 383). While it was not originally designed to measure flavonoid intake, the impact of missing foods was assessed by comparing those listed on the FFQ to those in the USDA database, as well as the addition of genistein and daidzein composition of tofu, fruits, vegetables, and grain products from this database and other sources from the literature. Widely available fruits and vegetables, chocolates, and tea were included on the instruments; thus providing some assurance that commonly-consumed flavonoid-rich products were assessed in this population. Additionally, while several studies have examined the association between flavonoids in relation to breast cancer risk, only two studies to date had examined flavonoids with the USDA Database, and those were in a Greek population (59) and Italian population (60), respectively. By examining the effect of flavonoids with this database on a U.S. population, it was possible to observe a stronger association.

Study Limitations

While the FFQ has recognized limitations in assessing diet, it was the best method available for conducting large epidemiologic studies such as the LIBCSP. The Block FFQ was originally designed to estimate fat intake and while there have been modifications made

to incorporate additional nutrients and foods, it does not assess all sources of flavonoids listed in the USDA Database for the Flavonoid Content of Selected Foods. Also, tofu is the only soy-based product on the LIBCSP Block FFQ and soybean products are the primary food source listed on the USDA – Iowa State University Database on the Isoflavone Content of Selected Foods. However, with the use of additional databases (from Dr. Mary Wolff and those found in the literature from other experts in the field), the inclusion of isoflavone-containing fruits, vegetables, nuts, beverages, and grain products were performed to ensure the most accurate estimates of flavonoid intake possible. Additionally, the FFQ did inquire about numerous flavonoid-rich fruits and vegetables, as well as tea, wine, and chocolate, all of which are commonly consumed products in the United States (392), so the amount of underestimation was minimal.

Other limitations include recall of past diet. There are many forms in which recall can be a problem with the use of FFQs. First, responses are dependent upon subjects' ability to remember food consumption over the past accurately, which varies in an unsystematic way from person to person (444). In addition, the diagnosis of breast cancer may have influenced how cases responded to the FFQ, possibly attributing their diagnosis to certain components of their diet, which could lead to a vast difference in diet between cases and controls and, perhaps, portray flavonoids as more protective than they really may be. The third issue related to recall is the desire of some to report a healthier diet. This could have lead to an underreporting of fat and sweets intake and over-reporting of fruit and vegetable intake because they believed this would be acceptable in the eyes of the interviewer; it was possible that this type of recall problem would make the cases and controls appear more homogeneous

with respect to dietary intake and make it difficult to detect an effect of flavonoids on breast cancer incidence and survival.

Additionally, the LIBCSP Block FFQ measured dietary intake in the year prior to the interview. Like many chronic diseases, it is hypothesized that breast cancer is a result of an accumulation of exposures and changes within the body, which can take many years to develop before a diagnosis is made. Thus, the FFQ may not have assessed the period of time most relevant to the development of breast cancer. This means the diet reported in the FFQ was assumed to be similar to not only the diet in the year proceeding diagnosis for cases, but also the years following diagnosis. However, diet does change over time, especially more likely after a diagnosis of breast cancer when lifestyle changes are often made in an attempt to prevent recurrence (445-447). This problem may have been more pronounced with the flavonoid intake and survival analysis because it could be inferred that women consumed more fruits and vegetables following diagnosis (445-447). This would have resulted in the FFQ underestimating their post-diagnosis flavonoid intake and perhaps make it easier to find a beneficial effect of flavonoids when consumed at very low levels.

Finally, with regard to survival, the advent of surgical and drug treatment has made immense improvements in the prognosis of breast cancer cases. Thus, these improvements alone, rather than flavonoids, may have been important for improving breast cancer survival. The best way to address this problem was to adjust for chemotherapy and radiation treatment so that the effect of flavonoids could be better observed.

Summary

Although several studies have examined flavonoids in relation to breast cancer risk, most have involved isoflavones in soy, and none have been published thus far with regard to breast cancer survival. Various classes of flavonoids have been reported to inhibit breast cancer cell replication, estradiol activity, and mammary tumorigenesis. However, except with respect to isoflavones, there is no sufficient evidence, experimental or otherwise, linking particular flavonoids or classes of flavonoids to specific actions in the process of mammary carcinogenesis (59). Consequently, the biologic plausibility of any inverse, protective associations found in the other classes of flavonoids and breast cancer risk and survival, were considered no more than suggestive (59).

The fundamental reason for conducting this analysis was to examine what components in particular foods and beverages, primarily fruits, vegetables, and tea; have biological mechanisms that impact the development of breast cancer. The hypotheses included the following, that the controls consume more flavonoids than the breast cancer cases, that increased flavonoid intake reduces the risk of breast cancer incidence, and that increased flavonoid intake improves the prognosis for breast cancer cases following diagnosis. While there are limitations to the FFQ, the amount of underestimation was likely to be minimal. The study population was sufficiently large to detect differences between cases and controls and it may be the first study published using an American population with the USDA Database for the Flavonoid Content of Selected Foods.

Because this area of research is vastly unexplored, results will hopefully provide reasoning for additional research that continues to focus upon what in the diet truly influences the progression, and perhaps suppression, of breast cancer. Flavonoids may play a pivotal role in this process. Eventually, in addition to simply adding to the literature regarding diet and

breast cancer, the possibility of discovering these dietary components could have a large public health impact in terms of prevention and survival.

Tables

Table 2.1. Classes and Dietary Sources of Flavonoids.

Flavonoid Class	Representative Flavonoids	Main Sources
Flavonols	Quercetin, Kaempherol, Myricetin, Isorhamnetin	Onions, Cherries, Apples, Broccoli, Tomato, Tea, Red Wine, Berries
Flavones	Luteolin, Apigenin	Parsley, Thyme, Cereal
Flavanones	Hesperetin, Naringenin, Eriodicyol	Citrus Fruits, (e.g., Oranges, Grapefruit, Tangerines), Cumin, Peppermint
Flavan-3-ols (Catechins)	(+)-Catechin, (+)-Gallocatechin, (-)-Epicatechin, (-)- Epigallocatechin, (-)-Epicatechin 3-gallate, (-)-Epigallocatehin 3-gallate, Theaflavin, Theaflavin 3-gallate, Theaflvain 3'-gallate, Theaflavin 3,3' gallate, Thearubigins	Apples, Tea, Chocolate, Red Wine, Hops, Nuts
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Blueberries, Cherries, Elderberries, Raspberries
Isoflavones	Genistein, Daidzein	Tofu
Lignans	Matairesinol, Secoisolariciresinol	Flaxseeds, Legumes, Whole Grains, Fruits, Vegetables

Adapted from Ren (49), Dwyer (448), and Ososki (449).

Table 2.2. Classification of FFQ Food and Beverage Contribution of Flavonoid Intake.

Category 1. Foods and beverages consumed in high quantities which are large contributors of flavonoids	
Apples, Applesauce, and Pears	Tea
Grapefruit	Wine
Oranges	
Broccoli	
Orange Juice and Grapefruit Juice	
Category 2. Foods and beverages consumed in high quantities which are small contributors of flavonoids	
Tomatoes and Tomato Juice	Spaghetti
Green Salad	Vegetable Soup
Category 3. Foods and beverages consumed in small quantities which are large contributors of flavonoids	
Cherries	Tofu, Frozen Tofu
Fresh Peaches, Apricots, and Nectarines	Chocolate Cake, Brownies, Cookies
Kale, Collards, and Turnip Greens	Chocolate Candy
Category 4. Foods and beverages consumed in small quantities which are small contributors of flavonoids	
Strawberries	Beans
Canned Peaches and Apricots	Cauliflower and Brussel Sprouts
Green Beans	Spinach (raw and cooked)
Peas	Coleslaw and Cabbage
Carrots	Red and Green Peppers
Hamburgers, Beef Burritos, and Meatloaf	Pizza
Beer	

Table 2.3. Example of Flavonoid Data in Excel Spreadsheet.

ID	strawberrytotalday	strawberryflavonol	strawberryflavone	Strawberryflavan-one
10027	7.538300	1.440000	0.000000	0.000000
10043	7.538300	1.440000	0.000000	0.000000
10056	7.538300	1.440000	0.000000	0.000000
10072	7.538300	1.440000	0.000000	0.000000
ID	**strawberryflavan3ol**	**Strawberryantho-cyanidin**	**strawberryisoflavone**	**strawberrylignan**
10027	4.470000	0.000000	0.050200	1.578100
10043	4.470000	0.000000	0.050200	1.578100
10056	4.470000	0.000000	0.050200	1.578100
10072	4.470000	0.000000	0.050200	1.578100

Table 2.4. Minimum Detectable Odds Ratios in the Proposed Case-Control Study of the LIBCSP Population, Alpha = 0.05.

Specific Aim	Estimated Prevalence of Exposure Among Controls (Percent)	Power	Minimum Detectable Odds Ratio
Aim #2. Based on Modified Block FFQ and Case-Control Data: To examine the association between each class of flavonoid intake and total dietary intake of flavonoids and risk of breast cancer.			
Quintile 5 vs. Quintile 1 (highest vs. lowest intake)	20%	0.49	0.80
	20%	0.70	0.75
	20%	0.87	0.70
	20%	0.96	0.65
	20%	0.99	0.60

Table 2.5. Power calculations (expressed as %) assuming different true hazard ratios of breast cancer mortality for certain variables of interest.*

Variable	Hazard Ratios (n = 186 deaths among 1,273 invasive cases)					
	0.9	**0.8**	**0.7**	**0.6**	**0.5**	**0.4**
Flavonoid Intake	7	16	31	53	75	90

*All calculations assume the survival rate in the unexposed group (lowest quintile of intake) is 0.85, based on the 186 deaths (14.6%) amongst the 1,273 invasive cases. Type 1 Error rate was assumed to be 5%. The accrual period was one year and the minimum follow-up time was five years. The percentage lost-to-follow-up was assumed to be 4%, based on the 55 cases (3.9%) of the 1,414 cases who gave permission to be re-contacted. The comparison for the hazard ratio is the lowest quintile of flavonoid intake to the highest quintile of flavonoid intake, amongst the invasive cases only.

Chapter III: DIETARY FLAVONOID INTAKE AND BREAST CANCER RISK AMONG WOMEN IN THE LONG ISLAND BREAST CANCER STUDY PROJECT

Abstract

Background: Flavonoids are phytochemicals found in a variety of foods that have demonstrated anti-carcinogenic properties in experimental studies. Few epidemiologic studies have examined whether flavonoid intake is associated with breast cancer in humans. This study investigated whether dietary flavonoid intake is associated with a reduced risk of breast cancer among a population-based sample of American women. **Methods:** A case-control study was conducted among women ages 20-98 years who resided in Nassau and Suffolk counties in Long Island, New York. Cases and controls were interviewed in-person about known and suspected breast cancer risk factors, and were asked to complete a self-administered food frequency questionnaire (FFQ) regarding their average frequency of food and beverage consumption in the prior 12 months. For those with known menopausal status, 1,434 breast cancer cases and 1,440 controls provided adequate dietary responses. **Results:** Breast cancer risk was decreased for the highest quintile of flavonol intake in post-menopausal women (odds ratio = 0.54, 95% confidence interval = 0.40, 0.73), but not pre-menopausal women (OR = 1.38, 95% CI = 0.88-2.15). Among post-menopausal women, risk was also decreased for flavones (OR = 0.61, 95% CI = 0.45-0.83), flavan-3-ols (OR = 0.74, 95% CI = 0.55-0.99), and lignans (OR = 0.69, 95% CI = 0.51-0.94). **Conclusion:** Intake of flavonols, flavones, flavan-3-ols, and lignans is associated with a reduced risk of incident post-menopausal breast cancer among Long Island women. These results coincide

with previous studies conducted among Mediterranean women. Our results suggest American women can consume sufficient levels of flavonoids to benefit from their potential chemopreventive effects.

Introduction

Flavonoids are a group of more than 4,000 polyphenolic compounds that occur naturally in fruits, vegetables, and beverages of plant origin (49, 72) In numerous laboratory studies, flavonoids have demonstrated the ability to decrease lifetime estrogen exposure (50-53), inhibit tumor cell proliferation (54, 55), and inhibit reactive oxygen species (ROS) (56-58), all of which are mechanisms thought to influence breast cancer development (46, 47, 51-55, 72, 268). Further, dietary intake of certain flavonoids has been reported to potentially protect humans from developing certain types of cancer (450-453), including breast cancer (59, 60).

Until very recently, epidemiologic research regarding flavonoids and breast cancer development in women was limited, primarily due to the difficulty in estimating flavonoid intake. Previous hospital-based, case-control studies in Greece (59) and Italy (60) have had their respective dietary data linked with two flavonoid databases from the United States Department of Agriculture (USDA) (377, 378). Reduced risks of breast cancer were observed for intake of two flavonoid classes, flavones (59, 60) and flavonols (60). Whether similar risk reductions are detectable among American women, for whom intake of flavonoid-rich foods is traditionally lower than in Mediterranean women, is unknown (454-456).

This analysis investigated whether breast cancer risk in a population-based case-control study of women in the Long Island Breast Cancer Study Project (LIBCSP) was reduced in relation to flavonoid intake.

Materials and Methods

Participants

The Long Island Breast Cancer Study Project was conducted on Long Island, New York, in Nassau and Suffolk counties (26). Cases were English-speaking women with newly-diagnosed in situ or invasive breast cancer between August 1, 1996 and July 31, 1997. Cases were identified using a rapid reporting system developed specifically for the study. Controls were randomly selected through random-digit-dialing methods for those under age 65 and Health Care Finance Administration lists for those age 65 years or older and frequency-matched to cases in 5-year age groups (371). The institutional review boards of all the participating institutions approved the study protocol, and the individual women all signed informed consent forms.

In-person interviews were completed for 1,508 breast cancer cases (81.2% of eligible cases) and 1,556 controls (62.8% of eligible controls). Reasons for non-participation included subject refusal, too ill, cognitively impaired, unlocatable or moved out of area, and deceased (26).

Exposure Assessment

Women were administered a standardized questionnaire and asked to report on a variety of known and suspected breast cancer risk factors. Cases who signed a medical record release form at the interview had their medical records reviewed for clinical and pathologic characteristics related to the breast cancer diagnosis and treatment, including estrogen (ER) and progesterone (PR) tumor receptor status.

Cases and controls were asked to recall their diet history in the previous 12 months, including assessment of frequency and portion size, with a modified version of the Block food frequency questionnaire (FFQ) (435). 1,481 cases (98.2%) and 1,518 controls (97.6%) completed this self-administered instrument. To facilitate comparison of our results with other studies, 18 cases and 18 controls with daily energy intakes above or below 3 standard deviations of the log-transformed mean in kilocalories per day (kcal/d) were excluded from the analysis (48). An additional 29 cases and 60 controls were excluded because their menopausal status was unknown, resulting in a total of 1,434 cases and 1,440 controls.

Dietary Flavonoid Intake Assessment

Food and beverage content of total flavonoids and seven classes of flavonoids (flavonols, flavones, flavan-3-ols, flavanones, anthocyanidins, isoflavones, and lignans) were estimated with a database created for use in the LIBCSP (457). The LIBCSP database included both the USDA Database for the Flavonoid Content of Selected Foods (377) and the USDA – Iowa State University Database on the Isoflavone Content of Selected Foods (378). Additional sources (270, 298, 379-382, 458-461) were utilized to include isoflavone content provided by fruits, vegetables, nuts, and grains, which are important dietary contributors among American women (392). These sources also provided content information for lignans, a class of flavonoids not included in the USDA databases, but for which laboratory evidence has demonstrated potential anti-carcinogenic properties (72, 462-466).

Using this database, a total of 50 items listed on the modified Block FFQ were found to contain measurable amounts of at least one flavonoid class. Individual foods and beverages were listed under each class they contained from the richest source to the smallest source (top to bottom) (457). The richest sources of total flavonoids include ‘tea, including herb tea’

(111.41 grams (g) of flavan-3-ols per 100 milligrams (mg)), 'cherries' (116.31 g of anthocyanidins per 100 mg), and 'grapefruit' (54.50 g of flavanones per 100 mg) (377).

Statistical Analysis

Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression (436), including terms for energy intake (kcal/d) and age (in five-year age group). Total flavonoids and each flavonoid class were categorized as quintiles or deciles based on the distribution of intake by controls, but produced similar results; thus, only the results for quintiles are reported here. Tests of trend were conducted using the continuous values in milligrams/day (mg/d).

Confounding was assessed using backward elimination with multivariable models. Potential confounders included menopausal status (pre- and post-menopausal), lifetime alcohol intake (grams/day), cigarette smoking (current, former, never), family history of breast cancer in a mother or sister, benign breast disease, average physical activity levels from menarche to reference date (hours/day), body mass index (BMI) [weight (kg) / height $(m)^2$] at reference date (date of interview), household income, education, parity, mammography use, oral contraceptive use, and fruits, vegetables, and antioxidants consumed in the previous 12 months. None of the potential confounders altered the estimates of effect by greater than 10%.

Effect modification was first examined through use of stratified analysis and then by comparing the log likelihood-statistic for regression models that included a multiplicative interaction term to those without (437). From the covariates listed above, only menopausal status was found to modify the association between flavonoid intake and breast cancer risk.

For the analyses, menopause-specific quintiles were created based on the respective intakes of pre- and post-menopausal control women.

Differences in risk estimates by hormone receptor status of case tumors were examined with stratified analyses. ER+PR+ cases were considered as one group and compared with all other hormonal receptor types combined (ER+PR-, ER-PR+, ER-PR-).

Results

The distribution of flavonoid intake among the breast cancer cases and controls is presented in Table 1. Overall, cases consumed a lower amount of total flavonoids per day than controls among both post-menopausal (mean = 220.74 mg/d and 242.66 mg/d, respectively) and pre-menopausal women (mean = 211.12 mg/d and 212.19 mg/d, respectively), though the differences were more pronounced among post-menopausal women. Flavan-3-ols were the largest contributor to total intake and were most disparate between post-menopausal cases (mean = 163.29 mg/d) and post-menopausal controls (mean = 182.68 mg/d).

As shown in Table 2, among post-menopausal women, breast cancer risk was decreased in relation to intake of all flavonoids except for flavanones and isoflavones. ORs (95% CIs) were reduced by 25% among post-menopausal women in the highest fifth of intake of total flavonoids (OR = 0.75, 95% CI = 0.56-1.01), by nearly 40% for flavones (OR = 0.61, 95% CI = 0.45-0.83), by nearly 50% for flavonols (OR = 0.54, 95% CI = 0.40-0.73), and by 30% for lignans (OR = 0.69, 95% CI 0.51-0.94). There was a significant decreasing trend across quintiles for total flavonoids, flavonols, flavones, and lignans. In contrast, among pre-

menopausal women, there was no evidence for a decreased risk of breast cancer for any class of flavonoids.

When stratified by ER/PR status, there was little or no heterogeneity in breast cancer risk in relation to flavonoid intake for post-menopausal women. A consistent trend towards a reduced risk was found for all hormonal receptor types in relation to flavonols, flavones, and total flavonoids (Table 3). The number of pre-menopausal women in the limited our ability to stratify by hormone receptor status in these younger women.

Discussion

Inverse associations were found for intake of total flavonoids and most flavonoid classes with breast cancer risk in post-menopausal women only. These results are consistent with two previous hospital-based, case-control studies conducted in Greece (21) and Italy (60) that found a slightly more modest reduction in risk with increasing flavones (59, 60) and flavonols (60). Both used the same two USDA databases (377, 378) to measure flavonoid intake and each had a study population size similar to ours. Our enhancement of these American databases to more fully capture intake of flavonoid-rich foods may have improved our ability to detect a stronger association between flavonoid intake and breast cancer risk in our American population.

In contrast, our data do not support an inverse association between isoflavones and breast cancer risk. Previous studies have also not observed an association (238, 370, 467-470), including a study conducted in a multiethnic population in the San Francisco Bay Area (470). The diet history instrument used in the LIBCSP was limited in its coverage of soy products, which may have resulted in a slight underestimation of intake of isoflavone-rich foods. This

non-differential misclassification would result in masking any potential beneficial effects of these compounds.

While previous efforts have been made to estimate the isoflavone content of soy-based products in the U.S. (298, 471), the continued growth of new soy products on the market, as well as non-traditional sources of soy such as soy flour in doughnuts and soy protein in fast food hamburgers, demonstrate the need for their inclusion in future dietary assessment tools. Furthermore, the Block FFQ did not include blueberries and raspberries, both rich sources of anthocyanidins (377). Omission of these berries may have contributed to the lower anthocyanidin intake reported in our study compared to those in Greece (59) and Italy (60), although neither of these studies found a risk reduction with anthocyanidins.

Additionally, flavonoid content in foods is variable, in part influenced by environmental conditions (472). Particularly, in fruits and vegetables, flavonoid content varies due to different cultivars, cultural practices, climatic conditions and geographic location, degree of ripeness, storage conditions, and industrial processing (292, 473-476). Thus, it is possible that there are differences in flavonoid content in the products consumed by the Long Island study population compared to those for which estimates were taken from and used in the creation of databases. However, it is unknown how large or small these differences were and where all products, especially fruits and vegetables, were grown or produced.

Our study did, however, expand the coverage of flavonoids compared to previous studies of flavonoids and breast cancer risk (59, 60) by including lignans, which are typically found in the woody portions of plants, the seed coat of seeds, and the bran layer in grains (382, 477). Lignans are thought to act through the same mechanisms as other flavonoids in preventing breast cancer (477). Our finding of a reduced breast cancer risk for increasing

lignan intake among women on Long Island supports data reported in animals (478-481) and humans (72, 295, 396, 462, 466, 482, 483).

Given the hypothesized anti-carcinogenic effects of flavonoids (46, 47, 50-58, 72, 268), consumption would be expected to benefit both pre- and post-menopausal women. However, the biological mechanism for the effect modification by menopausal status observed in our data is unclear. A previous study of fruit, vegetable, and micronutrient intake in the LIBCSP (48) found a decreased risk of breast cancer among post-menopausal women with increasing levels of vegetable intake and many micronutrients, including alpha and beta-carotene. Our findings suggest that the impact of flavonoids may also be greater in post-menopausal women. Further research based on large numbers of both pre- and post-menopausal women is needed to help clarify this issue.

Flavonoids are in numerous products, including fruits and vegetables, thus flavonoid consumption may reflect part of an overall healthy diet and lifestyle (33, 369). Furthermore, many lifestyle factors that may potentially confound the relationship between flavonoids and breast cancer are highly correlated with flavonoids (48, 484, 485), making it difficult to firmly establish their independent effects (486). The LIBCSP main questionnaire extensively assessed exposures over the life course including recreational physical activity levels from menarche to age at diagnosis, lifetime active and passive smoking exposure, and lifetime alcohol consumption (48). However, when these were controlled mutually or individually, our results were not substantially altered.

Our study relied on retrospective reporting of dietary intake, which is subject to error, particularly in the reporting by breast cancer cases, compared to controls. The controls may have over-reported consumption of flavonoid-rich foods, such as fruits and vegetables, in an

attempt to appear socially correct. This would overemphasize the benefits of flavonoids. However, if this had actually occurred, it would be expected that over-reporting would occur among all control women, regardless of menopausal status. The lack of an association in pre-menopausal women argues against this possibility. An additional concern with errors in recall is that case reports of food intake may be affected by whether they have initiated chemotherapy by the time of the study interview (375). However, in the LIBCSP, most of the case women were interviewed prior to any chemotherapy, and among those that had started, reported intake levels were not found to differ from those who had not started (48).

Very few studies have addressed the impact of dietary flavonoid intake on the risk of breast cancer, particularly in an American population. Only studies in Greece (59) and Italy (60) have used the USDA Database for the Flavonoid Content of Selected Foods and USDA – Iowa State University Database on the Isoflavone Content of Selected Foods together. Our work combined these two databases with additional literature (270, 298, 379-382, 392, 458-461) to provide a more comprehensive instrument for assessing flavonoid intake, including total flavonoids and lignans.

This study had the advantage of a large sample size with a population-based design, reducing selection bias and allowing for greater generalizability of results compared with hospital-based studies. The LIBCSP population consumed a wide variety and significant amounts of flavonoid-containing products, such as fruits, vegetables, and tea, enabling us to address our specific aims. Furthermore, the Block FFQ utilized in this study is a validated, reliable dietary assessment tool for estimating usual food group intake and ranking individuals into categories of intake (375, 383, 487).

In summary, this case-control study provides evidence that increased intake of flavonoids, and particularly flavones, flavonols, flavan-3-ols, and lignans, is associated with reduced risk of breast cancer in a population-based sample of post-menopausal women in the U.S. These findings support similar, but more modest reductions observed in Greece and Italy (59, 60). Most research to date has not utilized the two recently available USDA databases together, with additional sources, to study flavonoids and breast cancer incidence. Further research using these instruments needs to be conducted, particularly among American populations.

Tables

Table 3.1. Distribution of flavonoid intake (mg/d) for cases and controls of the Long Island Breast Cancer Study Project

Pre-menopausal Cases (n = 457)		**Pre-menopausal Controls (n = 487)**		
Variable	**Mean (mg/d)**	**Mean (mg/d)**	**p-value[†]**	**p-value[*]**
Total Flavonoids	211.12	212.19	0.94	0.53
Flavonols	10.09	10.11	0.96	0.35
Flavones	0.14	0.14	0.91	0.44
Flavanones	25.60	27.13	0.44	0.54
Flavan-3-ols	161.00	161.06	0.99	0.41
Anthocyanidins	3.16	3.03	0.75	0.64
Isoflavones	5.50	5.03	0.37	0.38
Lignans	5.97	5.92	0.85	0.50
Post-menopausal Cases (n = 977)		**Post-menopausal Controls (n = 953)**		
Variable	**Mean (mg/d)**	**Mean (mg/d)**	**p-value[a]**	**p-value[b]**
Total Flavonoids	220.74	242.66	0.02	0.02
Flavonols	9.68	10.70	0.002	0.0003
Flavones	0.13	0.15	0.0002	< 0.0001
Flavanones	34.12	34.17	0.97	0.99
Flavan-3-ols	163.29	182.68	0.03	0.009
Anthocyanidins	3.14	3.66	0.17	0.02
Isoflavones	4.58	4.86	0.46	0.69
Lignans	6.01	6.62	0.005	0.002

[†]P-value for t-test comparing means among pre-menopausal women
[a]P-value for t-test comparing means among post-menopausal women
[*]Wilcoxon rank sum test comparing medians among pre-menopausal women
[b]Wilcoxon rank sum test comparing medians among post-menopausal women

Table 3.2. Age and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between menopausal-specific flavonoid intake in relation to breast cancer incidence

	Pre-menopausal (n = 944)		**Post-menopausal (n = 1930)**
	OR (95% CI)		**OR (95% CI)**
Total Flavonoids[#]		**Total Flavonoids[#]**	
0-34.5	1.00	**0-51.8**	1.00
34.5-84.5	1.20 (0.79-1.84)	**51.8-119.1**	0.94 (0.71-1.24)
84.5-199.5	1.29 (0.84-1.97)	**119.1-253.3**	0.79 (0.60-1.05)
199.5-343.0	1.46 (0.96-2.22)	**253.3-377.2**	0.80 (0.60-1.06)
343.0+	1.12 (0.72-1.74)	**377.2+**	0.75 (0.56-1.01)
P for trend[*]	0.95		0.05
Total Flavonols[#]		**Total Flavonols[#]**	
0-3.7	1.00	**0-4.3**	1.00
3.7-6.0	1.32 (0.86-2.03)	**4.3-6.8**	0.56 (0.42-0.74)
6.0-10.2	1.48 (0.97-2.27)	**6.8-11.1**	0.62 (0.47-0.82)
10.2-15.1	1.53 (0.99-2.35)	**11.1-17.1**	0.63 (0.47-0.83)
15.1+	1.38 (0.88-2.15)	**17.1+**	0.54 (0.40-0.73)
P for trend[*]	0.92	**P for trend[*]**	0.009
Total Flavones[#]		**Total Flavones[#]**	
0-0.04	1.00	**0-0.04**	1.00
0.05-0.07	0.94 (0.62-1.43)	**0.05-0.08**	0.90 (0.68-1.19)
0.08-0.12	1.29 (0.86-1.84)	**0.09-0.14**	0.95 (0.72-1.26)
0.13-0.21	1.07 (0.70-1.63)	**0.15-0.21**	0.70 (0.52-0.94)
0.22+	1.07 (0.70-1.65)	**0.22+**	0.61 (0.45-0.83)
P for trend[*]	0.94	**P for trend[*]**	0.0007
Total Flavanones[#]		**Total Flavanones[#]**	
0-3.1	1.00	**0-5.3**	1.00
3.2-10.8	0.69 (0.46-1.04)	**5.4-18.8**	1.09 (0.82-1.46)
10.9-24.5	0.69 (0.46-1.04)	**18.9-32.1**	1.10 (0.83-1.46)
24.6-40.3	0.85 (0.57-1.26)	**32.2-54.2**	1.08 (0.81-1.43)
40.4+	0.80 (0.53-1.21)	**54.3+**	1.00 (0.75-1.34)
P for trend[*]	0.34	**P for trend[*]**	0.87
Total Flavan-3-ols[#]		**Total Flavan-3-ols[#]**	
0-5.1	1.00	**0-7.6**	1.00
5.2-26.4	1.22 (0.80-1.87)	**7.7-54.0**	0.94 (0.72-1.24)
26.5-120.8	1.32 (0.87-2.01)	**54.1-192.0**	0.80 (0.60-1.06)
120.9-264.1	1.52 (1.00-2.30)	**192.1-277.9**	0.82 (0.62-1.08)
264.2+	1.21 (0.78-1.86)	**278.0+**	0.74 (0.55-0.99)
P for trend[*]	0.87	**P for trend[*]**	0.06
Total Anthocyanidins[#]		**Total Anthocyanidins[#]**	
0-0.04	1.00	**0-0.03**	1.00
0.05-0.56	1.15 (0.77-1.72)	**0.04-0.56**	1.09 (0.83-1.44)
0.57-1.60	0.77 (0.50-1.17)	**0.57-1.84**	0.97 (0.73-1.28)
1.61-4.19	1.07 (0.71-1.61)	**1.85-4.84**	0.82 (0.62-1.09)
4.20+	1.08 (0.71-1.63)	**4.85+**	0.85 (0.64-1.14)
P for trend[*]	0.81	**P for trend[*]**	0.23
Total Isoflavones[#]		**Total Isoflavones[#]**	
0-0.31	1.00	**0-0.27**	1.00

0.32-1.10	1.03 (0.68-1.56)	**0.28-0.62**	0.97 (0.72-1.30)
1.11-3.17	0.98 (0.65-1.47)	**0.63-1.94**	1.16 (0.87-1.55)
3.18-7.62	0.88 (0.58-1.33)	**1.95-7.63**	1.14 (0.85-1.53)
7.63+	1.14 (0.76-1.72)	**7.64+**	1.02 (0.76-1.38)
P for trend[*]	0.56	**P for trend**[*]	0.72
Total Lignans[#]		**Total Lignans**[#]	
0-2.0	1.00	**0-2.4**	1.00
2.1-4.0	1.43 (0.95-2.17)	**2.5-4.2**	1.07 (0.81-1.40)
4.1-5.4	0.98 (0.63-1.51)	**4.3-6.4**	0.82 (0.61-1.09)
5.5-9.3	1.62 (1.07-2.45)	**6.5-10.2**	0.79 (0.59-1.05)
9.4+	1.24 (0.81-1.92)	**10.3+**	0.69 (0.51-0.94)
P for trend[*]	0.72	**P for trend**[*]	0.01

[*] P for trend for continuous variable

[#] In milligrams per day (mg/d)

Table 3.3. Age and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between flavonoid intake and breast cancer incidence among post-menopausal women, stratified by ER/PR status

	Controls	ER+PR+		ER+PR-, ER-PR+, ER-PR-	
	(n = 953)	Cases (n) (n = 378)	OR (95% CI)	Cases (n) (n = 274)	OR (95% CI)
Total Flavonoids[#]					
0-51.7	190	89	1.00	72	1.00
51.8-119.0	192	78	0.90 (0.62-1.31)	62	0.89 (0.59-1.32)
119.1-253.2	190	72	0.83 (0.57-1.21)	42	0.60 (0.39-0.93)
253.3-377.1	191	77	0.86 (0.59-1.25)	49	0.68 (0.44-1.04)
377.2+	190	62	0.75 (0.50-1.12)	49	0.72 (0.47-1.11)
P for trend[*]			0.35		0.09
Total Flavonols[#]					
0-4.2	191	113	1.00	93	1.00
4.3-6.7	190	66	0.59 (0.41-0.86)	47	0.51 (0.34-0.78)
6.8-11.0	190	67	0.60 (0.41-0.87)	42	0.46 (0.30-0.71)
11.1-17.0	191	74	0.66 (0.46-0.96)	46	0.49 (0.32-0.75)
17.1+	191	58	0.55 (0.37-0.82)	56	0.51 (0.33-0.79)
P for trend[*]			0.12		0.03
Total Flavones[#]					
0-0.04	191	101	1.00	69	1.00
0.05-0.08	190	74	0.76 (0.52-1.10)	72	1.05 (0.71-1.56)
0.09-0.14	191	85	0.89 (0.62-1.29)	55	0.83 (0.54-1.26)
0.15-0.21	191	61	0.64 (0.43-0.94)	44	0.67 (0.43-1.04)
0.22+	190	57	0.59 (0.40-0.89)	34	0.51 (0.32-0.82)
P for trend[*]			0.02		0.003
Total Flavanones[#]					
0-5.3	190	70	1.00	50	1.00
5.4-18.8	192	77	1.18 (0.80-1.74)	52	1.05 (0.68-1.63)
18.9-32.1	189	84	1.21 (0.83-1.78)	61	1.20 (0.78-1.84)
32.2-54.2	191	80	1.14 (0.77-1.67)	58	1.16 (0.75-1.80)
54.3+	191	67	0.95 (0.63-1.42)	53	1.06 (0.68-1.66)
P for trend[*]			0.77		0.49
Total Flavan-3-ols[#]					
0-7.6	190	93	1.00	71	1.00
7.7-54.0	192	75	0.81 (0.56-1.18)	62	0.88 (0.59-1.31)
54.1-192.0	189	65	0.71 (0.49-1.04)	48	0.69 (0.45-1.05)
192.1-277.9	192	81	0.86 (0.60-1.24)	48	0.66 (0.43-1.02)
278.0+	190	64	0.75 (0.51-1.10)	45	0.67 (0.43-1.03)
P for trend[*]			0.45		0.13
Total Anthocyanidins[#]					
0-0.03	189	77	1.00	58	1.00
0.04-0.56	192	88	1.19 (0.82-1.73)	70	1.22 (0.81-1.84)
0.57-1.84	190	88	1.25 (0.86-1.81)	44	0.80 (0.51-1.24)
1.85-4.84	191	69	0.93 (0.63-1.37)	50	0.90 (0.59-1.39)
4.85+	191	56	0.77 (0.51-1.16)	52	0.95 (0.62-1.46)
P for trend[*]			0.005		0.63
Total Isoflavones[#]					

0-0.27	190	82	1.00	55	1.00
0.28-0.62	191	63	0.78 (0.52-1.17)	64	1.19 (0.78-1.83)
0.63-1.94	191	81	1.09 (0.75-1.60)	50	0.98 (0.62-1.52)
1.95-7.63	191	88	1.21 (0.83-1.77)	58	1.16 (0.75-1.80)
7.64+	190	64	0.92 (0.61-1.37)	47	1.00 (0.63-1.58)
P for trend*			0.91		0.48
Total Lignans#					
0-2.4	215	89	1.00	72	1.00
2.5-4.2	167	81	1.09 (0.76-1.58)	68	1.07 (0.72-1.59)
4.3-6.4	190	76	0.96 (0.66-1.40)	48	0.74 (0.48-1.14)
6.5-10.2	191	71	0.89 (0.60-1.30)	43	0.64 (0.41-0.99)
10.3+	190	61	0.82 (0.55-1.24)	43	0.67 (0.43-1.05)
P for trend*			0.35		0.02

[#] P for trend for continuous variable

[*] In milligrams per day (mg/d)

CHAPTER IV: DIETARY FLAVONOID INTAKE AND BREAST CANCER SURVIVAL AMONG WOMEN IN THE LONG ISLAND BREAST CANCER STUDY PROJECT

Abstract

Background: Laboratory research and a growing number of epidemiologic studies have provided evidence for a reduced risk of breast cancer associated with dietary intake of certain classes of flavonoids. However, the effects of flavonoids on survival are not known. In a population-based study, we investigated whether dietary flavonoid intake prior to diagnosis is associated with breast cancer survival. **Methods:** Women age 25-98 years who were newly diagnosed with a first primary invasive breast cancer between August 1, 1996 and July 31, 1997 and participated in a population-based, case-control study (n = 1,210) were followed for vital status through December 31, 2002. At the case-control interview conducted shortly after diagnosis, respondents completed a food frequency questionnaire that assessed dietary intake in the previous twelve months. All-cause mortality (n = 173 deaths) and breast cancer-specific mortality (n = 113 deaths) were determined through the National Death Index. **Results:** Reduced hazard ratios (age-and energy adjusted HR, (and 95% confidence intervals (CI))) for all-cause mortality were observed among pre- and post-menopausal women for the highest quintile of intake, compared to the lowest, for flavones (0.63, (0.41-0.96)), isoflavones (0.52, (0.33-0.82)), and anthocyanidins (0.64, (0.42-0.98)). Effects were more pronounced among post-menopausal women for flavones 0.59 (0.35-0.99)) and isoflavones (0.44 (0.24-0.81)). Results were similar when analyses considered breast cancer-specific mortality only. **Conclusion:** This is the first study to provide evidence that mortality

is reduced in association with high levels of dietary flavones and isoflavones among breast cancer patients, particularly among those who were postmenopausal at diagnosis.

INTRODUCTION

Prior laboratory research suggests that flavonoids may inhibit breast cancer development by decreasing estrogen production (50-53), inhibiting breast cancer cell proliferation (54, 55, 488-492), and decreasing reactive oxygen species (ROS) production (56-58). Several population-based studies (59, 60, 493), including analyses from the Long Island Breast Cancer Study (LIBCSP) (493) reported inverse associations between dietary flavonoid intake and breast cancer risk, but to the best of our knowledge, there are no reports on the association between flavonoids and breast cancer survival.

Some (30, 32, 33, 305, 494), but not all (306, 361), observational studies have observed a reduced risk of all-cause mortality among breast cancer patients in relation to intake of fruit and vegetables, which are abundant in flavonoid content (377). A previous analysis of fruits, vegetables, and micronutrients in relation to survival of breast cancer cases who participated in the LIBCSP (494) found a reduced risk of mortality with increasing intakes of fruits, fruit juices, and vegetables at diagnosis. However, micronutrients, including vitamin C, vitamin E, and alpha- and beta-carotene, were not associated with mortality in this population.

The study of flavonoids may help to identify food sources that enhance breast cancer survival, and clarify inconsistent results from previous studies assessing fruits and vegetables and breast cancer survival. This study examined whether flavonoid intake reported near the time of diagnosis is associated with reduced all-cause and breast cancer-specific mortality in a population-based sample of women with incident breast cancer (371).

MATERIALS AND METHODS

Overview

This research draws upon data collected as part of the LIBCSP, which began as a case-control study (371) and now includes assessment of survival among the breast cancer cases. For this analysis, flavonoid intake in the year prior to the baseline case-control study interview was used to examine survival among LIBCSP participants diagnosed with invasive breast cancer in 1996-1997 (n = 1,273). Vital status through 2002 was determined using the National Death Index (NDI). Information on dietary intake and potential confounders and effect modifiers also was collected at the baseline interview, which took place shortly after diagnosis (mean = 96 days) (371). Treatment information was derived from baseline (1996-1997) and follow-up (2002-2004) interviews and medical records.

Study Subjects

Eligible cases for the parent LIBCSP case-control study (371) included English-speaking women newly diagnosed with a first invasive primary breast cancer between August 1, 1996 and July 31, 1997 who were residents of Nassau and Suffolk counties, Long Island, New York. Cases were identified through a rapid reporting system that was developed specifically for the LIBCSP. The attending physician was contacted to confirm study eligibility and to seek permission to contact each patient. Of the 1,837 eligible cases with physician consent, 1,508 (82%) agreed to participate and completed the main questionnaire (n = 1,273 invasive cases).

Exposure Assessment

Baseline, Case-Control Interview. Breast cancer cases and controls were administered a standardized questionnaire by trained interviewers that asked about a variety of known and suspected breast cancer risk factors. Participants were also asked to self-complete a modified version of the Block food frequency questionnaire (FFQ) (435), which included information on frequency and portion size of 100 food items. The instrument was modified to include questions regarding flavonoid-rich foods such as tofu, cherries, soups, fruit drinks, and alfalfa sprouts (457). Of the 1,273 invasive cases who completed the case-control questionnaire, 1,249 completed the FFQ at baseline. To facilitate comparisons with other studies, 38 invasive cases with daily energy intakes above or below 3 standard deviations of the log-transformed mean were excluded from the analysis (48). Of the remaining cases, 25 had unknown menopausal status and were also excluded, resulting in a final sample size of 1,210 women.

Dietary Flavonoid Intake Assessment at Baseline. Details on the food items included in each flavonoid class have been described previously (457). Briefly, food and beverage contents of total flavonoids and seven classes of flavonoids (flavonols, flavones, flavan-3-ols, flavanones, anthocyanidins, isoflavones, and lignans) were estimated using a database created for the LIBCSP (457) that included values from both the USDA Database for the Flavonoid Content of Selected Foods (377) and the USDA – Iowa State University Database on the Isoflavone Content of Selected Foods (378). Additional sources (270, 298, 379-382, 459-461) were utilized to estimate the isoflavone content of products not included on the USDA database including selected fruits, vegetables, nuts, and grains that are important dietary contributors of flavonoids among American women (392). These sources also provided information for lignans, a class of flavonoids for which laboratory and

epidemiologic evidence has demonstrated potential anti-carcinogenic properties (72, 462-466), that is not included in the USDA databases.

Fifty items listed on the modified Block FFQ were found to contain at least one flavonoid class. The richest sources of total flavonoids include 'tea, including herb tea', which consists primarily of flavan-3-ols (111.41 milligrams (mg) per 100 grams (g)); 'cherries', which consist primarily of anthocyanidins (116.31 mg per 100 g); and 'grapefruit', which consists primarily of flavanones (54.50 mg per 100 g) (377).

Treatment Data

Treatment information was based on data from respondent reports at the baseline case-control and follow-up interviews and the medical records collected as part of each study.

Case-control Interview. At baseline, medical records were abstracted to obtain information on disease stage (*in situ* versus invasive), initial course of breast cancer treatment, and estrogen receptor (ER) and progesterone receptor (PR) status. Three-fourths of the baseline case interviews occurred prior to the initiation of chemotherapy (371).

Follow-up Interview. Additional treatment information was obtained from follow-up telephone interviews of case participants or proxies in 2002-2004, and from medical records. Of the original 1,508 case participants, 1,414 gave permission to re-contacted them. Of these, a total of 1,098 cases (n = 868 invasive cases) were successfully re- interviewed by phone. The remaining cases refused to participate in the follow-up interview, were untraceable, or were deceased and had no identifiable proxy. During the follow-up telephone interview, respondents were asked their complete course of treatment for the initial breast cancer diagnosis. Respondents or proxies were asked to sign a Health Insurance Portability and Accountability Act (HIPAA)-approved medical record release form.

Follow-up medical records were retrieved and abstracted for 474 invasive cases to determine treatments for their first diagnosis of breast cancer. A high concordance was found between treatment reported by the respondent during the follow-up interview and information abstracted from the medical records for radiation (Kappa = 0.97), chemotherapy (Kappa = 0.96), and hormone therapy (Kappa = 0.92).

Study Outcome

The National Death Index (NDI) was used to ascertain vital status and the cause and date of death if deceased. 173 (14.3%) deaths occurred by December 31, 2002 among the 1,210 women diagnosed with invasive breast cancer in 1996-1997 with adequate dietary intake data available for analysis. Of these, 113 (65.3% of all deaths) were due to breast cancer based on ICD codes 174.9 and C-50.9 listed as a primary or secondary code on the death certificate. Other causes of death included cardiovascular disease (n = 24), lung cancer (n = 5), other cancers (n = 17), and other (n =21).

Statistical Analysis

Kaplan-Meier survival curves (437) were used to compare survival probabilities among cases with different levels of flavonoid intake at the baseline case-control interview with subsequent vital status. The effects of flavonoids on survival were also categorized in quintiles, deciles, quartiles, tertiles, and dichotomously at the median intake, and results were similar. Quintiles are presented here and were based on the distribution of flavonoid intake for pre- and post-menopausal invasive cases combined to facilitate comparisons between the two groups. When menopause-specific cut-points were examined, results were not substantially different than those shown. Total flavonoids and each of the seven flavonoid classes of interest were evaluated with log hazard plots to determine whether the proportional

hazards assumption was met. Cox proportional hazards regression (437) was used to estimate hazard ratios and 95% confidence intervals (CI) for the association between total flavonoids, as well as each of the seven flavonoid classes, with all-cause mortality and breast cancer-specific mortality. All models were adjusted for age at diagnosis (continuous) and dietary energy intake (continuous). Models were re-run with follow-up time limited to 5 years and the results were nearly identical to those where all follow-up time was included (data not shown).

Effect modification was examined through use of stratified analysis and by comparing the log-likelihood statistic for models that included multiplicative interaction terms to those without (437). Potential modifiers included covariates assessed at the baseline interview: menopausal status (pre- or post-menopausal), family history of breast cancer in a first-degree relative, physical activity level from menarche to date of diagnosis (hours/day), active/passive cigarette smoking, body mass index (BMI) [weight (kg) / height $(m)^2$] at diagnosis, average lifetime alcohol intake (grams/day), education, income, hormone replacement therapy (HRT), and co-morbidities including history of hypertension, diabetes, high cholesterol, myocardial infarction, and stroke. None of these covariates were found to modify the association between flavonoids and survival based on a p-value of 0.20. However, because breast cancer survival has been shown to vary with menopausal status in some studies (495, 496), results were stratified by menopausal status.

We also investigated potential effect modification by the primary treatment for breast cancer at diagnosis (obtained as part of the follow-up study), including radiation treatment and chemotherapy, and no effects were observed (data not shown). We examined associations between flavonoids and survival according to tumor characteristics, including

tumor size and hormone receptor status (ER/PR) obtained from the medical record as part of the case-control and follow-up studies. No effect measure modification was observed, even when cases were stratified by each individual hormone receptor type. Therefore, to maximize study power, ER+PR+ cases were considered as one group and the remaining three hormone receptor types were combined (ER+PR-, ER-PR+, ER-PR-) into another group.

Potential confounders included those considered as effect modifiers. None of the potential confounders altered effect estimates for flavonoid classes by more than 10% (data not shown). Thus, only the age- and energy-adjusted results are shown.

RESULTS

Invasive cases were pre-dominantly white (94.1%), ever married (96.4%), and post-menopausal at diagnosis (Table 1). The proportion of cases with at least some college education was approximately equal to the proportion with a high school diploma or less. Approximately 30% had a household income of at least $50,000 before taxes.

As shown in Table 2, flavones (HR = 0.63, 95% CI = 0.41-0.96), isoflavones (HR = 0.52, 95% CI = 0.33-0.82), and anthocyanidins (HR = 0.64, 95% CI = 0.42-0.98) were inversely associated with all-cause mortality when analyses included both pre- and post-menopausal women, although dose-response trends were not observed. When analyses were restricted to post-menopausal women only, risk of all-cause mortality was decreased in relation to flavones (HR = 0.59, 95% CI: 0.35-0.99) and isoflavones (HR = 0.44, 95% CI = 0.24-0.81), comparing the highest quintile of intake to the lowest quintile (Table 2). Total flavonoids (HR = 0.78, 95% CI = 0.49-1.25) and anthocyanidins (HR = 0.66, 95% CI = 0.40-1.08) were also associated with a modest reduction in mortality. Among pre-menopausal women,

similar reductions in all-cause mortality were observed for flavones (HR = 0.69, 95% CI = 0.32-1.47), isoflavones (HR = 0.71, 95% CI = 0.34-1.48), and anthocyanidins (HR = 0.62, 95% CI = 0.27-1.40), although confidence intervals were wide. Total flavonoids (HR = 1.77, 95% CI = 0.91-3.46), flavonols, flavan-3-ols, and lignans were positively associated with mortality; however, estimates were imprecise and no clear dose-response trends were evident.

With results stratified by hormone receptor status, effects were slightly more pronounced among those with ER+PR+ tumors, but the confidence intervals were wide (data not shown). For example, among post-menopausal women with ER+PR+ tumors, inverse associations with all-cause mortality were observed comparing the highest quintile of intake to the lowest quintile, for anthocyanidins (HR = 0.57, 95% CI = 0.28-1.17) and flavones (HR = 0.59, 95% CI = 0.29-1.21). More modest reductions in all-cause mortality were found for flavonols (HR = 0.77, 95% CI = 0.39-1.52), flavan-3-ols (HR = 0.80, 95% CI = 0.42-1.54), lignans (HR = 0.86, 95% CI = 0.45-1.67), and total flavonoids (HR = 0.81, 95% CI = 0.42-1.57). For women with all other hormone receptor types (ER+PR-, ER-PR+, and ER+PR+) (n = 458), no consistent associations were observed.

Results for breast cancer-specific mortality were similar to those for all-cause mortality, including an inverse association with mortality for flavones among post-menopausal women (HR = 0.49, 95% CI: 0.24-0.99) and all women (HR = 0.48, 95% CI = 0.27-0.84), comparing the highest quintile of intake to the lowest quintile (Table 3). Total flavonoids (HR = 0.62, 95% CI = 0.33-1.16), anthocyanidins (HR = 0.62, 95% CI = 0.33-1.18), and isoflavones (HR = 0.79, 95% CI = 0.43-1.44) were also associated with a modest reduction in breast cancer mortality among post-menopausal women, although the confidence intervals were wide.

Modest reductions in breast cancer mortality were observed among pre-menopausal women for flavones (HR = 0.45, 95% CI = 0.17-1.19) and anthocyanidins (HR = 0.81, 95% CI = 0.35-1.89), but again the confidence intervals were wide. Total flavonoids (HR = 1.75, 95% CI = 0.82-3.72), flavanols, flavan-3-ols, and lignans were positively associated with mortality, though no dose-response relationship existed.

DISCUSSION

To the best of our knowledge, this is the first study to examine the influence of dietary flavonoid intake prior to diagnosis on subsequent breast cancer survival. We found inverse associations for intake of flavones and isoflavones with all-cause mortality, that were more pronounced among post-menopausal women, although dose-response trends were not observed for either association. Total flavonoids and anthocyanidins also demonstrated modest inverse associations with mortality in this group.

The observation in our study of a reduced risk of mortality associated with total isoflavones in postmenopausal women is inconsistent with one recent study conducted in Shanghai, China (497). This Chinese study focused solely on the prognostic effects of soy, which is rich in isoflavones and traditionally consumed more frequently by Asian populations than in the U.S. The investigators found that soy intake prior to cancer diagnosis was unrelated to disease-free breast cancer survival among pre- and post-menopausal women (497). Reasons for the inconsistent results between the two studies are not clear, although it is possible that consumption of soy is uniformly high in this Asian population, which would make it more difficult to detect differences in mortality associated with only minor differences in intake. In contrast, prior research conducted in Italy (60), Greece (59), and the

U.S. (493) observed a decreased risk of developing breast cancer with increasing levels of flavone intake among post-menopausal women.

Study power was adequate for our analyses that were conducted among all women and for those restricted to post-menopausal women, but was reduced for our analyses that focused on pre-menopausal women only. Thus, any differences we observed by menopausal status could be due to the unstable estimates among the younger women. Power would have been modestly improved if we were able to consider breast cancer recurrence as an outcome. Although women were asked to report this data at the follow-up interview, we were unable to confirm these events in the medical records for many women. Thus, we focused our analyses on mortality, which is reliably and consistently reported in the NDI.

The Block FFQ has been demonstrated to be a valid and reliable dietary assessment tool for estimating usual food intake and ranking individuals into categories of intake of micronutrients (375, 383, 487). However, a potential limitation of this instrument is its lack of complete assessment of commonly consumed flavonoid-rich products. Although the Block FFQ was modified for the LIBCSP to include more flavonoid-rich foods, it did not include blueberries and raspberries, which are rich sources of anthocyanidins (377). In the future, FFQs and other dietary history assessment tools should incorporate newly developed and commonly consumed soy products to enhance coverage of isoflavones. These products include meatless hamburger, chicken, and sausage made from soy protein, as well as soy protein found in some fast food hamburgers. Inclusion of these foods on FFQs used in future studies would improve both the estimation of flavonoid intake and thus the ability to detect an association with breast cancer survival.

Flavonoid consumption may reflect part of an overall healthy diet and lifestyle (33, 369). Furthermore, many lifestyle factors that may potentially confound the relationship between flavonoids and breast cancer are highly correlated with high flavonoid intake, making it difficult to firmly establish their independent effects (486). However, in our analyses, age and energy-adjusted estimates were very similar to multivariate-adjusted results, indicating that confounding by the variables examined was not evident. However, residual confounding by unmeasured or poorly measured confounders could have biased the estimates. For the LIBCSP, stage of breast cancer was defined as in situ or regional invasive types rather than the more detailed staging system used by pathologists, ranging from Stage 0 to Stage 4 (498). Thus, there may be some confounding by stage in these data, if flavonoid intake is associated with stage at diagnosis.

Dietary modification following disease diagnosis is an increasingly commonplace behavior among survivors (499-501). Women concerned about breast cancer recurrence have been reported to consume more fruits and vegetables compared to those who are not as concerned (445-447, 501). Thus, it is possible that a diagnosis of breast cancer motivated dietary behavior change in some of the cases. Changes in lifestyle might also have affected other outcomes (e.g., lung cancer deaths in 2.3% of cases and cardiovascular disease deaths in 12.7% of cases). However, when we restricted our analyses to breast cancer-specific deaths only, results were similar to those observed for all-cause mortality.

Similarly, case reports of food intake may have been affected by whether or not a woman had initiated chemotherapy by the time of the study interview (375). However, in the LIBCSP, most of the case women (> 75%) were interviewed about their dietary history prior to any chemotherapy. In addition, among those that had started treatment, average intake

levels of flavonoid-rich fruits and vegetables did not differ from those who had not started (48).

This study had the advantage of a large sample size and population-based design, reducing the likelihood of selection bias and allowing for greater generalizability compared with smaller, hospital-based studies. The LIBCSP population consumed relatively large quantities of a wide variety of flavonoid-containing products, such as fruits, vegetables, and tea (457, 493) and intakes of several flavonoid classes were comparable to those from the populations in Italy (60) and Greece (59). However, our study population consumed, on average, higher levels of flavan-3-ols and isoflavones (457, 493).

In summary, this follow-up study of breast cancer patients supports a beneficial effect of increasing levels of flavones and isoflavones on all-cause mortality, with effects more pronounced among post-menopausal, rather than pre-menopausal women. These results are encouraging given that few modifiable lifestyle factors for breast cancer survival have been systematically evaluated. Future studies are needed that include thorough assessments of flavonoid-rich food intake at diagnosis and following diagnosis to determine the role of flavonoids intake on breast cancer prognosis.

Tables

Table 4.1. Demographic characteristics of invasive cases in the LIBCSP

Demographic Factor		Cohort (n=1,210)		Deaths (n=173)	
		N	%	N	%
Age at reference	< 44 years	176	14.5	21	12.1
	45-54 years	293	24.2	33	19.1
	55-64 years	301	24.9	34	19.7
	65-74 years	302	25.0	47	27.1
	75+ years	138	11.4	38	22.0
	Missing	0		0	
Race	White	1138	94.1	158	91.3
	Black	50	4.2	14	8.1
	Other	21	1.7	1	0.6
	Missing	1		0	
Education	< High school	161	13.3	36	20.5
	High school graduate	439	36.4	75	43.9
	Some college	283	23.5	34	19.9
	College graduate	149	12.3	16	9.3
	Post-college	175	14.5	11	6.4
	Missing	3		2	
Marital Status	Never Married	44	3.6	9	5.2
	Ever Married	1165	96.4	164	94.8
	Missing	1		0	
Religion	Catholic	698	57.7	108	62.4
	Protestant	293	24.2	45	26.0
	Jewish	196	16.2	16	9.2
	None	12	1.0	2	1.2
	Other	11	0.9	2	1.2
	Missing	0		0	
Income	Less than $15,000	95	7.9	29	16.8
	$15,000-$19,999	59	4.9	12	6.9
	$20,000-$24,999	80	6.6	15	8.7
	$25,.000-$34,999	212	17.5	40	23.1
	$35,000-$49,999	198	16.4	26	15.0
	$50,000-$69,999	183	15.1	19	11.0
	$70,000-$89,999	152	12.6	14	8.1
	$90,000 or more	229	19.0	18	10.4
	Missing	2		0	
ER/PR Status	ER+	668	73.4	83	73.4
	ER-	242	26.6	54	26.6
	Missing	300		36	

	PR+	582	64.2	64	35.8
	PR-	324	35.8	73	64.2
	Missing	304		36	
Tumor Size (cm)[b]	0-1.9	370	78.2	21	70.0
	2.0-5.0	84	19.9	8	26.7
	> 5.0	9	1.9	1	3.3
	Missing	737		737	

[a]Includes values for missing income, which were imputed using age, race, and education.
[b]Centimeters.

Table 4.2. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996-1997.

Variable (mg/day)	Deaths/ Cohort # deaths/ 376	Pre-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 834	Post-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 1,210	Pre and Post HR (95% CI)
Total Flavonoids*						
0-42.4	3/82	1.00	25/161	1.00	28/243	1.00
42.5-95.0	15/72	2.49 (1.32-4.69)	23/171	0.81 (0.52-1.28)	38/243	1.10 (0.77-1.57)
95.1-216.2	6/79	0.58 (0.24-1.36)	28/162	1.09 (0.71-1.65)	34/241	0.95 (0.66-1.39)
216.3-340.4	6/75	0.61 (0.26-1.46)	32/168	1.24 (0.83-1.86)	38/243	1.11 (0.77-1.59)
340.5+	13/68	1.77 (0.91-3.46)	22/172	0.78 (0.49-1.25)	35/240	0.96 (0.66-1.40)
Total Flavonols*						
0-3.4	4/58	1.00	31/185	1.00	35/243	1.00
3.5-5.9	12/81	1.65 (0.84-3.26)	23/162	0.89 (0.57-1.40)	35/243	1.03 (0.71-1.49)
6.0-10.1	8/83	0.78 (0.36-1.68)	25/159	0.99 (0.64-1.54)	33/242	0.94 (0.64-1.37)
10.2-14.4	5/76	0.47 (0.19-1.19)	26/164	1.02 (0.66-1.57)	31/240	0.86 (0.58-1.27)
14.5+	14/78	1.64 (0.84-3.17)	25/164	0.98 (0.62-1.53)	39/242	1.12 (0.78-1.62)
Total Flavones*						
0-0.03	7/61	1.00	32/180	1.00	39/241	1.00
0.04-0.07	9/80	1.07 (0.51-2.25)	29/163	1.24 (0.82-1.88)	38/243	1.20 (0.83-1.72)
0.08-0.12	11/75	1.36 (0.69-2.70)	27/167	1.13 (0.74-1.73)	38/242	1.17 (0.82-1.68)
0.13-0.19	7/70	0.87 (0.39-1.95)	25/172	0.92 (0.59-1.44)	32/242	0.88 (0.60-1.29)
0.20+	9/90	0.69 (0.32-1.47)	17/152	0.59 (0.35-0.99)	26/242	0.63 (0.41-0.96)
Total Flavanones*						
0-4.0	12/97	1.00	21/143	1.00	33/240	1.00
4.1-16.3	8/84	0.80 (0.37-1.73)	28/156	1.49 (0.97-2.29)	36/240	1.25 (0.86-1.81)
16.4-29.9	6/67	0.75 (0.32-1.78)	19/176	0.60 (0.37-0.98)	25/243	0.64 (0.42-0.97)
30.0-48.5	9/74	1.04 (0.50-2.17)	30/172	1.13 (0.75-1.71)	39/246	1.10 (0.77-1.57)
48.6+	8/54	1.08	32/187	0.99	40/241	1.03

		(0.48-2.43)		(0.66-1.49)		(0.72-1.48)
Total Flavan-3-ols*						
0-5.0	3/66	1.00	29/178	1.00	32/244	1.00
5.1-34.4	8/84	0.80 (0.37-1.74)	22/158	0.88 (0.56-1.39)	30/242	0.83 (0.56-1.23)
34.5-140.0	12/78	1.42 (0.73-2.77)	26/164	1.01 (0.66-1.56)	38/242	1.12 (0.78-1.61)
140.1-263.7	7/79	0.72 (0.32-1.63)	29/162	1.21 (0.80-1.83)	36/241	1.10 (0.76-1.59)
263.8+	13/69	1.76 (0.91-3.42)	24/172	0.84 (0.53-1.32)	37/241	1.01 (0.70-1.46)
Total Anthocyanidins*						
0-0.03	6/60	1.00	39/181	1.00	45/241	1.00
0.04-0.40	16/86	2.12 (1.14-3.93)	28/158	1.18 (0.77-1.79)	44/244	1.42 (1.01-2.00)
0.41-1.60	10/70	1.33 (0.66-2.71)	25/178	0.92 (0.59-1.42)	35/248	1.00 (0.69-1.45)
1.61-4.23	4/81	0.36 (0.13-1.01)	20/157	0.74 (0.46-1.19)	24/238	0.62 (0.40-0.95)
4.24+	7/79	0.62 (0.27-1.40)	18/160	0.66 (0.40-1.08)	25/239	0.64 (0.42-0.98)
Total Isoflavones*						
0-0.29	8/70	1.00	19/172	1.00	27/242	1.00
0.30-0.78	7/58	1.10 (0.49-2.48)	43/185	1.58 (1.09-2.30)	50/243	1.49 (1.07-2.08)
0.79-2.34	9/69	1.23 (0.59-2.56)	25/175	0.89 (0.58-1.38)	34/244	0.96 (0.66-1.39)
2.35-7.47	10/88	0.93 (0.46-1.90)	31/152	1.59 (1.06-2.38)	41/240	1.36 (0.96-1.94)
7.48+	9/91	0.71 (0.34-1.48)	12/150	0.44 (0.24-0.81)	21/241	0.52 (0.33-0.82)
Total Lignans*						
0-2.2	7/72	1.00	26/171	1.00	33/243	1.00
2.3-3.9	5/72	0.60 (0.24-1.53)	28/170	1.09 (0.72-1.65)	33/242	0.96 (0.65-1.40)
4.0-5.9	14/82	1.69 (0.89-3.21)	25/162	0.98 (0.63-1.51)	39/244	1.14 (0.80-1.63)
6.0-8.9	6/77	0.61 (0.26-1.45)	26/163	0.96 (0.62-1.48)	32/240	0.88 (0.60-1.30)
9.0+	11/73	1.27 (0.63-2.54)	25/168	0.98 (0.63-1.54)	36/241	1.03 (0.71-1.49)

Table 4.3. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to breast cancer-specific mortality.

Variable (mg/day)	Deaths/ Cohort # deaths/ 367	Pre-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 781	Post-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 1,148	Pre and Post HR (95% CI)
Total Flavonoids*						
0-42.4	2/81	1.00	16/152	1.00	18/233	1.00
42.5-95.0	13/70	2.88 (1.44-5.78)	16/164	0.97 (0.56-1.68)	29/234	1.37 (0.90-2.10)
95.1-216.2	5/78	0.61 (0.24-1.58)	14/148	0.90 (0.51-1.61)	19/226	0.81 (0.49-1.32)
216.3-340.4	4/73	0.50 (0.18-1.42)	21/156	1.40 (0.84-2.33)	25/229	1.10 (0.70-1.73)
340.5+	10/65	1.75 (0.82-3.72)	12/161	0.62 (0.33-1.16)	22/226	0.88 (0.55-1.42)
Total Flavonols*						
0-3.4	4/58	1.00	17/171	1.00	21/229	1.00
3.5-5.9	10/79	1.80 (0.85-3.80)	16/155	1.04 (0.60-1.81)	26/234	1.22 (0.78-1.89)
6.0-10.1	6/81	0.73 (0.30-1.77)	14/148	0.92 (0.52-1.65)	20/229	0.86 (0.53-1.39)
10.2-14.4	3/74	0.34 (0.10-1.12)	15/152	0.87 (0.49-1.55)	18/226	0.69 (0.41-1.16)
14.5+	11/75	1.64 (0.78-3.46)	17/155	1.02 (0.59-1.79)	28/230	1.20 (0.77-1.87)
Total Flavones*						
0-0.03	4/58	1.00	16/163	1.00	20/221	1.00
0.04-0.07	9/80	1.46 (0.67-3.15)	17/151	1.24 (0.72-2.13)	26/231	1.30 (0.83-2.01)
0.08-0.12	10/74	1.62 (0.77-3.39)	19/158	1.20 (0.71-2.03)	29/232	1.32 (0.86-2.02)
0.13-0.19	6/69	0.94 (0.39-2.27)	18/165	1.06 (0.62-1.80)	24/234	1.01 (0.64-1.59)
0.20+	5/86	0.45 (0.17-1.19)	9/144	0.49 (0.24-0.99)	14/230	0.48 (0.27-0.84)
Total Flavanones*						
0-4.0	10/95	1.00	12/133	1.00	22/228	1.00
4.1-16.3	7/83	0.89 (0.39-2.05)	19/146	1.52 (0.89-2.61)	26/229	1.27 (0.81-1.99)
16.4-29.9	6/67	0.97 (0.40-2.35)	9/166	0.47 (0.23-0.94)	15/233	0.60 (0.35-1.03)
30.0-48.5	7/72	1.03 (0.45-2.38)	19/161	1.21 (0.72-2.03)	26/233	1.15 (0.74-1.78)
48.6+	4/50	0.61	20/175	1.09	24/225	0.98

		(0.21-1.81)		(0.65-1.82)		(0.62-1.56)
Total Flavan-3-ols*						
0-5.0	2/65	1.00	19/168	1.00	21/233	1.00
5.1-34.4	6/82	0.76 (0.31-1.85)	13/149	0.83 (0.46-1.50)	19/231	0.78 (0.48-1.28)
34.5-140.0	11/77	1.75 (0.85-3.60)	14/152	0.90 (0.50-1.60)	25/229	1.14 (0.73-1.78)
140.1-263.7	5/77	0.63 (0.24-1.63)	21/153	1.46 (0.88-2.43)	26/230	1.19 (0.76-1.86)
263.8+	10/66	1.75 (0.83-3.69)	12/159	0.63 (0.34-1.18)	22/225	0.89 (0.55-1.43)
Total Anthocyanidins*						
0-0.03	4/58	1.00	21/163	1.00	25/221	1.00
0.04-0.40	11/81	1.80 (0.88-3.69)	15/145	1.05 (0.60-1.85)	26/226	1.28 (0.82-1.98)
0.41-1.60	8/68	1.33 (0.60-2.95)	21/173	1.27 (0.76-2.12)	29/241	1.30 (0.85-1.99)
1.61-4.23	4/81	0.46 (0.16-1.31)	11/148	0.65 (0.35-1.24)	15/229	0.58 (0.34-1.00)
4.24+	7/79	0.81 (0.35-1.89)	11/152	0.62 (0.33-1.18)	18/231	0.68 (0.41-1.13)
Total Isoflavones*						
0-0.15	7/76	1.00	11/150	1.00	18/226	1.00
0.16-0.26	5/71	0.96 (0.40-2.35)	21/165	1.02 (0.59-1.78)	26/236	0.99 (0.62-1.59)
0.27-0.37	8/67	1.69 (0.79-3.62)	15/159	0.99 (0.57-1.72)	23/226	1.17 (0.75-1.83)
0.38-0.59	8/71	0.48 (0.17-1.36)	24/158	1.08 (0.63-1.84)	32/229	0.86 (0.54-1.39)
0.60+	6/82	1.03 (0.46-2.28)	8/149	0.79 (0.43-1.44)	14/231	0.87 (0.54-1.41)
Total Lignans*						
0-2.2	6/71	1.00	15/160	1.00	21/231	1.00
2.3-3.9	4/71	0.60 (0.21-1.71)	18/160	1.17 (0.69-1.98)	22/231	0.99 (0.62-1.57)
4.0-5.9	12/80	1.92 (0.95-3.89)	16/153	1.04 (0.60-1.80)	28/233	1.28 (0.84-1.97)
6.0-8.9	4/75	0.50 (0.18-1.42)	15/151	0.88 (0.49-1.57)	19/226	0.76 (0.46-1.26)
9.0+	8/70	1.16 (0.52-2.58)	15/157	0.87 (0.49-1.55)	23/227	0.95 (0.60-1.51)

Chapter V: DISCUSSION

Summary

In the population-based case-control study of women in Nassau and Suffolk counties, New York, total flavonoid intake, including intake of flavonols, flavones, flavan-3-ols, and lignans, were associated with a reduced risk of developing breast cancer in post-menopausal women. Among post-menopausal women with ER+PR+ tumors, similar risk reductions were observed. Intake of flavanones and isoflavones were associated with a modest reduction in risk in pre-menopausal women.

In the follow-up study, among the post-menopausal breast cancer cases, intake of flavones and isoflavones at or just prior to diagnosis was associated with a subsequent reduced risk of all-cause mortality, and intake of flavones was associated with a reduced risk of breast cancer mortality. Similar, but more modest reductions in mortality were observed for these flavonoid classes among pre-menopausal women.

Study Strengths

Biologic Plausibility of the Hypothesis

A biologic mechanism by which flavonoids may affect breast cancer development and progression is through an estrogenic pathway. Endogenous hormones, particularly estrogens, are believed to play a significant role in the development of breast cancer, and serum levels differ substantially between pre- and post-menopausal women (169). Flavonoids have demonstrated the ability to lower endogenous hormone levels in pre- (49, 502) and post-menopausal women (503), inhibit transcriptional factors involved in cancer metastasis (504,

505), including vascular endothelial growth factor (VEGF), which is strongly associated with tumor angiogenesis (506). Thus, it is biologically plausible that dietary intake of these compounds may affect breast cancer risk and survival.

In this study of dietary flavonoid intake on breast cancer risk and survival, beneficial effects of flavonoids were more pronounced among post-menopausal women. The reasons for this heterogeneity by menopausal status are not entirely clear, but may due in part to their differences in the underlying levels of endogenous estrogen levels in part to their differences in the underlying levels of endogenous estrogen levels (or to other possible methodologically related considerations, which are discussed below).

Pre-menopausal women, for whom endogenous estrogen levels are very high, derive endogenous hormones primarily from ovarian hormone production and secondarily from conversion of androgens (testosterone and androstenedione) in adipose tissue. With the cessation of ovarian function, post-menopausal women produce much less estrogen, and thus have much lower levels of endogenous estrogens compared to pre-menopausal women. The lower levels of endogenous estrogens in post-menopausal women may be a reason why we observed a more dramatic reduction in breast cancer risk with increasing levels of flavonoid intake. In post-menopausal women, flavonoids have less estrogen to compete with for binding to estrogen receptors and therefore have a greater ability to decrease breast cell proliferation and the risk of DNA mutation, both of which are necessary precursors for preventing breast cancer (112, 507). The anti-estrogenic effects of flavonoids may be insufficient to influence the higher endogenous estrogen levels in pre-menopausal women, resulting in no evidence of an inverse association between flavonoids and breast cancer risk among this younger subgroup.

Although flavones were the smallest contributor to total flavonoid intake in our study, they have the strongest inverse association with breast cancer risk and a strong inverse association with mortality among post-menopausal women. With a mean intake of approximately 0.10 mg per day, it is uncertain if this amount is sufficient to exert anti-carcinogenic effects. However, flavones are potent inhibitors of enzymes involved in estrogen metabolism, aromatase and 17 β-hydroxysteroid oxidoreductase (53, 508), and inhibitors of enzymes involved in carcinogenesis, including cyclooxygenase (509, 510). The biological properties of this class of flavonoids, in addition to the consistency of our results with those reported in Greece (59) and Italy (60), provide evidence that flavone intake may be inversely related to breast cancer risk and mortality.

Novelty of the Hypothesis

To date, very few studies (59, 60, 511) have addressed the impact of dietary flavonoid intake on risk of breast cancer. Two of the studies (59, 60) focused solely on populations in Mediterranean countries. One very recently published investigation was conducted in an in an American population (511), but only one class of flavonoids, flavonols, were examined. Furthermore, prior to this dissertation, no published research had examined the association between flavonoid intake and breast cancer survival. However, a very recent investigation conducted among women in Shanghai, China, examined the influence of only a single flavonoid class, isoflavones (497).

Flavonoid Database

To estimate the flavonoid content of consumed food items, the two previous case-control studies, conducted in Greece (59) and Italy (60), relied on two sources: the USDA Database for the Flavonoid Content of Selected Foods and the USDA – Iowa State University

Database on the Isoflavone Content of Selected Foods. For this dissertation, flavonoid content of food consumed by women on Long Island was estimated using these same databases that were further augmented to provide more comprehensive coverage of flavonoid-containing foods and beverages. In particular, these enhancements included assessment of total flavonoids and lignans, neither of which were analyzed in the two previously conducted case-control studies.

Sample Size and Source of Population

This study also had the advantage of a sufficiently large sample size (n = 2,874) with adequate power to detect an association between flavonoids and breast cancer risk and survival. This sample size is slightly greater than that of the hospital-based Greek study (n = 2,368), but smaller than the hospital-based Italian study (n = 5,157). The population-based design of the LIBCSP, however, reduces selection bias and allows for greater generalizability of the results compared with the results from these two previously conducted hospital-based studies.

Interview and Dietary Data

The comprehensive interview data for the LIBCSP case-control study provided an efficient opportunity to examine an important, yet unresolved question in breast cancer research. The Block FFQ utilized in the LIBCSP is a validated, reliable dietary assessment tool for estimating usual food group intake and ranking individuals into categories of intake (375, 383, 487). The data from this dietary instrument indicated that the study population consumed a wide variety and significant amounts of flavonoid-containing products, including fruits, vegetables, and tea, enabling the specific aims of the dissertation to be addressed (457).

Measurement of All-Cause and Breast Cancer-Specific Mortality

All-Cause Mortality

All-cause mortality reflects the number of women who died during the follow-up period, regardless of cause of death. The reduced risk of all-cause mortality observed among post-menopausal women consuming high levels of flavones and isoflavones is of public health importance; it indicates the potential for fruit, vegetable, and soy consumption to reduce mortality, regardless of cause of death, following breast cancer diagnosis.

This reduced risk raises the issue that flavonoids may be reducing the risk of mortality due to diseases other than breast cancer, including heart disease. Thus, the hypothesized biologic effects of flavonoids may be more strongly related to other chronic diseases. Of the 173 deaths during the follow-up, 113 (65.3%) were due to breast cancer, and, the study results were similar for both all-cause mortality and breast cancer-specific mortality. Thus, the reduced risk of all-cause mortality likely must reflect, in part, a reduction in breast cancer mortality.

Breast Cancer-Specific Mortality

The assessment of breast cancer-specific mortality is of particular importance for the clinician and for researchers. Clinicians are concerned with diagnosis and treatment of breast cancer as well as prognosis. Identification of exposures which may affect the risk of mortality from breast cancer is important for advising breast cancer patients who are in the process of rehabilitation and recovery. For the researcher, the findings for breast cancer-specific mortality are important to advancing our scientific understanding of how these compounds may affect breast cancer progression, by elucidating the underlying biologic pathways. For example, high levels of flavone intake among post-menopausal women were

associated with a reduced risk of breast cancer-specific mortality. It is possible that flavones are interacting with endogenous estrogens and reducing their ability to stimulate breast cell proliferation and DNA mutation. However, further research of flavones and post-menopausal women needs to be conducted.

Study Limitations

Exposure Misclassification

Dietary Recall in the Case-Control Study

One limitation of the case-control analysis was that breast cancer cases and controls could have differentially reported dietary intake because of the differences in their health status. For example, cases could have potentially attributed their breast cancer diagnosis to a poor diet. In this instance, they could have overestimated their intake of seemingly unhealthy foods and beverages, resulting in relatively low estimates of flavonoid intake compared to estimates for controls. This could have potentially caused large disparities in reported intake by cases as compared with the controls, and potentially overemphasized the benefits of flavonoids.

Alternatively, controls may have over-reported consumption of flavonoid-rich foods, such as fruits and vegetables, in an attempt to appear socially correct. If this had occurred, it would have been expected that over-reporting would occur among all control women, regardless of menopausal status. Post-menopausal controls tended to consume greater levels of total flavonoids and all flavonoid classes per day than did pre-menopausal controls. Possible explanations for this finding include the following, older women may have better diet recall ability than younger women, and, as the women in the study population grew

older, they became more health-conscious and their intake of flavonoid-rich foods steadily increased. Furthermore, it would be expected that with increasing age, there is a greater likelihood that women will obtain routine medical examinations and screening tests, such as mammography. It is plausible that post-menopausal women would therefore receive more health care and more advice, including dietary recommendations, than pre-menopausal women.

The food frequency questionnaire was self-completed by the respondent as part of the in-home interview at the time of the case-control interview. Both breast cancer cases and controls may have been influenced by the presence of the trained interviewer, resulting in the over-reporting of healthier diets. This would have made the breast cancer cases and controls appear more homogeneous with respect to dietary intake and inhibited the ability to detect associations between flavonoids and breast cancer. However, inverse associations were found for increasing intake of total flavonoids and most flavonoid classes and breast cancer risk among post-menopausal women. However, the physical presence of the interviewer in the home at the time the FFQ was being completed by the respondent is likely to have improved the accuracy of reporting by both cases and controls, because any difficulties in completing the instrument could have been addressed immediately by the trained interviewer.

Dietary Recall Error

Any study attempting to obtain dietary information from participants about events in the past may be subject to error. Both breast cancer cases and controls were asked to recall their usual dietary intake in the previous 12 months. However, it is difficult to remember exactly what one consumes over such a long period of time, resulting in an estimate, at best, of what products and how often those products were truly consumed. Since this error in recalling diet

was likely present among all study subjects, the potential to misclassify both cases and controls within quintiles of flavonoid intake was equally probable. In this case, non-differential recall had an unpredictable effect on our results.

Time Period of Dietary Assessment for the Case-Control Study

At the time of the baseline, case-control interview, which was conducted shortly after the initial breast cancer diagnosis, dietary intake was assessed for the year prior to interview. This baseline assessment was used for both the case-control and follow-up analyses reported here. However, it is hypothesized that breast cancer is a result of an accumulation of exposures and changes within the body, which can take many years to develop before a diagnosis is made. A person's eating habits can change throughout life as certain products are added or deleted from the diet, or are increased or decreased in consumption. Thus, assessing the 12-month period prior to breast cancer diagnosis may not be as relevant with regard to breast cancer development as assessing average lifetime consumption of flavonoids. However, the difficulty in recalling lifetime consumption is a problem that affects all epidemiologic research. It is unknown how levels of flavonoid intake increased or decreased throughout each participant's life. Thus, it is uncertain if the estimated odds ratios and hazard ratios would be further from or closer to the null if this detailed consumption were estimated. Further, the dietary assessment tools, such as the Block FFQ, are currently considered among the best available for these types of studies.

Time Period of Dietary Assessment for the Follow-Up Study

The diagnosis of breast cancer has been reported to influence subsequent dietary behavior, including increased fruit and vegetable intake (445-447). In the analysis reported here, pre-diagnosis flavonoid intake showed modest reductions for risk of mortality in the follow-up

study. However, a more marked reduction may have been obscured if consumers of a low-flavonoid diet prior to diagnosis had since increased their flavonoid intake and subsequently improved their prognosis.

Alternatively, there has been concern expressed by some clinicians that use of multivitamins and supplements during treatment may inhibit treatment effectiveness. Thus, if women with high intake of flavonoids at baseline continue this practice, it is possible that any beneficial effects for flavonoid use at non-treatment could have been attenuated. Future studies would benefit from more careful assessment of post-diagnosis diet before, during, and after chemotherapy.

Omission of Flavonoid-Rich Foods and Beverages on the Block FFQ

Though the Block FFQ was modified to include products such as tofu for the LIBCSP, other flavonoid-rich sources were omitted. The omission of blueberries and raspberries, both rich in anthocyanidins (377), may have resulted in underestimation of anthocyanidin intake in these analyses. Isoflavone intake may also have been underestimated as numerous soy products, including soy milk and meatless soy products, were not included on the FFQ. Although, the instrument was specifically modified to increase the number of food items containing isoflavones, these may not be the flavonoid-rich foods that are most commonly consumed by American women.

Other Nutrients

Since flavonoids are present in fruits and vegetables, any association found between flavonoids and breast cancer may be due to other well-studied components in these products. In other words, the flavonoid and breast cancer association results may have been confounded by nutrients that are derived from common food sources. However, assessments

of micronutrients including vitamin C, vitamin E, alpha and beta-carotene, lutein, and lycopene in the LIBCSP (48, 512) found no reduced risk of breast incidence or mortality.

Fiber, which is rich in fruits and vegetables, has been hypothesized to decrease breast cancer risk by inhibiting intestinal re-absorption of estrogens, resulting in lower circulating estrogen levels (112). However, when the flavonoid and breast cancer incidence analysis was adjusted by fiber intake, the inverse associations remained (Table A.23). Further, adjustment for fiber intake did not affect the association between flavonoid intake and breast cancer survival (Table A.24).

Though not a well-established risk or prognostic factor, inadequate folate intake may result in abnormal DNA synthesis and repair, potentially increasing the risk for breast cancer (112, 513). However, in unadjusted analyses of folate, no associations with breast cancer incidence and survival in the LIBCSP were observed.

Serum Flavonoid Levels

Bioavailability of flavonoids varies widely among dietary sources (514). The polyphenols that are most well absorbed in the gut by humans are isoflavones, followed by flavan-3-ols, flavanones, and flavonols (514). The least well-absorbed flavonoids are the anthocyanidins (514). Flavonoids are measured in the blood as well as urine (72). Having serum or urinary biomarkers of flavonoid intake may have been useful to compare with estimates from the FFQ. However, serum and urinary levels reflect short-term intake of flavonoids, usually 24 hours to 1 week (515), whereas the FFQ asks about intake in the 12 months prior to the interview. Given that the biomarkers and the FFQ do not correspond to the same time frame, low correlations among the measures would be expected. In addition, it is unknown whether the diagnosis of breast cancer, or the treatment for the disease, would alter the biomarker

levels of these compounds. Thus, for estimating usual dietary intake of flavonoids in the prior year or more, the FFQ remains the most practical assessment tool.

Classification of Flavonoids

For this analysis, all flavonoids were combined together to obtain a measure of total flavonoid intake. However, it is possible that the different flavonoid classes may have different biological effects and thus, if true, it would be erroneous to combine them. Little research, however, has focused on the flavonoid classes other than isoflavones. Even among the isoflavones, there could be dual effects, both anti-estrogenic and endocrine disruptive. Until further research is done, usefulness of the total flavonoid intake measure is unclear.

Covariate Misclassification

Treatment Information

We attempted to obtain detailed information on the primary course of treatment, which was collected as part of the LIBCSP case-control and follow-up interviews, and was obtained as part of the medical record retrieval. Most of the data was collapsed into dichotomous 'yes/no' variables to enhance study power. Therefore, the level of detail was not as fine as the data that is collected in a clinical trial, although it was comparable to what is often reported to the SEER registries. However, the treatment data available did not prove to be an important confounder or effect modifier in these data.

In the follow-up study, case subjects were asked to recall treatment modalities undergone for the initial breast cancer diagnosis. For cases that had died or were too ill to be interviewed, proxies were interviewed. The recall of treatment by proxy respondents, however, may be less accurate than the recall of the cases themselves. For respondents and their proxies who had provided written permission, medical records were retrieved and

abstracted. A high concordance was found between treatment reported by respondents (cases and proxies) during the follow-up interview and the information abstracted from the medical record (radiation (98.5%), chemotherapy (98.3%), hormone therapy (96.4%)).

Co-morbidities

Post-menopausal patients frequently have one or more pre-existing co-morbidities at the time of diagnosis (e.g. diabetes, hypertension, and heart disease) (516). Prior research has found that co-morbidity is an independent predictor of survival among breast cancer patients (517-520). More African-American breast cancer patients die from co-morbidities, including diabetes and hypertension, than Caucasian patients (520). In our survival analysis, however, 94% of the study population was Caucasian and only 4% was African-American. Thus, we were unable to examine differences by race. The main, case-control questionnaire had extensive assessment of medical history, which included history of hypertension and diabetes, as well as high cholesterol, myocardial infarction, and stroke. When these factors were controlled for, the results from the survival analyses were not substantially altered (Table A.25).

Lifestyle Factors

Many lifestyle factors that may confound the relationship between flavonoids and breast cancer are highly correlated with the exposure of interest (48, 484, 485), inhibiting the ability to firmly establish independent effects of flavonoids on breast cancer risk (486). The main, case-control questionnaire had extensive assessment of exposures over the life course including recreational physical activity from menarche to age at diagnosis, lifetime active and passive smoking exposure, and lifetime alcohol consumption (48). When these factors were controlled for mutually or individually, the results were not substantially altered.

Although, given that many of the lifestyle variables are difficult to measure in an epidemiologic study, and thus misclassification of these exposures is of concern, it is likely that there is some residual confounding present in the results shown.

Social Support and Health Care Factors

Social support, quality of life, and other psychosocial factors have been demonstrated to impact survival (521). The absence of this type of information in this study is another potential source of residual confounding. Factors of concern include social support mechanisms, stress, complimentary and alternative medicine (CAM), and health care coverage. It is believed that social support from family and friends, low stress, and adequate health care coverage improve quality of life and prolong survival (344, 521, 522). Therefore, these factors may have played a role in reducing the risk of mortality among the post-menopausal women of the LIBCSP, for whom high intakes of flavones and isoflavones appeared to be beneficial.

It is also possible that these support and health care factors motivated cases to improve the quality of their diet. This may have led to an increase in flavonoid intake. Therefore, the intake assessed at the baseline, case-control interview may be an underestimate and the inverse associations observed among post-menopausal cases may be stronger than what are presented. Furthermore, studies of social support and stress have reported weak, inconclusive results regarding survival (523-526). Overall, social support appears to improve quality of life rather than quantity of life (523, 525, 526). Thus, since these various social and health care factors do not appear to be strongly related to breast cancer survival, it is unlikely they confounded the association between dietary flavonoid intake and breast cancer survival.

Outcome Misclassification

The analysis on flavonoids and breast cancer survival may have had outcome misclassification if any deaths were not ascertained by the National Death Index (NDI). However, studies testing the effectiveness of the NDI (388-391) found the service to correctly identify the vital status of nearly 100% of all participants, distinguishing it as the "gold standard" of mortality ascertainment.

Sample Size Considerations

Study power was adequate for both the case-control and case-only analyses that were conducted among all women and for those restricted to post-menopausal women. However, power was reduced for our analyses that focused on pre-menopausal women only. Thus, any differences we observed by menopausal status could be due to the imprecise and unstable estimates among the younger women. Power would have been modestly improved if we were able to consider breast cancer recurrence as an outcome.

Future Directions

The present study contributed to the understanding of an important modifiable lifestyle factor, dietary flavonoid intake, on breast cancer incidence and survival. Flavonoid intake near the time of breast cancer diagnosis had never been evaluated among a large sample of American women. Given the paucity of the evidence with regard to dietary flavonoid intake and breast cancer incidence and survival, more research is warranted to better understand these relationships.

To improve our understanding of the relationship between dietary flavonoid intake and breast cancer incidence and survival, future investigations should include sufficiently large sample sizes and comprehensive dietary assessment instruments. In particular, food

frequency questionnaires and diet histories need to inquire about intake of as many flavonoid-containing foods and beverages as possible. Items that are currently absent from some instruments which should be included are, berries (e.g., blueberries, raspberries, blackberries, and elderberries); soy foods and beverages, including meatless soy products, and non-traditional sources of soy (e.g., fast food hamburgers).

More relevant to breast cancer survival, it would be beneficial to improve measurement of co-morbidities, complimentary and alternative medicine, family and social support mechanisms, health insurance coverage, and stress. Sufficiently long follow-up periods would also allow for both pre- and post-diagnosis dietary information to be collected. It is unknown how dietary flavonoid intake changes over time among survivors and it is not established that increased intake improves prognosis. Evaluating dietary patterns throughout a woman's life (pre- and post-diagnosis) may help us better understand if there is a critical period for dietary flavonoid intake with regard to survival.

Most research to date addressing diet and breast cancer incidence has focused on fruits, vegetables, micronutrients, and fat. While fruits and vegetables have been reported to decrease breast cancer risk, it remains unclear what components in these products are driving this effect. If flavonoids are involved, then intake of products other than fruits and vegetables may also be beneficial in reducing risk, such as grains (i.e., bread and rice), nuts, soy, red wine, tea, coffee, and chocolate. Fortification, already a common practice with many vitamins and minerals, may also be a method for adding flavonoid content to products available in the marketplace.

Further advancement into this area of research may help physicians and other health professionals recommend dietary behaviors that will provide more options to women for

reducing their risk of breast cancer and potentially improving the prognosis for those who already have been diagnosed with breast cancer. Gaining a more precise knowledge of the role of dietary flavonoid intake on breast cancer incidence and survival may also help researchers better understand the mechanisms associated with breast cancer etiology and prognosis.

Appendix I:

Additional Tables and Figures

Table A.1. Primary cause of death for invasive cases according to NDI records.

Number of Invasive Cases	1273
Number of Deaths (%)	188 (14.8%)
Cause of Death	
Breast Cancer	121 (64.4%)
Other Causes	
Lung Cancer	5
Other Cancer	17
Cardiovascular Disease	24
Other Causes	21
Total from Non-breast cancer causes	67 (35.6%)

Table A.2. Distribution of flavonoid intake (mg/d) for cases and controls of the Long Island Breast Cancer Study Project

Pre-menopausal Cases (n = 457)		**Pre-menopausal Controls (n = 487)**		
Variable	**Mean (mg/d)**	**Mean (mg/d)**	**p-value[†]**	**p-value[*]**
Total Flavonoids	211.12	212.19	0.94	0.53
Flavonols	10.09	10.11	0.96	0.35
Flavones	0.14	0.14	0.91	0.44
Flavanones	25.60	27.13	0.44	0.54
Flavan-3-ols	161.00	161.06	0.99	0.41
Anthocyanidins	3.16	3.03	0.75	0.64
Isoflavones	5.50	5.03	0.37	0.38
Lignans	5.97	5.92	0.85	0.50
Post-menopausal Cases (n = 977)		**Post-menopausal Controls (n = 953)**		
Variable	**Mean (mg/d)**	**Mean (mg/d)**	**p-value[a]**	**p-value[b]**
Total Flavonoids	220.74	242.66	0.02	0.02
Flavonols	9.68	10.70	0.002	0.0003
Flavones	0.13	0.15	0.0002	< 0.0001
Flavanones	34.12	34.17	0.97	0.99
Flavan-3-ols	163.29	182.68	0.03	0.009
Anthocyanidins	3.14	3.66	0.17	0.02
Isoflavones	4.58	4.86	0.46	0.69
Lignans	6.01	6.62	0.005	0.002

[†]P-value for t-test comparing means among pre-menopausal women
[a]P-value for t-test comparing means among post-menopausal women
[*]Wilcoxon rank sum test comparing medians among pre-menopausal women
[b]Wilcoxon rank sum test comparing medians among post-menopausal women

Table A.3. Distribution of geometric means of flavonoid intake for cases and controls of the LIBCSP

Pre-menopausal Cases (n = 457)			**Pre-menopausal Controls (n = 487)**				
Variable	**Geometric Mean (mg/d)**		**Geometric Mean (mg/d)**				**p-value**[†]
Total Flavonoids	121.51		113.55				0.39
Flavonols	7.91		7.56				0.37
Flavones	0.10		0.10				0.45
Flavanones	16.29		16.68				0.78
Flavan-3-ols	49.54		43.67				0.34
Anthocyanidins	0.91		1.03				0.34
Isoflavones	1.78		1.65				0.48
Lignans	4.28		4.14				0.60
Post-menopausal Cases (n = 977)			**Post-menopausal Controls (n = 953)**				
Variable	**Geometric Mean (mg/d)**		**Geometric Mean (mg/d)**				**p-value**[*]
Total Flavonoids	126.87		143.27				0.02
Flavonols	7.08		8.16				0.001
Flavones	0.09		0.10				0.003
Flavanones	22.85		22.54				0.81
Flavan-3-ols	42.81		55.46				0.007
Anthocyanidins	0.90		1.03				0.16
Isoflavones	1.29		1.35				0.56
Lignans	4.31		4.77				0.02

[†]P-value for t-test comparing geometric means among cases
[*]P-value for t-test comparing geometric means among controls

Table A.4. Foods and beverages included in each flavonoid class, listed according to flavonoid content (highest to lowest)

Total Flavonols	Total Flavones	Total Flavanones	Total Flavan-3-ols	Total Antho-cyanidins	Total Isoflavones	Total Lignans
Mustard greens, turnip greens, collards, kale	Spinach (raw)	Grapefruit	Tea, including herb tea (hot or iced)	Cherries (fresh in season)	Tofu	Tea, including herb tea (hot or iced)
Spinach (raw)	Red or green peppers	Oranges	Chocolate candy	Wine	Low-fat, frozen tofu	Strawberries (fresh in season)
Broccoli	Tomatoes, tomato juice, V-8 juice	Orange Juice or Grapefruit Juice	Cherries (fresh in season)		Green peas	Whole-wheat or other whole grain bread
Tea, including herb tea (hot or iced)	Cauliflower or brussel sprouts		Chocolate cake, brownies, cookies		Other beans (baked, pinto, kidney, lima, blackeyed, chili w/beans)	Coffee, regular or decaf
Hamburgers, Cheeseburgers, meat loaf, tacos	Green salad		Apples, applesauce, pears		Peanuts, peanut butter	Broccoli
Apples, applesauce, pears	Hamburgers, cheeseburgers meat loaf, tacos		Wine		White bread, rye, pumpernickel bread, sandwiches, bagels	Peanuts, peanut butter
Green salad	Cole slaw, cabbage, sauerkraut		Peaches, apricots (canned, frozen, or dried)		Whole-wheat or other whole grain bread	Winter squash, baked squash
String beans, green beans			Strawberries (fresh in season)		Cole slaw, cabbage, sauerkraut	Carrots, or mixed vegetables containing carrots
Strawberries (fresh in season)			Other beans (baked, pinto, kidney, lima, blackeyed, chili w/beans)		Other potatoes (boiled, baked, mashed, potato salad)	Orange Juice or Grapefruit Juice
Tomatoes, tomato juice, V-8 juice			Peaches, apricots (canned, frozen, or dried)		Brown Rice	Brown Rice
Cherries					White rice	Sweet

(fresh in season)						potatoes, yams
Pizza						Grapefruit
Spaghetti, lasagna, other pasta with tomato sauce						Hamburgers, Cheeseburgers, meat loaf, tacos
Grapefruit						Red or green peppers
Peaches, apricots (canned, frozen, or dried)						Cantaloupe
Wine						Wine
Cauliflower or brussel sprouts						Spaghetti, lasagna, other pasta with tomato sauce
Red or green peppers						Pizza
Tomato and vegetable soups						High fiber, bran or granola cereals
Cole slaw, cabbage, sauerkraut						Green salad
Green peas						Cauliflower or brussel sprouts
Beer						String beans, green beans
Other potatoes (boiled, baked, mashed, potato salad)						White bread, rye, pumpernickel bread, sandwiches, bagels
Orange Juice or Grapefruit Juice						Oranges
Carrots, or mixed vegetables containing carrots						Bananas
						Corn bread, corn muffins, corn tortillas
						Tomatoes, tomato

						juice, V-8 juice
						Other beans (baked, pinto, kidney, lima, blackeyed, chili w/beans)
						Apples, applesauce, pears
						Cole slaw, cabbage, sauerkraut
						Corn, including corn on the cob
						Alfalfa Sprouts
						Other potatoes (boiled, baked, mashed, potato salad)
						Green peas
						White rice

Table A.5. Cases total flavonoid intake and class intake per day (in mg) by ER/PR status.

Variable	N	Mean (mg/d)	Median (mg/d)	Minimum	Maximum
ER+PR+					
Total Flavonoids	258	208.98	143.01	5.16	870.24
Flavonols	258	9.37	7.67	0.41	33.01
Flavones	258	0.14	0.10	0.00	0.74
Flavanones	258	33.66	23.06	0.00	216.03
Flavan-3-ols	258	150.52	106.33	0.14	652.10
Anthocyanidins	258	3.78	0.87	0.00	69.79
Isoflavones	258	1.06	0.31	0.00	53.76
Lignans	258	5.68	4.66	0.10	19.81
ER+PR-					
Total Flavonoids	68	216.98	154.87	8.09	732.67
Flavonols	68	10.30	9.85	0.83	29.01
Flavones	68	0.13	0.10	0.01	0.58
Flavanones	68	26.41	24.09	0.00	149.33
Flavan-3-ols	68	164.52	115.57	0.12	646.87
Anthocyanidins	68	4.74	0.74	0.00	93.13
Isoflavones	68	0.71	0.32	0.03	7.25
Lignans	68	4.84	6.38	0.33	19.45
ER-PR+					
Total Flavonoids	22	266.61	231.59	26.24	709.25
Flavonols	22	11.59	10.20	1.96	27.05
Flavones	22	0.14	0.13	0.01	0.37
Flavanones	22	32.47	32.59	0.00	95.94
Flavan-3-ols	22	205.97	193.42	3.07	645.49
Anthocyanidins	22	3.51	2.20	0.00	11.17
Isoflavones	22	0.85	0.35	0.03	7.30
Lignans	22	6.86	6.23	0.34	19.16
ER-PR-					
Total Flavonoids	94	200.89	114.55	10.38	733.17
Flavonols	94	8.95	6.47	0.67	28.93
Flavones	94	0.12	0.10	0.00	0.57
Flavanones	94	30.08	25.82	0.00	132.08
Flavan-3-ols	94	149.29	52.81	0.00	654.60
Anthocyanidins	94	3.55	0.90	0.00	93.59
Isoflavones	94	0.78	0.31	0.03	14.69
Lignans	94	5.56	4.19	0.17	17.27

Table A.6. Controls total flavonoid intake and class intake per day (in mg) by ER/PR status.

Variable	N	Mean (mg/d)	Median (mg/d)	Minimum	Maximum
ER+PR+					
Total Flavonoids	274	222.12	151.28	4.65	809.24
Flavonols	274	10.21	9.26	0.79	33.02
Flavones	274	0.16	0.13	0.00	1.03
Flavanones	274	36.58	28.24	0.00	196.25
Flavan-3-ols	274	161.26	111.54	0.19	664.33
Anthocyanidins	274	3.16	0.75	0.00	52.92
Isoflavones	274	0.73	0.30	0.03	25.81
Lignans	274	5.98	4.83	0.10	17.08
ER+PR-					
Total Flavonoids	62	221.40	132.78	5.60	801.15
Flavonols	62	10.17	7.91	0.70	37.74
Flavones	62	0.15	0.13	0.00	0.62
Flavanones	62	26.56	22.44	0.00	116.29
Flavan-3-ols	62	170.53	69.99	0.35	654.20
Anthocyanidins	62	3.48	0.70	0.00	78.80
Isoflavones	62	0.91	0.36	0.02	23.44
Lignans	62	6.31	4.90	0.08	20.30
ER-PR+					
Total Flavonoids	26	294.50	209.34	7.55	756.72
Flavonols	26	12.72	8.63	1.80	35.12
Flavones	26	0.14	0.11	0.01	0.34
Flavanones	26	29.20	16.03	0.00	123.40
Flavan-3-ols	26	236.38	116.47	2.17	650.91
Anthocyanidins	26	3.67	0.80	0.00	22.11
Isoflavones	26	0.81	0.38	0.10	7.02
Lignans	26	7.99	5.55	0.61	18.58
ER-PR-					
Total Flavonoids	102	223.84	139.00	0.83	714.67
Flavonols	102	10.55	7.50	0.39	27.00
Flavones	102	0.15	0.13	0.00	0.86
Flavanones	102	32.44	23.12	0.00	172.52
Flavan-3-ols	102	165.62	59.55	0.09	644.73
Anthocyanidins	102	4.02	0.73	0.00	69.82
Isoflavones	102	0.76	0.31	0.01	11.63
Lignans	102	6.31	4.74	0.04	18.49

Table A.7. Case and control distribution for each quintiled flavonoid exposure stratified by menopausal status.[*]

	Pre-menopausal (n=944)		Post-menopausal (n=1,930)	
Total Flavonoids[#]	**Cases**	**Controls**	**Cases**	**Controls**
0-44.6	99	124	197	160
44.6-101.2	90	94	211	191
101.2-230.2	101	91	192	198
230.2-364.7	91	89	196	202
364.7+	76	89	181	202
Total	457	487	977	953
Total Flavonols[#]				
0-4.0	82	116	260	170
4.0-6.4	101	99	168	187
6.4-10.7	92	90	189	197
10.7-16.2	98	91	196	197
16.2+	84	91	164	202
Total	457	487	977	953
Total Flavones[#]				
0-0.05	85	101	238	187
0.05-0.09	94	107	204	182
0.09-0.14	106	101	208	186
0.14-0.22	84	84	182	204
0.22+	88	94	145	194
Total	457	487	977	953
Total Flavanones[#]				
0-4.5	123	107	176	177
4.5-15.2	97	125	167	163
15.2-30.0	80	95	209	191
30.0-50.3	94	81	211	206
50.3+	63	79	214	216
Total	457	487	977	953
Total Flavan-3-ols[#]				
0-6.5	81	108	222	177
6.5-39.5	99	108	185	177
39.5-189.8	100	87	197	201
189.8-267.9	97	96	204	195
267.9+	80	88	169	203
Total	457	487	977	953
Total Anthocyanidins[#]				
0-0.04	84	91	221	200
0.04-0.56	109	103	216	179
0.56-1.75	88	109	189	179
1.75-4.57	86	97	172	194
4.57+	90	87	179	201
Total	457	487	977	953
Total Isoflavones[#]				
0-0.17	101	100	202	185
0.17-0.26	80	95	184	198

0.26-0.38	93	99	211	185
0.38-0.61	85	84	203	206
0.61+	98	109	177	179
Total	457	487	977	953
Total Lignans[#]				
0-2.3	88	118	213	173
2.3-4.2	109	94	235	195
4.2-6.2	86	103	171	175
6.2-9.8	97	83	194	206
9.8+	77	89	164	204
Total	457	487	977	953

[#] In milligrams per day (mg/d).
[*]29 cases and 60 controls missing data for menopausal status.

Table A.8. A summary of the preliminary evaluation of confounding and effect modification of flavonoids and breast cancer incidence by selected covariates.

Covariate	Relationship between Covariate and Outcome (Incidence)? OR (95% CI)	FLAVONOID EXPOSURES		
		Relationship between covariate and Total Flavonoids? OR (95% CI)	Evidence of Effect Measure Modification? p-value from Likelihood Ratio Test	Does the OR for Total Flavonoids change by more than 10% when Covariate is added to model?
Menopausal Status	Borderline	YES	YES	No
Age	YES	YES	YES	No
Alcohol	No	No	No	No
Smoking	No	No	No	No
Family History	YES	No	No	No
BBD	YES	No	No	No
Physical Activity	Borderline	YES	No	No
BMI	No	No	No	No
Income	Borderline	Borderline	No	No
Education	Borderline	Borderline	No	No
Parity	YES	Borderline	No	No
Mammography	YES	Borderline	No	No
OC Use	No	No	No	No
Fruits	Borderline	YES	No	No
Vegetables	Borderline	YES	No	No
Antioxidants	No	YES	No	No

Table A.9. Age and energy-adjusted ORs and 95% CIs for the association between menopausal-specific flavonoid intake in relation to breast cancer incidence

	Pre-menopausal (n = 944)		**Post-menopausal (n = 1930)**
	OR (95% CI)		**OR (95% CI)**
Total Flavonoids[#]		**Total Flavonoids[#]**	
0-34.5	1.00	**0-51.8**	1.00
34.5-84.5	1.20 (0.79-1.84)	**51.8-119.1**	0.94 (0.71-1.24)
84.5-199.5	1.29 (0.84-1.97)	**119.1-253.3**	0.79 (0.60-1.05)
199.5-343.0	1.46 (0.96-2.22)	**253.3-377.2**	0.80 (0.60-1.06)
343.0+	1.12 (0.72-1.74)	**377.2+**	0.75 (0.56-1.01)
P for trend[*]	0.95	**P for trend[*]**	0.05
Total Flavonols[#]		**Total Flavonols[#]**	
0-3.7	1.00	**0-4.3**	1.00
3.7-6.0	1.32 (0.86-2.03)	**4.3-6.8**	0.56 (0.42-0.74)
6.0-10.2	1.48 (0.97-2.27)	**6.8-11.1**	0.62 (0.47-0.82)
10.2-15.1	1.53 (0.99-2.35)	**11.1-17.1**	0.63 (0.47-0.83)
15.1+	1.38 (0.88-2.15)	**17.1+**	0.54 (0.40-0.73)
P for trend[*]	0.92	**P for trend[*]**	0.009
Total Flavones[#]		**Total Flavones[#]**	
0-0.04	1.00	**0-0.04**	1.00
0.05-0.07	0.94 (0.62-1.43)	**0.05-0.08**	0.90 (0.68-1.19)
0.08-0.12	1.29 (0.86-1.84)	**0.09-0.14**	0.95 (0.72-1.26)
0.13-0.21	1.07 (0.70-1.63)	**0.15-0.21**	0.70 (0.52-0.94)
0.22+	1.07 (0.70-1.65)	**0.22+**	0.61 (0.45-0.83)
P for trend[*]	0.94	**P for trend[*]**	0.0007
Total Flavanones[#]		**Total Flavanones[#]**	
0-3.1	1.00	**0-5.3**	1.00
3.2-10.8	0.69 (0.46-1.04)	**5.4-18.8**	1.09 (0.82-1.46)
10.9-24.5	0.69 (0.46-1.04)	**18.9-32.1**	1.10 (0.83-1.46)
24.6-40.3	0.85 (0.57-1.26)	**32.2-54.2**	1.08 (0.81-1.43)
40.4+	0.80 (0.53-1.21)	**54.3+**	1.00 (0.75-1.34)
P for trend[*]	0.34	**P for trend[*]**	0.87
Total Flavan-3-ols[#]		**Total Flavan-3-ols[#]**	
0-5.1	1.00	**0-7.6**	1.00
5.2-26.4	1.22 (0.80-1.87)	**7.7-54.0**	0.94 (0.72-1.24)
26.5-120.8	1.32 (0.87-2.01)	**54.1-192.0**	0.80 (0.60-1.06)
120.9-264.1	1.52 (1.00-2.30)	**192.1-277.9**	0.82 (0.62-1.08)
264.2+	1.21 (0.78-1.86)	**278.0+**	0.74 (0.55-0.99)
P for trend[*]	0.87	**P for trend[*]**	0.06
Total Anthocyanidins[#]		**Total Anthocyanidins[#]**	
0-0.04	1.00	**0-0.03**	1.00
0.05-0.56	1.15 (0.77-1.72)	**0.04-0.56**	1.09 (0.83-1.44)
0.57-1.60	0.77 (0.50-1.17)	**0.57-1.84**	0.97 (0.73-1.28)
1.61-4.19	1.07 (0.71-1.61)	**1.85-4.84**	0.82 (0.62-1.09)
4.20+	1.08 (0.71-1.63)	**4.85+**	0.85 (0.64-1.14)
P for trend[*]	0.81	**P for trend[*]**	0.23
Total Isoflavones[#]		**Total Isoflavones[#]**	
0-0.31	1.00	**0-0.27**	1.00

0.32-1.10	1.03 (0.68-1.56)	**0.28-0.62**	0.97 (0.72-1.30)
1.11-3.17	0.98 (0.65-1.47)	**0.63-1.94**	1.16 (0.87-1.55)
3.18-7.62	0.88 (0.58-1.33)	**1.95-7.63**	1.14 (0.85-1.53)
7.63+	1.14 (0.76-1.72)	**7.64+**	1.02 (0.76-1.38)
P for trend[*]	0.56	**P for trend**[*]	0.72
Total Lignans[#]		**Total Lignans**[#]	
0-2.0	1.00	**0-2.4**	1.00
2.1-4.0	1.43 (0.95-2.17)	**2.5-4.2**	1.07 (0.81-1.40)
4.1-5.4	0.98 (0.63-1.51)	**4.3-6.4**	0.82 (0.61-1.09)
5.5-9.3	1.62 (1.07-2.45)	**6.5-10.2**	0.79 (0.59-1.05)
9.4+	1.24 (0.81-1.92)	**10.3+**	0.69 (0.51-0.94)
P for trend[*]	0.72	**P for trend**[*]	0.01

[*] P for trend for continuous variable.

[#] In milligrams per day (mg/d).

Table A.10. Age and energy-adjusted ORs and 95% CI for the association between flavonoid intake and breast cancer incidence among post-menopausal women, stratified by ER/PR status

	Controls	ER+PR+		ER+PR-, ER-PR+, ER-PR-	
	(n = 953)	Cases (n) (n = 378)	OR (95% CI)	Cases (n) (n = 274)	OR (95% CI)
Total Flavonoids[#]					
0-51.7	190	89	1.00	72	1.00
51.8-119.0	192	78	0.90 (0.62-1.31)	62	0.89 (0.59-1.32)
119.1-253.2	190	72	0.83 (0.57-1.21)	42	0.60 (0.39-0.93)
253.3-377.1	191	77	0.86 (0.59-1.25)	49	0.68 (0.44-1.04)
377.2+	190	62	0.75 (0.50-1.12)	49	0.72 (0.47-1.11)
P for trend[*]			0.35		0.09
Total Flavonols[#]					
0-4.2	191	113	1.00	93	1.00
4.3-6.7	190	66	0.59 (0.41-0.86)	47	0.51 (0.34-0.78)
6.8-11.0	190	67	0.60 (0.41-0.87)	42	0.46 (0.30-0.71)
11.1-17.0	191	74	0.66 (0.46-0.96)	46	0.49 (0.32-0.75)
17.1+	191	58	0.55 (0.37-0.82)	56	0.51 (0.33-0.79)
P for trend[*]			0.12		0.03
Total Flavones[#]					
0-0.04	191	101	1.00	69	1.00
0.05-0.08	190	74	0.76 (0.52-1.10)	72	1.05 (0.71-1.56)
0.09-0.14	191	85	0.89 (0.62-1.29)	55	0.83 (0.54-1.26)
0.15-0.21	191	61	0.64 (0.43-0.94)	44	0.67 (0.43-1.04)
0.22+	190	57	0.59 (0.40-0.89)	34	0.51 (0.32-0.82)
P for trend[*]			0.02		0.003
Total Flavanones[#]					
0-5.3	190	70	1.00	50	1.00
5.4-18.8	192	77	1.18 (0.80-1.74)	52	1.05 (0.68-1.63)
18.9-32.1	189	84	1.21 (0.83-1.78)	61	1.20 (0.78-1.84)
32.2-54.2	191	80	1.14 (0.77-1.67)	58	1.16 (0.75-1.80)
54.3+	191	67	0.95 (0.63-1.42)	53	1.06 (0.68-1.66)
P for trend[*]			0.77		0.49
Total Flavan-3-ols[#]					
0-7.6	190	93	1.00	71	1.00
7.7-54.0	192	75	0.81 (0.56-1.18)	62	0.88 (0.59-1.31)
54.1-192.0	189	65	0.71 (0.49-1.04)	48	0.69 (0.45-1.05)
192.1-277.9	192	81	0.86 (0.60-1.24)	48	0.66 (0.43-1.02)
278.0+	190	64	0.75 (0.51-1.10)	45	0.67 (0.43-1.03)
P for trend[*]			0.45		0.13
Total Anthocyanidins[#]					
0-0.03	189	77	1.00	58	1.00
0.04-0.56	192	88	1.19 (0.82-1.73)	70	1.22 (0.81-1.84)
0.57-1.84	190	88	1.25 (0.86-1.81)	44	0.80 (0.51-1.24)
1.85-4.84	191	69	0.93 (0.63-1.37)	50	0.90 (0.59-1.39)
4.85+	191	56	0.77 (0.51-1.16)	52	0.95 (0.62-1.46)
P for trend[*]			0.005		0.63
Total Isoflavones[#]					
0-0.27	190	82	1.00	55	1.00

0.28-0.62	191	63	0.78 (0.52-1.17)	64	1.19 (0.78-1.83)
0.63-1.94	191	81	1.09 (0.75-1.60)	50	0.98 (0.62-1.52)
1.95-7.63	191	88	1.21 (0.83-1.77)	58	1.16 (0.75-1.80)
7.64+	190	64	0.92 (0.61-1.37)	47	1.00 (0.63-1.58)
P for trend*			0.91		0.48
Total Lignans#					
0-2.4	215	89	1.00	72	1.00
2.5-4.2	167	81	1.09 (0.76-1.58)	68	1.07 (0.72-1.59)
4.3-6.4	190	76	0.96 (0.66-1.40)	48	0.74 (0.48-1.14)
6.5-10.2	191	71	0.89 (0.60-1.30)	43	0.64 (0.41-0.99)
10.3+	190	61	0.82 (0.55-1.24)	43	0.67 (0.43-1.05)
P for trend*			0.35		0.02

*P for trend for continuous variable.

In milligrams per day (mg/d).

Table A.11. Age, fruit, fruit juice, vegetable, antioxidant, and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to breast cancer incidence.

	Pre-menopausal	Post-menopausal	Pre- and Post-menopausal
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Total Flavonoids[#]			
0-44.6	1.00	1.00	1.00
44.6-101.2	1.24 (0.81-1.89)	0.92 (0.68-1.25)	1.04 (0.82-1.33)
101.2-230.2	1.38 (0.90-2.10)	0.80 (0.59-1.09)	1.02 (0.80-1.30)
230.2-364.7	1.34 (0.88-2.04)	0.80 (0.59-1.08)	0.99 (0.78-1.25)
364.7+	1.10 (0.71-1.72)	0.77 (0.56-1.05)	0.91 (0.71-1.17)
P for trend[*]	0.91	0.06	0.17
Total Flavonols[#]			
0-4.0	1.00	1.00	1.00
4.0-6.4	1.43 (0.94-2.19)	0.63 (0.47-0.84)	0.83 (0.66-1.05)
6.4-10.7	1.39 (0.89-2.16)	0.70 (0.52-0.94)	0.88 (0.69-1.12)
10.7-16.2	1.51 (0.97-2.36)	0.71 (0.53-0.96)	0.93 (0.73-1.18)
16.2+	1.30 (0.82-2.05)	0.58 (0.43-0.80)	0.79 (0.61-1.01)
P for trend[*]	0.66	0.06	0.13
Total Flavones[#]			
0-0.05	1.00	1.00	1.00
0.05-0.09	0.92 (0.61-1.40)	0.94 (0.70-1.25)	0.94 (0.75-1.19)
0.09-0.14	0.98 (0.63-1.52)	1.00 (0.73-1.36)	1.00 (0.78-1.29)
0.14-0.22	0.78 (0.47-1.29)	0.84 (0.59-1.19)	0.84 (0.64-1.12)
0.22+	0.60 (0.33-1.08)	0.74 (0.49-1.12)	0.74 (0.53-1.03)
P for trend[*]	0.04	0.19	0.06
Total Flavanones[#]			
0-4.5	1.00	1.00	1.00
4.5-15.2	0.66 (0.44-0.97)	1.05 (0.77-1.44)	0.90 (0.71-1.14)
15.2-30.0	0.74 (0.44-1.23)	1.09 (0.77-1.54)	0.96 (0.73-1.27)
30.0-50.3	1.00 (0.54-1.83)	1.06 (0.71-1.58)	1.07 (0.77-1.48)
50.3+	0.72 (0.34-1.54)	1.06 (0.66-1.69)	1.01 (0.68-1.49)
P for trend[*]	0.53	0.66	0.75
Total Flavan-3-ols[#]			
0-6.5	1.00	1.00	1.00
6.5-39.5	1.18 (0.78-1.78)	0.86 (0.65-1.16)	0.97 (0.77-1.22)
39.5-189.8	1.51 (0.99-2.30)	0.79 (0.60-1.05)	1.00 (0.79-1.25)
189.8-267.9	1.33 (0.88-2.02)	0.84 (0.63-1.11)	1.01 (0.80-1.27)
267.9+	1.22 (0.79-1.89)	0.70 (0.52-0.94)	0.86 (0.68-1.09)
P for trend[*]	0.97	0.06	0.17
Total Anthocyanidins[#]			
0-0.04	1.00	1.00	1.00
0.04-0.56	1.12 (0.74-1.69)	1.10 (0.83-1.46)	1.09 (0.87-1.37)
0.56-1.75	0.80 (0.52-1.21)	1.02 (0.76-1.35)	0.96 (0.76-1.20)
1.75-4.57	0.88 (0.57-1.35)	0.86 (0.65-1.15)	0.88 (0.70-1.12)
4.57+	0.95 (0.61-1.48)	0.89 (0.67-1.19)	0.93 (0.74-1.18)
P for trend[*]	0.84	0.47	0.43
Total Isoflavones[#]			
0-0.17	1.00	1.00	1.00

0.17-0.26	0.79 (0.51-1.20)	0.93 (0.69-1.24)	0.88 (0.69-1.11)
0.26-0.38	0.87 (0.57-1.32)	1.13 (0.84-1.53)	1.01 (0.80-1.28)
0.38-0.61	0.91 (0.59-1.43)	1.02 (0.75-1.39)	0.98 (0.77-1.26)
0.61+	0.79 (0.51-1.22)	1.10 (0.79-1.53)	1.00 (0.78-1.30)
P for trend*	0.62	0.56	0.19
Total Lignans#			
0-2.3	1.00	1.00	1.00
2.3-4.2	1.52 (1.02-2.26)	0.98 (0.74-1.30)	1.14 (0.91-1.43)
4.2-6.2	1.09 (0.72-1.65)	0.80 (0.59-1.08)	0.87 (0.69-1.10)
6.2-9.8	1.57 (1.03-2.39)	0.77 (0.57-1.03)	0.99 (0.79-1.25)
9.8+	1.16 (0.76-1.78)	0.67 (0.49-0.91)	0.82 (0.65-1.05)
P for trend*	0.92	0.01	0.07

In milligrams per day (mg/d).

* P for trend for continuous variable.

Table A.12. Age and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) stratified by ER/PR status for the association between flavonoid intake and breast cancer incidence among post-menopausal women.

Variable	Controls	ER+ PR+		ER+ PR-		ER- PR+		ER- PR-	
	(n = 953)	Cases (n) (n=378)	OR (95% CI)	Cases (n) (n=117)	OR (95% CI)	Cases (n) (n=29)	OR (95% CI)	Cases (n) (n=128)	OR (95% CI)
Total Flavonoids*									
0 - 230.2	549	228	1.00	75	1.00	16	1.00	82	1.00
230.2+	404	150	0.91 (0.71-1.17)	42	0.74 (0.49-1.11)	13	1.02 (0.48-2.18)	46	0.82 (0.56-1.22)
P for trend#			0.32		0.18		0.58		0.08
Total Flavonols*									
0 - 10.7	554	240	1.00	77	1.00	15	1.00	85	1.00
10.7+	399	138	0.84 (0.65-1.08)	40	0.70 (0.46-1.07)	14	1.16 (0.54-2.50)	43	0.77 (0.51-1.15)
P for trend#			0.11		0.03		0.39		0.04
Total Flavones*									
0 - 0.14	555	252	1.00	79	1.00	16	1.00	95	1.00
0.14+	398	126	0.72 (0.56-0.94)	38	0.68 (0.45-1.04)	13	1.02 (0.48-2.17)	33	0.52 (0.34-0.80)
P for trend#			0.02		0.006		0.52		0.01
Total Flavanones*									
0 – 30.0	531	218	1.00	60	1.00	16	1.00	77	1.00
30.0+	422	160	0.89 (0.69-1.14)	57	1.12 (0.75-1.66)	13	0.99 (0.46-2.13)	51	0.88 (0.60-1.31)
P for trend#			0.75		0.55		0.27		0.22
Total Flavan-3-ols*									
0 – 189.8	555	228	1.00	76	1.00	16	1.00	81	1.00
189.8+	398	150	0.94 (0.73-1.21)	41	0.72 (0.48-2.10)	13	1.06 (0.50-2.25)	47	0.87 (0.59-1.29)
P for trend#			0.41		0.14		0.47		0.16
Total Anthocyanidins*									
0 – 1.75	558	248	1.00	75	1.00	15	1.00	82	1.00
1.75+	395	130	0.75 (0.58-0.96)	42	0.81 (0.54-1.22)	14	1.28 (0.61-2.68)	46	0.83 (0.56-1.22)
P for			0.005		0.36		0.55		0.11

trend[#]									
Total Isoflavones[*]									
0 – 0.38	568	235	1.00	71	1.00	14	1.00	81	1.00
0.38+	385	143	0.96 (0.73-1.25)	46	0.98 (0.64-1.51)	15	1.37 (0.62-3.04)	47	0.98 (0.65-1.48)
P for trend[#]			1.00		0.74		0.06		0.58
Total Lignans[*]									
0 – 6.2	543	235	1.00	79	1.00	16	1.00	85	1.00
6.2+	410	143	0.83 (0.65-1.07)	38	0.62 (0.41-0.94)	13	0.99 (0.46-2.10)	43	0.72 (0.48-1.07)
P for trend[#]			0.32		0.05		0.55		0.02

Table A.13. Age and energy-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between flavonoid intake and breast cancer incidence among post-menopausal women, stratified by ER/PR.

	Controls	ER+PR+, ER+PR-, ER-PR+		ER-PR-	
	(n = 953)	Cases (n) (n = 524)	OR (95% CI)	Cases (n) (n = 128)	OR (95% CI)
Total Flavonoids[#]					
0-44.6	160	107	1.00	32	1.00
44.6-101.2	191	111	1.09 (0.83-1.42)	29	1.18 (0.76-1.85)
101.2-230.2	198	101	0.89 (0.68-1.16)	21	0.75 (0.46-1.23)
230.2-364.7	202	104	0.89 (0.68-1.16)	27	1.03 (0.65-1.63)
364.7+	202	101	0.95 (0.72-1.25)	19	0.70 (0.42-1.19)
P for trend[*]			0.28		0.09
Total Flavonols[#]					
0-4.0	170	144	1.00	39	1.00
4.0-6.4	187	97	0.92 (0.70-1.21)	21	0.79 (0.48-1.30)
6.4-10.7	197	91	0.82 (0.62-1.08)	25	0.96 (0.60-1.54)
10.7-16.2	197	101	0.90 (0.69-1.18)	24	0.95 (0.59-1.53)
16.2+	202	91	0.84 (0.63-1.12)	19	0.70 (0.42-1.19)
P for trend[*]			0.07		0.05
Total Flavones[#]					
0-0.05	187	137	1.00	33	1.00
0.05-0.09	182	110	1.13 (0.86-1.47)	30	1.28 (0.82-1.99)
0.09-0.14	186	100	0.99 (0.76-1.30)	32	1.39 (0.90-2.15)
0.14-0.22	204	96	0.85 (0.65-1.12)	22	0.81 (0.50-1.33)
0.22+	194	81	0.72 (0.54-0.97)	11	0.40 (0.21-0.76)
P for trend[*]			0.01		0.01
Total Flavanones[#]					
0-4.5	177	89	1.00	24	1.00
4.5-15.2	163	87	1.04 (0.78-1.39)	25	1.16 (0.72-1.87)
15.2-30.0	191	118	1.14 (0.88-1.48)	28	1.11 (0.71-1.74)
30.0-50.3	206	117	1.02 (0.79-1.32)	25	0.90 (0.57-1.44)
50.3+	216	113	0.91 (0.70-1.18)	26	0.93 (0.58-1.49)
P for trend[*]			0.86		0.23
Total Flavan-3-ols[#]					
0-6.5	177	133	1.00	28	1.00
6.5-39.5	177	87	0.87 (0.65-1.15)	30	1.34 (0.86-2.08)
39.5-189.8	201	100	0.87 (0.67-1.14)	23	0.81 (0.50-1.31)
189.8-267.9	195	110	1.00 (0.76-1.30)	28	1.12 (0.71-1.76)
267.9+	203	94	0.86 (0.65-1.14)	19	0.70 (0.41-1.17)
P for trend[*]			0.34		0.16
Total Anthocyanidins[#]					
0-0.04	200	108	1.00	33	1.00
0.04-0.56	179	121	1.28 (0.98-1.67)	31	1.37 (0.88-2.13)
0.56-1.75	179	109	1.18 (0.90-1.54)	18	0.71 (0.42-1.20)
1.75-4.57	194	99	0.92 (0.70-1.21)	22	0.82 (0.50-1.33)
4.57+	201	87	0.75 (0.57-0.99)	24	0.92 (0.57-1.49)
P for trend[*]			0.09		0.10
Total Isoflavones[#]					

0-0.17	185	105	1.00	26	1.00
0.17-0.26	198	108	0.99 (0.76-1.30)	20	0.70 (0.42-1.16)
0.26-0.38	185	107	1.03 (0.79-1.35)	35	1.60 (1.05-2.45)
0.38-0.61	206	109	0.96 (0.73-1.26)	28	1.10 (0.70-1.74)
0.61+	179	95	1.03 (0.77-1.37)	19	0.86 (0.50-1.47)
P for trend*			0.53		0.56
Total Lignans#					
0-2.3	173	110	1.00	33	1.00
2.3-4.2	195	124	1.17 (0.90-1.51)	31	1.20 (0.77-1.86)
4.2-6.2	175	96	1.02 (0.77-1.35)	21	0.92 (0.56-1.52)
6.2-9.8	206	99	0.83 (0.63-1.09)	27	1.00 (0.63-1.58)
9.8+	204	95	0.87 (0.66-1.15)	16	0.57 (0.32-0.99)
P for trend*			0.19		0.03

* P for trend for continuous variable.

In milligrams per day (mg/d).

Table A.14. Number and percentage of eligible invasive breast cancer cases for each categorical characteristic included in the LIBCSP follow-up study.

Characteristic	N (%) (n = 1,273)	Characteristic	N (%)
Race		**Alcohol Use**	
White	1191 (93.8%)	Never	498 (39.1%)
Black	57 (4.5%)	Ever	775 (60.9%)
Other	22 (1.7%)		
Missing	3	**Family History of BC**	255 (20.7%)
		Missing	39
Estrogen Receptor Status			
Negative	255 (26.8%)	**Education**	
Positive	695 (73.2%)	Less than High School	171 (13.5%)
Missing	323	High School Graduate	456 (36.0%)
		Some College	302 (23.8%)
Progesterone Receptor Status		College Graduate	157 (12.4%)
Negative	341 (36.0%)	Post-college Education	182 (14.3%)
Positive	605 (64.0%)	*Missing*	5
Missing	327		
		Household Income/yr.	
Age at Diagnosis (years)		Less than $15,000	103 (9.4%)
< 35	36 (2.8%)	$15,000-$19,999	59 (5.4%)
35-39	38 (3.0%)	$20,000-$24,999	68 (6.2%)
40-44	109 (8.6%)	$25,.000-$34,999	161 (14.7%)
45-50	192 (15.1%)	$35,000-$49,999	169 (15.4%)
≥ 51	898 (70.5%)	$50,000-$69,999	158 (14.4%)
		$70,000-$89,999	140 (12.8%)
Menopausal Status		$90,000 or more	237 (21.7%)
Pre-menopausal	387 (31.0%)	*Missing*	178
Post-menopausal	861 (69.0%)		
Missing	25	**Any Chemotherapy Prior to Interview**	418 (48.7%)
		Missing	415
Nulliparous	165 (13.0%)		
		Any Radiation Therapy Prior to Interview	563 (65.4%)
Ever Breastfed	388 (31.4%)	*Missing*	412
Age at menarche: < 12 years	338 (26.6%)	**Ever Married**	1222 (96.1%)
Ever Used Oral Contraceptives	541 (42.6%)		
Ever Smoker			
Never	568 (44.6%)		
Past/Former	453 (35.6%)		
Current	252 (19.8%)		

Table A.15. Number and percentage of invasive breast cancer cases for each categorical characteristic included in the LIBCSP follow-up study.

Characteristic	N (%) (n = 1,210)	Characteristic	N (%)
Race		**Alcohol Use**	
White	1138 (94.1%)	Never	466 (38.5%)
Black	50 (4.2%)	Ever	744 (61.5%)
Other	21 (1.7%)		
Missing	1	**Family History of BC**	239 (20.4%)
		Missing	37
Estrogen Receptor Status			
Negative	242 (26.6%)	**Education**	
Positive	668 (73.4%)	Less than High School	161 (13.3%)
Missing	300	High School Graduate	439 (36.4%)
		Some College	283 (23.5%)
Progesterone Receptor Status		College Graduate	159 (12.3%)
Negative	324 (35.8%)	Post-college Education	175 (14.5%)
Positive	582 (64.2%)	*Missing*	3
Missing	304		
		Household Income/yr.	
Age at Diagnosis (years)		Less than $15,000	95 (9.1%)
< 35	35 (2.9%)	$15,000-$19,999	56 (5.4%)
35-39	36 (3.0%)	$20,000-$24,999	64 (6.1%)
40-44	143 (11.8%)	$25,.000-$34,999	154 (14.8%)
45-50	141 (11.7%)	$35,000-$49,999	160 (15.3%)
≥ 51	855 (70.6%)	$50,000-$69,999	155 (14.9%)
		$70,000-$89,999	135 (13.0%)
Menopausal Status		$90,000 or more	223 (21.4%)
Pre-menopausal	376 (31.1%)	*Missing*	168
Post-menopausal	834 (68.9%)		
		Any Chemotherapy Prior to Interview	424 (51.5%)
Nulliparous	154 (12.7%)	*Missing*	387
Ever Breastfed	381 (31.5%)	**Any Radiation Therapy Prior to Interview**	539 (65.3%)
		Missing	384
Age at menarche: < 12 years	310 (25.6%)		
		Ever Married	1165 (96.4%)
Ever Used Oral Contraceptives	515 (42.6%)		
Missing	2		
Ever Smoker			
Never	541 (44.7%)		
Past/Former	435 (36.0%)		
Current	234 (19.3%)		

Table A.16. Invasive case distribution for each quintile of flavonoid exposure stratified by menopausal status.

Variable	Pre-menopausal (n=376)	Post-menopausal (n=834)	Pre- and Post-menopausal (n=1,210)
	Cases	Cases	Cases
Total Flavonoids*			
0-42.5	82	161	243
42.5-95.1	72	171	243
95.1-216.3	79	162	241
216.3-340.5	75	168	243
340.5+	68	172	240
Total	376	834	1210
Total Flavonols*			
0-3.5	58	185	243
3.5-6.0	81	162	243
6.0-10.2	83	159	242
10.2-14.5	76	164	240
14.5+	78	164	242
Total	376	834	1210
Total Flavones*			
0-0.04	61	180	241
0.04-0.08	80	163	243
0.08-0.13	75	167	242
0.13-0.20	70	172	242
0.20+	90	152	242
Total	376	834	1210
Total Flavanones*			
0-4.1	97	143	240
4.1-16.4	84	156	240
16.4-30.0	67	176	243
30.0-48.6	74	172	246
48.6+	54	187	241
Total	376	834	1210
Total Flavan-3-ols*			
0-5.1	66	178	244
5.1-34.5	84	158	242
34.5-140.1	78	164	242
140.1-263.8	79	162	241
263.8+	69	172	241
Total	376	834	1210
Total Anthocyanidins*			
0-0.04	60	181	241
0.04-0.41	86	158	244
0.41-1.61	70	178	248
1.61-4.24	81	157	238
4.24+	79	160	239
Total	376	834	1210
Total Isoflavones*			
0-0.16	78	160	238

0.16-0.27	71	172	243
0.27-0.38	70	175	245
0.38-0.60	72	172	244
0.60+	85	155	240
Total	376	834	1210
Total Lignans*			
0-2.3	72	171	243
2.3-4.0	72	170	242
4.0-6.0	82	162	244
6.0-9.0	77	163	240
9.0+	83	168	241
Total	376	834	1210

* In milligrams per day (mg/d).

Table A.17. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996-1997.

Variable (mg/day)	Deaths/ Cohort # deaths/ 376	Pre-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 834	Post-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 1,210	Pre and Post HR (95% CI)
Total Flavonoids*						
0-42.4	3/82	1.00	25/161	1.00	28/243	1.00
42.5-95.0	15/72	2.49 (1.32-4.69)	23/171	0.81 (0.52-1.28)	38/243	1.10 (0.77-1.57)
95.1-216.2	6/79	0.58 (0.24-1.36)	28/162	1.09 (0.71-1.65)	34/241	0.95 (0.66-1.39)
216.3-340.4	6/75	0.61 (0.26-1.46)	32/168	1.24 (0.83-1.86)	38/243	1.11 (0.77-1.59)
340.5+	13/68	1.77 (0.91-3.46)	22/172	0.78 (0.49-1.25)	35/240	0.96 (0.66-1.40)
Total Flavonols*						
0-3.4	4/58	1.00	31/185	1.00	35/243	1.00
3.5-5.9	12/81	1.65 (0.84-3.26)	23/162	0.89 (0.57-1.40)	35/243	1.03 (0.71-1.49)
6.0-10.1	8/83	0.78 (0.36-1.68)	25/159	0.99 (0.64-1.54)	33/242	0.94 (0.64-1.37)
10.2-14.4	5/76	0.47 (0.19-1.19)	26/164	1.02 (0.66-1.57)	31/240	0.86 (0.58-1.27)
14.5+	14/78	1.64 (0.84-3.17)	25/164	0.98 (0.62-1.53)	39/242	1.12 (0.78-1.62)
Total Flavones*						
0-0.03	7/61	1.00	32/180	1.00	39/241	1.00
0.04-0.07	9/80	1.07 (0.51-2.25)	29/163	1.24 (0.82-1.88)	38/243	1.20 (0.83-1.72)
0.08-0.12	11/75	1.36 (0.69-2.70)	27/167	1.13 (0.74-1.73)	38/242	1.17 (0.82-1.68)
0.13-0.19	7/70	0.87 (0.39-1.95)	25/172	0.92 (0.59-1.44)	32/242	0.88 (0.60-1.29)
0.20+	9/90	0.69 (0.32-1.47)	17/152	0.59 (0.35-0.99)	26/242	0.63 (0.41-0.96)
Total Flavanones*						
0-4.0	12/97	1.00	21/143	1.00	33/240	1.00
4.1-16.3	8/84	0.80 (0.37-1.73)	28/156	1.49 (0.97-2.29)	36/240	1.25 (0.86-1.81)
16.4-29.9	6/67	0.75 (0.32-1.78)	19/176	0.60 (0.37-0.98)	25/243	0.64 (0.42-0.97)
30.0-48.5	9/74	1.04 (0.50-2.17)	30/172	1.13 (0.75-1.71)	39/246	1.10 (0.77-1.57)
48.6+	8/54	1.08 (0.48-2.43)	32/187	0.99 (0.66-1.49)	40/241	1.03 (0.72-1.48)
Total Flavan-3-ols*						
0-5.0	3/66	1.00	29/178	1.00	32/244	1.00
5.1-34.4	8/84	0.80 (0.37-1.74)	22/158	0.88 (0.56-1.39)	30/242	0.83 (0.56-1.23)
34.5-140.0	12/78	1.42 (0.73-2.77)	26/164	1.01 (0.66-1.56)	38/242	1.12 (0.78-1.61)
140.1-263.7	7/79	0.72 (0.32-1.63)	29/162	1.21 (0.80-1.83)	36/241	1.10 (0.76-1.59)

263.8+	13/69	1.76 (0.91-3.42)	24/172	0.84 (0.53-1.32)	37/241	1.01 (0.70-1.46)
Total Anthocyanidins*						
0-0.03	6/60	1.00	39/181	1.00	45/241	1.00
0.04-0.40	16/86	2.12 (1.14-3.93)	28/158	1.18 (0.77-1.79)	44/244	1.42 (1.01-2.00)
0.41-1.60	10/70	1.33 (0.66-2.71)	25/178	0.92 (0.59-1.42)	35/248	1.00 (0.69-1.45)
1.61-4.23	4/81	0.36 (0.13-1.01)	20/157	0.74 (0.46-1.19)	24/238	0.62 (0.40-0.95)
4.24+	7/79	0.62 (0.27-1.40)	18/160	0.66 (0.40-1.08)	25/239	0.64 (0.42-0.98)
Total Isoflavones*						
0-0.29	8/70	1.00	19/172	1.00	27/242	1.00
0.30-0.78	7/58	1.10 (0.49-2.48)	43/185	1.58 (1.09-2.30)	50/243	1.49 (1.07-2.08)
0.79-2.34	9/69	1.23 (0.59-2.56)	25/175	0.89 (0.58-1.38)	34/244	0.96 (0.66-1.39)
2.35-7.47	10/88	0.93 (0.46-1.90)	31/152	1.59 (1.06-2.38)	41/240	1.36 (0.96-1.94)
7.48+	9/91	0.71 (0.34-1.48)	12/150	0.44 (0.24-0.81)	21/241	0.52 (0.33-0.82)
Total Lignans*						
0-2.2	7/72	1.00	26/171	1.00	33/243	1.00
2.3-3.9	5/72	0.60 (0.24-1.53)	28/170	1.09 (0.72-1.65)	33/242	0.96 (0.65-1.40)
4.0-5.9	14/82	1.69 (0.89-3.21)	25/162	0.98 (0.63-1.51)	39/244	1.14 (0.80-1.63)
6.0-8.9	6/77	0.61 (0.26-1.45)	26/163	0.96 (0.62-1.48)	32/240	0.88 (0.60-1.30)
9.0+	11/73	1.27 (0.63-2.54)	25/168	0.98 (0.63-1.54)	36/241	1.03 (0.71-1.49)

* In milligrams per day (mg/d).

Table A.18. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to breast cancer-specific mortality.

Variable (mg/day)	Deaths/ Cohort # deaths/ 367	Pre-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 781	Post-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 1,148	Pre and Post HR (95% CI)
Total Flavonoids*						
0-42.4	2/81	1.00	16/152	1.00	18/233	1.00
42.5-95.0	13/70	2.88 (1.44-5.78)	16/164	0.97 (0.56-1.68)	29/234	1.37 (0.90-2.10)
95.1-216.2	5/78	0.61 (0.24-1.58)	14/148	0.90 (0.51-1.61)	19/226	0.81 (0.49-1.32)
216.3-340.4	4/73	0.50 (0.18-1.42)	21/156	1.40 (0.84-2.33)	25/229	1.10 (0.70-1.73)
340.5+	10/65	1.75 (0.82-3.72)	12/161	0.62 (0.33-1.16)	22/226	0.88 (0.55-1.42)
Total Flavonols*						
0-3.4	4/58	1.00	17/171	1.00	21/229	1.00
3.5-5.9	10/79	1.80 (0.85-3.80)	16/155	1.04 (0.60-1.81)	26/234	1.22 (0.78-1.89)
6.0-10.1	6/81	0.73 (0.30-1.77)	14/148	0.92 (0.52-1.65)	20/229	0.86 (0.53-1.39)
10.2-14.4	3/74	0.34 (0.10-1.12)	15/152	0.87 (0.49-1.55)	18/226	0.69 (0.41-1.16)
14.5+	11/75	1.64 (0.78-3.46)	17/155	1.02 (0.59-1.79)	28/230	1.20 (0.77-1.87)
Total Flavones*						
0-0.03	4/58	1.00	16/163	1.00	20/221	1.00
0.04-0.07	9/80	1.46 (0.67-3.15)	17/151	1.24 (0.72-2.13)	26/231	1.30 (0.83-2.01)
0.08-0.12	10/74	1.62 (0.77-3.39)	19/158	1.20 (0.71-2.03)	29/232	1.32 (0.86-2.02)
0.13-0.19	6/69	0.94 (0.39-2.27)	18/165	1.06 (0.62-1.80)	24/234	1.01 (0.64-1.59)
0.20+	5/86	0.45 (0.17-1.19)	9/144	0.49 (0.24-0.99)	14/230	0.48 (0.27-0.84)
Total Flavanones*						
0-4.0	10/95	1.00	12/133	1.00	22/228	1.00
4.1-16.3	7/83	0.89 (0.39-2.05)	19/146	1.52 (0.89-2.61)	26/229	1.27 (0.81-1.99)
16.4-29.9	6/67	0.97 (0.40-2.35)	9/166	0.47 (0.23-0.94)	15/233	0.60 (0.35-1.03)
30.0-48.5	7/72	1.03 (0.45-2.38)	19/161	1.21 (0.72-2.03)	26/233	1.15 (0.74-1.78)
48.6+	4/50	0.61 (0.21-1.81)	20/175	1.09 (0.65-1.82)	24/225	0.98 (0.62-1.56)
Total Flavan-3-ols*						
0-5.0	2/65	1.00	19/168	1.00	21/233	1.00
5.1-34.4	6/82	0.76 (0.31-1.85)	13/149	0.83 (0.46-1.50)	19/231	0.78 (0.48-1.28)
34.5-140.0	11/77	1.75 (0.85-3.60)	14/152	0.90 (0.50-1.60)	25/229	1.14 (0.73-1.78)
140.1-263.7	5/77	0.63 (0.24-1.63)	21/153	1.46 (0.88-2.43)	26/230	1.19 (0.76-1.86)

263.8+	10/66	1.75 (0.83-3.69)	12/159	0.63 (0.34-1.18)	22/225	0.89 (0.55-1.43)
Total Anthocyanidins*						
0-0.03	4/58	1.00	21/163	1.00	25/221	1.00
0.04-0.40	11/81	1.80 (0.88-3.69)	15/145	1.05 (0.60-1.85)	26/226	1.28 (0.82-1.98)
0.41-1.60	8/68	1.33 (0.60-2.95)	21/173	1.27 (0.76-2.12)	29/241	1.30 (0.85-1.99)
1.61-4.23	4/81	0.46 (0.16-1.31)	11/148	0.65 (0.35-1.24)	15/229	0.58 (0.34-1.00)
4.24+	7/79	0.81 (0.35-1.89)	11/152	0.62 (0.33-1.18)	18/231	0.68 (0.41-1.13)
Total Isoflavones*						
0-0.15	7/76	1.00	11/150	1.00	18/226	1.00
0.16-0.26	5/71	0.96 (0.40-2.35)	21/165	1.02 (0.59-1.78)	26/236	0.99 (0.62-1.59)
0.27-0.37	8/67	1.69 (0.79-3.62)	15/159	0.99 (0.57-1.72)	23/226	1.17 (0.75-1.83)
0.38-0.59	8/71	0.48 (0.17-1.36)	24/158	1.08 (0.63-1.84)	32/229	0.86 (0.54-1.39)
0.60+	6/82	1.03 (0.46-2.28)	8/149	0.79 (0.43-1.44)	14/231	0.87 (0.54-1.41)
Total Lignans*						
0-2.2	6/71	1.00	15/160	1.00	21/231	1.00
2.3-3.9	4/71	0.60 (0.21-1.71)	18/160	1.17 (0.69-1.98)	22/231	0.99 (0.62-1.57)
4.0-5.9	12/80	1.92 (0.95-3.89)	16/153	1.04 (0.60-1.80)	28/233	1.28 (0.84-1.97)
6.0-8.9	4/75	0.50 (0.18-1.42)	15/151	0.88 (0.49-1.57)	19/226	0.76 (0.46-1.26)
9.0+	8/70	1.16 (0.52-2.58)	15/157	0.87 (0.49-1.55)	23/227	0.95 (0.60-1.51)

* In milligrams per day (mg/d).

Table A.19. A summary of the preliminary evaluation of confounding and effect modification of flavonoids and breast cancer survival by selected covariates.

Covariate	Relationship between Covariate and Outcome (Mortality)? HR (95% CI)	FLAVONOID EXPOSURES		
		Relationship between covariate and Total Flavonoids? HR (95% CI)	Evidence of Effect Measure Modification? p-value from Likelihood Ratio Test	Does the HR for Total Flavonoids change by more than 10% when Covariate is added to model?
Menopausal Status	YES	Borderline	YES	No
Age	YES	YES	YES	No
Alcohol	No	No	No	No
Smoking	No	No	No	No
Family History	No	No	No	No
Physical Activity	No	No	No	No
BMI	No	No	No	No
Income	No	No	No	No
Education	No	No	No	No
Parity	No	No	No	No
OC Use	No	No	No	No
ER Status	Borderline	Borderline	No	No
PR Status	Borderline	Borderline	No	No
Chemotherapy	No	No	No	No
Radiation Therapy	No	No	No	No
Fruits	No	No	No	No
Hypertension	No	No	No	No
Diabetes	No	No	No	No
High Cholesterol	No	No	No	No
Myocardial Infarction	No	No	No	No
Stroke	No	No	No	No
Vegetables	No	Borderline	No	No
Antioxidants	No	Borderline	No	No

Table A.20. Age, fruit, fruit juice, vegetable, antioxidant, and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality.

Variable	Pre-menopausal (n=376)	Post-menopausal (n=834)	Pre- and Post-menopausal (n=1,210)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total Flavonoids*			
0-42.5	1.00	1.00	1.00
42.5-95.1	2.50 (1.32-4.76)	0.84 (0.53-1.33)	1.08 (0.75-1.56)
95.1-216.3	0.52 (0.22-1.26)	1.08 (0.71-1.66)	0.94 (0.65-1.38)
216.3-340.5	0.61 (0.26-1.48)	1.23 (0.82-1.84)	1.08 (0.75-1.55)
340.5+	1.72 (0.88-3.39)	0.81 (0.50-1.30)	1.02 (0.70-1.48)
P for trend#	0.09	0.82	0.49
Total Flavonols*			
0-3.5	1.00	1.00	1.00
3.5-6.0	1.64 (0.81-3.31)	0.94 (0.59-1.48)	1.03 (0.71-1.50)
6.0-10.2	0.77 (0.36-1.68)	0.99 (0.64-1.53)	0.93 (0.64-1.37)
10.2-14.5	0.47 (0.18-1.22)	1.05 (0.68-1.62)	0.86 (0.58-1.26)
14.5+	1.64 (0.83-3.23)	1.07 (0.67-1.69)	1.26 (0.87-1.82)
P for trend#	0.21	0.80	0.67
Total Flavones*			
0-0.04	1.00	1.00	1.00
0.04-0.08	1.31 (0.58-2.97)	1.14 (0.74-1.74)	1.10 (0.76-1.60)
0.08-0.13	1.41 (0.70-2.86)	1.14 (0.74-1.74)	1.18 (0.82-1.68)
0.13-0.20	0.70 (0.31-1.62)	1.03 (0.65-1.62)	0.92 (0.62-1.37)
0.20+	0.61 (0.25-1.51)	0.70 (0.39-1.27)	0.71 (0.43-1.15)
P for trend#	0.18	0.78	0.66
Total Flavanones*			
0-4.1	1.00	1.00	1.00
4.1-16.4	0.90 (0.39-2.08)	1.59 (0.99-2.56)	1.23 (0.82-1.84)
16.4-30.0	0.79 (0.33-1.90)	0.61 (0.37-0.99)	0.66 (0.44-1.01)
30.0-48.6	1.01 (0.45-2.24)	1.21 (0.79-1.85)	1.11 (0.77-1.62)
48.6+	0.79 (0.31-2.03)	1.04 (0.61-1.78)	1.07 (0.67-1.69)
P for trend#	0.52	0.54	0.43
Total Flavan-3-ols*			
0-5.1	1.00	1.00	1.00
5.1-34.5	0.78 (0.35-1.76)	0.90 (0.57-1.42)	0.81 (0.55-1.20)
34.5-140.1	1.43 (0.72-2.84)	1.01 (0.65-1.55)	1.11 (0.77-1.58)
140.1-263.8	0.72 (0.31-1.64)	1.22 (0.80-1.84)	1.07 (0.74-1.54)
263.8+	1.82 (0.93-3.57)	0.84 (0.54-1.33)	1.07 (0.74-1.53)
P for trend#	0.06	0.85	0.45
Total Anthocyanidins*			
0-0.04	1.00	1.00	1.00
0.04-0.41	2.25 (1.20-4.22)	1.14 (0.74-1.74)	1.48 (1.06-2.08)
0.41-1.61	1.36 (0.66-2.79)	0.91 (0.59-1.42)	1.01 (0.70-1.46)
1.61-4.24	0.33 (0.12-0.93)	0.76 (0.47-1.23)	0.63 (0.41-0.97)
4.24+	0.60 (0.26-1.37)	0.69 (0.42-1.15)	0.63 (0.41-0.96)
P for trend#	0.06	0.60	0.13
Total Isoflavones*			

0-0.16	1.00	1.00	1.00
0.16-0.27	0.72 (0.30-1.76)	0.83 (0.53-1.31)	0.78 (0.52-1.17)
0.27-0.38	1.70 (0.85-3.37)	1.15 (0.77-1.72)	1.29 (0.91-1.81)
0.38-0.60	0.41 (0.16-1.08)	1.26 (0.84-1.91)	1.00 (0.69-1.45)
0.60+	1.11 (0.52-2.36)	0.74 (0.44-1.23)	0.87 (0.58-1.30)
P for trend[#]	0.72	0.21	0.19
Total Lignans[*]			
0-2.3	1.00	1.00	1.00
2.3-4.0	0.61 (0.24-1.55)	1.08 (0.71-1.64)	0.94 (0.64-1.37)
4.0-6.0	1.52 (0.79-2.94)	0.99 (0.64-1.53)	1.12 (0.78-1.61)
6.0-9.0	0.62 (0.26-1.51)	0.94 (0.61-1.46)	0.88 (0.60-1.29)
9.0+	1.31 (0.65-2.63)	1.01 (0.65-1.59)	1.06 (0.73-1.54)
P for trend[#]	0.08	0.74	0.69

[*] In milligrams per day (mg/d).
[#] P for trend for continuous variable.

Table A.21. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by ER/PR status for the association between flavonoid intake in relation to all-cause mortality.

Variable	ER+PR+		ER+PR-		ER-PR+		ER-PR-	
	Cases (n) Deaths (n)	HR (95% CI)	Cases (n) Deaths (n)	HR (95% CI)	Cases (n) Deaths (n)	HR (95% CI)	Cases (n) Deaths (n)	HR (95% CI)
Total Flavonoids*								
0-216.3	329 32	1.00	87 18	1.00	30 4	1.00	128 25	1.00
216.3+	215 25	1.08 (0.63-1.84)	45 9	0.94 (0.41-2.15)	18 3	1.16 (0.25-5.49)	69 22	1.48 (0.82-2.68)
P for trend#		0.19		0.36		0.89		0.47
Total Flavonols*								
0-10.2	336 36	1.00	87 18	1.00	27 4	1.00	126 28	1.00
10.2+	208 21	0.88 (0.50-1.55)	45 9	0.94 (0.41-2.15)	21 3	0.82 (0.16-4.18)	71 19	1.17 (0.63-2.16)
P for trend#		0.35		0.36		0.70		0.69
Total Flavones*								
0-0.13	357 41	1.00	86 18	1.00	28 6	1.00	134 35	1.00
0.13+	187 16	0.63 (0.35-1.14)	46 9	0.85 (0.37-1.96)	20 1	0.18 (0.02-1.59)	63 12	0.77 (0.39-1.51)
P for trend#		0.60		0.86		0.19		0.43
Total Flavanones*								
0-30.0	343 30	1.00	71 17	1.00	29 3	1.00	118 26	1.00
30.0+	201 27	1.24 (0.72-2.14)	61 10	0.63 (0.29-1.37)	19 4	2.52 (0.49-13.06)	79 21	1.04 (0.56-1.90)
P for trend#		0.23		0.16		0.75		0.45
Total Flavan-3-ols*								
0-140.1	328 33	1.00	87 18	1.00	29 4	1.00	125 23	1.00
140.1+	216 24	1.03 (0.61-1.76)	45 9	0.97 (0.43-2.19)	19 3	1.03 (0.21-4.96)	72 24	1.70 (0.95-3.05)
P for trend#		0.24		0.51		0.98		0.47
Total Anthocyanidins*								
0-1.61	342 42	1.00	88 22	1.00	32 6	1.00	124 35	1.00
1.61+	202 15	0.53 (0.29-0.96)	44 5	0.41 (0.16-1.08)	16 1	0.30 (0.04-2.54)	73 12	0.54 (0.28-1.06)
P for trend#		0.04		0.52		0.39		0.11
Total Isoflavones*								
0-0.38	332	1.00	78	1.00	26	1.00	122	1.00

	30		13		4		34	
0.38+	212 27	1.26 (0.71- 2.23)	54 14	1.69 (0.73- 3.92)	22 3	0.77 (0.16- 3.78)	75 13	0.53 (0.27- 1.03)
P for trend*		0.39		0.47		0.41		0.25
Total Lignans*								
0-6.0	331 33	1.00	89 20	1.00	30 4	1.00	126 28	1.00
6.0+	213 24	1.08 (0.63- 1.85)	43 7	0.67 (0.28- 1.62)	18 3	1.15 (0.23- 5.71)	71 19	1.11 (0.61- 2.03)
P for trend[#]		0.28		0.53		0.97		0.77

***** In milligrams per day (mg/d).

[#] P for trend for continuous variable.

Table A.22. Age and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by ER/PR status for the association between flavonoid intake in relation to breast cancer-specific mortality.

Variable	ER+PR+		ER+PR-		ER-PR+		ER-PR-	
	Cases (n) Deaths (n)	HR (95% CI)	Cases (n) Deaths (n)	HR (95% CI)	Cases (n) Deaths (n)	HR (95% CI)	Cases (n) Deaths (n)	HR (95% CI)
Total Flavonoids*								
0-216.3	315 18	1.00	81 12	1.00	30 4	1.00	121 18	1.00
216.3+	205 16	1.18 (0.59-2.34)	41 5	0.76 (0.26-2.20)	17 2	0.74 (0.13-4.21)	63 16	1.62 (0.81-3.24)
P for trend#		0.30		0.24		0.79		0.37
Total Flavonols*								
0-10.2	320 20	1.00	81 12	1.00	27 4	1.00	118 20	1.00
10.2+	200 14	0.93 (0.46-1.91)	41 5	0.70 (0.24-2.03)	20 2	0.49 (0.08-3.02)	66 14	1.27 (0.61-2.63)
P for trend#		0.46		0.24		0.64		0.63
Total Flavones*								
0-0.13	338 23	1.00	78 10	1.00	27 5	1.00	125 26	1.00
0.13+	182 11	0.70 (0.33-1.47)	44 7	1.08 (0.39-3.01)	20 1	0.22 (0.02-1.95)	59 8	0.63 (0.28-1.42)
P for trend#		0.95		0.95		0.26		0.30
Total Flavanones*								
0-30.0	330 18	1.00	64 10	1.00	28 2	1.00	111 19	1.00
30.0+	190 16	1.22 (0.60-2.47)	58 7	0.74 (0.28-1.94)	19 4	3.96 (0.59-26.56)	73 15	1.07 (0.53-2.17)
P for trend#		0.58		0.44		1.00		0.31
Total Flavan-3-ols*								
0-140.1	314 19	1.00	81 12	1.00	29 4	1.00	118 16	1.00
140.1+	206 15	1.06 (0.54-2.12)	41 5	0.77 (0.27-2.21)	18 2	0.64 (0.11-3.68)	66 18	1.98 (1.00-3.92)
P for trend#		0.30		0.27		0.84		0.39
Total Anthocyanidins*								
0-1.61	325 25	1.00	79 13	1.00	31 5	1.00	115 26	1.00
1.61+	195 9	0.49 (0.22-1.05)	43 4	0.51 (0.17-1.58)	16 1	0.35 (0.04-2.12)	69 8	0.47 (0.21-1.05)
P for trend#		0.14		0.25		0.49		0.09
Total Isoflavones*								
0-0.38	318	1.00	74	1.00	26	1.00	111	1.00

	16		9		4		23	
0.38+	202 18	1.39 (0.66- 1.93)	48 8	1.18 (0.42- 3.35)	21 2	0.48 (0.08- 2.92)	73 11	0.62 (0.29- 1.31)
P for trend*		0.42		0.50		0.43		0.34
Total Lignans*								
0-6.0	316 18	1.00	82 13	1.00	30 4	1.00	119 21	1.00
6.0+	204 16	1.23 (0.62- 2.44)	40 4	0.52 (0.17- 1.64)	17 2	0.71 (0.12- 4.23)	65 13	1.10 (0.54- 2.22)
P for trend[#]		0.47		0.32		0.85		0.56

***** In milligrams per day (mg/d).

[#] P for trend for continuous variable.

Table A.23. Age, fiber, and energy-adjusted ORs and 95% CIs for the association between menopausal-specific flavonoid intake in relation to breast cancer incidence

	Pre-menopausal (n = 944)		**Post-menopausal (n = 1930)**
	OR (95% CI)		**OR (95% CI)**
Total Flavonoids[#]		**Total Flavonoids[#]**	
0-34.5	1.00	**0-51.8**	1.00
34.5-84.5	1.19 (0.79-1.78)	**51.8-119.1**	0.93 (0.69-1.24)
84.5-199.5	1.42 (0.95-2.13)	**119.1-253.3**	0.81 (0.61-1.10)
199.5-343.0	1.36 (0.90-2.04)	**253.3-377.2**	0.80 (0.60-1.07)
343.0+	1.13 (0.74-1.72)	**377.2+**	0.78 (0.57-1.05)
P for trend[*]	0.87	**P for trend[*]**	0.07
Total Flavonols[#]		**Total Flavonols[#]**	
0-3.7	1.00	**0-4.3**	1.00
3.7-6.0	1.56 (1.04-2.35)	**4.3-6.8**	0.60 (0.45-0.80)
6.0-10.2	1.60 (1.04-2.45)	**6.8-11.1**	0.65 (0.49-0.87)
10.2-15.1	1.78 (1.15-2.74)	**11.1-17.1**	0.66 (0.49-0.89)
15.1+	1.56 (0.99-2.43)	**17.1+**	0.55 (0.41-0.75)
P for trend[*]	0.67	**P for trend[*]**	0.02
Total Flavones[#]		**Total Flavones[#]**	
0-0.04	1.00	**0-0.04**	1.00
0.05-0.07	1.01 (0.67-1.52)	**0.05-0.08**	0.89 (0.67-1.18)
0.08-0.12	1.30 (0.86-1.96)	**0.09-0.14**	0.90 (0.68-1.20)
0.13-0.21	1.22 (0.79-1.90)	**0.15-0.21**	0.72 (0.54-0.97)
0.22+	1.27 (0.78-2.07)	**0.22+**	0.60 (0.43-0.84)
P for trend[*]	0.47	**P for trend[*]**	0.005
Total Flavanones[#]		**Total Flavanones[#]**	
0-3.1	1.00	**0-5.3**	1.00
3.2-10.8	0.68 (0.47-0.99)	**5.4-18.8**	1.06 (0.79-1.44)
10.9-24.5	0.73 (0.49-1.09)	**18.9-32.1**	1.11 (0.83-1.49)
24.6-40.3	1.00 (0.66-1.51)	**32.2-54.2**	1.05 (0.79-1.41)
40.4+	0.73 (0.45-1.16)	**54.3+**	1.07 (0.79-1.45)
P for trend[*]	0.63	**P for trend[*]**	0.50
Total Flavan-3-ols[#]		**Total Flavan-3-ols[#]**	
0-5.1	1.00	**0-7.6**	1.00
5.2-26.4	1.24 (0.83-1.86)	**7.7-54.0**	0.86 (0.64-1.15)
26.5-120.8	1.59 (1.05-2.41)	**54.1-192.0**	0.80 (0.60-1.05)
120.9-264.1	1.42 (0.94-2.14)	**192.1-277.9**	0.84 (0.63-1.11)
264.2+	1.28 (0.83-1.98)	**278.0+**	0.70 (0.52-0.93)
P for trend[*]	0.86	**P for trend[*]**	0.06
Total Anthocyanidins[#]		**Total Anthocyanidins[#]**	
0-0.04	1.00	**0-0.03**	1.00
0.05-0.56	1.13 (0.75-1.69)	**0.04-0.56**	1.08 (0.81-1.42)
0.57-1.60	0.87 (0.58-1.32)	**0.57-1.84**	0.98 (0.74-1.31)
1.61-4.19	0.96 (0.63-1.46)	**1.85-4.84**	0.82 (0.62-1.09)
4.20+	1.11 (0.72-1.72)	**4.85+**	0.85 (0.64-1.12)
P for trend[*]	0.65	**P for trend[*]**	0.36
Total Isoflavones[#]		**Total Isoflavones[#]**	
0-0.31	1.00	**0-0.27**	1.00

0.32-1.10	1.14 (0.73-1.80)	**0.28-0.62**	0.96 (0.72-1.28)
1.11-3.17	1.06 (0.69-1.62)	**0.63-1.94**	1.28 (0.96-1.71)
3.18-7.62	1.09 (0.72-1.65)	**1.95-7.63**	1.18 (0.88-1.60)
7.63+	1.33 (0.86-2.08)	**7.64+**	1.12 (0.82-1.52)
P for trend[*]	0.36	**P for trend**[*]	0.94
Total Lignans[#]		**Total Lignans**[#]	
0-2.0	1.00	**0-2.4**	1.00
2.1-4.0	1.55 (1.04-2.30)	**2.5-4.2**	0.97 (0.74-1.29)
4.1-5.4	1.15 (0.76-1.72)	**4.3-6.4**	0.81 (0.60-1.09)
5.5-9.3	1.69 (1.12-2.57)	**6.5-10.2**	0.77 (0.57-1.02)
9.4+	1.21 (0.79-1.85)	**10.3+**	0.67 (0.50-0.91)
P for trend[*]	0.70	**P for trend**[*]	0.01

[*] P for trend for continuous variable.

[#] In milligrams per day (mg/d).

Table A.24. Age, fiber, and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996-1997.

Variable (mg/day)	Deaths/ Cohort # deaths/ 376	Pre-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 834	Post-menopausal HR (95% CI)	Deaths/ Cohort # deaths/ 1,210	Pre and Post HR (95% CI)
Total Flavonoids*						
0-42.4	3/82	1.00	25/161	1.00	28/243	1.00
42.5-95.0	15/72	2.58 (1.36-4.90)	23/171	0.80 (0.51-1.25)	38/243	1.08 (0.75-1.56)
95.1-216.2	6/79	0.55 (0.23-1.32)	28/162	1.11 (0.73-1.70)	34/241	0.97 (0.66-1.42)
216.3-340.4	6/75	0.61 (0.26-1.46)	32/168	1.24 (0.83-1.85)	38/243	1.11 (0.77-1.58)
340.5+	13/68	1.77 (0.90-3.45)	22/172	0.80 (0.50-1.29)	35/240	0.98 (0.67-1.44)
Total Flavonols*						
0-3.4	4/58	1.00	31/185	1.00	35/243	1.00
3.5-5.9	12/81	1.69 (0.85-3.36)	23/162	0.87 (0.55-1.36)	35/243	1.01 (0.70-1.47)
6.0-10.1	8/83	0.78 (0.36-1.68)	25/159	1.01 (0.65-1.56)	33/242	0.94 (0.65-1.38)
10.2-14.4	5/76	0.46 (0.18-1.18)	26/164	1.03 (0.67-1.59)	31/240	0.87 (0.59-1.28)
14.5+	14/78	1.62 (0.83-3.17)	25/164	1.03 (0.65-1.63)	39/242	1.17 (0.80-1.69)
Total Flavones*						
0-0.03	7/61	1.00	32/180	1.00	39/241	1.00
0.04-0.07	9/80	1.12 (0.52-2.41)	29/163	1.21 (0.79-1.83)	38/243	1.17 (0.81-1.69)
0.08-0.12	11/75	1.39 (0.69-2.77)	27/167	1.12 (0.73-1.72)	38/242	1.16 (0.81-1.67)
0.13-0.19	7/70	0.87 (0.39-1.95)	25/172	0.92 (0.59-1.44)	32/242	0.88 (0.60-1.29)
0.20+	9/90	0.58 (0.25-1.35)	17/152	0.61 (0.35-1.06)	26/242	0.62 (0.39-0.98)
Total Flavanones*						
0-4.0	12/97	1.00	21/143	1.00	33/240	1.00
4.1-16.3	8/84	0.81 (0.37-1.74)	28/156	1.46 (0.95-2.24)	36/240	1.23 (0.84-1.79)
16.4-29.9	6/67	0.76 (0.32-1.80)	19/176	0.59 (0.36-0.96)	25/243	0.63 (0.41-0.96)
30.0-48.5	9/74	1.03 (0.49-2.16)	30/172	1.13 (0.75-1.70)	39/246	1.10 (0.77-1.58)
48.6+	8/54	1.03	32/187	1.08	40/241	1.09

		(0.44-2.42)		(0.70-1.66)		(0.74-1.60)
Total Flavan-3-ols*						
0-5.0	3/66	1.00	29/178	1.00	32/244	1.00
5.1-34.4	8/84	0.81 (0.37-1.77)	22/158	0.89 (0.56-1.41)	30/242	0.83 (0.56-1.23)
34.5-140.0	12/78	1.40 (0.71-2.78)	26/164	1.02 (0.66-1.56)	38/242	1.13 (0.79-1.62)
140.1-263.7	7/79	0.73 (0.32-1.65)	29/162	1.20 (0.80-1.82)	36/241	1.10 (0.76-1.59)
263.8+	13/69	1.76 (0.91-3.41)	24/172	0.85 (0.54-1.34)	37/241	1.02 (0.71-1.48)
Total Anthocyanidins*						
0-0.03	6/60	1.00	39/181	1.00	45/241	1.00
0.04-0.40	16/86	2.15 (1.16-4.01)	28/158	1.14 (0.75-1.75)	44/244	1.40 (0.99-1.98)
0.41-1.60	10/70	1.33 (0.65-2.70)	25/178	0.90 (0.58-1.40)	35/248	1.00 (0.69-1.45)
1.61-4.23	4/81	0.36 (0.13-1.01)	20/157	0.74 (0.46-1.19)	24/238	0.62 (0.40-0.95)
4.24+	7/79	0.60 (0.26-1.37)	18/160	0.68 (0.41-1.12)	25/239	0.65 (0.42-1.00)
Total Isoflavones*						
0-0.29	8/70	1.00	19/172	1.00	27/242	1.00
0.30-0.78	7/58	1.13 (0.50-2.57)	43/185	1.55 (1.06-2.26)	50/243	1.47 (1.05-2.06)
0.79-2.34	9/69	1.23 (0.59-2.57)	25/175	0.91 (0.59-1.42)	34/244	0.97 (0.66-1.41)
2.35-7.47	10/88	0.94 (0.46-1.91)	31/152	1.63 (1.08-2.45)	41/240	1.37 (0.96-1.96)
7.48+	9/91	0.65 (0.29-1.42)	12/150	0.45 (0.25-0.83)	21/241	0.52 (0.33-0.84)
Total Lignans*						
0-2.2	7/72	1.00	26/171	1.00	33/243	1.00
2.3-3.9	5/72	0.60 (0.23-1.53)	28/170	1.10 (0.72-1.66)	33/242	0.96 (0.66-1.40)
4.0-5.9	14/82	1.71 (0.90-3.24)	25/162	0.98 (0.63-1.52)	39/244	1.14 (0.80-1.63)
6.0-8.9	6/77	0.58 (0.24-1.41)	26/163	0.95 (0.62-1.47)	32/240	0.89 (0.60-1.30)
9.0+	11/73	1.30 (0.64-2.62)	25/168	1.00 (0.64-1.57)	36/241	1.03 (0.71-1.50)

* In milligrams per day (mg/d).

Table A.25. Age, co-morbidity^, and energy-adjusted hazard ratios (HR) and 95% confidence intervals (CI) stratified by menopausal status for the association between flavonoid intake in relation to all-cause mortality among breast cancer cases diagnosed in 1996-1997.

Variable	Pre-menopausal (n=376)	Post-menopausal (n=834)
	HR (95% CI)	HR (95% CI)
Total Flavonoids*		
0-42.4	1.00	1.00
42.5-95.0	2.89 (1.50-5.55)	0.90 (0.57-1.41)
95.1-216.2	0.60 (0.25-1.43)	1.05 (0.69-1.60)
216.3-340.4	0.64 (0.27-1.52)	1.24 (0.83-1.86)
340.5+	1.55 (0.78-3.09)	0.80 (0.50-1.29)
Total Flavonols*		
0-3.4	1.00	1.00
3.5-5.9	1.67 (0.84-3.30)	0.91 (0.58-1.42)
6.0-10.1	0.83 (0.38-1.80)	0.95 (0.62-1.48)
10.2-14.4	0.51 (0.20-1.30)	1.04 (0.68-1.60)
14.5+	1.46 (0.74-2.90)	1.00 (0.64-1.58)
Total Flavones*		
0-0.03	1.00	1.00
0.04-0.07	1.08 (0.51-2.28)	1.29 (0.85-1.96)
0.08-0.12	1.36 (0.68-2.71)	1.07 (0.70-1.64)
0.13-0.19	0.92 (0.41-2.09)	0.89 (0.57-1.39)
0.20+	0.66 (0.31-1.41)	0.63 (0.37-1.06)
Total Flavanones*		
0-4.0	1.00	1.00
4.1-16.3	0.87 (0.40-1.89)	1.60 (1.03-2.48)
16.4-29.9	0.81 (0.34-1.93)	0.62 (0.38-1.01)
30.0-48.5	1.14 (0.54-2.40)	1.05 (0.69-1.58)
48.6+	0.99 (0.43-2.29)	1.03 (0.68-1.55)
Total Flavan-3-ols*		
0-5.0	1.00	1.00
5.1-34.4	0.92 (0.42-2.03)	0.96 (0.60-1.53)
34.5-140.0	1.49 (0.76-2.91)	0.99 (0.65-1.52)
140.1-263.7	0.72 (0.32-1.64)	1.14 (0.75-1.72)
263.8+	1.59 (0.80-3.14)	0.90 (0.57-1.42)
Total Anthocyanidins*		
0-0.03	1.00	1.00
0.04-0.40	1.89 (1.00-3.57)	1.27 (0.83-1.93)
0.41-1.60	1.35 (0.66-2.75)	0.89 (0.57-1.38)
1.61-4.23	0.38 (0.14-1.08)	0.70 (0.43-1.13)
4.24+	0.67 (0.30-1.52)	0.70 (0.42-1.16)
Total Isoflavones*		
0-0.29	1.00	1.00
0.30-0.78	1.27 (0.56-2.88)	1.37 (0.94-2.02)
0.79-2.34	1.29 (0.62-2.72)	0.93 (0.60-1.45)
2.35-7.47	0.99 (0.48-2.02)	1.53 (1.01-2.31)
7.48+	0.66 (0.31-1.42)	0.49 (0.27-0.89)
Total Lignans*		

0-2.2	1.00	1.00
2.3-3.9	0.56 (0.22-1.43)	1.06 (0.70-1.61)
4.0-5.9	1.99 (1.04-3.84)	1.00 (0.65-1.56)
6.0-8.9	0.64 (0.27-1.52)	0.95 (0.62-1.46)
9.0+	1.12 (0.54-2.30)	1.02 (0.65-1.60)

* In milligrams per day (mg/d).

^Co-morbidities adjusted for included hypertension, diabetes, high cholesterol, myocardial infarction, and stroke.

Figure A.1. Flavonoids ability to reduce breast cancer through the estrogen pathway.

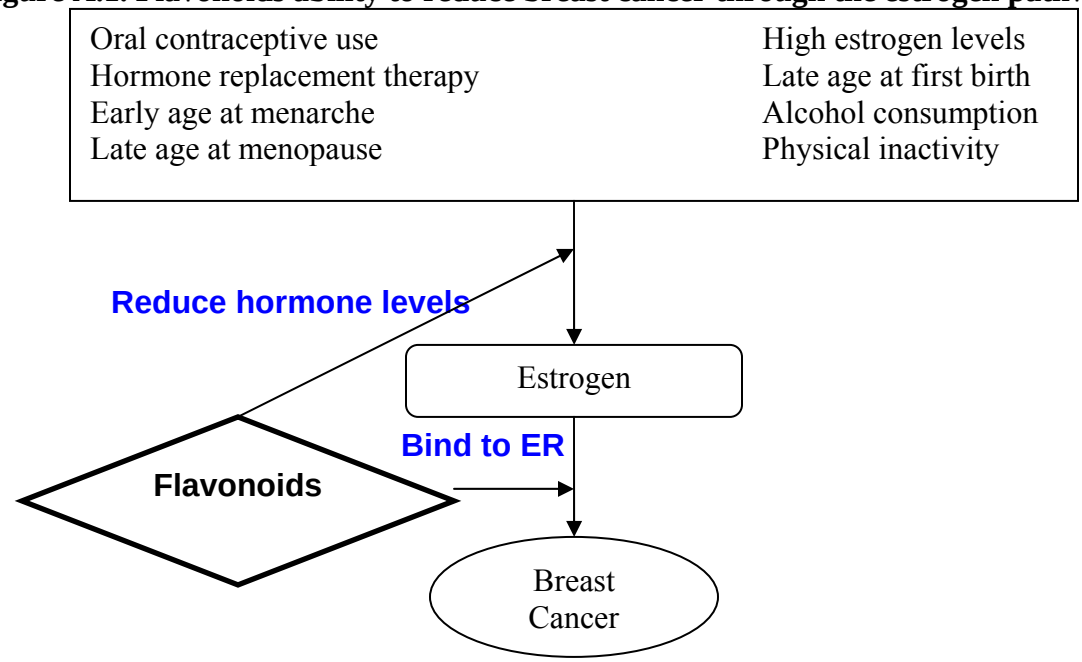
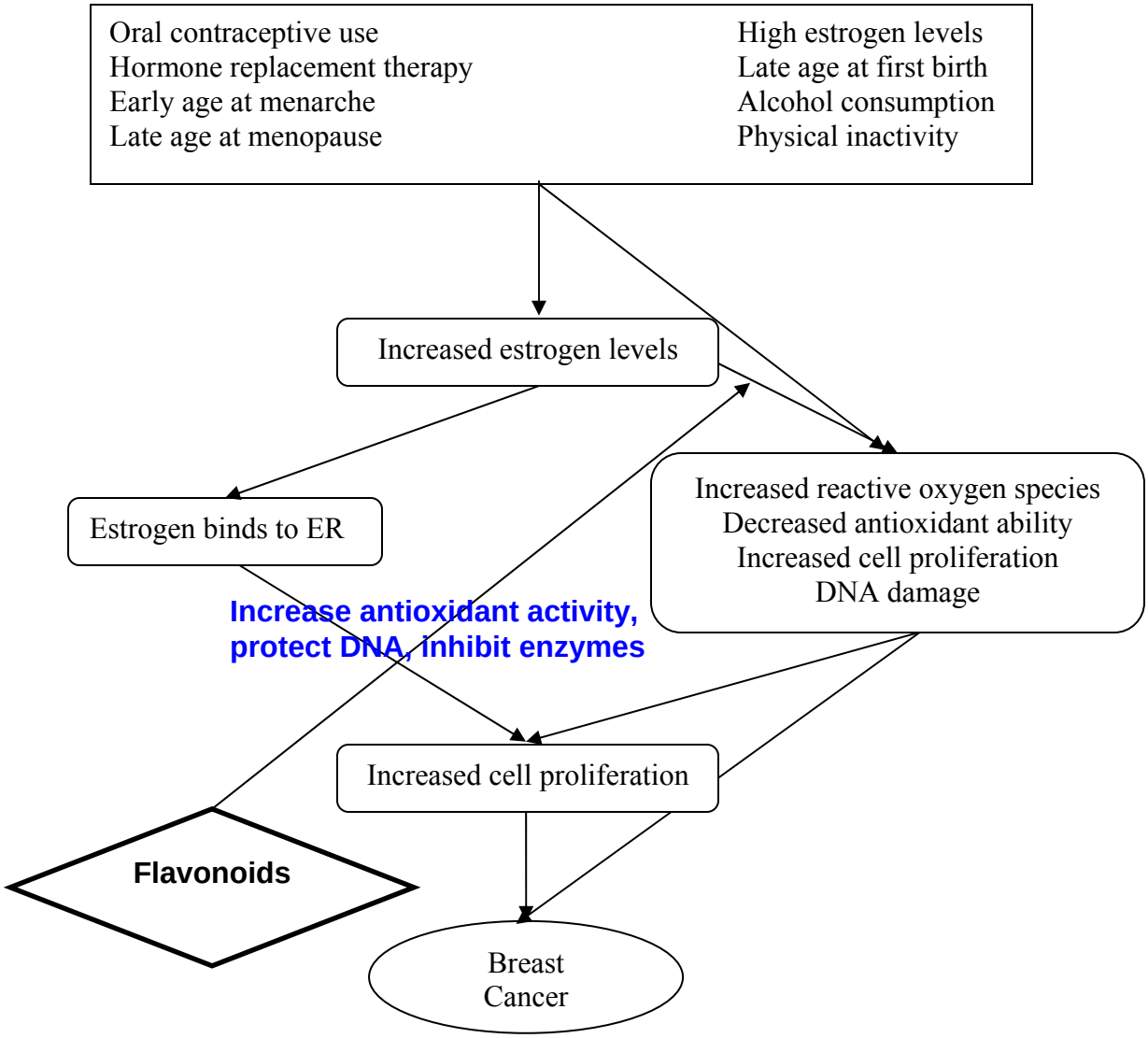


Figure A.2. Flavonoids ability to reduce breast cancer through the oxidative stress pathway.



Appendix II:

Construction of a flavonoid database for assessing intake in a population-based sample of women on Long Island, New York

Title: Construction of a flavonoid database for assessing intake in a population-based sample of women on Long Island, New York

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This work was supported in part by grants from the National Cancer Institute and the National Institutes of Environmental Health and Sciences (Grant nos. UO1CA/ES66572, UO1CA66572, CA52283, and P30ES10126), the National Institutes of Health (Grant no. 5T32CA009330-25), and from the Lance Armstrong Foundation.

ABSTRACT

Background: Flavonoids have been hypothesized to reduce the risk of cancer. However, their quantification in epidemiologic research has been limited because there are no standardized food intake methods. Previous studies of cancer risk have not included all flavonoid classes, thereby overlooking flavonoids that constitute a large proportion of intake in the U.S.

Objective: We developed a database to quantify flavonoid content for the modified Block food frequency questionnaire (FFQ).

Methods: Using available literature and USDA databases, we estimated content for seven flavonoid classes, including 30 individual flavonoids, for 50 of 100 food group items in the LIBCSP FFQ. We estimated individual daily flavonoid intake for the 1,500 population-based control women without breast cancer.

Results: Total flavonoid content of food items ranged from 0 to129 milligrams (mg) / 100 grams (g), with flavan-3-ols the largest contributor. Individual intake estimates, from highest to lowest, were flavan-3-ols (median 101 mg/day), flavanones, flavonols, lignans, isoflavones, anthocyanidins, and flavones.

Conclusion: Flavonoid intake exhibits a wide range of levels and classes in the population-based sample of women. Highest intake was found for flavan-3-ols and moderate intake for lignans, a class previously excluded in flavonoid intake estimates. This database will be useful to quantify flavonoid intake for other studies using the Block FFQ.

INTRODUCTION

Flavonoids are a group of more than 4,000 polyphenolic compounds that occur naturally in foods of plant origin (49). Evidence from laboratory studies and epidemiological investigations implicate flavonoids in cancer prevention (49, 51-58, 269-271, 273-277). Many mechanisms of action have been identified, including carcinogen activation, anti-proliferation, cell cycle arrest, induction of apoptosis and cell differentiation, inhibition of angiogenesis, and antioxidation (49).

Most human studies have only been able to quantitate intake of a small portion of flavonoids or intake of a small portion of foods containing flavonoids, because of the lack of a flavonoid food composition database. Due to their to potential health benefits, growing interest in flavonoids has led to the improvement of flavonoid intake assessment and to the creation of the USDA – Iowa State University Database on the Isoflavone Content of Selected Foods in 1999 and the USDA Database for the Flavonoid Content of Selected Foods in 2003.

While these are useful tools to estimate flavonoid intake, coverage of foods and beverages containing these flavonoids remains incomplete. Unless these databases are supplemented with additional information available in the literature, underestimation of intake is likely. For example, isoflavone coverage in the USDA Isoflavone Database includes primarily soybeans and soy-based products, as well as legumes such as beans and peas. However, isoflavones also occur in foods more frequently consumed by American populations (392), including fruits, vegetables, nuts, and cereals, although in relatively smaller amounts. Without accounting for the isoflavone content in these commonly-consumed products, results among an American population could be underestimates of flavonoid intake.

Isoflavones have demonstrated the ability to suppress luteinizing hormone (LH) and follicular stimulating hormone (FSH), increasing the length of the follicular phase and thus delaying menstruation (289, 290). A change in menstrual cycle length alters the duration of mammary epithelial cells in the luteal phase of the cycle where breast cells are more proliferative (40, 287). Reducing the number of menstrual cycles in a woman's lifetime may reduce her breasts' exposure to estrogen (40, 287). Additionally, isoflavones have been shown to increase serum levels of sex hormone-binding globulin (SHBG), which decreases the amount of bioavailable estrogen by decreasing levels of free estradiol (39, 42, 279-282).

Another class of flavonoids, lignans, have shown inverse associations with breast cancer risk in case-control studies in Finland, China, and Australia (72, 462, 466). Inverse associations have also been found with ovarian cancer (465), endometrial cancer (463), and thyroid cancer (464). Recent studies of flavonoids and breast cancer conducted in Greece and Italy (59, 60) exclude lignans, but include the following six classes, flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, and isoflavones. Lignans are found in fruits, vegetables, nuts, grains, tea, and coffee (382). However, lignans are not included in a USDA database.

Lignans, have demonstrated the ability to reduce circulating hormone levels in the body through aromatase inhibition (41, 51-53, 278). This research has led to the hypothesis that flavonoids, such as lignans and isoflavones, compete with estradiol for binding to estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) and thus inhibit cell proliferation and tumorigenesis via gene transcription (269).

In order to study dietary flavonoid intake, particularly in American populations, we created an enhanced flavonoid database. To improve the comprehensiveness of flavonoid

coverage in foods and beverages, additional sources of literature were reviewed and incorporated into the USDA databases.

METHODS

The aim of this report was to develop an expanded flavonoid database to estimate the mean intake of flavonoids among participants of the Long Island Breast Cancer Study Project (LIBCSP). The LIBCSP was a population-based study of women of Nassau and Suffolk counties in Long Island, New York (371). We report here values for control participants only. Controls were identified using random digit dialing for women under the age of 65 years and Health Care Finance Administration rosters for women 65 years or older, and were frequency-matched to the expected distribution of case women by 5-year age group (371). Because the original study was focused on breast cancer, a disease frequently diagnosed in post-menopausal women (112), the age range of our controls was 20-95 years and the mean age (57 years) was older than that of the underlying general population of women in the United States (mean = 40-44 years) (527).

The LIBCSP collected information on dietary intake in the year prior to the case-control interview utilizing a modified version of the 100-item Block food frequency questionnaire (FFQ) (435). Important flavonoid-containing foods included in this version were beef stew, soups, cherries, fruit drinks, alfalfa sprouts, corn, and tofu.

Databases and Literature Used

USDA Database for the Flavonoid Content of Selected Foods

The database is the product of a two-stage project undertaken by the Nutrient Data Laboratory (NDL) and the Food Composition Laboratory (FCL) of the Beltsville Human Nutrition Research Center (BHNRC) of the Agricultural Research Service (ARS) and U.S.

Department of Agriculture (USDA), in collaboration with epidemiology and nutrition groups from universities, institutes, and corporations (377). The first phase consisted of an extensive survey of the literature for articles containing data on the flavonoid content of foods. Only data from analytical studies which used acceptable procedures defined as those which lead to good separation of flavonoid compounds, such as column chromatography or high-performance liquid chromatography (HPLC), were used (377). The second phase of this government-sponsored analysis, currently underway, includes approximately sixty fruits, vegetables, and nuts at the FCL (377).

The USDA Database for the Flavonoid Content of Selected Foods contains values for five classes of flavonoids: flavanols, flavones, flavanones, flavan-3-ols, and anthocyanidins (Table 1). Twenty-six individual flavonoids comprise these classes and they are measured in 225 foods and beverages. Values are reported as milligrams per 100 grams (mg/100g) of fresh weight of edible portion of food and values of beverages were adjusted by their specific gravities and reported as served. This database provided the flavonoid content for these five classes in the foods and beverages included in the LIBCSP FFQ.

USDA - Iowa State University Database on the Isoflavone Content of Selected Foods

The USDA - Iowa State University Database on the Isoflavone Content of Selected Foods was a collaborative effort between the FCL and NDL of the ARS/USDA and the Department of Food Science and Human Nutrition of the Iowa State University (378). Data on the isoflavone content of foods were collected from scientific articles published in refereed journals and by extensive sampling of soy-containing foods and subsequent analyses at the Iowa State University (378). The data was then compiled for daidzein, genistein, and glycitein and their glucosides.

Additional Literature

Additional sources of literature were used to broaden the coverage of flavonoid content provided by the two USDA databases. De Kleijn et al. (382) estimated the mean intake of dietary isoflavones, coumestans, and lignans in healthy, Western, pre-menopausal women. To do this, they first conducted a literature search to locate published laboratory data on flavonoid content of food and beverage items (382). The isoflavones, daidzein and genistein, as well as two lignan precursors, matairesinol and secoisolariciresinol, were included to form a database.

In 2000 and 2002, Liggins et al. (379-381) published papers on the daidzein and genistein content of fruits, nuts and vegetables, and cereals. Of all the foods analyzed, 36 fruits and nuts, 66 vegetables, and 57 cereals contained measurable quantities of daidzein and genistein. When multiple references reported different values for a specific food or beverage, the mean of the published values was used.

Additional databases (528) provided isoflavone and lignan content of selected foods and beverages assessed in previous studies. The initial values were derived from Pillow et al. (298) and were updated and refined using extensive literature searches and published laboratory data. These databases improved the comprehensiveness of coverage of lignan content of the foods and beverages inquired about on the FFQ because they included data on secoisolariciresinol and matairesinol, precursors of the lignans enterodiol and enterolactone, respectively.

Database Construction

The traditional construction of a database for analysis in association studies involves the linking of FFQ food data, specifically frequency and portion size, with existing databases

for the dietary components being studied. For our present purposes, the modified Block FFQ food data was linked to the flavonoid content data in the two USDA databases and additional literature sources.

A total of 50 items from the 100-item modified Block FFQ were found to contain at least one class of flavonoids (Table 2). Quantifiable flavonoid contents for flavones, flavanones, flavonols, flavan-3-ols, and anthocyanidins from the USDA Database for the Flavonoid Content of Selected Foods were found for 31 of the 50 (62.0%) FFQ items. Isoflavone content was retrieved from the literature and utilized for 19 of the 50 (38.0%) FFQ food group items (378, 382). The USDA – Iowa State University Database on the Isoflavone Content of Selected Foods was utilized to obtain isoflavone content of the following foods from the FFQ: tofu, frozen tofu, green peas, and other beans (baked, pinto, kidney, lima, black-eyed, chili with beans). Isoflavone content of apples, cauliflower, cabbage, tea, carrots, and peanut butter, strawberry, cantaloupe, broccoli, other potatoes (boiled, baked, mashed, potato salad), whole-wheat or other whole grain bread, white bread, tomatoes, brown rice, and white rice were obtained from separate databases (379-382). Lignan content for 39 of the 50 (78.0%) FFQ items was obtained from two databases (382, 528).

Derivation of Weights for Foods and Beverages

Weights were assigned to the flavonoid content of the foods and beverages from the USDA databases and literature which most accurately represented the LIBCSP FFQ item. This was necessary because some items listed in the modified Block FFQ include multiple foods or beverages rather than single foods (e.g., 'Cauliflower or brussel sprouts'). Weights (percentages) were assigned to the respective database items (e.g., give equal weight to both

foods by assigning 0.50 to ‘Cauliflower, raw’ and 0.50 to ‘Brussel sprouts, raw’ from the USDA Database for the Flavonoid Content of Selected Foods) to provide their flavonoid contribution when a subject reports its consumption.

The Foods Commonly Eaten in the United States: Quantities Consumed Per Eating Occasion and in a Day, 1994-1996 was utilized to aid in the assignment of weights to these multiple food items (392). This publication contains estimates of food intakes by individuals residing in households in the entire United States (392). The estimates were based on information from 14,262 non-breast fed individuals ages 2 and above for whom 2 days of dietary intake information was obtained in the 1994-1996 USDA Continuing Survey of Food Intakes by Individuals (CSFII 1994-96) (392). Since the LIBCSP participants consisted of females ages 20 and older, only intake estimates pertaining to females in the following age categories listed within the CSFII were reviewed: Age 20-39, Age 40-59, and Age 60 and older. The average of these categories was calculated and used to assign weights.

RESULTS

Table 2 presents content of total flavonoids and of the 7 classes of flavonoids for each of the 50 FFQ items and the 100 foods and beverages they represent. Food items in the database with a 0.00 value indicate that any flavonoid content was below the limit of detection in laboratory analysis (377). Cherries have the greatest total flavonoid content per 100 g (129.13 mg), followed by tea (118.06 mg), grapefruit (55.62 mg), and tofu (28.61 mg). Total isoflavone content was highest in tofu, frozen tofu (16.87 mg), and green peas (2.42 mg). Lignan content was highest in tea (2.72 mg), strawberries (1.58 mg), and coffee (0.72 mg) but, similar to isoflavones, small amounts are present in many other items.

Among the controls in the LIBCSP, the distribution of flavonoid intake is presented in Table 3. The controls consumed a mean of 230.43 mg of total flavonoids per day. Flavan-3-ols (173.82 mg/day, 75.4%) and flavanones (31.43 mg/day, 31.6%) were the classes of flavonoids consumed the most by this population. Isoflavones and lignans contributed 2.1% and 2.8%, respectively, to the mean intake of total flavonoids. Individual foods and beverages (see Appendix 1) are listed from the richest source of flavonoids to the smallest source (top to bottom) for each flavonoid class. The richest sources of total flavonoids in this database include 'tea, including herb tea', which contains 111.41 mg of flavan-3-ols per 100 g; 'cherries', which contains 116.31 mg of anthocyanidins per 100 g; and 'grapefruit', which contains 54.50 mg of flavanones per 100 g. For total flavonoids, intakes ranged from 0.8 to 44.3 mg/day for the lowest 20% of consumers and from 364.5 to 902.0 mg/day for the highest 20% of consumers (data not shown).

For purposes of summarizing and reporting flavonoid consumption patterns in the LIBCSP, the items on the modified Block FFQ were aggregated on the basis of the classes of flavonoids which they contained. Table 4 lists the major food and beverage contributors of the specific flavonoids in the diets of the control women in the LIBCSP. Tea, including herb tea was the greatest contributor of lignans, flavonols, and flavan-3-ols.

DISCUSSION

Flavonoid intake in our American population was comparable to the levels of intake observed in Greece (59) and Italy (26). The median intake of flavan-3-ols for the Greek study was 23.5 mg/day, and for the Italian study it was 44.1 mg/day. Similar to the LIBCSP, flavan-3-ols were the greatest source of flavonoid intake in the Italian study (26). The LIBCSP controls consumed a median of 100.77 mg/day of flavan-3-ols, strongly influenced

by tea consumption. Median isoflavone intake in our study (1.49 mg/day) was greater than both of the aforementioned studies, with frozen tofu and tofu serving as the largest contributors.

Soy products are the richest source of isoflavones (298) and there is increasing prevalence of soy in non-traditional sources (470), such as soy flour in doughnuts and soy protein in fast food hamburgers. To elucidate whether isoflavone intake is associated with various diseases such as cancer, future research should include assessing intake of as many of these products as possible. Future databases will also need to be developed to include the estimated flavonoid content of these products.

Two recently published studies of flavonoids and breast cancer risk (59, 60) have used both the USDA Database for the Flavonoid Content of Selected Foods and the USDA - Iowa State University Database on the Isoflavone Content of Selected Foods to estimate flavonoid intake, with the Italian study (60) supplementing the databases with additional sources of data (379-381). The database described here used these sources along with additional sources to increase the coverage of isoflavones and include a category of flavonoids not measured by the previous studies (59, 60). Although they represented a small proportion of intake overall, lignans (41, 51-53, 278) and isoflavones (39, 40, 42, 279, 280, 282, 289-291) are known to have strong biologic activity and both were consumed at some level by all LIBCSP control participants. The expanded coverage of our database may enhance the ability to address etiologic questions with regard to breast cancer and other maladies.

While this database is more comprehensive than those used in previous studies, it may not reflect true intake for several reasons. Flavonoid content in foods is variable, in part

being influenced by environmental conditions (472). Particularly, in fruits and vegetables, flavonoid distributions vary due to the different cultivars, cultural practices, climatic conditions and geographic location, degree of ripeness, storage conditions, and industrial processing (292, 473-476).

The FFQ does not include all flavonoid-containing foods. Although we modified the Block FFQ for the LIBCSP to include some flavonoid-containing foods, it did not include blueberries and raspberries, both rich sources of anthocyanidins (377). Omission of these berries from the modified Block FFQ may have contributed to the lower anthocyanidin intake reported in our study population compared to those in Greece (59) and Italy (60).

The reported properties of flavonoids suggest that increased consumption of flavonoid-containing foods and beverages may decrease the risk of many diseases, including cancer and heart disease (298). This database will facilitate research on the associations between flavonoids and disease in observational studies.

Table 1. Flavonoid database values for total flavonoids and total flavonoid classes (in mg per 100 g).

Block FFQ Item	Total Flavo-noids	Total Flavo-nols	Total Flav-ones	Total Flavan-ones	Total Flavan-3-ols	Total Antho-cyanidins	Total Isoflav-ones	Total Lig-nans
Apples, applesauce, pears	9.78	2.52	0.00	0.00	7.20	0.00	0.01	0.05
Bananas	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.07
Peaches, apricots, nectarines (fresh in season)	6.21	0.85	0.00	0.00	5.36	0.00	0.00	0.00
Strawberries (fresh in season)	7.54	1.44	0.00	0.00	4.47	0.00	0.05	1.58
Cherries (fresh in season)	129.13	1.24	0.00	0.00	11.58	116.31	0.00	0.00
Peaches, apricots (canned, frozen, or dried)	1.87	0.00	0.00	0.00	1.87	0.00	0.00	0.00
Oranges	22.02	0.00	0.00	21.94	0.00	0.00	0.00	0.08
Grapefruit	55.62	0.90	0.00	54.50	0.00	0.00	0.00	0.22
Orange Juice or Grapefruit Juice	19.68	0.05	0.00	19.33	0.00	0.00	0.00	0.30
Other beans (baked, pinto, kidney, lima, blackeyed, chili w/beans)	3.67	0.00	0.00	0.00	2.01	0.00	1.60	0.06
String beans, green beans	2.02	1.93	0.00	0.00	0.00	0.00	0.00	0.10
Green peas	2.53	0.10	0.00	0.00	0.00	0.00	2.42	0.01
Corn, including corn on the cob	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.04
Tomatoes, tomato juice, V-8 juice	1.57	1.26	0.21	0.00	0.00	0.00	0.05	0.06
Broccoli	4.64	4.17	0.00	0.00	0.00	0.00	0.03	0.44
Cauliflower or brussel sprouts	1.09	0.77	0.21	0.00	0.00	0.00	0.02	0.10
Spinach (raw)	5.99	4.88	1.11	0.00	0.00	0.00	0.00	0.00
Mustard greens, turnip greens, collards, kale	12.33	12.33	0.00	0.00	0.00	0.00	0.00	0.00

Cole slaw, cabbage, sauerkraut	0.24	0.13	0.03	0.00	0.00	0.00	0.05	0.04
Carrots, or mixed vegetables containing carrots	0.38	0.04	0.00	0.00	0.00	0.00	0.00	0.35
Red or green peppers	1.18	0.33	0.66	0.00	0.00	0.00	0.00	0.20
Green salad	2.22	1.97	0.15	0.00	0.00	0.00	0.00	0.10
Other potatoes (boiled, baked, mashed, potato salad)	0.11	0.06	0.00	0.00	0.00	0.00	0.04	0.01
Tofu	28.61	0.00	0.00	0.00	0.00	0.00	28.61	0.00
Hamburgers, cheeseburgers meat loaf, tacos	3.01	2.74	0.07	0.00	0.00	0.07	0.00	0.21
Spaghetti, lasagna, other pasta with tomato sauce	1.32	1.17	0.00	0.00	0.00	0.00	0.00	0.15
Pizza	1.36	1.21	0.00	0.00	0.00	0.00	0.00	0.15
Tomato and vegetable soups	0.14	0.14	0.00	0.00	0.00	0.00	0.00	0.00
Chocolate cake, brownies, cookies	10.03	0.00	0.00	0.00	10.03	0.00	0.00	0.00
Chocolate candy	23.39	0.00	0.00	0.00	23.39	0.00	0.00	0.00
Beer	0.10	0.10	0.00	0.00	0.00	0.00	0.00	0.00
Wine	12.27	0.85	0.00	0.00	6.64	4.63	0.00	0.16
Tea, including herb tea (hot or iced)	118.06	3.89	0.00	0.00	111.41	0.00	0.03	2.72
Whole-wheat or other whole grain bread	0.97	0.00	0.00	0.00	0.00	0.00	0.09	0.88
Cantaloupe	0.19	0.00	0.00	0.00	0.00	0.00	0.00	0.18
Watermelon	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.05
Winter squash, baked squash	0.38	0.00	0.00	0.00	0.00	0.00	0.00	0.38
Sweet potatoes, yams	0.30	0.00	0.00	0.00	0.00	0.00	0.00	0.30
Alfalfa	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.03

Sprouts								
High fiber, bran or granola cereals	0.11	0.00	0.00	0.00	0.00	0.00	0.00	0.11
White rice	0.04	0.00	0.00	0.00	0.00	0.00	0.02	0.02
Brown Rice	0.32	0.00	0.00	0.00	0.00	0.00	0.03	0.30
Potato chips, corn chips, popcorn	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.02
Coffee, regular or decaf	0.72	0.00	0.00	0.00	0.00	0.00	0.00	0.72
White bread, rye, pumpernickel bread, sandwiches, bagels	0.58	0.00	0.00	0.00	0.00	0.00	0.50	0.09
Peanuts, peanut butter	1.28	0.00	0.00	0.00	0.00	0.00	0.87	0.41
Low-fat, frozen tofu	16.87	0.00	0.00	0.00	0.00	0.00	16.87	0.00
Corn bread, corn muffins, corn tortillas	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.07
Other cooked cereals and grits	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.05
French Fries and Fried Potatoes	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.02

Table 2. Distribution of flavonoid intake among a representative sample of women without breast cancer (n = 1500) in the Long Island Breast Cancer Study Project

Variable	Mean[#]	Median[#]	Minimum[#]	Maximum[#]	Standard Deviation[#]
Total Flavonoids	230.43	148.95	0.83	902.03	216.49
Flavonols	10.44	8.39	0.39	37.74	7.47
Flavones	0.15	0.12	0.00	1.44	0.13
Flavanones	31.43	22.90	0.00	227.69	33.97
Flavan-3-ols	173.82	100.77	0.00	685.19	199.67
Anthocyanidins	3.51	1.46	0.00	139.57	8.35
Isoflavones	4.90	1.49	0.01	106.41	8.24
Lignans	6.36	4.84	0.04	20.30	4.68

[#]In milligrams (mg) per day.

Table 3. Major contributors of flavonoids by flavonoid class among the control women in the LIBCSP

Rank	Food Aggregate	Percent	Cumulative Percent
	Flavonols		
1	Tea, including herb tea	56	56
2	Green salad	8	64
3	Broccoli	7	71
4	Mustard greens, turnip greens, collards, kale	1	72
	Flavones		
1	Green salad	41	41
2	Tomatoes, tomato juice, V-8 juice	30	71
3	Red or green peppers	10	81
4	Spinach (raw)	6	87
5	Cauliflower or brussel sprouts	5	92
	Flavanones		
1	Orange juice or grapefruit juice	52	52
2	Grapefruit	35	87
3	Oranges	13	100
	Flavan-3-ols		
1	Tea, including herb tea	97	97
2	Apples, applesauce, pears	1	98
	Anthocyanidins		
1	Cherries (fresh, in season)	73	73
2	Wine	26	99
3	Hamburgers, cheeseburgers, meat loaf, tacos	1	100
	Isoflavones		
1	Low-fat, frozen tofu	85	85
2	Tofu	7	92
3	Peas	1	93
	Lignans		
1	Tea, including herb tea	99	99
2	Strawberries	0.5	99.5
3	Whole-wheat or other whole grain bread	0.3	99.8

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