

## ABSTRACT

Title of Dissertation: RACIAL AND ETHNIC DISPARITIES OF BREAST CANCER RISK: THE ROLE OF INDIVIDUAL AND NEIGHBORHOOD-LEVEL CARDIOMETABOLIC FACTORS

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**Background:** Observed racial and ethnic disparities in breast cancer are complex, in part, due to biological and behavioral factors at the individual and neighborhood level. Cardiometabolic factors such as the use of cholesterol-lowering drugs and engaging in healthy lifestyle behaviors may reduce breast cancer risk, however, the current understanding of these factors among diverse racial and ethnic populations remains limited. Moreover, at the neighborhood-level, the extent to which neighborhood socioeconomic status (nSES) influences inflammatory profiles among racially and ethnically diverse populations remains unclear. Using data from the Multiethnic Cohort Study (MEC), this dissertation investigates cholesterol-lowering drug use (Aim I) and a Healthy Lifestyle Index (HLI) (Aim II) in relation to postmenopausal breast cancer risk by race and ethnicity; and, assesses associations between nSES and inflammatory biomarkers among adults (Aim III).

**Methods:** Prospective cohort analyses were conducted among postmenopausal women who completed the third MEC follow-up questionnaire in 2003 (Aim 1, n=41,394) or the baseline

questionnaire in 1993-1996 (Aim 2, n=65,561) and were followed until 2017 for invasive breast cancer diagnoses (n=1,681 and 4,555 cases, respectively). Multivariable adjusted hazard ratios [HR] and 95% confidence intervals [95% CI] were estimated using Cox proportional hazards regression. For Aim III, multivariable linear regression assessed cross-sectional associations between nSES and inflammatory serum biomarkers (adiponectin, leptin and C-reactive protein) among adults residing in California (n=6,919) and Hawaii (n=6,899) (2000-2017).

**Results:** Cholesterol-lowering drug use (Aim 1) and duration was not associated with breast cancer risk among all women with no statistically significant heterogeneity in associations by race and ethnicity (p-interaction >0.05). In Aim 2 analyses, women with a higher HLI score (Tertile (T)) had a reduced risk of breast cancer (HR<sub>T3 vs T1</sub>: 0.76; 95% CI: 0.69, 0.84; HR<sub>T2 vs T1</sub>: 0.88; 95% CI: 0.79, 0.97) compared to women in the lowest HLI tertile with a significant dose-response observed (p-trend <0.01). Similar patterns were observed across all racial and ethnic groups of women. In California and Hawaii, individuals living in low nSES neighborhoods had higher serum levels of CRP (p-trend <0.001; p-trend = 0.02, respectively) and leptin (p-trend <0.001) while adiponectin levels were lower (p-trend <0.01; p-trend = 0.03, respectively) compared to individuals living in neighborhoods with high nSES. Additional adjustment for body mass index attenuated these associations (p-trend >0.05) (Aim III).

**Public Health Impact:** Findings from this dissertation further support engaging in healthy lifestyle behaviors as a preventative strategy for breast cancer reduction among multiethnic populations of postmenopausal women whereas cholesterol-lowering drug use was not associated with reductions in risk. In addition, residing in low nSES neighborhoods was associated with less favorable inflammatory biomarkers levels.

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by

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## Dedication

To all the women who have been diagnosed with breast cancer, family members and friends included, your resiliency is unmatched, and your strength is an inspiration for this work. May this research contribute to the greater good and health of humanity and serve as a steppingstone for future research in racial and ethnic disparities research.

## Acknowledgements

Firstly, all the glory and honor belong to my Lord and Savior, Jesus Christ. God Almighty is my pillar of strength, my source of wisdom, my fountain of encouragement, and my blanket of assurance.

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To my family and friends, who have been my support system, I thank you all dearly. To my children, Enoch (5) and Elyse (3), thank you. Your bright faces and limitless imagination encouraged mommy in so many ways throughout this journey. You inspired my resiliency. To my mom, dad, brother and mother-in-law, my support system, I appreciate you endlessly for your continued support and dedication to help in the many ways I needed as a working wife and mother.

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## List of Abbreviations

AI/AN	American Indian/Alaska Natives
nSES	Neighborhood socioeconomic status
HER2	Human epidermal growth factor receptor 2
ER	Estrogen-receptor
PR	Progesterone-receptor
CRP	C-reactive protein
BMI	Body mass index
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
CVD	Cardiovascular disease
IBS	Invasive breast cancer
DCIS	Ductal carcinoma <i>in situ</i>
ILC	Invasive lobular carcinoma
HR	Hormone receptor
NGS	Nottingham Grading System
SEER	Surveillance, Epidemiology, and End Results
SRP	Surveillance Research Program
NCI	National Cancer Institute
NST	No special type
DCCPS	Division of Cancer Control and Population Sciences
MHT	Menopausal hormone therapy
MetS	Metabolic syndrome
BBD	Benign breast disease
BRCA1	BReast CAncer gene 1
BRCA2	BReast CAncer gene 2
ACL	Adenosine triphosphate-citrate lyase inhibitors
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
SREBP	Sterol regulatory element binding proteins

VLDL	Very-low density lipoproteins
NHANES	National Health and Nutrition Examination Survey
HLI	Health Lifestyle Index
VAT	Visceral adipose tissue
SAT	Subcutaneous adipose tissue
IL-6	Interlukin-6
IL-8	Interlukin-8
DEXA	Dual x-ray absorptiometry

# Chapter 1: Introduction

## Background and rationale

Breast cancer is a complex, multi-dimensional disease that affects approximately one in eight women in the United States [1]. The incidence rates of breast cancer by race and ethnicity vary with comparable rates for White and African American women, 131 per 100,000 and 125 per 100,000, respectively [2]. Breast cancer incidence rates among aggregated Asian and Pacific Islanders (102 per 100,000), Hispanic/Latinos (99 per 100,000) and American Indian/Alaska Natives (AI/AN) (80 per 100,000) are relatively lower compared to White and African American women [2]. More specifically, among women representing disaggregated Asian and Pacific Islander groups, breast cancer incidence rates vary: Chinese (74 per 100,000), Japanese (103 per 100,000), Filipina (98 per 100,000), Korean (46 per 100,000), South Asian (77 per 100,000) and Vietnamese (60 per 100,000) [3]. Observed disparities by race and ethnicity are more disparate when breast cancer risk and prognosis are examined by hormone receptor type.

Racial and ethnic disparities in breast cancer are complex, in part, due to interrelated factors at the genetic, biological, social and environmental level. These disparities are further complicated by racial and ethnic differences observed in the prevalence of cardiometabolic factors, such as obesity [4], insulin resistance [5], diabetes [6, 7], high cholesterol [8, 9] and hypertension [10]. In addition, lifestyle-related modifiable factors such as dietary intake [11], physical activity [12], sedentary behavior [13], obesity [14, 15], smoking [16], alcohol intake [17] and sleep behavior [18] are associated with cardiometabolic risk factors. Specifically, obesity is a strong well-established risk factor for postmenopausal breast cancer [19, 20] and a higher prevalence of obesity has been observed among non-Hispanic African

American women along with an overall higher prevalence of cardiometabolic risk factors compared to White women [21] and non-Hispanic Asian adults [22, 23]. Furthermore, non-Hispanic African American women report higher prevalence of elevated blood pressure whereas among Mexican American women, a higher prevalence of elevated waist circumference, elevated triglycerides, reduced high density lipoprotein and elevated fasting glucose has been observed. [20]. However, cholesterol-lowering drug use has been shown to decrease cholesterol levels and in turn reduce the risk of cardiovascular disease and related health outcomes[24]. Overall, racial and ethnic minorities experience poor cumulative health and increased cardiometabolic risk at each income level and health insurance coverage status compared to White adults [25].

Breast cancer is influenced by a myriad of individual and neighborhood-level factors. Genetic factors, characterized as non-modifiable factors, play a vital role in the risk of developing cardiometabolic factors and breast cancer [26, 27]. Modifiable lifestyle behaviors and social and environmental determinants of health also contribute to and influence individual-level disease risk profiles including cardiometabolic factors. Beyond the individual-level behavioral factors, the neighborhood-level environment, defined as the conditions in which people are born, live, learn work, play and worship [28], has emerged as a critical focus of epidemiologic research to expand the understanding of neighborhood-level attributes such as neighborhood socioeconomic status and the obesogenic environment. There are plausible biological pathways previously established [29-31] by which the association of the neighborhood environment influences individual health through the "obesogenic environment" defined by the collective influence of structural and built surroundings, economic, political and social conditions on promoting obesity [32]. The

obesogenic environment has previously been characterized using neighborhood socioeconomic status (nSES) in relation to obesity as increasing evidence suggests the role of nSES as a determinant of health [33]. However, limited studies have examined individual-level and neighborhood-level factors in relation to postmenopausal breast cancer risk and obesity related biological pathways among diverse multiethnic populations.

Modifiable lifestyle factors including physical activity, sedentary behavior, body mass index (BMI), alcohol consumption, smoking status, sleep and diet have been shown to influence cardiometabolic risk and have been examined in relation to breast cancer risk [34-37]. The direction and strength of association vary among these cardiometabolic factors with breast cancer risk and may suggest certain factors may have stronger influence on breast cancer risk than other factors. Physical activity is a well-established protective factor with consistent inverse associations observed particularly among postmenopausal breast cancer [35, 38]. However, sedentary behavior has been shown to increase the risk of incident breast and other types of cancers [39], and is more prevalent among African American women [40, 41]. Obesity and metabolic dysfunction have been linked as an underlying mechanism in the association between sedentary behavior and cancer with greater BMI significantly increasing the breast cancer risk, especially among postmenopausal women [42]. Other modifiable lifestyle factors such as smoking and alcohol consumption are correlated and have been associated with increased risk of breast cancer among women who are current users irrespective of racial and ethnic groups [43-47]. Adequate sleep, an emerging breast cancer risk factor, is essential for overall health [48]. Studies have shown sleep duration or sleep difficulties are associated with poor health outcomes including obesity [49], type II diabetes [50], immune dysfunction and heart disease [51]. Particularly, short sleep duration has been

associated with risk of incident breast cancer among postmenopausal women [52]. Given the prevalence of these modifiable lifestyle factors vary by race and ethnicity and may contribute to differences in breast cancer risk by race and ethnicity, it is critically important to expand this field of research by collectively assessing these modifiable lifestyle factors in relation to breast cancer risk among multiethnic populations of postmenopausal women.

Cholesterol-lowering drugs, such as statins, typically prescribed for elevated low-density lipoprotein (LDL) cholesterol and to reduce the risk of heart disease or cardiovascular events [26], have been shown to decrease overall cancer incidence among statin users [28] and to reduce the risk of breast cancer among postmenopausal women [27]. Epidemiologic data suggests statin use may reduce mortality in women diagnosed with breast cancer [29]. However, evidence from prior studies conducted among primarily White women does not support an association with breast cancer risk. Despite the higher prevalence of cardiovascular disease (CVD) and CVD-related events among racial and ethnic minorities namely, African American, Latina and Hispanic women, the association of cholesterol-lowering drug use as a protective factor for breast cancer risk is not well understood among racial and ethnic minorities.

At the neighborhood level, indicators such as neighborhood socioeconomic status (nSES) have been used to characterize the neighborhood obesogenic environment [53]. nSES is characterized as the economic, physical, and social characteristics of the place where a person lives and more specifically, is assessed using a composite measure of socioeconomic factors that capture multiple domains of housing, education, poverty, employment, occupation and income[33]. There is also growing evidence in support of the association between nSES and breast cancer risk [54, 55] and other chronic diseases such as obesity [30].

Low nSES neighborhoods generally lack adequate community resources such as healthy food options, community centers and medical facilities and may have reduced walkability and comprised safety which can influence an individual's ability to engage in physical activity [56]. While prior studies support the role of neighborhood and obesogenic environments in obesity and inflammatory-related diseases, the underlying biological mechanisms remain unclear. Inflammatory biomarkers such as C-reactive protein (CRP) and adipokines have been associated with obesity and inflammation [57]. Previous studies have reported higher levels of CRP and adipokines associated with disadvantaged neighborhood conditions [58] and the built environment [59] among African Americans. However, studies have not examined neighborhood socioeconomic status in relation to inflammatory biomarker levels across diverse racial and ethnic groups.

### Specific aims

The **overall objective** of this dissertation was to improve the knowledge of individual and neighborhood level cardiometabolic risk factors among a diverse multiethnic population. Aims 1 and 2 focused on postmenopausal breast cancer risk, while Aim 3 investigated a key neighborhood contextual factor, nSES, in relation to inflammation, an important carcinogenic pathway. The **central hypothesis** was stated as postmenopausal women who use cholesterol-lowering drugs and who engage in healthier lifestyle behaviors would have inverse associations with breast cancer risk. In addition, individuals living in low nSES neighborhoods would have less favorable levels of biomarker serum levels. These associations would vary by race and ethnicity.

The **rationale** for this dissertation was to assess cholesterol-lowering drug use and healthy lifestyle factors as potential preventative strategies for breast cancer risk reduction and

to assess biological relationships of neighborhood socioeconomic status and inflammation among racially and ethnically diverse adults. This dissertation underscores the importance for research among racial and ethnic groups with a high prevalence of cardiometabolic risk factors such as obesity, smoking, alcohol intake, physical inactivity, and unhealthy diet. The specific aims of this dissertation are:

1. To examine the association between cholesterol-lowering drug use (status and duration) and breast cancer risk, overall and by race and ethnicity among postmenopausal women in the Multiethnic Cohort (MEC) study (2003-2017).  
Hypothesis: Postmenopausal women who are former or current cholesterol-lowering drug users will have reduced breast cancer risk and risk will vary across racial and ethnic groups.
2. To assess a Healthy Lifestyle Index (HLI) comprised of seven components (dietary intake, physical activity, body mass index, smoking status, alcohol consumption, sleep duration and sedentary behavior) in relation to breast cancer risk among postmenopausal women in the MEC study, overall and by race and ethnicity.  
Hypothesis: Postmenopausal women with a higher HLI score will have reduced breast cancer risk and with risk reductions varying across racial and ethnic groups.
3. To examine cross-sectional associations between neighborhood socioeconomic status (nSES) and circulating inflammatory biomarkers including C-reactive protein, adiponectin and leptin among healthy adults (men and women) in the MEC (1998 – 2000) residing in California and Hawaii.

Hypothesis: Levels of inflammatory biomarkers will differ by nSES (i.e., a higher nSES will be associated with lower levels of CRP and leptin and higher adipokine levels) and will differ across state and race and ethnicity.

Significance and innovation

The dissertation research presented herein uses one of the largest prospective cohort studies with diverse racial and ethnic representation of African American, Japanese American, Latino, Native Hawaiian and White adults. Aim 1 expands the current understanding of cholesterol-lowering drug use and duration, a potential chemopreventive agent, in relation to breast cancer risk among racial and ethnic groups of postmenopausal women. Aim 2 emphasizes the public health implications of maintaining a healthy lifestyle to reduce the risk of breast cancer and contributes further evidence for women across different racial and ethnic groups to consider engaging in healthy lifestyle behaviors to influence their own risk reduction. Aim 3 focuses on examining the relationships between the neighborhood socioeconomic status and circulating biomarkers. This research can further the understanding of biological pathways contributing to obesity and inflammatory-related diseases among diverse racial and ethnic populations. Collectively, findings from this dissertation contribute to expanding the knowledge of potentially modifiable breast cancer risk factors and help inform prevention strategies focused on establishing positive health outcomes among racial and ethnic groups adults, specifically postmenopausal women.

## Chapter 2: Background

### Overview of breast cancer

In 2022, approximately 15% of new cancer cases in women were diagnosed as breast cancer; specifically, 287,850 new cases of invasive and 51,400 new cases of non-invasive ductal carcinoma in situ (DCIS) breast cancer were estimated [60]. Invasive breast cancer (IBC) is the most common type of breast cancer categorized into two main types: invasive ductal carcinoma (which originates in cells within the milk duct of the breast) and invasive lobular carcinoma (ILC) (which originates in the lobules of the breast). DCIS is defined as a premalignant proliferation of neoplastic epithelial cells within the lumen of mammary ducts. The main difference between DCIS and IBC is the gatekeeping effect of the myoepithelium; in DCIS tumor suppressive effects prevent expansion of tumor cells, whereas in IBC there is a loss of suppressive effects that enable tumor cells to progress and multiply [61].

### Hormone and HER2 receptors

Breast cancer cells have receptors, or proteins, which bind to hormones (estrogen and progesterone) or other proteins (human epidermal growth factor receptor 2 (HER2) to promote cancer cell growth. Approximately 70-80% of incident breast tumors are hormone receptor- positive defined as estrogen receptor positive (ER+) and progesterone receptor- positive (PR+). Approximately 25% of incident cases of breast cancer are hormone receptor- negative defined as ER- and PR- [62]. Breast cancer cells with estrogen and/or progesterone receptors are referred to as ER+ and/or PR+, while breast cancer cells that do not possess either hormone receptor are referred to as ER- and/or PR-. Some breast cancer cells contain an abundance of the protein receptors, HER2, which promotes cancer cells to divide and multiply; this breast cancer type is referred to as HER2+, and HER2- if the HER2 receptors

are absent on breast cancer cells. Invasive breast cancer is further classified into four main molecular subtypes including luminal A (ER+ and/or PR+ and HER2-), luminal B (ER+ and/or PR+ and HER2 +/-), HER2-enriched (ER- and PR- and HER2+) and triple negative breast cancer (TNBC) tumors (ER-, PR- and HER2-) which are the most aggressive. TNBC tumors, which lack estrogen, progesterone and HER2 receptors, and high-grade tumors are more likely to be diagnosed in African American women [63]. Women with breast tumors that are ER+ and/or PR+ positive tend to have a lower risk of mortality after diagnosis compared to women with ER- and/or PR- tumors [64], in part due to available adjuvant therapy. White women are most commonly diagnosed with HR+/HER2- (76%) while African American women have the lowest prevalence of this subtype (61%), and among other racial and ethnic groups the prevalence of breast cancer by molecular subtype is relatively similar, ranging from 69% to 71%: Hispanic (69%) American Indian/Alaska Native (70%), and Asian and Pacific Islanders (71%). The different subtypes of breast cancer identified have been associated with varied prognosis and survival, which in turn may contribute to existing racial and ethnic disparities in breast cancer outcomes [63, 65].

Shown in **Figure 1** are the molecular subtypes of breast cancer. IBC is classified according to tumor growth patterns and the degree of differentiation, and by histological type and grade. The Nottingham (Elston-Ellis) modification of Scarff-Bloom-Richardson grading system, known most as the Nottingham Grading System (NGS), is the internationally recommended grading system in breast cancer [66]. NGS is based on evaluation of three morphological features: a) degree of gland formation, b) nuclear pleomorphism, and c) mitotic count formation [67].

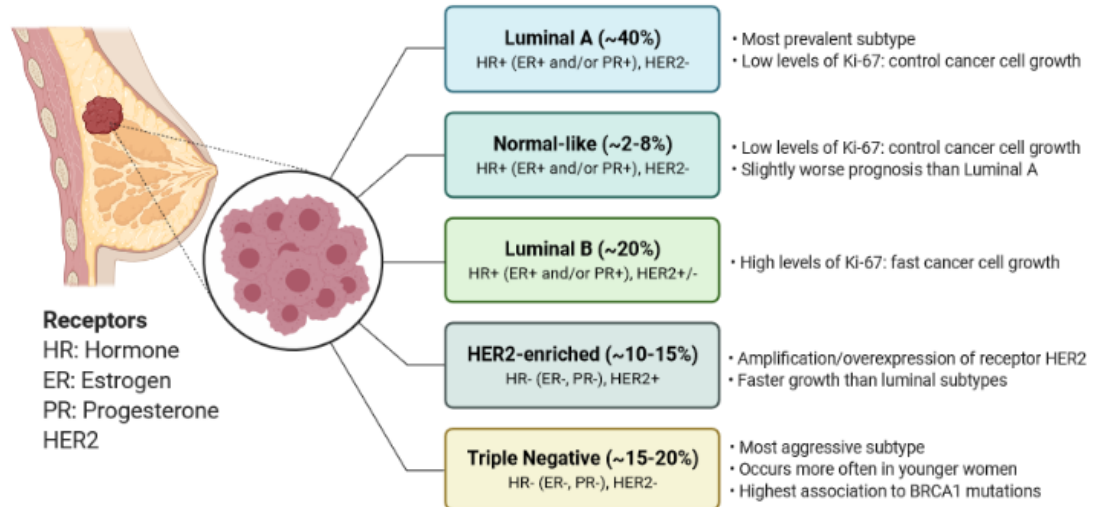


Figure 1. Molecular subtypes of breast cancer [68]

Nearly 60% to 75% of tumors are classified as no special type (NST) of characteristics, whereas tumors classified by specific types are less common. Grade 1 is classified as well-differentiated tumors that demonstrate high similarity to the normal breast ducts and lobules, tubule formation (>75%), a mild degree of nuclear pleomorphism, and low mitotic count. Grade II is defined as moderately differentiated tumors and Grade III is defined as poorly differentiated tumors with a marked degree of cellular pleomorphism and frequent mitoses and no tubule formation (<10%)[67].

There are four main breast cancer subtypes: luminal A, luminal B, HER2-enriched and TNBC (basal). Luminal A is the most commonly diagnosed breast cancer that tends to have less aggressive tumor cell growth compared to the other subtypes and subsequently, the most favorable outcome [69, 70]. Luminal B subtype which has a higher grade with poorer prognosis and is also referred to as hormone receptor-positive (HR+), has recently shown to be positively associated with pKi67 and/or HER2 [69, 70]. TNBC does not have hormone or HER2 receptors and among TNBC tumors, nearly 75% are classified as having the basal-like subtype defined by gene expression profiling [71]. **Table 1** shows the four intrinsic subtypes

of breast cancer and their respective immunohistochemistry, grade, outcome/prognosis and prevalence rates.

Table 1. Intrinsic subtypes of breast cancer

Intrinsic subtype	IHC status	Grade	Outcome	Prevalence*
Luminal A*	[ER+ PR+] HER2-KI67-	1 2	Good	71%
Luminal B*	[ER+ PR+] HER2+ KI67+	2 3	Poor	12%
HER2 enriched*	[ER-PR-] HER2+	2 3	Poor	5%
Basal* (Triple negative)	[ER-PR-] HER2-	3	Poor	12%

\*American Cancer Society Breast Cancer Facts and Figures 2017 – 2018 [60]; IHC: Immunohistochemistry; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor-2

### Descriptive epidemiology of breast cancer

#### *Breast cancer incidence rates by race and ethnicity*

Breast cancer incidence in the United States has steadily increased with each decade. The following figures utilize the 2000-2018 Surveillance, Epidemiology, and End Results (SEER) Program to visualize the breast cancer incidence rates by race and ethnicity. SEER provides information on cancer statistics among the U.S. population and is supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS). Ogbenna, BT (2021) created Figures 2 through 15. **Figures 2-4** which show the incidence of breast cancer by 10-year age strata between 2000 to 2018 for women < 50 years of age (**Figure 2**), 50 – 64 years (**Figure 3**) and women 65 years and older (**Figure 4**). The breast cancer incidence rates in Figures 2 through 15 include aggregated Asian and Pacific Islander data which is not reflective of the varying rates across disaggregated Asian groups. Specifically, breast cancer incidence among Filipina, Native Hawaiian and Japanese women has increased from 1984 to 2013 compared to trends observed among White women, while rates among Chinese women have decreased [65]. The incidence of breast cancer was

highest among non-Hispanic White women less than 50 years of age until 2016, Asian/Pacific Islanders (including Hispanic) had the highest breast cancer incidence in 2017 and 2018. The trend for breast cancer incidence among African American women was similar to White women over time, while American Indian had the lowest incidence.

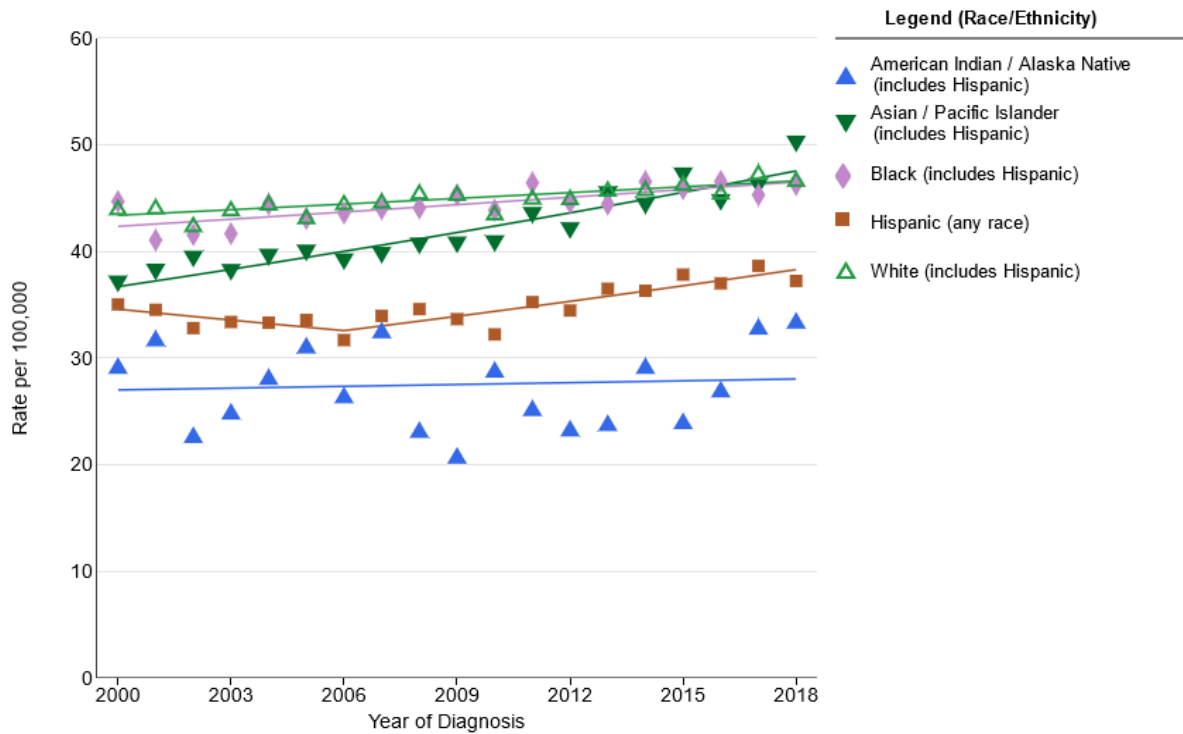


Figure 2 Breast cancer incidence rates, 2000-2018 by race/ethnicity, delay-adjusted SEER incidence rate, Ages <50 years, All stages

Women between ages 50 and 64 years had steady breast cancer incidence rates during the 2000-2018 time period. However, non-Hispanic White women had notable decreasing incidence rates from 2000 to 2003 and between 2003 and 2018 incidence rates plateaued. African American women had the second highest incidence rates, which gradually increased over time. Asian/Pacific Islander and Hispanic women had similar incidence rates until 2007, however incidence of breast cancer among Asian/Pacific Islander women increased more

rapidly than Hispanic women. American Indian women had the lowest incidence of breast cancer over the years.

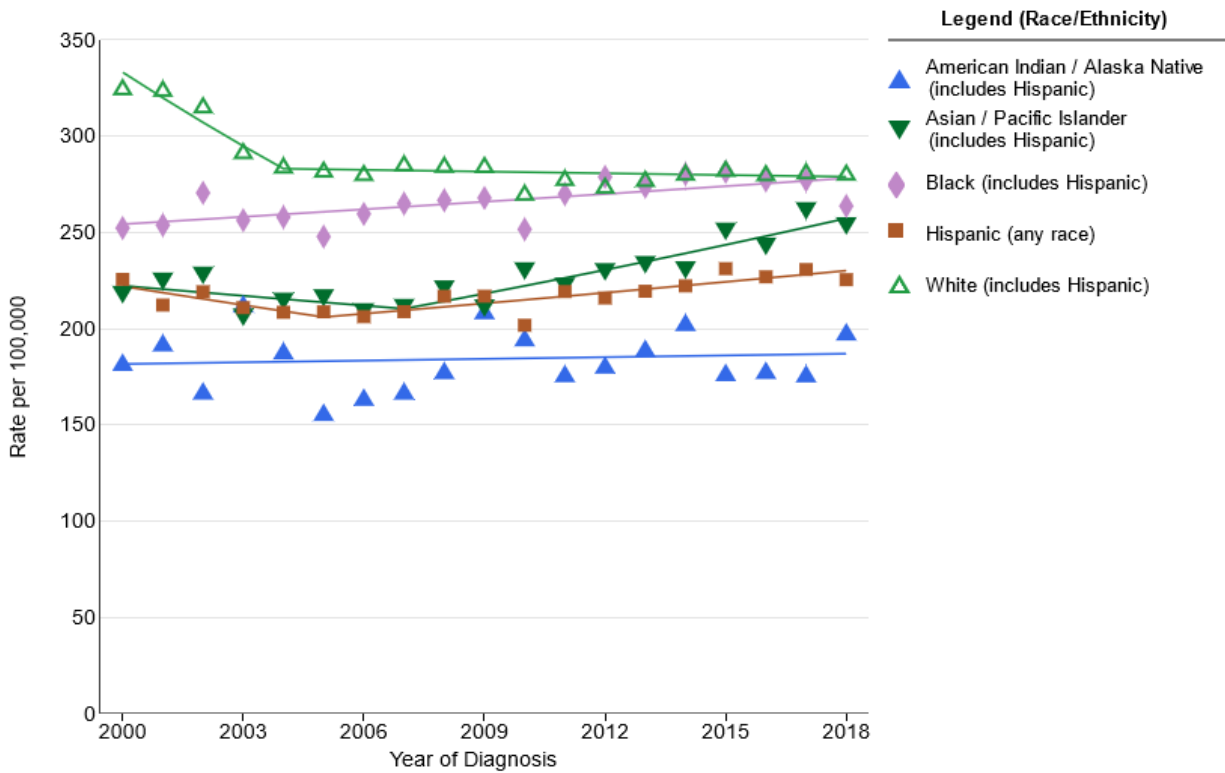


Figure 3 Breast cancer incidence rates, 2000-2018 by race/ethnicity, delay-adjusted SEER incidence rate, Ages 50-64, All stages

Breast cancer incidence among women 65 years old and older across all racial and ethnic groups increased steadily over time. Incidence rates decreased only among White women from 2000 to 2004; thereafter rates followed a gradual upward trend. African American women had the second highest rates, followed by Hispanic, American Indian and Asian/Pacific Islander women.

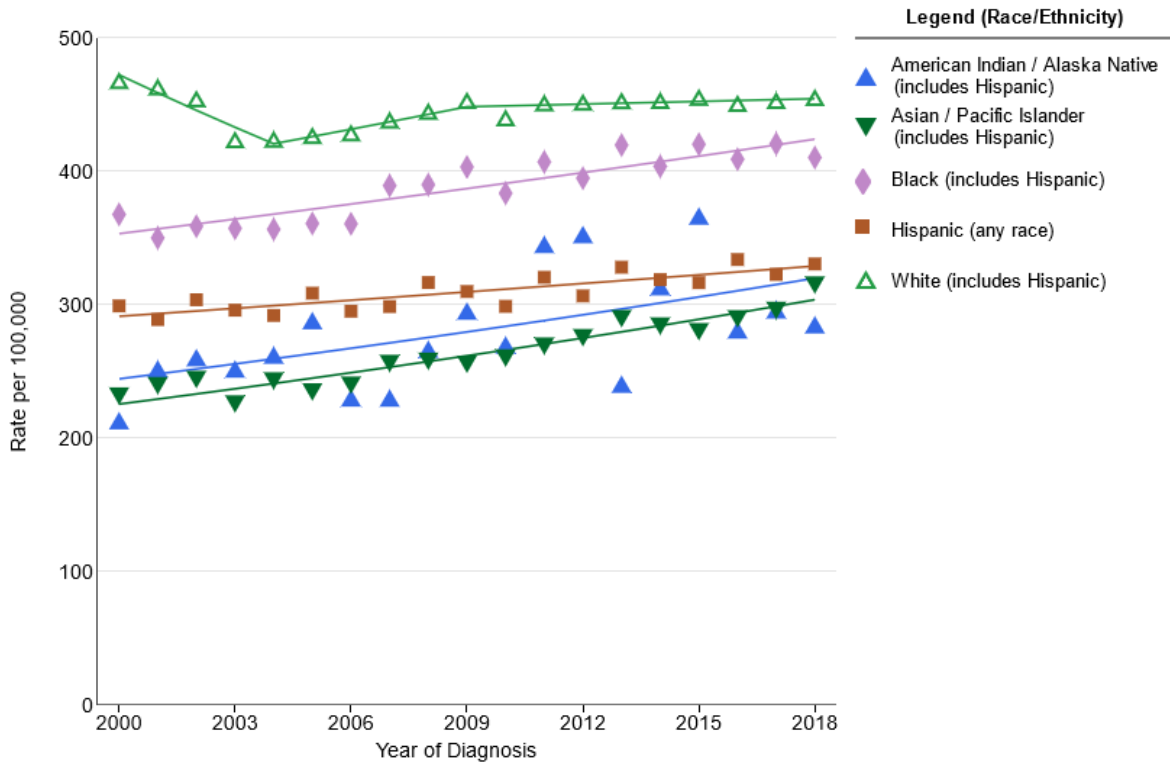


Figure 4 Breast cancer incidence rates, 2000-2018 by race/ethnicity, delay-adjusted SEER incidence rate, Ages 65+, All stages

Breast cancer incidence rates by subtype and race and ethnicity

Ogbenna, BT (2021) created **Figures 5– 7** using SEER data of age-adjusted breast cancer incidence rates between 2010 and 2018. In **Figure 5**, women with luminal A who were ER+, PR+ and HER2- had the highest incidence rate with increasing trends over time. Women with HER2 enriched breast cancer who were ER, PR- and HER2+ had the lowest incidence rates. Women with triple negative breast cancer and ER+, PR+ and HER2+ had similar incidence rates over time. Breast cancer incidence rates for White women were remarkably similar to rates for all races shown in **Figure 6**.

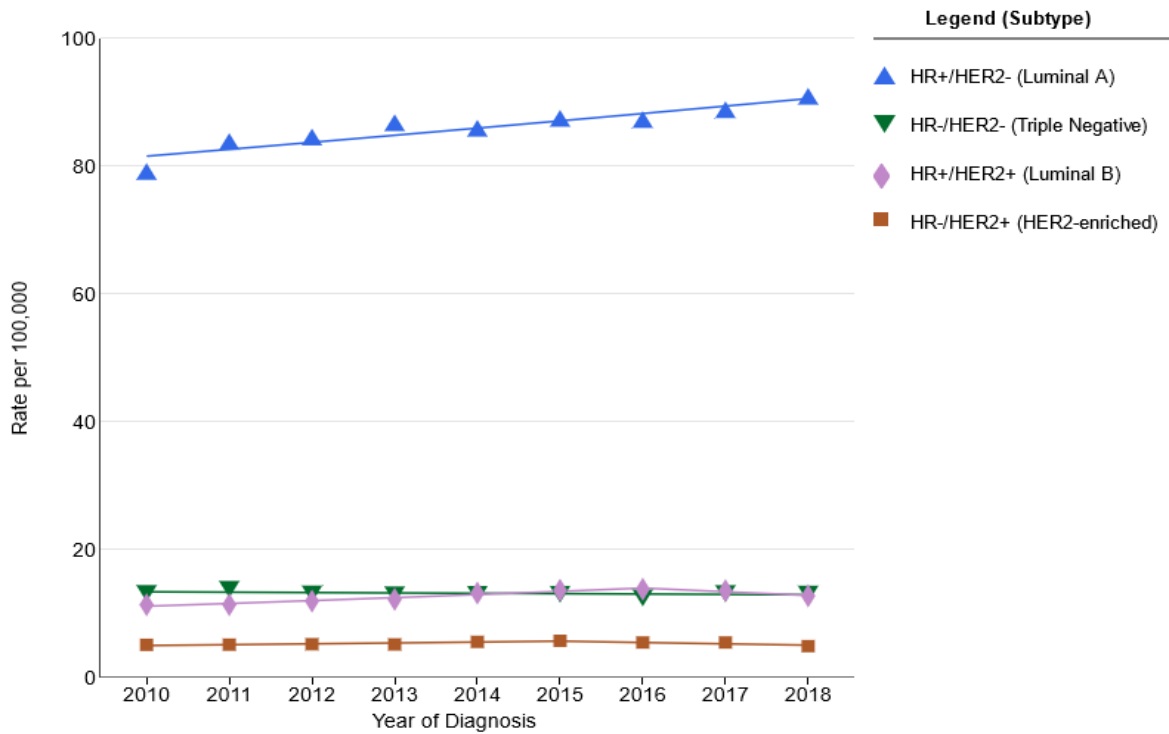


Figure 5 Breast cancer age-adjusted incidence rates, 2010-2018 by subtype, delay-adjusted SEER incidence rate, All Ages, All Races

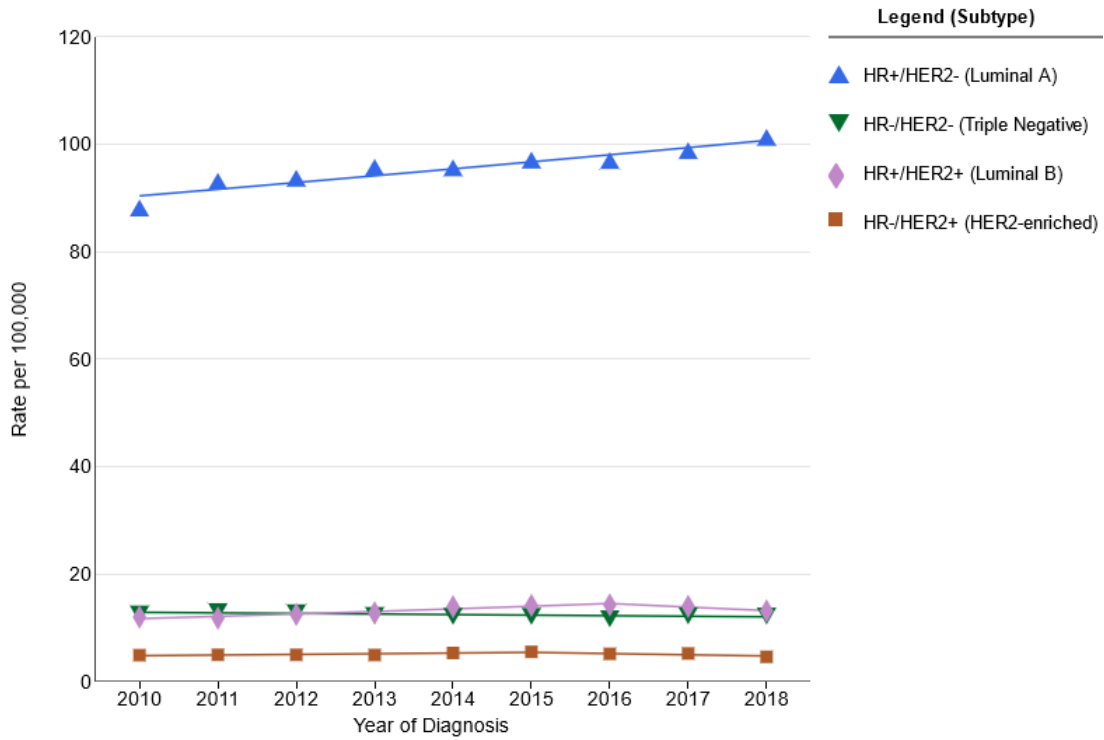


Figure 6 Breast cancer age-adjusted incidence rates, 2010-2018 by subtype, delay-adjusted SEER incidence rate, All Ages, White

**Figure 7** shows breast cancer incidence among African American women of all ages, by subtype. Similar to White women, women with ER+, PR+ and HER2- breast cancer had the highest incidence rates. However, the incidence rates by subtype were distinct and steady over time. African American women with triple negative breast cancer had the second highest breast cancer incidence rate overall, followed by women with ER+, PR+ and HER2+ breast cancer and HER2 enriched breast cancer. Breast cancer incidence in Asian/Pacific Islander women appeared to increase among those with ER+, PR+ and HER2 tumors, while the other subtypes were steady

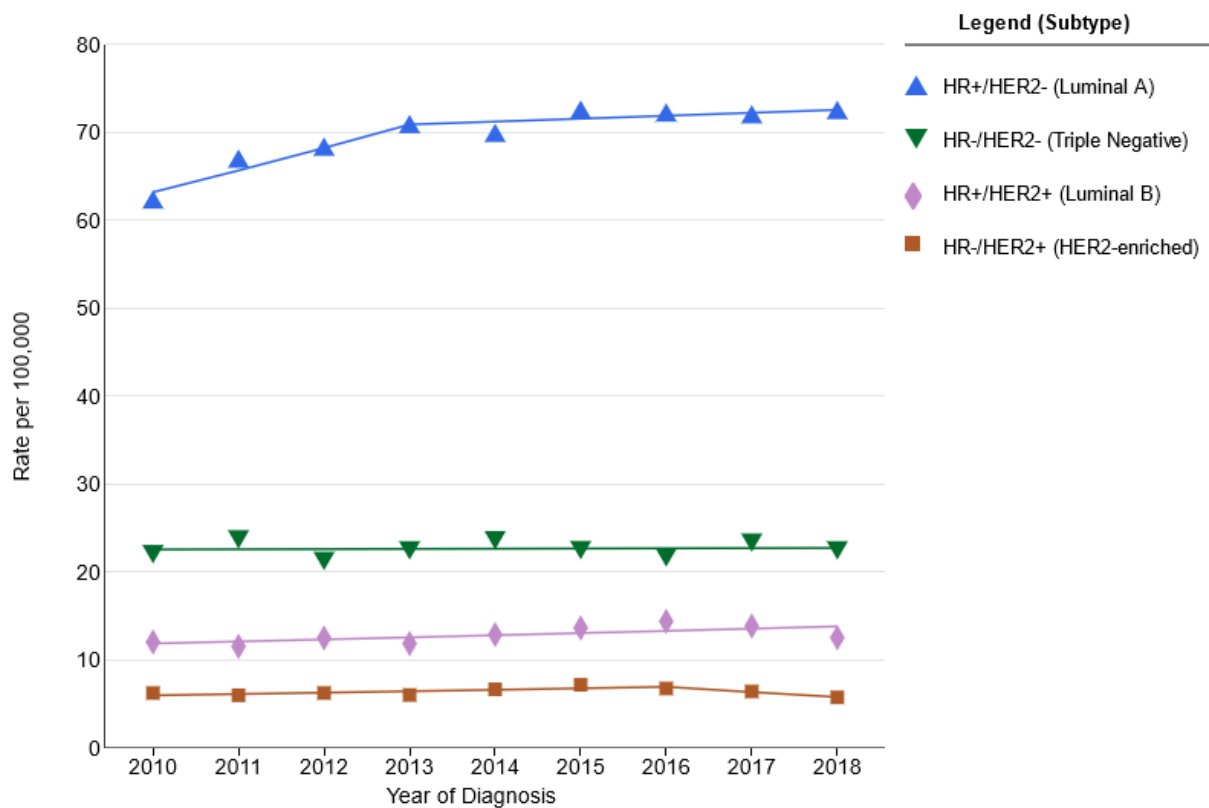


Figure 7 Breast cancer age-adjusted incidence rates, 2010-2018 by subtype, delay-adjusted SEER incidence rate, Black, All Ages

**Figure 8** shows breast cancer incidence among American Indian women of all ages, by subtype. Incidence rates remained constant over the years. With higher incidence among women with ER+, PR+ and HER2- breast cancer. Breast cancer incidence for the other subtypes remained below 10 per 100,000 over time. Among Asian/Pacific Islander women, breast cancer incidence

increased most notably among women with luminal A over time, whereas luminal B, is steadily increasing and triple negative and HER2-enriched subtypes are stagnant shown in **Figure 9**.

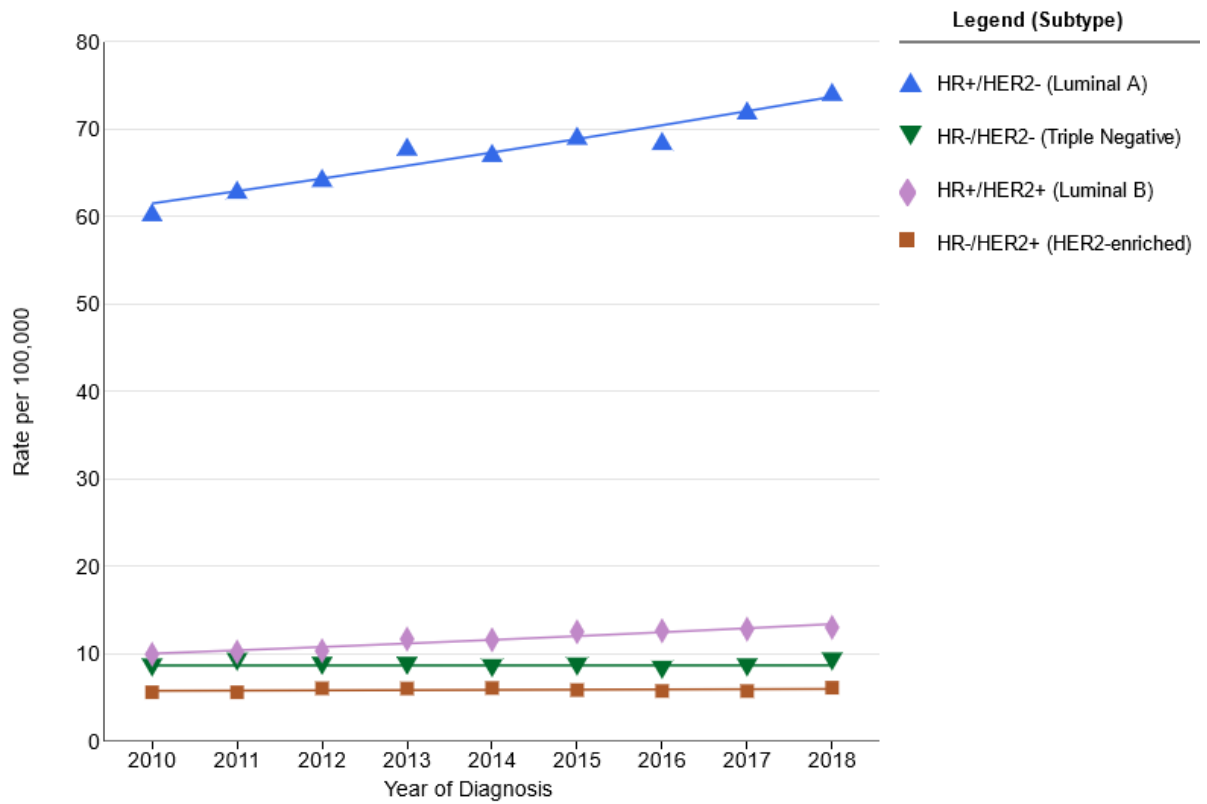


Figure 8 Breast cancer age-adjusted incidence rates, 2010-2018 by subtype, delay-adjusted SEER incidence rate, American Indian, All Ages

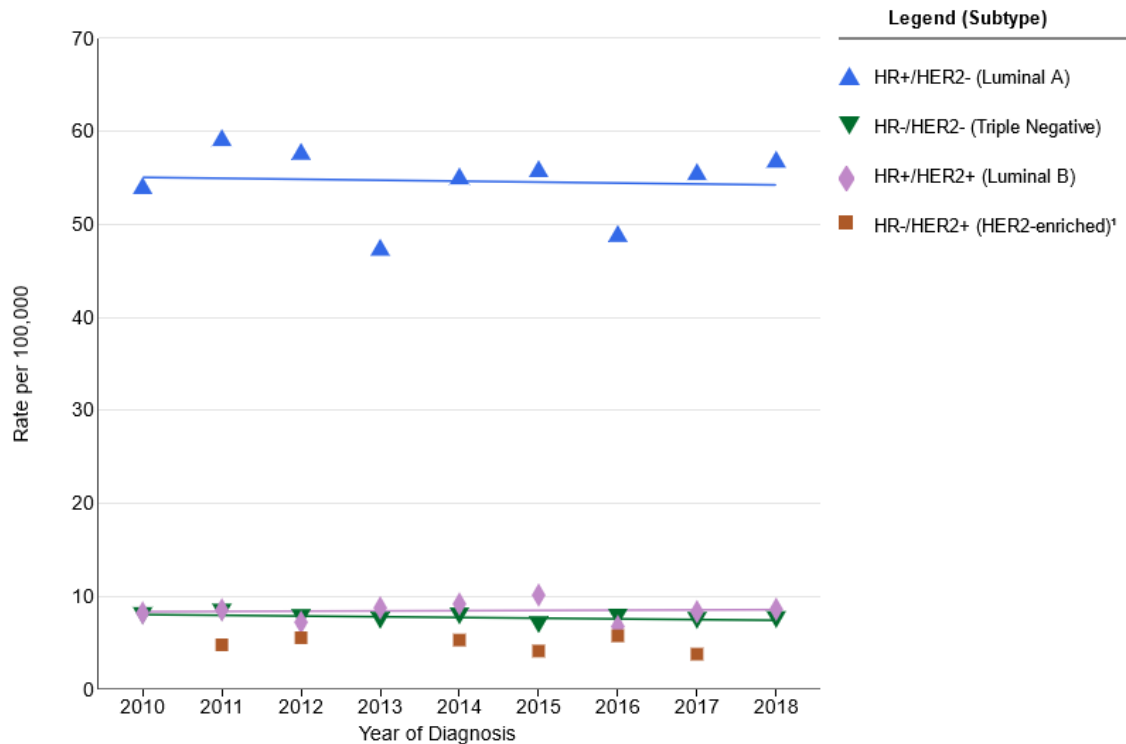


Figure 9 Breast cancer age-adjusted incidence rates, 2010-2018 by subtype, delay-adjusted SEER incidence rate, Asian/Pacific Islander, All Ages

#### Incidence rates by stage at diagnosis

**Figures 10– 14** show age-adjusted breast cancer incidence rates between 2004 and 2018. Across all racial groups, incidence rate for women with localized breast cancer increased more rapidly than women with regional, distant and unstaged breast cancer over time (**Figure 10**). Trends in breast cancer by subtype among White women were similar to trends across all racial groups (**Figure 11**). Incidence rates were highest among African American women with localized breast cancer with an increased trend over time. In 2017, among African American women with localized and regional breast cancer the incidence rate decreased. Distant and unstaged had the lowest breast cancer incidence. (**Figure 12**). Breast cancer incidence rates among Asian/Pacific Islander women by stage at diagnosis had similar trends compared to White women and overall (**Figure 13**). American Indian women with localized breast cancer has distinct fluctuations in incidence rates over time. This pattern is also observed among American Indian women with

regional breast cancer. Data for unstaged and distant stages were sparse and were difficult to interpret (**Figure 14**).

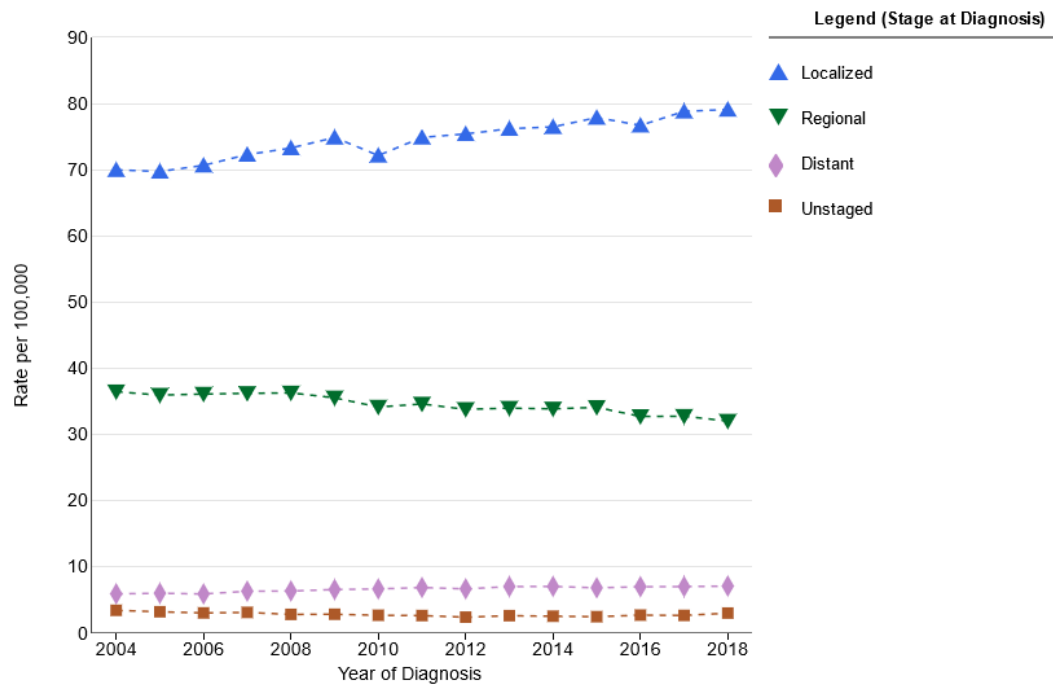


Figure 10 Breast cancer age-adjusted incidence rates, 2004 -2018 by Stage at Diagnosis, All Ages, All Races

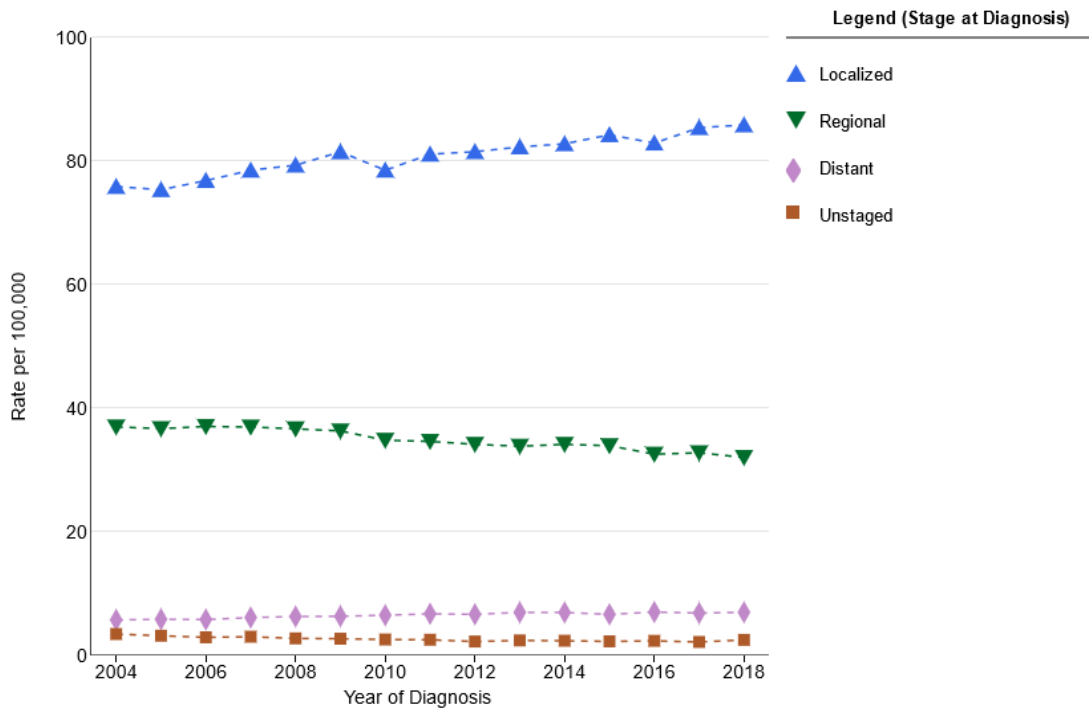


Figure 11 Breast cancer age-adjusted incidence rates, 2004-2018 by Stage at Diagnosis, All Ages, White

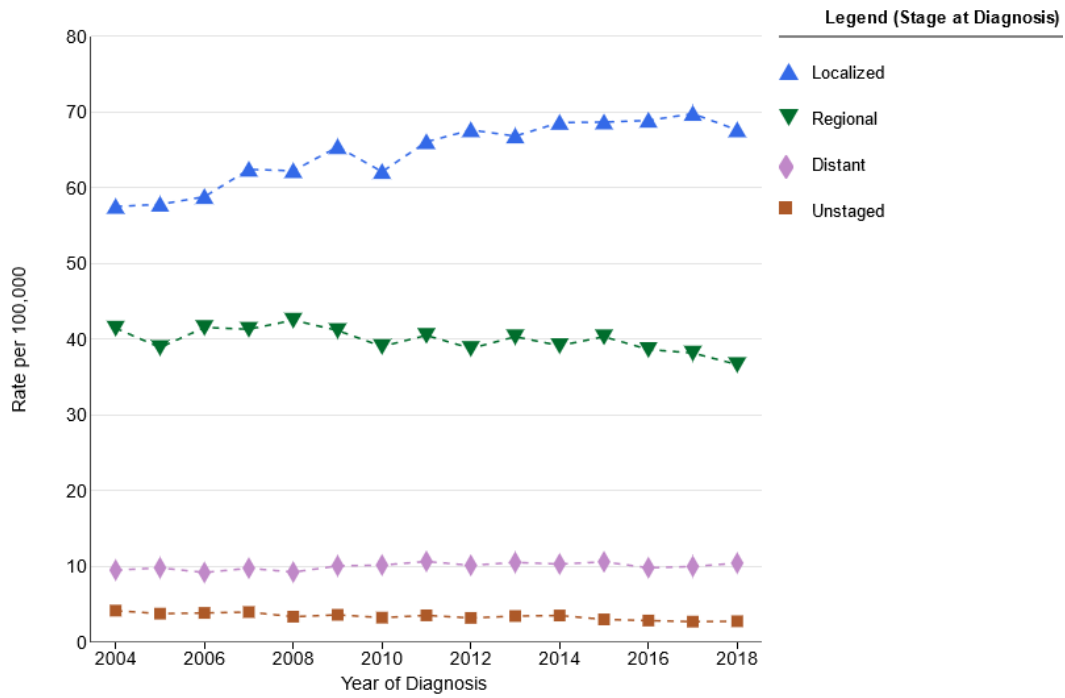


Figure 12 Breast cancer age-adjusted incidence rates, 2004-2018 by Stage at Diagnosis, All Ages, Black

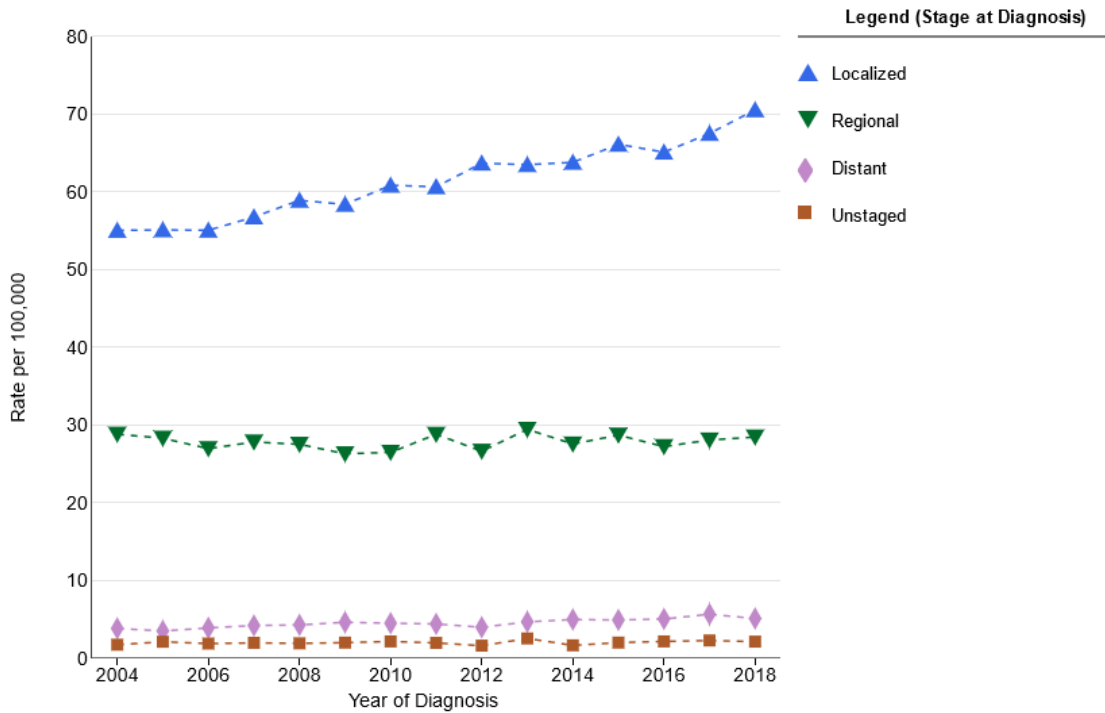


Figure 13 Breast cancer age-adjusted incidence rates, 2004-2018 by Stage at Diagnosis, All Ages, Asian Pacific Islander

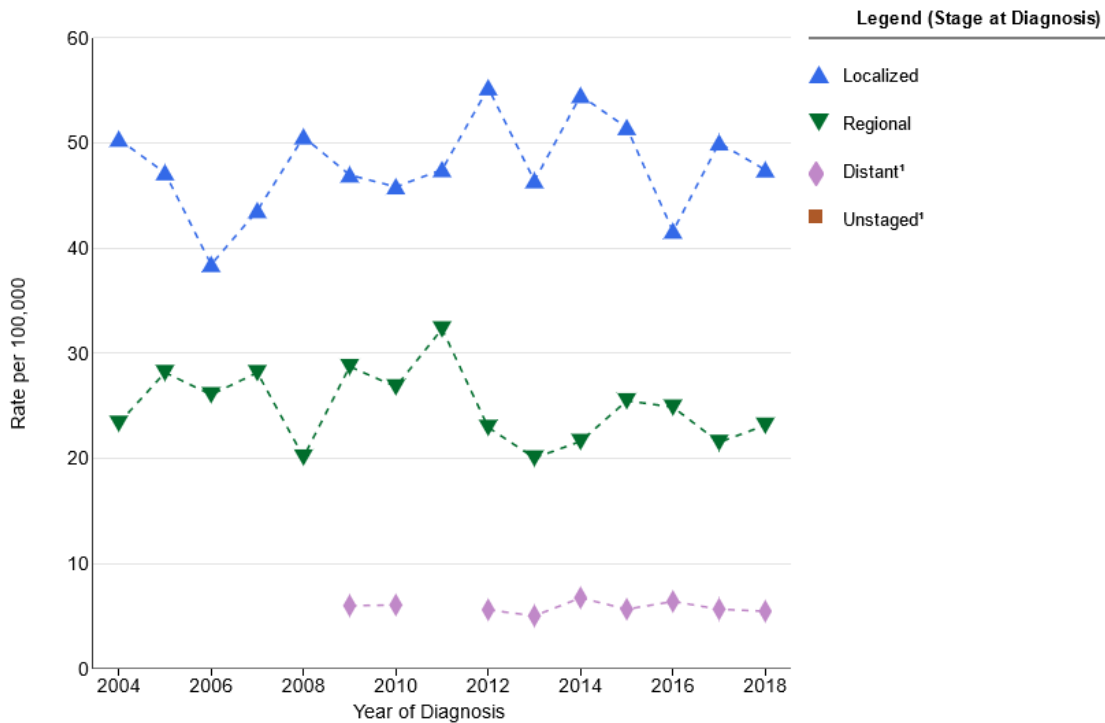


Figure 14 Breast cancer age-adjusted incidence rates, 2004-2018 by Stage at Diagnosis, All Ages, American Indian/Alaska

Breast cancer mortality rates

Incident cases of breast cancer have been gradually increasing over the last decade by about 0.5% per year, however death rates (mortality rates) have declined [72]. More specifically, mortality rates among racial and ethnic populations vary, with increased rates observed among African American women [73-75]. According to the SEER registry mortality data from 1993 through 1998, African American women had a two-fold higher risk, Latina women had a 30% higher risk and Asian Americans had a 10% reduced risk of death after breast cancer diagnosis compared to Non-Hispanic Whites [76]. The disparity in mortality rates between African American and White women has persisted since 2011. African American women have 40% higher mortality than White women [77]. While the incidence of breast cancer among women overall has increased and is highest among White women, mortality rates are disproportionately higher among African American and other racial and ethnic groups (American Indian and Alaska Native, Non-Hispanic, Asian and Pacific Islander and Hispanic) compared to White women [78]. The racial and

ethnic disparities in breast cancer still persists despite innovation and improvements in breast cancer screenings and treatment. The gap in survival rates between White and African American breast cancer survivors have remained constant for the last four decades [78].

Explanations for observed racial and ethnic disparities are complex but may include stage at breast cancer diagnosis and differences in tumor characteristics and aggressiveness. For some women, the stage at diagnosis may be related to inadequate screening and diagnostic services, differences in post-diagnosis care quality, individual and nSES and community infrastructure including healthcare-related facility access and proximity [79]. Additionally, the differences in tumor characteristics and histology may be linked to genetic susceptibility and tumor biology differences across racial and ethnic groups [80]. These existing disparities in breast cancer mortality pose a serious and critical need for further research regarding the contributing factors. It is important to strategize ways to reduce and eliminate these disparities, however the scope of this dissertation focused on breast cancer risk and therefore mortality was not described in detail.

Key risk factors for postmenopausal breast cancer

Risk factors for breast cancer can be classified as either “modifiable” and “non-modifiable.” Potentially modifiable risk factors are influenced by behavior such as alcohol use, smoking and physical activity [81]. Non-modifiable risk factors are determined and cannot be changed or altered such as a person’s age, biological sex and genetic profiles [82]. A summary of established and suspected potentially modifiable and non-modifiable factors for postmenopausal breast cancer is provided in **Table 2**.

Table 2 Non-modifiable and modifiable individual and behavioral		
Risk Factor	Direction of association	Reference
<b>Non-modifiable</b>		
Age	↑	[83]
Earlier age at menarche	↑	[84]

Risk Factor	Direction of association	Reference
Later age at menopause	↑	[85]
Increased Body height	↑	[86]
BRCA1/BRCA2 genetic carrier	↑	[87]
Breast density	↑	[88]
Family history of breast cancer	↑	[89]
Previous benign breast biopsy	↑	[90]
High polygenic risk score	↑	[91]
Nulliparous	↑	[92]
Younger age at first birth	↓	[93]
Breastfeeding	↓	[94]
<b>Modifiable</b>		
Increased alcohol consumption	↑	[95]
Obesity	↑	[96]
Menopausal hormone therapy	↑	[97]
Smoking status	↑	[45]
Physical activity	↓	[98]
Healthy diet	↓	[99]

Modifiable risk factors offer potential avenues for breast cancer risk reduction. Women who consume higher to moderate levels of alcohol have increased risk for breast cancer, across all racial and ethnic groups [100-105]. Higher body mass index (BMI), a measure of excess fat and a metric used to classify obesity [96, 106, 107], has been associated with increased postmenopausal breast cancer risk with variations in risk by menopausal status. With regards to breastfeeding and physical activity, both factors have consistently been inversely associated with breast cancer risk [94, 108]. Women with higher levels of circulating estradiol [109] and menopausal hormone therapy use [110] have an increased risk of breast cancer. Modifiable and some non-modifiable factors influence breast cancer risk via estrogen pathways [111]. The risk factors by race and ethnicity are discussed in section *Racial and ethnic disparities in breast cancer risk factors*.

### Molecular and hormonal factors of breast cancer

In terms of non-modifiable risk factors, breast cancer risk increases with age up until about age 70 years [60]. As an individual ages, the greater the likelihood of cell abnormalities and mutations occur which can then lead to the development of cancer [112]. Menstrual and reproductive health encompass important health events in a women's breast cancer risk profile. The younger a woman is at the initial start of her menstrual cycle (age at menarche) and the older she is at the start of menopause (the absence of a women's menstrual cycle for 12 consecutive months), the longer a woman's ovaries produce steroid hormones (estrogen and progesterone) which in turn leads to prolonged lifetime exposure to circulating steroid hormones which can increase the risk of breast cancer. It is likely that the alteration in risk from these events is mediated by changes in estrogen secretion and availability [111, 113, 114]. Body height may be an indicator of body growth and related to nutritional energy during childhood and associated with pre-puberty growth and may affect age at menarche [86].

The tumor suppressor genes, BRCA1 (BReast CAncer gene 1) and BRCA2 (BReast CAncer gene 2), produce proteins to assist DNA repair in the body. However, mutations in these genes have been most notably associated with increased risk of breast cancer and other types of cancer [115]. As women age, mammographic density decreases and involution of breast tissue increases; both are associated with breast cancer risk, but breast density has been shown to be a strong risk factor [116-118]. Women with a family history of breast cancer among direct relatives (mother, aunt, or sibling) have increased risk of breast cancer due to genetic profile similarities [89, 119]. Additionally, benign breast disease (BBD) or a previous benign breast biopsy may be an indicator of breast tissue overgrowth which is linked to increased risk for breast cancer [90]. Furthermore, there are personal, biological, cultural, religious, and societal factors that influence a women's decision to become pregnant, as well as biological factors that influence the age at which

a woman has her first birth. Women experience hormonal fluctuations and changes during pregnancy, birth and the post-partum period (and while breastfeeding) that affect breast growth and changes overtime [120].

### Circulating sex steroids

Sex steroids, such as estrogens (estradiol and estriol), have been associated with hormone-driven breast cancers [121]. Epidemiologic studies have shown that exposures to early age at menarche, delayed menopause and use of menopausal hormone therapy (MHT) may increase the risk of developing breast cancer and may be more evident in postmenopausal women due to increasing risk of adiposity with age [122]. Circulating sex hormone concentrations in postmenopausal women are strongly associated with several established or suspected risk factors for breast cancer and may mediate the effects of these factors on breast cancer.

The EPIC cohort conducted by Key et al. (2002) found a two-fold increased risk of breast cancer overall in postmenopausal women with concentrations of circulating estrogens and androgens [123]. Serum levels of total and bioavailable testosterone and estradiol were associated with risks of ER-positive, PR-positive, and joint ER+ PR+, as well as of ER-negative, PR-negative, and joint ER-PR- breast tumors. However, postmenopausal obesity was consistently associated with increased risk of hormone receptor-positive breast cancer versus hormone-receptor negative breast cancer, which may suggest increased estrogen synthesis in adipose tissue storage and greater bioavailability. Reproduction-related exposures were associated with increased risk of ER-positive, but not ER-negative tumors. Nulliparity and delayed childbearing were more consistently associated with increased breast cancer risk for ER-positive than ER-negative tumors, and early menarche was more consistently associated with ER-positive/PR-positive than ER-negative/PR-negative tumors [124, 125].

In premenopausal women, estrogen is produced in the granulosa cells of the ovary, the aromatase enzyme converts testosterone to estradiol and androstenedione to estrone. The follicle stimulating hormone levels regulates the ovarian production of estradiol. Premenopausal women experience cyclic fluctuations of circulating estradiol and progesterone through the menstrual cycle as oocytes, immature egg cells, mature and are released. In postmenopausal women, estrogen and progesterone secretion from the ovary declines and production of circulating estradiol continues in non-reproductive tissues such as the liver, heart, brain, muscle and bone, and adipose tissue [126]. Circulating estradiol remain low (10-60 pmol/l) and constant compared to levels in younger women (70 – 1500 pmol/l). In postmenopausal women, the adrenal production of androgens in adipose tissue to estrogen continues after menopause but declines with age [126].

#### Racial and ethnic disparities in breast cancer risk factors

The differences in breast cancer rates may be influenced by the varying prevalence of modifiable and non-modifiable risk factors by race and ethnicity. There are known breast cancer risk factors that vary by race and ethnicity which include: age at menarche, age at menopause, age at first childbirth, body weight, breastfeeding, number of childbirths and menopausal hormone therapy [127-134]. Age is the strongest breast cancer risk factor whereby incidence increases with age until about 70 years across all age groups. Particularly African American women under 45 years of age have higher breast cancer incidence than White women. The median age at diagnosis for African American women is 58 years and 62 years for White women. BMI has been shown to increase postmenopausal breast cancer among all women however, African American, Native Hawaiian and Latina women have a higher prevalence than White women[135]. With regards to lifetime estrogen exposure, a younger age at menarche and later age at menopause are associated with increased risk of breast cancer due to longer duration of exposure to circulating estrogen.

African American and Hispanic girls are more likely to be younger at menarche, whereas White and Asian girls are more likely to be older at menarche [128]. There are varying hormone concentrations at various stages of the menstrual cycle observed across race and ethnic groups of females. African American women have been shown to have higher follicular phase oestradiol concentrations compared to Latina and White women. African American women also have considerably higher levels of luteal phase oestradiol and progesterone compared to Latina and White women, which may suggest greater exposure to endogenous steroid hormones is more likely observed among young African American and Latina women compared to White women [130] and may increase breast cancer risk. African American and Latina women are more likely to have more children at a younger age and are less likely to breastfeed [136] which may contribute to increased risk of breast cancer. Asian women are more likely to use menopausal hormone therapy (MHT) [137] and African American women are more likely to use MHT and report lower quality of life whereas White women using MHT reported higher quality of life [138].

The genetic influence of family history of breast cancer is a well-established risk factor. Women with immediate relatives (i.e., mother or sister) or intermediate relatives (i.e., grandmother, aunt) with breast cancer have increased risk of developing breast cancer [139]. The BRCA1 and BRCA2 gene mutations are linked to most autosomal dominant inherited breast cancers due to DNA alterations that result in increased risk for developing cancer [63]. These mutations vary by race and ethnicity and are most prevalent among Hispanic women and least prevalent among Asian women [140].

In addition to the non-modifiable factors which vary by race and ethnicity, sociodemographic factors influence risk of breast cancer and prevention strategies at the neighborhood-level. Neighborhood attributes contribute to overall health and well-being and the

risk for developing breast cancer. Economic stability, poverty, education access and quality, healthcare access and quality, social and community context provide information on the collective effects that disproportionately affect women of racial and ethnic minorities compared to White women [129]. Typically, women who are low income have significantly lower rates of preventive screening for breast cancer, are more likely to be diagnosed at a later stage and often receive inadequate or disparate treatment, which may result in poorer survivorship outcomes for women of all races. Increased risk of breast cancer has also been observed among women with higher socioeconomic status and education level. This elevated risk has been attributed to increased alcohol consumption [103], fewer children [141], later age at first child [142], use of oral contraceptives [143] and use of menopausal hormone therapy [144]. Neighborhood socioeconomic status defined as area-based characteristics of education, income, poverty, occupation or composite index of multiple socioeconomic sociodemographic factors has been associated with breast cancer risk. More specifically, women residing in high SES neighborhoods areas have reported to have a two-fold increased risk of breast cancer risk compared to women living in low SES neighborhoods [145].

#### Overview of cardiometabolic risk factors

Cardiometabolic risk factors are influenced by a constellation of potentially modifiable factors including smoking, physical inactivity, and metabolic syndrome (MetS) [146]. According to the National Cholesterol Education Program's Adult Panel III, MetS is composed of six cardiometabolic risk factors that are related to cardiovascular disease (CVD): 1) abdominal obesity, 2) dyslipidemia, 3) insulin resistance and 4) elevated blood pressure, 5) proinflammatory state and 6) prothrombotic state [147]. The latter two are considered emerging metabolic risk factors compared to other definitions by the World Health Organization (WHO), European Group

for the Study of Insulin Resistance (EGIR) and International Diabetes Foundation (IDF).

Irrespective of the definition of MetS among these organizations, at least three of the following criteria must be met for an individual to be clinically diagnosed with MetS: insulin resistance or diabetes, increased waist circumference, increased fasting glucose, dyslipidemia, and hypertension [148].

Obesity and obesity-related disorders, as measured by excess weight particularly abdominal fat and waist circumference, are associated with physical inactivity and an atherogenic diet, high in cholesterol, saturated fats, trans fats and salt, and contributes to CVD and cardiometabolic risk factors [147]. Among the common MetS cardiometabolic risk factors, hypertension is the most prevalent. **Table 3** shows defining thresholds for the main cardiometabolic risk factors. Guidelines from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommend a blood pressure (BP) goal of <140/90 mm Hg for most women and <130/80 mm Hg for patients with diabetes and/or chronic kidney disease. Abdominal obesity, the strongest factor associated with metabolic syndrome, is commonly measured using waist circumference. Studies have shown the presence of abdominal obesity is more correlated with the metabolic risk factors than high BMI (>30 kg/m<sup>2</sup>) [147]

Table 3 Defining cardiometabolic risk factors

Cardiometabolic Risk Factors	Threshold Definition
Hypertension	≥130/≥85 mmHg
Elevated blood glucose	≥110 mg/dL
High-density lipoprotein cholesterol	< 50 mg/dL
Triglycerides	<50 mg/dL
Abdominal obesity	>35 in

MetS has three potential etiological categories: obesity and obesity-related conditions, insulin resistance and dyslipidemia. The obesity epidemic largely contributes to the increasing prevalence of MetS. Using a population sample of 17,048 adults from the National Health and Nutrition Examination Survey (NHANES), in 2011 - 2012 the prevalence of MetS was 32.5% (95% CI:29.0 – 36.2) and increased to 36.9% (95% CI: 33.9 – 39.9) in 2015 – 2016 [21]. Obesity increases the risk of developing CVD two-fold among individuals with MetS compared to individuals without MetS [149]. Insulin resistance is characterized by having an elevated level of insulin concentration and abnormally high blood glucose levels. Changes in receptor binding or post receptor mechanisms may contribute to the existence of insulin resistance and has been linked to impaired glucose, diabetes and risk of CVD [150].

#### Epidemiology of cardiometabolic risk factors by race and ethnicity

Studies have examined cardiometabolic risk factors associated with breast cancer to understand the underlying mechanisms contributing to disparities in risk, prognosis and survival. Race and ethnicity are social constructs used to group individuals based on their inherited physical characteristics and is a principal factor to understand in the complex matrix of breast cancer etiology. In cross-sectional analyses using the National Health and Nutrition Examination Survey between 1988 to 2012, Moore et al (2017) observed higher prevalence of cardiometabolic risk factors or MetS among non-Hispanic African American and Mexican American women. These women also had 20% greater odds of developing MetS than non-Hispanic White women [20].

Overall, Non-Hispanic African American adults have the highest prevalence of cardiovascular disease (57.1%) followed by Hispanic (43.7%) and non-Hispanic White (43.6%) adults [151]. Native Hawaiians have a 10% greater likelihood of being diagnosed with cardiovascular disease and a 68% greater likelihood of being diagnosed with coronary heart

disease compared to the general population [152]. The prevalence of obesity and overweight has emerged as a critical public health epidemic. Over, 71% of American adults were classified with overweight or obesity ( $\geq 25$  kg/m<sup>2</sup> and  $\geq 30$  kg/m<sup>2</sup>) and the prevalence is disproportionately affecting racial and ethnic minorities: Native Hawaiian (49%) [152], Non-Hispanic African American (44.8%), Hispanic (44.8%), Non-Hispanic Whites (42.1%) and Asian (17.4%) adults [151, 153]. Similarly, the prevalence of diabetes among adults are higher among non-Hispanic African Americans (16.4%) Asian (14.9%), Hispanic (14.7%) and Non-Hispanic White (11.9%) adults [154].

At the neighborhood-level, the influence of the neighborhood environment is a key indicator of overall health and is correlated with individual health and health outcomes [33]. African American women are more likely to reside in neighborhoods with lower socioeconomic status or impoverished neighborhoods compared to White women [155]. Due to the impacts of geographical demarcation of boundaries and racial segregation, African American and other racial and ethnic minoritized groups have resulted in concentrated poverty [155]. Neighborhood socioeconomic status has been linked to cardiometabolic risk factors through mechanistic pathways of obesity [30], and inflammation [156].

#### Epidemiology of cardiometabolic risk factors and breast cancer risk

Cardiometabolic risk factors have been examined in relation to postmenopausal breast cancer [157]. A meta-analysis conducted among 50 studies, 15 cohort studies involving 214,203 subjects and 3,414,806 person years, and 35 case-control studies involving 71,216 subjects [157], assessed the association between BMI and breast cancer risk. Although there was a null association between BMI and risk of breast cancer among premenopausal women, among postmenopausal

women who were overweight or obese the risk of developing breast cancer increased 20% compared to women who were not overweight and obese [157].

Zhoa et al (2020) conducted a recent systematic review and meta-analysis of 25 studies (14 cohort and 11 case-control) examining the association of MetS and breast cancer risk between 1992 and 2012 with sample sizes ranging from n=129 to n=94,555. Population samples were recruited from cohort and case-control studies in United States, China, Japan, Korea, Italy, Netherlands, France, Israel, Brazil, Uruguay and Canada. The overall risk for breast cancer increased 49% among adult women with MetS (relative risk = 1.49, 95% CI: 1.31 – 1.70, p< 0.0001). The racial and ethnic composition of the samples were not stated although country was identified. Recent studies have shown patients diagnosed with MetS are more likely to develop cardiovascular disease overall and by race. Three studies examining the relationship between MetS and breast cancer types found null associations, which was likely attributed to small sample sizes used in these studies. In terms of the relationship between MetS and breast cancer risk by menopausal status, three studies found null associations among premenopausal women, and of nine studies that examined this association among postmenopausal women, eight studies showed a two-fold risk in breast cancer among women with breast cancer [27].

Zhoa et al (2020) also examined the association between the individual components of MetS: BMI >24 kg/m<sup>2</sup> or obesity, higher waist circumference, high triglycerides, low high-density lipoprotein, high blood pressure and high fasting blood glucose and diabetes and breast cancer. Across cohort and case-control studies, BMI (n=9), high blood pressure (n=14) and high fasting blood glucose (n=10) were positively associated with breast cancer, while studies examining higher waist circumference (n=7) and higher triglycerides (n=10) were not associated with breast cancer. These study findings do not support prior studies that have shown a positive association

between abdominal obesity and breast cancer. Therefore, the level of heterogeneity across studies and a portion of the studies with small samples size were considered limitations and may have impacted studies results in the meta-analysis.

### Specific cardiometabolic risk factors

The following sub-sections describe the main individual and neighborhood-level factors examined in each specific aim of the dissertation. Sub-section describes cholesterol-lowering drug classifications, pharmacokinetics, biological mechanisms that lead to cholesterol-related health issues and conditions, prevalence of cholesterol-lowering drug use in the United States, relevant study findings and current gaps. Sub-section describes healthy lifestyle factors, specifically dietary intake, physical activity and sedentary behavior, obesity measured by BMI, smoking status, alcohol consumption and sleep, and independent associations with breast cancer. This section focuses on highlighting the current literature to elucidate current gaps related to understanding the association of independent and collective healthy lifestyle factors and breast cancer. Section describes the association between neighborhood socioeconomic status and inflammatory biomarkers (CRP, adiponectin and leptin) among adults.

### Cholesterol-lowering drugs: medication use

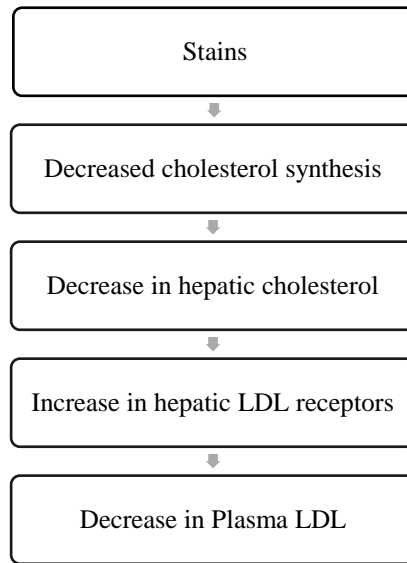
#### *Cholesterol-lowering drug classifications*

There are currently eight different cholesterol-lowering drugs classes: 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) inhibitor (statins), proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) inhibitors, fibric acid derivatives (fibrates), bile acid sequestrants (bile acid resins), nicotinic acid (niacin), selective cholesterol absorption inhibitors, Omega 3 fatty acids and fatty acid esters, and adenosine triphosphate-citrate lyase (ACL) inhibitors. Of these, statins are most commonly prescribed to treat lipid disorders and

to significantly lower low-density lipoprotein (LDL) levels by inhibiting HMG-CoA reductase activity which in turn decreases hepatic cholesterol levels. This process leads to an up-regulation of hepatic LDL receptors which results in uptake of LDL and clearance from the blood stream.[158] Statins also effectively reduce adverse cardiovascular disease outcomes such as stroke and CVD mortality [159].

Statins have been the most efficient agent for reducing plasma cholesterol associated with hypercholesterolemia. The dissertation focused on cholesterol lowering drug use of which statins are the most commonly prescribed. In the United States, there are currently seven HMG-CoA reductase inhibitors (statins) approved for lowering cholesterol: lovastatin, simvastatin, pravastatin, atorvastatin, rosuvastatin, fluvastatin and pitavastatin. The recommended statin prescribed depends on the patient's needs and potential for drug-drug interactions and allergies. Statins have different pharmacokinetic properties, which refers to the time course of absorption, distribution, metabolism and excretion (ADME) of a drug, compound or new chemical entity (NCE) after being administered into the body [160]. Pravastatin and rosuvastatin are the only statins that are hydrophilic (dissolve in water), while most other statins are lipophilic (dissolve in lipids).

Figure 15 Mechanisms for the decrease in LDL Levels using statin



**Figure 15** shows the primary mechanisms that decrease LDL levels [161]. Statins inhibit HMG-CoA reductase when administered in the bloodstream, which leads to decreased cholesterol synthesis in the liver and a decrease in cholesterol in the endoplasmic reticulum. This process results in sterol regulatory element binding proteins (SREBPs) to move from the endoplasmic reticulum to the Golgi where they are cleaved by proteases into active transcription factors [162]. The SREBPs then translocate to the nucleus where they increase the expression of several genes including HMG-CoA reductase and, most importantly, the LDL receptor [162]. The increased expression of HMG-CoA reductase restores hepatic cholesterol synthesis towards normal while the increased expression of the LDL receptor result in a greater number of LDL receptors on the plasma membrane of hepatocytes; this leads to increased clearance of LDL accounts for the reduction in plasma LDL-C and triglyceride levels [162].

For statins, the target organ is the liver. Liver metabolism varies by statin types as some statins have relatively high dose retention by the liver: >80% simvastatin, >70% fluvastatin and lovastatin, and 46% pravastatin, and others may have relatively low circulating concentrations: 5%

for simvastatin and lovastatin, 20-30% for fluvastatin, 17% for pravastatin, and 12% for atorvastatin. Cerivastatin has a higher circulating concentration compared to other statins [163].

In general statins have been shown to reduce LDL cholesterol by 10% with a daily dose of 1mg and have demonstrated a dose-efficacy. Lovastatin, simvastatin, atorvastatin and rosuvastatin have been shown to reduce LDL-C level by 30% - 70% with a dose range of 10-80 mg daily. [164] All statins reduce triglycerides relative to the triglyceride baseline. The apolipoprotein B (apo B) represents a key structural component of the lipoprotein particles which include LDL, very-low density lipoproteins (VLDL), and intermediate-density lipoproteins (IDL) [165]. Each of these particles carries an apo B molecule, and as a clinical marker of cardiovascular events, measures the total apo B level that represent the total circulating lipoprotein particles at a given time [166]. LDL-C, HDL-C, apo B levels decrease when using statins and triglycerides also decrease relative to the baseline comparison. A summary of prospective randomized statin trials in primary prevention studies describing the study type, type of statin, study design and study outcome is shown in **Appendix A Table A-1** [167]

#### *Cholesterol-lowering drugs: prevalence and biological mechanisms*

In the United States, there are nearly 43.3 million adults currently taking cholesterol-lowering drugs according to a 2005 – 2012 National Health and Nutrition Examination Survey (NHANES). Women were more likely to use cholesterol-lowering drugs compared to men and cholesterol-lowering drug use was more prevalent among non-Hispanic Whites than non-Hispanic African Americans and Mexican Americans. Adults with reportedly healthier diet and exercise also had the highest percentage of cholesterol-lowering drug use [168]. Dyslipidemia, abnormal cholesterol levels in the blood, is an established risk factor for cardiovascular disease and a common comorbidity among individuals with diabetes, obesity and other chronic disease like

cancer [169]. Among the MetS conditions, obesity has been strongly associated with breast cancer risk among postmenopausal women[170].

A typical obese individual with dyslipidemia would present with abnormal levels of the established clinical measures such as increased triglycerides and free fatty acids, increased LDL-C and decreased HDL-C, and increased concentration of plasma apo B [9]. Cholesterol binds to LDL-C and HDL-C and travels in the bloodstream throughout the body. Cholesterol circulating in the blood is absorbed and metabolized by the liver, which is then expelled from the body [171]. Studies have shown conflicting results that suggest null [172-174] and inverse associations [175] between total cholesterol and breast cancer risk. Differences in study design, methodology, sample size, follow-up duration and confounding factors considered may contribute to these differences in findings with total cholesterol. Further research is needed to expand the knowledge and evidence in the field.

Cholesterol-lowering drugs, namely statins (3-hydroxy 3-methylglutaryl Coenzyme A (HMG – CoA) reductase inhibitors) are commonly prescribed to individuals with hypertension and diabetes. Hypertension is a potentially modifiable risk factor of cardiovascular disease and has been associated with atherosclerosis in middle-aged adults. Hypertension also increases the likelihood of later in life CVD events [176]. As increased risk of CVD outcomes in adulthood occur, the risk for other chronic diseases and conditions increases with age. Diabetes mellitus (DM) is a metabolic disorder that occurs as a result of decreased insulin activity or insulin secretion. DM is categorized into two main subtypes: type I and type II. Type I DM is most commonly treated with insulin replacement therapy and is a result of genetic abnormalities. Type II DM is often treated with lifestyle changes such as diet and exercise in combination with oral hypoglycemics [177]. Individuals diagnosed with these chronic conditions may be suitable

candidates for disease management and drug therapy to prevent future CVD-related and DM health outcomes and may have a more complex health risk profile compared to individual not taking cholesterol-lowering drugs in relation to breast cancer.

Lipid metabolism affects synthesis of membranes and contribution of lipids to energy homeostasis and activation of inflammation-related pathways. Statins inhibit HMG-CoA reductase expression, which has been observed in breast cancer tumors, and may lead to apoptosis and inhibition of tumorigenesis in breast cancer. HMG-CoA is a key enzyme in the mevalonate pathway. Statins block the conversion of HMG-CoA to mevalonic acid which leads to a reduction in hepatic cholesterol synthesis and in turn increases the production of microsomal HMG-CoA reductase and LDL receptor expression. This biological process aids in the clearance of LDL-C from the bloodstream and subsequently reduces circulating LDL-C levels and had been shown to reduce the risk of cardiovascular related events and chronic disease such as dyslipidemia [178] .

*Cholesterol-lowering drugs and breast cancer risk: existing knowledge and gaps*

Cholesterol-lowering drugs have been shown to exhibit anticancer properties, however inconsistent associations between cholesterol-lowering drugs and breast cancer risk have been observed and limited research has examined these associations among postmenopausal women by race and ethnicity.

Eight epidemiological studies published between 2006 and 2017 examined statin use and breast cancer risk shown in **Table 5**. Of the eight studies, there were four cohorts [192, 193,194, 198], three systematic reviews [179-182], and one case-control study [183]. The sample size for the cohort studies ranged from 14,773 to 154,587 across multiple countries and were composed primarily of European and predominantly White women. Of the four cohort studies, three studies [193, 194, 198] found null associations between cholesterol-lowering drug use and breast cancer

risk, while one study found cholesterol-lowering drug use reduces the risk of breast cancer recurrence [184]. Islam et al. [180] conducted a review comprised of 36 epidemiological studies (11 prospective cohort, 16 case-control and nine randomized control trials) which examined the association between statin use and breast cancer risk. Despite relatively large sample populations (ranging from n=189 to n = 269,836) representing four continental regions, the results of this meta-analysis suggest statin use has no association with breast cancer risk. However, the reported findings did not stratify by menopausal status, a known effect modifier of breast cancer risk. The findings from Islam et al (2017) are listed below in Table 4.

Table 4 Epidemiologic studies included in Islam et al (2017) systematic review of cholesterol-lowering drugs and breast cancer risk [180]

<b>Study Characteristics</b>	<b>Number of studies</b>	<b>Pooled estimates</b>
<b>All studies</b>	36	0.94 (0.86–1.03)
<b>Case-control</b>	16	0.87 (0.73–1.05)
<b>Cohort</b>	11	1.0 (0.96–1.05)
<b>Randomized control trial</b>	9	1.04 (0.78–1.38)
<b>Region</b>		
<b>North America</b>	21	0.92 (0.84–1.02)
<b>Europe</b>	9	1.01 (0.97–1.05)
<b>Asia</b>	5	0.85 (0.48–1.52)
<b>Oceania</b>	1	1.13 (0.44–2.92)
<b>Duration of statin therapy</b>		
<b>&lt; 5 years</b>	8	0.94 (0.70–1.28)
<b>&gt; 5 years</b>	8	0.74 (0.52–1.04)
<b>Individual statin use</b>		
<b>Atorvastatin</b>	7	1.06 (0.95–1.18)
<b>Simvastatin</b>	10	0.90 (0.80–1.01)
<b>Pravastatin</b>	10	1.02 (0.92–1.12)
<b>Lovastatin</b>	5	0.88 (0.67–1.15)
<b>Fluvastatin</b>	5	0.84 (0.62–1.14)

The existing studies assessing cholesterol-lowering drugs and breast cancer risk have focused on study populations comprised of predominately White participants and have not consider multiethnic populations of postmenopausal women and the measurement of cholesterol-lowering drug use has not examined the combination of cholesterol-lowering drugs as duration of

use by each status type (former user and duration of use and current user and duration of use). Moreover, the differences in hormone receptor status may influence the hormonal and biological pathways in the presence of cholesterol-lowering drug use and may vary by duration of use. To date, only one study has examined cholesterol-lowering drug use and breast cancer risk by hormone receptor type. A summary of previous epidemiological studies examining cholesterol-lowering drug use and breast cancer risk are included in **Table 5**.

Table 5 Summary of epidemiological studies examining cholesterol-lowering drug use and breast cancer risk

<i>Author, Year</i>	<b>Study Population</b>	<b>Exposure Outcome</b>	<b>Participant Characteristics</b>	<b>Race/Ethnicity (Nationality)</b>	<b>Outcomes (Findings)</b>
[179] <i>Islam, 2017</i>	Published articles between 2003 and 2016  Systematic review and Meta-analysis  n = 36 studies	Statin therapy  Breast cancer risk	Adult women	North America (n=21), Europe (n=9), Asia (n=5) and Oceania (n=1)	The results from the meta-analysis suggest there is no association between statin use and breast cancer risk.
[185] <i>Borgquist, 2016</i>	Nurse's Health Study  n = 79,518 823,086 person-years of follow-up  3,055 cases of invasive breast cancer	Statin use  Breast cancer risk	U.S. registered nurses ages 30 to 55	United States Predominately	Statin use was not associated with risk of invasive breast cancer, irrespective of histologic subtype and ER status.
<i>Qu et al [182]</i>	Systematic review and Meta-analysis  n = 34 studies	Statin use  Breast cancer risk	Adult women	North America (n=22), Europe (n=9), Asia (n=2) and Oceania (n=1)	No significant association was observed in the relationship between statin use and breast cancer risk. Statin use may be associated with decrease mortality of breast cancer patients.
[186] <i>Desai, 2013</i>	Women's Health Initiative (WHI) cohort from 1993 to 1998  n = 154,587 7,430 breast cancer cases	Statin use (self-reported, verified with prescription medications and matched to the Master Drug Database (First Databank, Inc)  Breast cancer case (confirmed by medical record review)	Postmenopausal women ages 50 to 79 years	Race not stated.  United States	Findings from the WHI suggest no general association between statin use and breast cancer risk, and no association with simvastatin or lipophilic statins and breast cancer risk. Conversely, results showed a modest protective effect associated with statin use less than 1-year duration compared to multiple years.
[187] <i>Jacobs, 2011</i>	Cancer Prevention Study-II Nutrition Cohort	Statin use (self-reported; never, former, current <5	Predominantly White and over age 60.	United States	Long term use of cholesterol-lowering drugs was not associated with breast cancer,

<i>Author, Year</i>	<b>Study Population</b>	<b>Exposure Outcome</b>	<b>Participant Characteristics</b>	<b>Race/Ethnicity (Nationality)</b>	<b>Outcomes (Findings)</b>
	Recruitment from 1992 to 1993 N= 60,059 (men) N= 73,196 (women)	years, current > 5 years) Breast cancer			among other cancers such as prostate, colorectal, lung bladder, pancreatic or renal cell cancer.
<i>[183] Eaton, 2009</i>	North Dakota Cancer Registry Case-control study n= 189 95 Cases diagnosed between 2005 and 2008 North Dakota	Statin use (self-report) Breast cancer risk (histologically confirmed as primary site)	51 – 81 years old Overweight or Obese postmenopausal women who had never used HRT	95% White North Dakota	Findings suggest no association between statin use and breast cancer risk. Consistent with two other observational studies, this study showed an increased risk of breast cancer among overweight women who used statins for 4 years or less and progesterone receptor tumors among obese statin users compared to non-users.
<i>[188] Cauley, 2006</i>	Multi-site (40 clinical centers) Women’s Health Initiative recruitment was conducted between October 1,1993 and December 31, 1998. N=88, 322 women (observational study) N = 68 029 women (clinical trials) Total N=156 351 women	Potency, duration and type of statin use Breast cancer risk Secondary study Other lipid-lowering agents Breast cancer	Postmenopausal women between 50-79 years old	>81% White United States >44% of women between 60-69 years old	Overall, statins considered together as a class, were not significantly associated with breast cancer incidence. However, women who have ever used hydrophobic statins were associated with lower breast cancer incidence.

## Healthy lifestyle factors: independent associations with breast cancer

### Dietary intake

Dietary intake has long been studied in relation to breast cancer, however, inconsistent findings suggest further research is needed to elucidate the association between diet and breast cancer risk. A systematic literature review composed of 185 epidemiological and pre-clinical studies focused on food, nutrients, and breast cancer risk [189]. Consumption of carbohydrates, saturated fats, and red and processed meats increase circulating levels of endogenous estrogen, insulin-like growth factor (IGF)-1 and pro-inflammatory cytokines which may increase the risk of breast cancer. In contrast, consumption of fruits and vegetables have been shown to increase dietary exposure to fiber,  $\omega$ -3 poly unsaturated fatty acids (PUFAs), vitamins C and E, and thus, may reduce oxidative stress and lower chronic inflammation [190]. However, a review of 15 prospective studies examining fruit and vegetable intake and breast cancer risk found weak associations [191]. Additional studies found an inverse association among an Italian cohort in relation to breast cancer risk [192], and among 75, 929 postmenopausal women 38 to 63 years old [193]. The existing findings are inconsistent and suggest additional research is needed to understand the association between fruit and vegetable intake and breast cancer.

A meta-analysis of 17 prospective studies found unprocessed red meat and processed meat consumption were positively associated increased breast cancer risk [194]. Moreover, a cohort composed of 262,195 women in the United Kingdom found processed meat was positively associated with increased risk of breast cancer overall and among postmenopausal women, but not premenopausal women. However, red meat consumption was not associated with breast cancer risk [195]. The Women's Health Initiative conducted one of the largest randomized controlled trials composed of 48,835 postmenopausal women to examine dietary

fat intake and breast cancer risk. Study findings suggest a low-fat diet may suggest the risk of reducing breast cancer although the results were not statistically significant [196]. In addition, a meta-analysis study found increased risk of breast cancer among postmenopausal women who have diets high in total fat and polyunsaturated fats [197].

The association between intake of total carbohydrates or carbohydrates including total sugars or specific sugars, and breast cancer risk is inconsistent, and studies have yielded mixed findings. In a recent meta-analysis [198], null associations were found between glycemic index and breast cancer risk among premenopausal and postmenopausal women. In addition, majority of studies found that carbohydrate intake is not related to increased breast cancer risk in pre- or postmenopausal women. However, stratification by hormonal receptor status yields a positive association for women with ER- and/or PR- breast cancer tumors [198]. More research is needed to understand the association and the modifying effect of hormone receptor status, although current findings suggest there is no association between carbohydrate intake and glycemic intake and breast cancer risk overall.

Dietary intake is complex and challenging to measure within epidemiological studies and requires a comprehensive assessment of diet to yield an accurate representation of an individual's diet. Despite these challenges, dietary indices, and validated assessments [199, 200] have been developed to increase the validity of these measures, however given the existing study findings, results are inconsistent and more research is needed, especially among ethnic/racial populations.

#### Physical activity and body mass index

Studies of physical activity have consistently supported reductions in breast cancer risk [35, 201] and recurrence [202] along with improvements in survival [203]. The

American Cancer Society recommends 150 to 300 minutes of moderate-intensity physical activity per week or 75 to 150 minutes of vigorous-intensity physical activity. Limiting sedentary behavior, such as sitting, lying down, and watching television, and other forms of screen-based entertainment is also recommended.

Two systematic reviews, one conducted by Friedenrich et al. summarizing 24 cohort and 56 case-control studies [201] and another review by Renehan et al. summarizing 31 prospective studies [204], suggest there are positive associations between BMI and breast cancer risk [204]. In addition, Freidenrich et al observed a reduction in breast cancer risk among women who reported higher physical activity. Obesity has a well-established association with breast cancer risk, however depending on a women's menopausal status, the influence of BMI on breast cancer risk varies [205]. Epidemiologic evidence supports reduced risk of breast cancer among premenopausal women who have higher BMI [206]. African American women are more likely to have a higher BMI and more likely to be diagnosed with premenopausal breast cancer [207]. Among postmenopausal women, overweight or obesity have been associated with an increased risk of breast cancer [96, 208]. These associations also vary by race and ethnicity. In postmenopausal women, the prominent origin of estrogen production is derived from adipose tissue. As a woman ages, the risk for obesity increases and in menopause, this can lead to greater levels of estrogen and pro-tumorigenic effects [209].

### Smoking status

In the United States, cigarette smoking is the leading cause of preventable disease and death, despite a decline in the prevalence of current smokers over the past several decades [210, 211]. In 2018, the prevalence of current smoking was 13.7%; however the use of

electronic, combustible and noncombustible tobacco products is more widespread in the United states [212]. According to the 2019 National Health Interview Survey (NHIS), 50.6 million adults (20.8%) reported using any type of tobacco product [213]. Cigarette smoking has well-documented systemic health effects due to the circulating tobacco carcinogens such as polycyclic aromatic hydrocarbons, aromatic amines and N-nitrosamines found in blood of current smokers [214]; Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic class of chemicals naturally occurring in crude oil, coal and gasoline, and also produced when these elements as well as garbage, wood and tobacco are burned [215]. Tobacco smokers are exposed to PAHs by inhaling the tobacco smoke into their lungs and absorbed into the skin. Tobacco carcinogens have been used as biomarkers to understand the mechanisms of tobacco-related diseases and induced cancers [214, 216]. These toxic carcinogens have also been found in mammary tissue where the mammary epithelial cells metabolize and activate these compounds that lead to DNA damage within the breast cells [217].

In terms of the mechanisms of breast cancer, tobacco use has been shown to increase the frequency of p53 gene mutations in breast tumors to proportionally similar levels found in individuals with lung cancer [218]. Tobacco smoking is a well-established risk factor for cancers including lung [219], head and neck [220] and bladder [221]. However, study findings of the association between tobacco smoking and breast cancer have been inconsistent [37, 45, 47, 222-225].

A previous MEC study examined smoking and breast cancer risk by race/ethnicity and estrogen and progesterone receptor status in 67,313 women, ages 45-75 years old with a mean follow-up of 16.7 years. Smoking status was similar across racial and ethnic groups

and by ER and PR status and increased risk of breast cancer [45]. A meta-analysis comprised of seventy-five studies (31 prospective, 44 case– control) investigated the association between active smoking and breast cancer risk, and 31 studies (11 prospective and 20 retrospective) investigated the association between exposure to passive smoking and breast cancer incidence (some studies reported data on both types of exposure). Active smoking is defined as inhaling tobacco smoke directly from the end of a cigarette and passive smoking is defined as secondhand smoke , when an individual inhales smoke produced from an active tobacco cigarette, and tertiary hand smoking, when an individual inhales or is exposed to residual debris and smoke embedded within clothing or porous surfaces that absorb tobacco smoke[226] The results suggest active cigarette smoking is associated with increased risk of breast cancer among prospective and retrospective studies, and were stable across subgroups (childhood, household and occupation exposures, nationality, and menopausal status) when adjusted for alcohol consumption [227].

Three large prospective cohorts: the Nurses’ Health Study, the Women’s Health Initiative Observational Study [228] and the Cancer Prevention Study II Nutrition Cohort [43] examined the relationship between tobacco use and breast cancer risk and found a relatively consistent positive association observed in women who initiate smoking at a younger age [47], or who smoke for a long time prior to their first pregnancy [229] [224]. Given previous study findings, it is important to consider smoking as a lifestyle factor in the healthy lifestyle index in relation to breast cancer risk, especially among groups.

#### Alcohol consumption

In the United States, a standard drink of alcohol consists of 0.6 ounces or commonly consumed as 12-ounces of beer (5% alcohol content), 8-ounces of malt liquor (7% alcohol

content), 5-ounces of wine (12% alcohol content) or 1.5-ounces of 80-proof (40% alcohol content) [230]. The Dietary Guidelines for Americans recommends adults  $\leq 2$  drinks for men and  $\leq 1$  drink for women per day. Excessive and heavy drinking exceed these guidelines and increase the risk of immediate harmful health conditions that can lead to long-term health risks that include cardiovascular disease [231], cancer [232-234], weakened immune system [235-238], mental health issues [239, 240] and alcohol use disorders [241-243].

Alcohol consumption has been shown to promote mammary tumor growth [244] and insulin sensitivity [245] via hereditary and genetic factors that include family history of breast cancer and inherited BRCA1, BRCA2 and other breast cancer susceptibility gene mutations. A meta-analysis of 22 cohort studies identified between 1992 and 2017 examining alcohol consumption and breast cancer encompassed a total of 45,350 breast cancer cases. In support of previous studies and meta-analyses of epidemiological studies, found a positive dose-response association between total alcohol intake and breast cancer incidence. An increase of 20g of total alcohol increased the relative risk of breast cancer among all women and a relatively larger increase specifically among postmenopausal women [246]. However, a more recent meta-analysis evaluated 97 epidemiological studies (59 cohort and 38 case-control), published between 1984 and 2012, that examined the relationship between alcohol consumption and breast cancer. The majority of the study findings reported risk for broadly defined alcohol consumption and breast cancer associations: 85 (87.6%) reported both harmful and protective relative risk estimates, 11 (11.3%) reported only harmful estimates, but only one study (1.0%) reported protective effects [247]. Despite previous research that suggests alcohol consumption increases the risk

of breast cancer, additional research is needed to understand this relationship, namely in ethnic/racial populations.

Healthy Lifestyle Index: existing knowledge and gaps

According to the American Cancer Society diet and physical activity guidelines for cancer prevention and the U.S. Surgeon General’s report on smoking, a healthy lifestyle for overall health and well-being and to reduce the risk of breast cancer includes: 1) regular physical activity; 2) maintaining a healthy weight; 3) consuming a variety of vegetables and fruits, whole grains and good fats with limited red meat and processed meat, sugar-sweetened beverages and highly processed foods; 4) avoiding alcohol; and 5) never smoking or quitting smoking [248] (shown in **Figure 16**). The association between the listed lifestyle factors and breast cancer have been examined in previous studies, however, more information is needed to elucidate the collective impact on breast cancer risk in racial and ethnic groups.

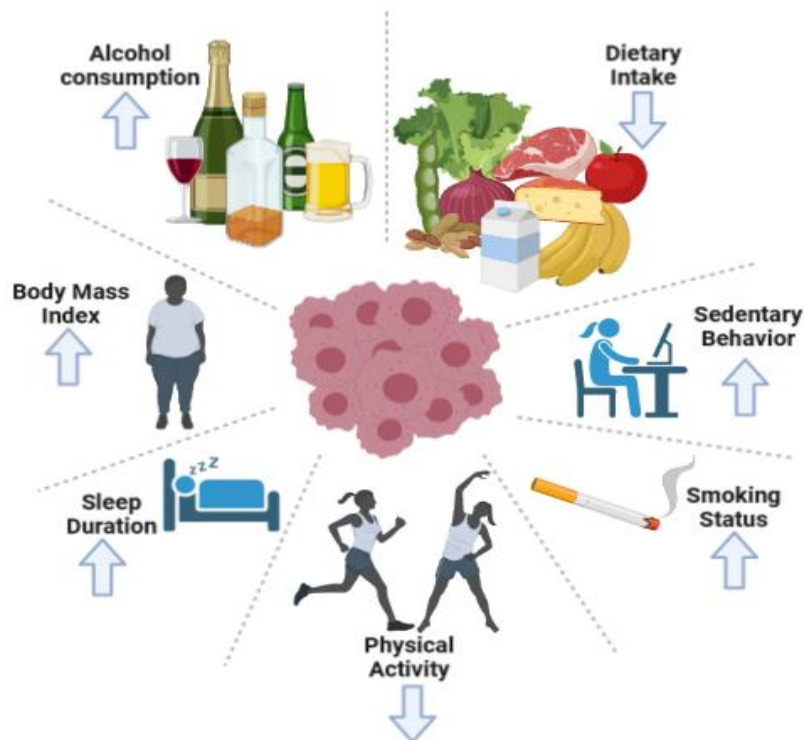


Figure 16. Lifestyle factors independently assessed in relation to breast cancer risk.[249]

There are limited studies examining the association between the healthy lifestyle index and breast cancer. Six epidemiological studies [54, 250-253] published between 2011 and 2020 examined healthy lifestyle index and breast cancer risk across various countries and study populations. Of the six studies, three utilized a prospective cohort design [250, 254, 255], two were population-based case-control studies [256, 257] and one a case-control study [228]. The prospective cohort study samples ranged from n=53,345 to n=146,326 of which two studies were conducted among participants living in the United Kingdom [255, 258] and the other study was comprised of White women in the United States. Inverse associations among women with the highest healthy lifestyle index score a reduction in breast cancer risk ranging from 16 to 32% across cohort studies. Among the two population-based case-control studies, the population sample ranges from 1,050 to 3,064 women cases. The remaining studies sample population ranged from 600 to 131,883. All six studies examined a healthy lifestyle index, and included dietary intake and physical activity assessment, and the risk of breast cancer. Studies used different factors to compose the HLI: one study did not assess smoking [229], another study did not consider alcohol consumption [227] and two studies did not assess BMI [227, 230]. Out of the six studies, only three studies assessed all five components [225, 226, 228]. There were similarities across studies that suggest a healthy lifestyle index (a lifestyle that maintains a healthy diet and physical activity) is inversely associated with breast cancer summarized in **Table 6**.

Table 6 Summary of studies examining the association between healthy lifestyle index and breast cancer risk

<i>Author, Year</i>	<b>Study Population</b>	<b>Exposure/ Outcome</b>	<b>Healthy Lifestyle Index components</b>	<b>Participant Characteristics</b>	<b>Race (Nationality )</b>	<b>Covariates</b>	<b>Outcomes/ (Findings)</b>
[251] <i>Ghosn, 2020</i>	Healthcare centers in Isfahan n= 1050; cases (n=350) Population-based case-control study Iran	<b>Healthy lifestyle factors</b> <b>Breast cancer</b> (confirmed by physical exam and mammography)	Diet (106-item Willett format FFQ specifically validated for Iranian women), physical activity (interview-based International physical activity questionnaire; categorical), Smoking (self-reported; categorical)  Operationalized all components as binary variables (0/1)  Overall score: 0-3	>30 years old adult women	Iranian	Age (continuous), residence (urban/rural), marital status (non/married/not married), SES (poor/middle/high class), education (educated/not educated), family history of BC (yes/no), menopausal status (yes/no), breast feeding (yes/no), history of disease (yes/no) and supplement use (yes/no), BMI (measured at study)	There is an inverse association between adherence to healthy lifestyle score and breast cancer risk odds. When stratified by menopausal status, the relationship remained significant among postmenopausal women and no association was found among premenopausal women.
[252] <i>Khalis, 2019</i>	BreCaFez Study February 2016 until August 2017 n= 600 Case-control Fez-region, Morocco	<b>Lifestyle index score</b> <b>Breast cancer risk</b>	Diet (intake of red and processed meat, white meat, cream, cheese, fish and vegetables (excluding potatoes) (tertiles), Physical activity (tertiles), BMI (tertiles), smoking (tertiles), alcohol consumption (tertiles), and breastfeeding (tertiles)[259]  Overall: 1 -11	Adult women	Moroccan	Age (continuous), number of live births (nulliparous, 1 to 3, $\geq 4$ ), menopausal status combined with age at menopause (premenopausal, postmenopausal $\leq 47$ years, and postmenopausal $>47$ years), history of oral contraceptives (yes, no), family history of BC (yes/no), wealth score (continuous), age at first full-term pregnancy (nulliparous, $<20$ years, $\geq 20$ years) and energy intake (continuous)	High HLI was inversely associated with breast cancer risk among premenopausal and postmenopausal women.
[250]	Women's Health Initiative	<b>Healthy Lifestyle Index score</b>	Diet (quintiles), alcohol consumption (categorical),	50 – 79 years old	White (> 83%)	Demographic characteristics, menstrual history, reproductive	All components of the HLI score were also associated with risk of breast cancer,

<i>Author, Year</i>	<b>Study Population</b>	<b>Exposure/ Outcome</b>	<b>Healthy Lifestyle Index components</b>	<b>Participant Characteristics</b>	<b>Race (Nationality )</b>	<b>Covariates</b>	<b>Outcomes/ (Findings)</b>
<i>Arthur, 2018</i>	Prospective cohort design  n= 131,883 postmenopausal women  United States	<b>Breast cancer clinicopathologic characteristics</b>	physical activity (quintiles), BMI (Categorical), and smoking (categorical)  Overall score: 0-20		African American Other	history, exogenous hormone use, family history, medical history, and diet and lifestyle factors	consistent with previous findings from the WHI study, postmenopausal women who had relatively high alcohol intake, who were obese, or who smoked cigarettes, had an increased risk of breast cancer, whereas those with a relatively high physical activity level had a reduced risk.
<i>[54] Arthur, 2017</i>	Canadian Study of Diet, Lifestyle and Health (CSDLH)  Case-cohort design  Baseline cohort (n = 39,618 women) Breast cancer cases (n = 1,936 postmenopausal women)  Canada	<b>Healthy Lifestyle Index score</b> (self-reported)  <b>Breast cancer</b> (cases confirmed via record linkage to Canadian Cancer Registry and Ontario Cancer Registry)	Diet (FFQ-derived information operationalized into quintiles), alcohol consumption (categorical), physical activity (quintiles), BMI (Categorical), and smoking (categorical)  Overall score: 0- 20	Adult women	Canadian	Education (High school or less, post/secondary/some college, graduate school), non-alcohol energy intake (continuous), age at menarche (continuous), parity (continuous), breastfeeding (yes/no), menopausal status (premenopausal, postmenopausal; for ovarian and endometrial cancer analyses only), HRT use ever (yes/no), oral contraceptive use ever (yes/ no), and family history of breast cancer in a first degree relative (yes/no).	Alcohol consumption and physical activity were not associated with any of the outcomes. There were weak associations with breast cancer, but the lifestyles factors are important in influencing risk.
<i>[253] McClain, 2017</i>	Long Island Breast Cancer Study Project (LIBCSP)	<b>Healthy lifestyle factors</b>	Alcohol consumption (frequency and duration, categorical),	20 – 98 years old	White (93.8%)	Age, BMI, and mammography	Associations for BMI and RPA with postmenopausal breast cancer in older women were more

<i>Author, Year</i>	<b>Study Population</b>	<b>Exposure/ Outcome</b>	<b>Healthy Lifestyle Index components</b>	<b>Participant Characteristics</b>	<b>Race (Nationality )</b>	<b>Covariates</b>	<b>Outcomes/ (Findings)</b>
	August 1996 – July 1997  n= 3064 women  1508 <i>In situ</i> and invasive breast cancer cases  Long Island, New York	<b>Postmenopausal breast cancer</b>	BMI (self-reported continuous)  Recreational physical activity (quintiles)  Nonsteroidal anti-inflammatory drug (NSAID) use (self-reported; binary)				pronounced among non-HRT users.
[259] Sanchez, 2011	Multicenter population-based case-control study January 2004 to December 2007  Mexico City, Monterrey, and Veracruz	<b>Healthy lifestyle factors</b>  <b>Breast cancer risk</b>	Diet (semi-quantitative FFQ for Mexicans), physical activity (semi-structured interviews; binary), alcohol consumption (self-reported; tertiles), and tobacco smoking (self-reported; binary)	35-69 years old	Mexican	Age category, health care system, and region, as well as for socioeconomic status, breastfeeding, BMI, family history of breast cancer, history of diabetes, folate consumption in diet, total daily calories consumption, height, and waist-to-hip ratio.	There is a decreased odds of having breast cancer with increasing quintiles of the Healthy Lifestyle index.

Although findings from epidemiological studies have been inconsistent with factors such as diet [109, 247], the American Cancer Society recommends maintaining a healthy lifestyle by eating healthy, staying active and avoiding tobacco use [3]. The healthy lifestyle index is a metric to assess the collective association these lifestyle factors have on breast cancer risk. Previous studies have used dietary intake, physical activity, hip-and-waist circumference, smoking, and alcohol intake, collectively, to measure a healthy lifestyle in relation to breast cancer risk [228, 248, 249] and other chronic disease [228, 237], but have not considered sleep and sedentary behavior as components in the indices utilized. Additionally, limited studies have assessed the collective association of healthy lifestyle factors and breast cancer risk among racial and ethnic groups of women. Moreover, the seven-component HLIs have not been examined with regard to breast cancer risk overall and specifically among racial and ethnic minorities. **Table 7** Summarizes prior studies that utilized an HLI and how the lifestyle factor variables were operationalized to create a summary HLI score.

Table 7 Operationalization of the Healthy Lifestyle Index (HLI) used in prior epidemiologic studies

Author Year	Operationalization of HLI score					
	Dietary Intake	Physical Activity	Smoking	Alcohol Intake	BMI	Healthy Lifestyle Score
[251] Ghosn, 2020	<p>106-item Willett format semi-quantitative dish-based food frequency questionnaire (FFQ)</p> <p>HELI-2010 (12 components (total and whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, and empty calories)</p> <p>Classified energy adjusted intakes of HEI-2010 into deciles categories. Fruits, vegetables, whole grains, nuts and legumes, long chain omega-3 fats and polyunsaturated fatty acids were given the score of 10 (highest decile) and score one indicated the lowest.</p> <p>Sugar, sweetened drinks and fruit juice, red and processed meat, trans fat, sodium intake, added sugars and saturated fatty acids were the lowest deciles were scored as ten. Summary score for individual items (10 to 100). Between 64-100 were considered to have a healthy diet</p>	<p>Interview-based International Physical activity (PA) questionnaire; responses were reported as metabolic equivalent hour/week</p> <p>Domains: Job-related PA; transportation PA; activities for housework, and house maintenance; recreation, sports, and leisure-time PA; and time spent sitting. Consider vigorous and moderate activities within the last 7 days.</p> <p>PA – low risk defined as active and moderately active lifestyle.</p>	<p>Pretest self-administered questionnaire, using, “Are you a smoker or not a smoker or an ex-smoker?”</p> <p>Smokers or non-smokers (non-smokers and ex-smokers)</p>	<p>Not included in HLI score.</p>	<p>Not included in HLI score.</p>	<p><b>Dietary Intake</b> Upper 2/5 of HEI-2010 (Q4, Q5) =1 Lower 3/5 of HEI-2010 (Q1, Q2, Q3) = 0</p> <p><b>Smoking</b> Non-smoker = 1 Smoker = 0</p> <p><b>Physical Activity</b> Active/ moderately active = 1 Inactive=0</p> <p><b>HLI</b> 0 to 3</p>
[252] Khalis, 2019*	<p>Limiting intake of red meat and avoiding processed meat (red and processed meat &lt;500 g/week and processed meat intake &lt;3 g/day), consuming more white meat (≥2 times per week), consuming more fish (≥2 times per week), high fruit and vegetable consumption (at least 5 servings per day), no cream or cheese consumption,</p>	<p>Having a high physical activity level (at least 60 min of moderate or 30 min of vigorous physical activity daily)</p> <p>&lt;30 min of moderate exercise or &lt;15 min of vigorous exercise per day.</p> <p>30 to &lt;60 min of moderate exercise or 15 to &lt;30 min of vigorous exercise per day.</p>	<p>Never having smoked: Current Former never</p>	<p>No alcohol consumption, daily: ≥10 g/day &lt;10 g/day Never</p>	<p>Healthy BMI (&lt; 25 kg/m<sup>2</sup>) ≥30 kg/m<sup>2</sup> 25 – 29 kg/m<sup>2</sup> 2 &lt;25 kg/m<sup>2</sup></p>	<p>Eleven components were used related to dietary intake. Factors were assigned 0, 0.5 or 1. The lifestyle index score ranged from 0 (least healthy) to eleven points (most healthy).</p> <p>Tertiles (lower, medium, upper)</p>

Author Year	Operationalization of HLI score					
	Dietary Intake	Physical Activity	Smoking	Alcohol Intake	BMI	Healthy Lifestyle Score
		≥60 min of moderate exercise or ≥30 min of vigorous exercise per day.				
[250] Arthur, 2018	Dietary intake of fruits and vegetables, grains, red and processed meat, the ratio of polyunsaturated to saturated fat, trans-fats, and glycemic load, The residuals from the linear regression models of each of dietary components on total energy intake were categorized into deciles and scored from 0 (lowest decile) to 9 (highest decile; vice versa for red/processed meat, trans-fat, and glycemic load). The individual scores were then totaled and categorized into quintiles.  The HLI score was then constructed by summing the scores of diets (5th quintile = 4, 4th quintile = 3, 3rd quintile = 2, 2nd quintile = 1, 1st quintile = 0)	Physical activity based on metabolic equivalent tasks [5th quintile = 4, 4th quintile = 3, 3rd quintile = 2, 2nd quintile = 1, 1st quintile = 0	Smoking: never smoked = 4, ex-smokers quit 10 years = 3, ex-smokers quit > 10 years = 2, current smoking 15 cigarettes/day = 1, current smoking > 15 cigarettes/day = 0	Alcohol intake (g/ day): none = 4, >0.0–4.9 = 3, >4.9–9.9 = 2, >9.9–19.9 = 1, >19.9 = 0	BMI (kg/m <sup>2</sup> ): 18.5–24.9 = 4, <18.5 = 3, 25.0–29.9 = 2, 30.0–34.9 = 1, 35+ = 0	The final score ranged from 0 to 20 with twenty being the healthiest behavior. The healthiest behavior was characterized by consuming a healthy diet (fifth quintile), avoidance of smoking, no alcohol consumption, high physical activity level (5th quintile), and a healthy BMI (18.5–24.9 kg/m <sup>2</sup> ).
[54] Arthur, 2017	FFQ-derived information on intake of cereal fiber, red and processed meat, margarine (as a marker of industrially produced trans fats), and fruits and vegetables. The residuals from the linear regression models of cereal fiber, red and processed meat, polyunsaturated and saturated fat, margarine, glycemic load, and fruits and vegetables on total energy intake were categorized into deciles and scored from 0 (lowest decile) to 9 (highest decile) (vice versa for red/processed meat, trans fat, and glycemic load).  Individual scores were summed and categorized into quintiles. (5th quintile = 4, 4th quintile = 3, 3rd quintile = 2, 2nd quintile = 1, 1st quintile = 0)	Physical activity based on metabolic equivalent tasks (5th quintile = 4, 4th quintile = 3, 3rd quintile = 2, 2nd quintile = 1, 1st quintile = 0)	Smoking status (never smoked = 4, ex-smokers quit > 10 years = 3, ex-smokers quit ≤ 10-years = 2, current smoking ≤15 cigarettes/day = 1, current smoking > 15 cigarettes/day = 0)	Alcohol intake (< 4.9 g/day = 4, 5.0–9.9 g/day = 3, 10.0–19.9 g/day = 2, 20.0–29.9 g/day = 1, 30+ g/day = 0)	BMI (kg/m <sup>2</sup> ) (< 22 = 4, 22.0 – 23.9 = 3, 24.0–25.9 = 2, 26.0–29.9 = 1, 30+ = 0)	Final score ranged from 0 to 20 with 20 being the healthiest behavior, which was characterized by consuming a healthy diet (5th quintile), avoidance of smoking, low alcohol intake (< 6.0 g/day), high physical activity level (5th quintile), and a healthy BMI (18.5–24.9 kg/m <sup>2</sup> ).

<i>Author Year</i>	<b>Operationalization of HLI score</b>					
	<b>Dietary Intake</b>	<b>Physical Activity</b>	<b>Smoking</b>	<b>Alcohol Intake</b>	<b>BMI</b>	<b>Healthy Lifestyle Score</b>
[253] <i>McClain, 2017</i>	Not included as risk factor	This information was summed up for all activities for each year of the woman's lifetime. The amount of lifetime physical activity was defined as exercise duration, in hours per week, from menarche to the reference date	Not included as risk factor	Lifetime alcohol intake was constructed using the number of years spent in the age interval as weights for total grams of alcohol consumed per day in each time period	Weight (kg)/height (m) <sup>2</sup> was calculated from the self-reported height and weight 1 year before the date of diagnosis for cases	No score used
[259] <i>Sanchez, 2011</i>	Validated semiquantitative food frequency questionnaire for Mexicans, which included 104 items and 10 multiple choice consumption frequency categories, as described by Willett.  Forty food groups were defined and certain foods were considered individually (e.g., eggs, mayonnaise, coffee, and beer) when they did not belong to a specific group or dietary pattern (e.g., oils, liquor, and animal origin fats;	Physical activity was divided into three categories: (a) light-intensity physical activities [1.1–2.9 metabolic equivalents of energy expenditure (METS)], (b) moderate-intensity physical activities (3.0–5.9 METS), and (c) vigorous-intensity physical activities (6 or more METS; ref. 37). The number of hours of physical activity per week, in each of the three categories, was calculated. Moderate and vigorous-intensity physical activities in hours per week.	Tobacco smoking was obtained as a dichotomous variable inquiring whether subjects had "consumed more than 100 cigarettes in their lifetime" (yes/no).  Low-risk group was defined as those subjects who had never smoked or had smoked 100 or less cigarettes in their lifetime.	Alcohol was measured in grams and, for this study, was divided into three categories: (a) did not consume, (b) consumed less than 1 g/d, and (c) consumed 1 g/d or more.  Women who did not consume alcohol were considered to have the lowest risk.	Not included in the HLI.	Summarized into quintiles Q1 (least) Q2 Q3 Q4 Q5(upper)

\*Additional components included in the HLI - longer cumulative duration of breastfeeding ( $\geq 24$  months)

## Hormonal and inflammatory biomarkers and obesity

### *Biomarkers*

Over the last several decades, epidemiological studies suggest adiposity, excess body fat, is associated with adverse health conditions and diseases, including cancer [260]. The American Institute for Cancer Research estimates more than 120,000 cases of cancer occurring in the United States are attributable to excess body fat [261] and an estimated 15-20% of all cancer deaths [262]. Adipose tissue is connective tissue composed primarily of adipocytes and is categorized into two main types: subcutaneous fat (under the skin) and visceral fat (between the internal organs). Adipose tissue can increase or decrease the release of free fatty acids, the energy which fuels skeletal muscle and other tissues and interacts and reacts via endocrine and metabolic signals from other organs. Importantly, adipose tissue serves as a regulator of energy balance and lipid metabolism via the release of peptide hormones. The correlation between adipose tissue and inflammation has long been studied using biomarkers to understand indicators for disease risk, prognosis, and survival. C-reactive protein (CRP) and hormonal proteins, adiponectin and leptin, are important markers of inflammation, a consequence of obesity.

### *C-reactive protein*

C-reactive protein synthesized by the liver, induced primarily by the cytokine interleukin – 6, is correlated with the inflammatory response in the body [263]. Epidemiologic data suggests higher CRP levels are associated with cardiovascular disease [264], diabetes [265], obesity [266] and cancer [267]. Studies have also observed a dose-response between aging and CRP levels. CRP levels in men and men increase with age [268] and are higher among women compared to men [269]. Similarly, higher levels of CRP have

been associated with BMI and increase as BMI increases [270]. African American men and women compared to other racial and ethnic groups typically have higher serum concentrations of CRP [271] whereas lower CRP concentrations have been seen among Asian men and women [272]. CRP production is strongly, positively related to insulin resistance and can change with insulin levels independently of changes in obesity [273].

### *Adiponectin*

Adiponectin is secreted by adipose tissue and plays an essential role in energy and metabolic processes [274]. Typically, lower serum concentrations of adiponectin have been associated with metabolic conditions such as obesity [275] and diabetes [265]. Studies have shown adiponectin secretion decreases proportional to the amount of adipose tissue [275]. Women typically have higher levels of adiponectin compared to men and levels increase with age [276]. With regards to race, Asian women have lower levels of adiponectin compared to White women [272]. However, both African American women and men tend to have significantly lower adiponectin levels compared to white adults [271].

### *Leptin*

Leptin is an adipocyte-secreted hormone which regulates food intake, circulating at proportional levels to adipose tissue accumulation, reproductive functioning and is vital in proinflammatory immune responses [277]. Epidemiologic data suggests serum concentrations of leptin decrease with aging with higher leptin levels observed in women compared to men [276] [278]. Leptin is closely linked to adipose tissue and among overweight or obese individuals serum concentration levels are significantly increased [275]. Leptin levels are significantly higher among African American women [271] and lower among Asian women compared to White women [272].

Neighborhood-level factors: neighborhood-socioeconomic status

The "obesogenic environment" defined by the collective influence of structural and built surroundings, economic, political and social conditions on promoting obesity [32]. The link between characteristics and features of the neighborhood-built environment and obesity have been widely researched as contributing factors to obesity and its growing epidemic [279]. The IPEN (International Physical Activity and Environment Network) Adult Study provides evidence for the association between built environments and physical activity and weight status in 12 countries. Neighborhood environment attributes, measured objectively and by self-report, were strongly associated with all physical activity outcomes (including accelerometer-assessed total physical activity and walking for transport and leisure) and with overweight/obesity [280]. This suggests the growing evidence of environmental attributes on modifiable health diseases, such as obesity and the critical need to understand the mechanisms that contribute to the obesogenic environment. Appendix A Table 1A summarized the prior studies assessing neighborhood attributes and the obesogenic environment.

Environmental attributes used to define neighborhood social characteristics vary by geographical location, but a relatively common attribute used is neighborhood poverty defined as neighborhoods with inadequate community-level or government economic resources related to infrastructure [281]. Neighborhood socioeconomic status is defined using socioeconomic factors such as a composite measure which captures multiple domains of housing, education, poverty, employment, occupation and income[33]. Attributes of the community built environment include recreational facilities, supermarkets, functioning sidewalks, and accessibility to parks [282]. Such neighborhood attributes include the proximity of grocery stores to residential areas, walkability index, population density, and

land use. These factors contribute to the obesogenic environment and can promote obesity and obesity-related conditions such as changes to the gut microbiome composition [283-285], induced stress [286-288], and disrupted circadian rhythm [49, 289, 290]. Studies have examined these environmental attributes among different populations to understand the biological link and association with obesity [30, 53, 280, 291, 292].

Neighborhood environment may contribute to the prevalence of obesity and chronic disease prevalence [293]. A systematic review and meta-analysis of 21 studies published from 2005 to 2018 with sample sizes ranging from 144 to 948,062 individuals across seven countries (USA, Canada, Germany, Australia, Sweden, France, United Kingdom and New Zealand) examined neighborhood-SES and obesity measured by BMI. The findings of the review supported previous studies that reported higher odds of overweight/obesity as well as other poor health outcomes in individuals living in low SES neighborhoods than individuals living in high SES neighborhoods [294].

Psychosocial stress in response to one's environment can have deleterious effects over chronic exposure. In women, stress may lead to unhealthy behaviors such as smoking or increased smoking, alcohol consumption, lack of sleep and exercise, as well as poor diet, which in turn puts them at an increased risk of cancer [295]. Chronic stress introduced via physiological and psychological stressors may change the body's state of homeostasis. Biomarkers have been used to assess the metabolic mechanisms of obesity and provide an objective measure to explore the association of obesity and the obesogenic environment [296].

The relationship between neighborhood attributes comprises an individual's environment and is complex and multifactorial. Neighborhood socioeconomic status

characterizes the socioeconomic environment of neighborhood. The social infrastructure relates to the physical construction and maintenance of facilities to enable services to the neighborhood and community. Neighborhoods lacking social infrastructure may reflect inadequate social cohesion and capital, which are interrelated to safety and crime, networks, and segregation [297]. These contributing social factors influence individual physical activity and involvement in outdoor activities, healthy eating options, and social behaviors such as smoking tobacco and drinking alcohol influence energy balance (intake and expenditure) and may lead to obesity and other chronic diseases such as cardiovascular disease, diabetes, and cancer.

*Neighborhood socioeconomic status and biomarkers: Evidence and gaps*

Prior studies have assessed CRP [156, 298-302], however three studies were conducted among predominately White populations [156, 298, 302] while two cross-sectional studies examined among African American adults [299] and Mexican American women [300] and a longitudinal study assessed change among White, African American, Hispanic and Chinese adults. The only prior study to date assessed serum levels of adiponectin among African American adults [303]. To date, no prior studies have examined the association between nSES and leptin in addition to CRP and adiponectin among African American, Japanese American, Latino, Native Hawaiian, and White adults. **Table 8** provides a summary of studies to date that have examined neighborhood socioeconomic status and biomarkers in adult men and women.

Table 8 Summary of prior studies examining neighborhood socioeconomic status and biomarkers

Author	Study Period	Study Design	Exposure	Outcome (Biomarkers Assessed)	Study Population	Measure of association	Adjustment factors
<i>Lyer et al (2022) [156]</i>	1990 - 1994 Males 1986 - 1990 Females	Prospective cohort	Neighborhood socioeconomic status	Adiponectin, C-reactive protein, interleukin-6, soluble tumor necrosis factor receptor-2	White women (NHS)	Neighborhood socioeconomic status was inversely associated with CRP ( $\beta = -8.38\%$ , 95% CI: $-10.99\%$ , $-5.69\%$ ),	age, fasting status, smoking status (current smokers, former smokers, never smokers), history of hypertension (binary), history of hypercholesterolemia (binary), BMI (<23, 23–<25, 25–<27.5, 27.5–<30, 30 kg/m <sup>2</sup> ), census region (Northeast, Midwest, South, West), population density (<1000 people/mi <sup>2</sup> , 1000 people/mi <sup>2</sup> ), post-menopausal hormone use (women only: pre-menopause and missing, post-menopause and never use, current use, past use), case status (binary), and any use of anti-inflammatory medications (binary)
<i>Roberts et al (2021) [302]</i>	2009-2010	Cross-sectional	BMS Neighborhood Psychosocial Hazards scale	Interferon gamma (IFN- $\gamma$ ), tumor necrosis factor alpha (TNF $\alpha$ ) interleukin-6 (IL-6) C-reactive protein (CRP) Serum amyloid A (SAA) Soluble intercellular adhesion molecule-1 (sICAM-1)	59% White; 36.8% Black	Model 1: 1.20 (1.04, 1.39) * Model 2: 1.25 (1.01, 1.55) * Model 3: 0.54, (0.22, 1.35) Model 4: 1.21 (1.01, 1.45)* Model 4: 1.13 (0.37, 3.48) Model 5: 1.24 (0.96, 1.59) Model 5: 0.91 (0.31, 2.68)	Model 1: disorder Model 2: disadvantage Model 3: normalized difference vegetation index (NDVI) Model 4: disorder and NDVI Model 5: disadvantage and NDVI
<i>Chaparro et al (2018) [298]</i>	2009 - 2012	Longitudinal	Carstairs index, Multiple Environmental Deprivation Index (MEDIX)	Lung function, blood pressure, body mass index (BMI), and levels of C-reactive protein (CRP).	United Kingdom (race/ethnicity not stated)	B (95% CI) 0.056 (0.044, 0.068)	age, gender, and the log of household equivalized income
<i>Cozier et al (2016) [299]</i>	1995 - 2013	Prospective cohort	Neighborhood socioeconomic status	C-reactive protein (CRP), hemoglobin A1C (hgA1C), and high-density lipoprotein (HDL) cholesterol.	African American women (BWHS)	Quintile 1: M1: 2.72 (2.18–3.41); M2: 2.60 (2.07–3.28) Quintile 2: M1: 2.19 (1.75–2.74); M2: 2.07 (1.73–2.47) Quintile 3: M1: 2.25 (1.77–2.87);	M1: Age M2: age, menopausal status, alcohol consumption, vigorous physical activity, moderate physical activity, walking for exercise, sitting/television viewing, insurance status, cigarette smoking, history of diabetes, female hormone use, household income, number of people in the household,

						<p>M2: 2.43 (2.02–2.93)            Quintile 4:            M1: 1.85 (1.41–2.43);            M2: 1.82 (1.41–2.35)            Quintile 5:            M1: 1.48 (1.03–2.13);            M2: 1.57 (1.11–2.22)            P trend: M1: 0.004; M2:            0.013</p>	<p>history of hypertension, years of education,            body mass index, western dietary pattern,            and prudent dietary pattern</p>
<p><i>Gallo et al</i>            (2012)            [300]</p>	<p>2006 -            2009</p>	<p>Cross-            sectional</p>	<p>household            income,            educational            attainment),            wealth (home            ownership), and            deprivation            (public            assistance)</p>	<p>Circulating levels of            plasma CRP, IL-6, and            sICAM-1</p>	<p>Mexican            American            women</p>	<p>% Difference (95% CI)            M1: -23.56** [-36.47;            -10.65]            M2: -12.98* [-25.85; -0.11]            M3: -9.00 [-21.25; 3.25]</p>	<p>M1: Age, language, nativity, smoker            (yes/no), duration of current residence            (neighborhood SES models only)            M2: M1 + BMI and waist circumference            M3: Dietary fat, fruit and vegetable            servings and physical activity</p>
<p><i>Nazmi et</i>  <i>al</i> (2010)            [301]</p>	<p>2000 -            2002</p>	<p>Cross-            sectional</p>	<p>Neighborhood            deprivation            score             Neighborhood            of residence            (proxied by            census tract)</p>	<p>fibrinogen, IL-6 and            CRP)</p>	<p>38% white,            28% Black,            22%            Hispanic            and 12%            Chinese.</p>	<p>Neighborhood deprivation            score:            M1: 9 (5.3, 12.8)            M2: 5.5 (1.7, 9.4)            M3: -0.8 (-4.0, 2.5)            M4: -3.6 (-6.9, -0.3)            M5: -3.0 (-6.2, 0.2)</p>	<p>Model 1: age and sex; Model 2: Model 1+            family income and education            Model 3: Adjusted for Model 1+            race/ethnicity            Model 4: Model 2 + race/ethnicity            Model 5: Model 4 + BMI, waist            circumference, physical activity, dietary            pattern score, smoking, alcohol intake,            recent acute infection, medication use,            impaired glucose tolerance, and diabetes</p>

## Chapter 3: General Methods

### *The Multiethnic Cohort Study*

The MEC is a prospective cohort study comprised of men and women from five racial and ethnic groups: African Americans, Japanese Americans, Latinos, Native Hawaiians, and Whites residing in largely in Los Angeles, California and Hawaii. Over 215,000 study participants, ages 45 to 75 years old at baseline, were recruited from 1993 to 1996 [200].

The sampling frame for the MEC included using driver's licenses, voters' registration files, census tracts and the Health Care Financing Administration (HCFA) files. To avoid oversampling of White participants in Los Angeles, an ethnic-specific surname identifier list was used from prior epidemiologic studies, population-based tumor registries and commercial publications to identify participants ethnicity. Participants' ethnicity was determined by their questionnaire responses [200].

Participants were mailed a twenty-six-page baseline questionnaire with questions pertaining to demographic characteristics, anthropometrics, reproductive history, and other lifestyle factors. Subsequent follow-up questionnaires varied in length and were mailed approximately every two to four years. Participants were followed prospectively for diagnosis of incident invasive breast cancer through routine linkage with the CA and HI statewide cancer registries participating in the NCI's SEER program, and for vital status through linkages to the National Death Index and death certificate files [200].

The prospective MEC data are robust and contain invaluable information on chronic disease among underrepresented and under-researched ethnic and racial minorities. This dissertation utilizes this ethnically and racially diverse data source to expand the knowledge

and understanding of cardiometabolic factors and breast cancer in a field that has historically researched primarily White, homogenous racial groups.

*Aim 1: Cholesterol-lowering drug use and breast cancer risk*

Study design and population

Aim 1 utilized a prospective cohort design whereby the start of the study was defined as the third MEC follow-up questionnaire (2003-2008) and the end of follow-up was defined as the study exit (December 31, 2017). Information on cholesterol-lowering drug use and duration of use was ascertained from the third MEC follow-up questionnaire.

Inclusion and exclusion criteria

The derivation of the analytic sample for Aim 1 is listed in **Figure 17**. The sample exclusions were hierarchically applied to the participants who completed the third MEC follow-up questionnaire in accordance with standard MEC exclusions for breast cancer risk studies.

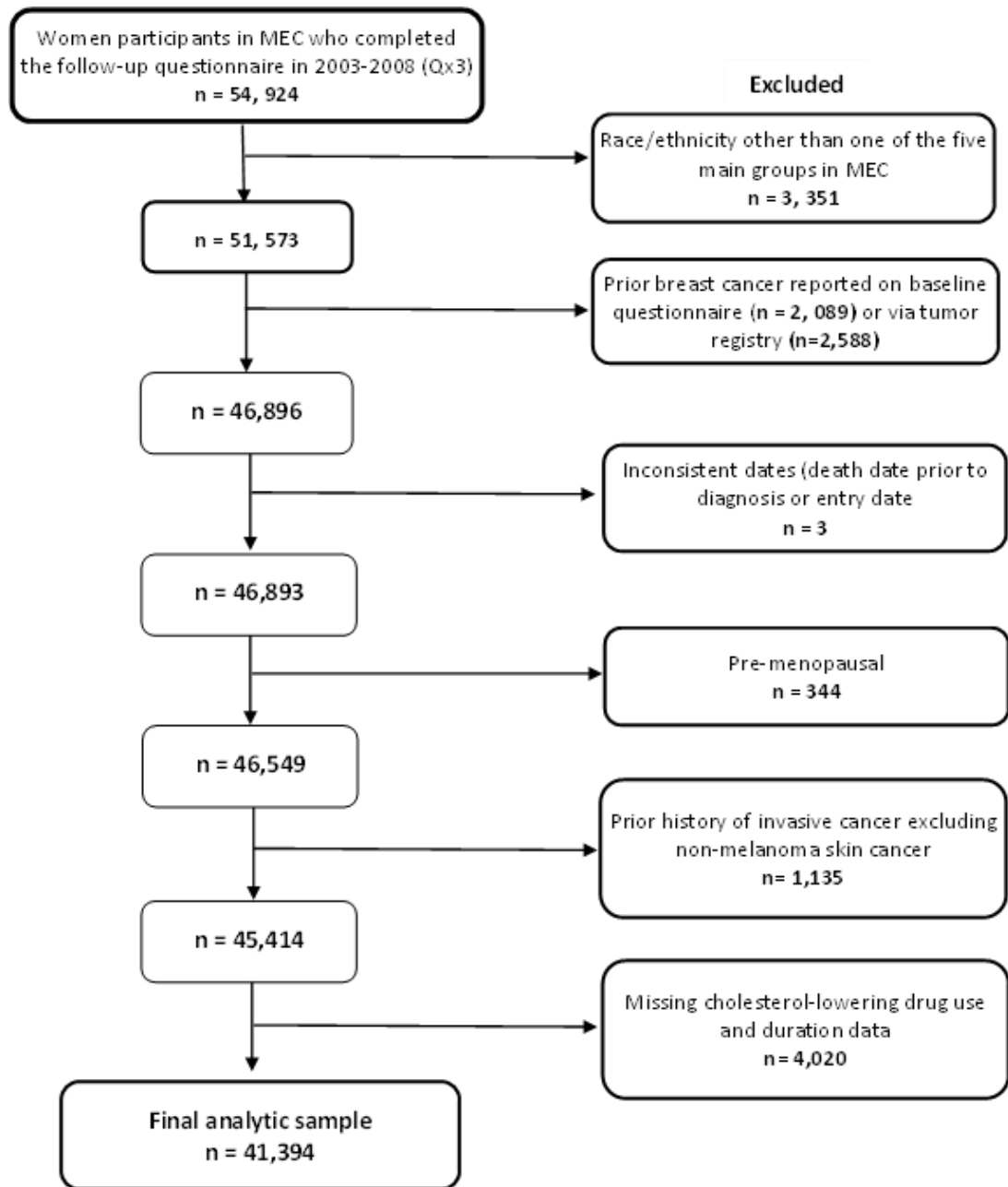


Figure 17 Flowchart of exclusion criteria for derivation of analytic sample

### Power calculations

The total analytic sample included n= 41,394 postmenopausal women and n=1,681 breast cancer cases occurring during the 11-year follow-up period. With a fixed sample size of postmenopausal women who use cholesterol-lowering drugs (n=18,301) and postmenopausal women who do not use cholesterol-lowering drugs (n=23,093) there is a

power of 99% or greater to detect a minimum HR=1.08. The average study duration (follow-up period) was 11.1 years (ranging from 2003 to 2017). The accrual time was one year (2003 to 2004) for participants to complete the third MEC follow-up questionnaire. The alternative hypothesis states that women who do not take cholesterol-lowering drugs relative to women who do take cholesterol-lowering drugs have an increased risk of breast cancer (hazard ratio = 1.08). The null hypothesis is that age at breast cancer diagnosis is the same in the unexposed (never cholesterol-lowering drug users) and exposed (cholesterol-lowering drug users) group. Alpha was defined as 0.05. The sample size for the overall analysis is n=41,394 women and by race: African American (n=5,665) Japanese American (n=13,112), Latina (n=7,544), Native Hawaiian (n=3,183) and White (n= 11,890). During the follow-up period, 1,681 postmenopausal were diagnosed with invasive breast cancer between the third MEC follow-up questionnaire until December 31, 2017.

#### Statistical hypotheses

The Aim I study assessed four exposure cholesterol-lowering drug use and duration variables: 1) status: never/ever, 2) status: never/former/current, 3) duration: never/< 3 years/> 3 years, and 4) status and duration: never/ former, <3 years /former, ≥3 years/current, <3 years/current, ≥3 years, and breast cancer risk. The alternative hypotheses are stated for overall, race and ethnicity stratified models and the hormone receptor sub-group analysis for the associations between each cholesterol-lowering drug exposure variable and breast cancer risk.

#### *Alternative hypotheses:*

For cholesterol-lowering drug status (ever/never), postmenopausal women who are ever cholesterol-lowering drug users have lower risk of invasive breast cancer compared to

postmenopausal women who are never users. By race and ethnicity, postmenopausal women who are ever cholesterol-lowering drug users have varying risk of breast cancer compared to postmenopausal women who are never users. By hormone receptor status, postmenopausal women who are ever cholesterol-lowering drug users have lower risk of invasive HR+ and HR- breast cancer compared to postmenopausal women who are never users.

For cholesterol-lowering drug status (never/former/current), overall, postmenopausal women who are former or current cholesterol-lowering drug users have lower risk of invasive breast cancer compared to postmenopausal women who are never users. By race and ethnicity, postmenopausal women who are former or current cholesterol-lowering drug users have varying risk of breast cancer compared to postmenopausal women who are never users. By hormone receptor status, postmenopausal women who are former or current cholesterol-lowering drug users have lower risk of invasive HR+ and HR- breast cancer compared to postmenopausal women who are never users.

For cholesterol-lowering drug use duration (never/< 3 years/≥3 years), overall, postmenopausal women who use cholesterol-lowering drug for < 3 or ≥3 years have lower risk of invasive breast cancer compared to postmenopausal women who are never users. By race and ethnicity, postmenopausal women who use cholesterol-lowering drug for < 3 or ≥3 years have varying risk of breast cancer compared to postmenopausal women who are never users. By hormone receptor status, postmenopausal women who use cholesterol-lowering drug for < 3 or ≥3 years have lower risk of invasive HR+ and HR- breast cancer compared to postmenopausal women who are never users.

For cholesterol-lowering drug status and duration (never/ former, <3 years /former, ≥3 years/current, <3 years/current, ≥3 years), overall postmenopausal women who are former

or current cholesterol-lowering drug users for  $< 3$  or  $\geq 3$  years have lower risk of invasive breast cancer compared to postmenopausal women who are former or current cholesterol-lowering drug users for  $< 3$  or  $\geq 3$  years have varying risk of breast cancer compared to postmenopausal women who are never users. By hormone receptor status, postmenopausal women who are former or current cholesterol-lowering drug users for  $< 3$  or  $\geq 3$  years have lower risk of invasive HR+ and HR- breast cancer compared to postmenopausal women who are never users.

#### Statistical approach

The Aim1 statistical methods is described in Chapter 4 methods – statistical analysis. In brief, multivariable Cox proportional hazard regression estimated the hazard ratios and 95% confidence intervals for the association between the cholesterol-lowering drug use and breast cancer risk among postmenopausal women. Overall, race and ethnicity-stratified analyses were conducted and trend and heterogeneity in associations by race and ethnicity were assessed. Additional descriptive and Cox proportional hazards regression assessing BMI, BMI stratified by waist circumference are in Appendix.

#### Confounding

The confounders for specific aim I analyses were identified *a priori* from previous literature, including prior MEC studies, and are known breast cancer risk or protective factors. Static covariate and confounder information were ascertained from baseline demographic data (race and ethnicity, education, and marital status). Whereas information on age, Alternative Healthy Eating Index (AHEI) score, alcohol intake, smoking status, physical activity, family history of breast cancer, breastfeeding and reproductive history including age at menarche, age at first childbirth, number of children for parous women, oral contraceptive

and menopause hormone therapy were obtained at the third MEC follow-up questionnaire. AHEI score and alcohol intake data were missing for n=1,469 participants, the largest number of participants with unknown covariate data. In the MEC, postmenopausal were more likely to not drink alcohol and to score in between the third and fourth AHEI score quartiles. Approximately 3.5% of participants were missing AHEI score and alcohol intake data, which is unlikely to pose a threat to residual confounding effects that would affect the measure of association; however, it is important to note when interpreting the adjustment factors included in the model. The possibility of missing values included in the analysis could lead to unbalanced differences in the analytic population by exposure or outcome. All categorical covariates with missing were retained in the model by classifying the missing in to a “unknown” category. Age at baseline was the only continuous variable included in the model and had no missing data. In addition, prescription drugs are vital component of healthcare. Individuals who were prescribed drugs may have been more likely to have access to healthcare insurance to support healthcare costs and thus may seek overall care compared to individuals without healthcare insurance [304]. This may have had non-differential misclassification effect due to the likelihood of access to healthcare insurance and healthcare is likely balanced between exposure groups.

The directed acyclic graph (DAG) illustrates the relationship between cholesterol-lowering drugs and breast cancer risk, potential confounders and effect modification by race and ethnicity. **Figure 18** shows the relationship between cholesterol-lowering drug use and breast cancer risk and the suspected confounders, effect modifiers and mediators. Bivariate associations were assessed to understand the direction and magnitude of association with cholesterol-lowering drug use and breast cancer.

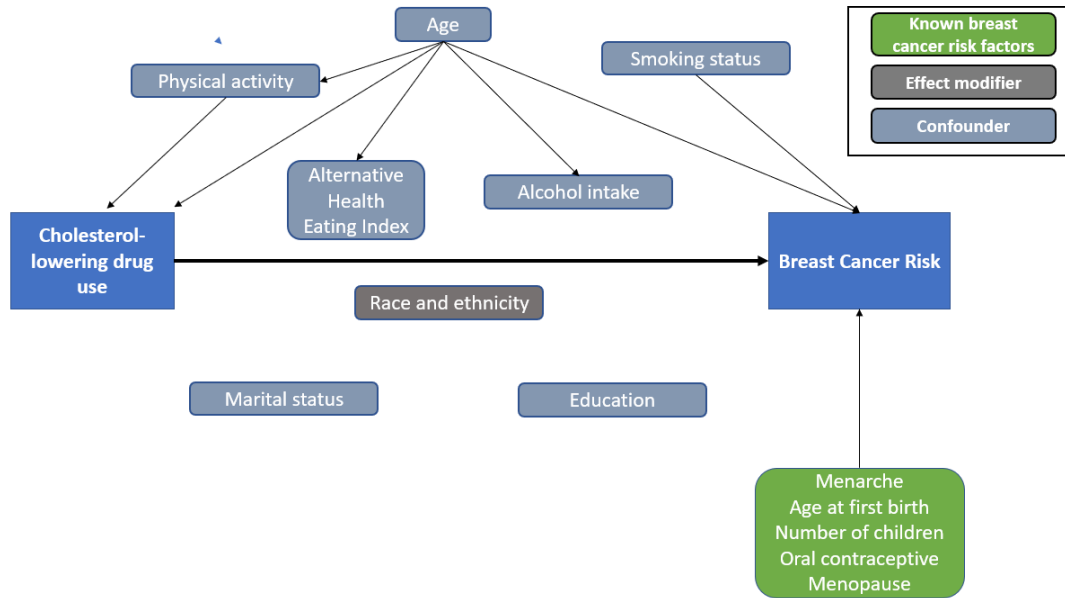


Figure 18 Directed acyclic graph of confounders and effect modifiers

Bivariate associations were assessed to understand the direction and magnitude of association with cholesterol-lowering drug use and breast cancer diagnosis. The possibility of missing values included in the analysis could lead to unbalanced differences in the analytic population by exposure or outcome. All categorical covariates with missing were retained in the model by retaining the missing values as an “unknown” category. Age at baseline was the only continuous variable included in the model and had no missing data.

### Potential biases

#### *Selection Bias: Loss-to-follow-up*

Loss-to-follow-up due to study drop-out or relocation could result in differential misclassification bias inherent to the prospective cohort design. Although information on reasons for drop-out or loss-to-follow-up due to relocation was not available, retention rates were high suggesting differential misclassification was unlikely.

*Information bias: social desirability bias*

Self-reported data is commonly obtained in questionnaires to gather information about the participant's health/disease history, behavioral, socioeconomic, and sociodemographic background. The data obtained from questionnaires can provide insight into an individual's health and lifestyle through the participant's perspective, views and opinions that would otherwise not be included in medical records or objective measure such as clinical examinations. However, self-reported data may be subject to social desirability bias. This type of bias occurs when questions are asked about private or sensitive topics such as dietary intake, lifestyle behaviors and income and the participant may report socially acceptable responses rather than an accurate representation of the individual's personal background and health history. An effective strategy used to reduce social desirability is to ensure all questionnaires remain confidential and anonymous. Additionally, the use of validated data collection instruments such the Health Eating Index 2010, based on evidence-based recommendations to focus on food and nutrients to predict chronic disease, was used to collect detailed dietary intake [305].

*Information bias: Misclassification of cholesterol-lowering drug*

The exposure ascertainment of cholesterol lowering drug use occurred at the time the participant completed third MEC questionnaire prior to invasive breast cancer diagnosis. Cholesterol-lowering drug use data was not available at the MEC. Additionally, information on duration and specific types of cholesterol lowering drug use was limited and restricted to use within the last year. With limited data on duration of use prior to completion of Qx3, the Aim I analysis was unable to assess classification of reason for cholesterol-lowering drug use and intensity of cholesterol-lowering drug regime. Moreover, the indication for cholesterol-

lowering drugs was not considered in the analyses due to the data not being available. Ideally, the exposure groups by use could be categorized by drug classification and drug indication to gain insight chronic conditions or health history that may make an individual a candidate for cholesterol-lowering drug prescription. This information would enhance the understanding of specific sub-populations and the association between cholesterol-lowering drugs and breast cancer risk. Despite this limitation, the exposure ascertainment in the current Aim 1 study extends information about cholesterol-lowering drug use compared to existing studies by combining the cholesterol-lowering drug status and duration at each level of status, whereas previous studies examine cholesterol-lowering drug use by either status or duration and if status and duration was combined, only duration for current users were assessed.

Moreover, cholesterol-lowering drug use was self-reported and collected at study entry as this single timepoint. The possibility of non-differential misclassification may result from exposure ascertainment based on a single timepoint rather than at multiple timepoints. Ideally, cholesterol-lowering drug use would have been measured every one to two years to capture changes and patterns in cholesterol-lowering drug use and duration. There is likely an equal number of participants prescribed or discontinuing cholesterol-lowering drugs [306].

### *Aim II: Healthy Lifestyle Index and breast cancer risk*

#### Study design and study population

The Aim II study design was a prospective cohort study. The baseline questionnaire (1993-1996) was defined as the study start and participants were followed until December 31, 2017, the study exit. The healthy lifestyle index exposure was based on information on seven lifestyle behaviors ascertained at the baseline questionnaire.

### Inclusion and exclusion criteria

The derivation of the analytic sample for Aim 2 is listed in **Figure 19**. The sample exclusions were hierarchically applied to the participants who completed the baseline questionnaire in accordance with standard MEC exclusions for breast cancer risk studies.

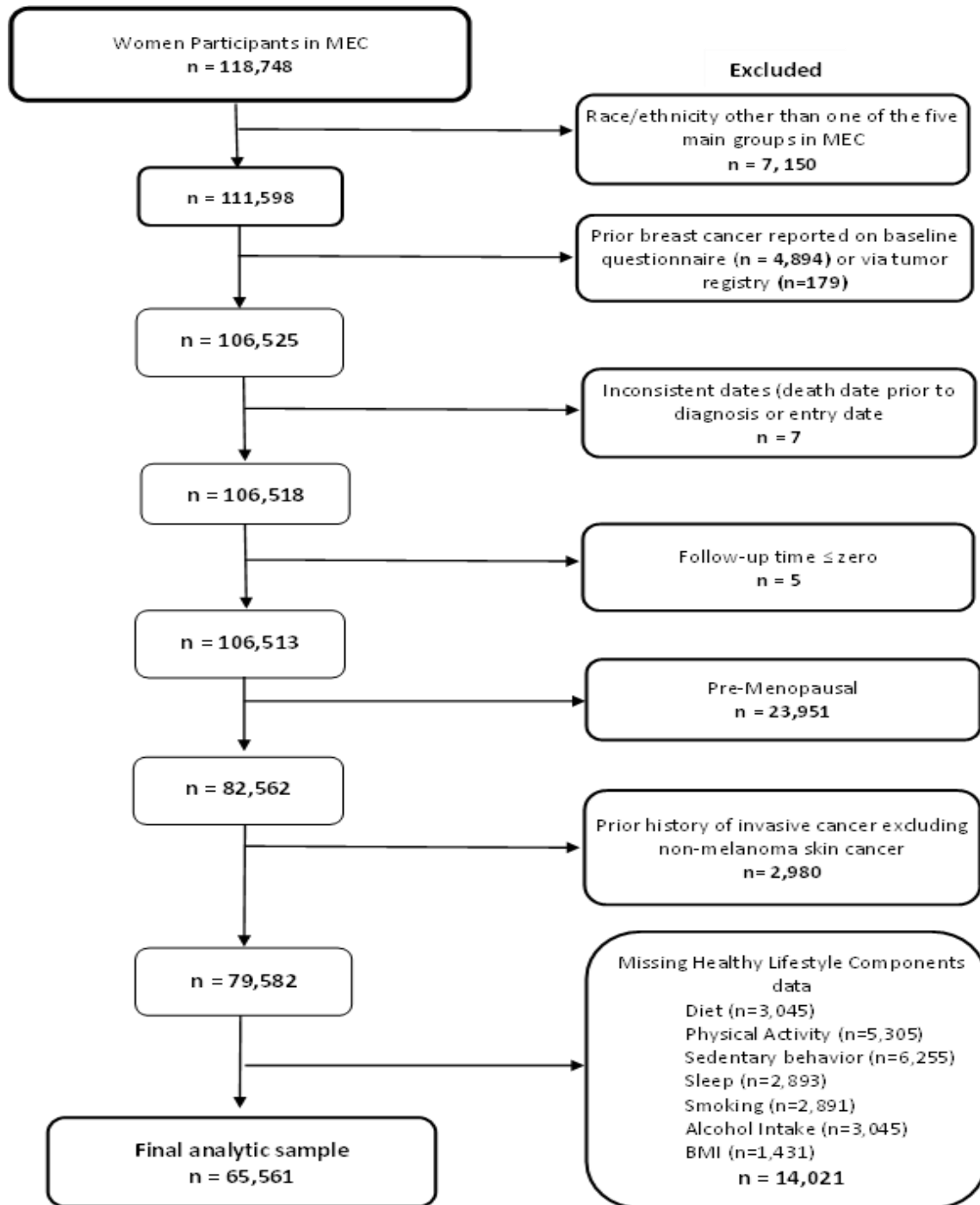


Figure 19 Derivation of analytic population

### Power calculation

The total analytic sample include n= 65,561 postmenopausal women and n=4,555 breast cancer cases occurring during the 24-year follow-up period.

With a fixed sample size of postmenopausal women who had a low HLI score (tertile 1) (n=7,386) and postmenopausal women had a high HLI score (n=34,718) there is a power of 99% or greater to detect a minimum HR=0.76. The average study duration (follow-up period) was 19.2 years (ranging from 1993 to 2017). The accrual time was three years (1993-1996) for participants to complete the MEC baseline questionnaire. The alternative hypothesis states low HLI score (Tertile 1) relative to women who have high HLI score (Tertile 3) have reduced risk of breast cancer (HR: 0.76). The null hypothesis is that age at breast cancer diagnosis is the same among unexposed (women with low HLI scores Q1) and exposed (women with high HLI scores Q3) group and Alpha was defined as 0.05. The sample size for the overall analysis is n=65,561 women and by race: African American (n=12,236) Japanese American (n=18,531), Latina (n=13,836), Native Hawaiian (n=4,365) and White (n= 16,593). During the follow-up period, 4,555 postmenopausal were diagnosed with invasive breast cancer between the MEC baseline questionnaire until December 31, 2017.

### Alternative hypotheses

The Aim II study assessed the exposure to the HLI comprised of seven lifestyle components and breast cancer risk. The alternative hypotheses are stated for overall, race and ethnicity stratified models and the hormone receptor sub-group analysis for the associations between the HLI score and breast cancer risk.

Overall, postmenopausal women who have a higher HLI score (T3 and T2) have lower risk of invasive breast cancer compared to postmenopausal women with a lower HLI

score (T1). By race and ethnicity, postmenopausal women who have a higher HLI score (T3 or T2) have varying risk reduction of breast cancer compared to postmenopausal women with a lower HLI score (T1). By hormone receptor status, postmenopausal women with a higher HLI score (T3 and T2) have lower risk of invasive HR+ and HR- breast cancer compared to postmenopausal women with a low HLI score (T1).

#### Statistical approach

The Aim 2 statistical methods are described in Chapter 5: methods – statistical analysis. In brief, multivariable Cox proportional hazard regression estimated the hazard ratios and 95% confidence intervals for the association between the HLI score and breast cancer risk among postmenopausal women. Overall, race and ethnicity-stratified analyses were conducted and trend and heterogeneity in associations by race and ethnicity were assessed.

#### Exposure ascertainment

The HLI was developed based on existing scientific knowledge and on public health guidelines for cancer prevention. The Healthy Lifestyle Index (HLI) was comprised of seven components: dietary intake, moderate and vigorous physical activity, sedentary behavior, smoking status and duration, alcohol consumption, BMI, and sleep duration. Additional details on each question from the MEC baseline questionnaire used to define the HLI component are described below.

The average dietary intake during last year (prior to baseline)[307, 308] was measured using the Healthy Eating Index-2010 (HEI-2010) composed of 12 components: total and whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, and empty calories. Physical

activity was defined as total metabolic equivalents (METs) in activities involving moderate or vigorous movement per day, on average, during the last year (prior to baseline [309, 310]. Sedentary behavior was defined as the total hours in sitting activities per day, on average, during the last year (prior to baseline)[311]. Smoking status and the number of pack-years was defined by operationalizing the smoking status variable and the number of pack-years into one variable to account for frequency and duration. This combined variable was categorized into quintiles [45, 312, 313]. Alcohol consumption was measured in grams of ethanol (per day) and categorized into tertiles based on the National Institute on Alcohol Abuse and Alcoholism Drinking level definitions [102, 314, 315]. BMI was defined using the Quetelet index and categorized into tertiles based on National Heart, Lung, and Blood Institute (NHLBI) guidelines [314]. Sleep duration was defined as the number of hours per day spent sleeping (including naps), on average, during the last year (prior to baseline)[48, 316]. The HLI score was composite sum of each of the seven components (**Table 9**).

Table 9 Operationalization of Healthy Lifestyle Index components

<b>Healthy Lifestyle Component</b>	<b>Minimum – Maximum Score</b>
Dietary intake (HEI-2010 score)	1-4
Moderate and vigorous physical activity (METs/week)	1-3
Sedentary behavior (hours/week)	1-3
Smoking status and pack-years (pack-years)	1-5
Alcohol consumption (g/day)	1-3
BMI (kg/m <sup>2</sup> )	1-3
Sleep duration (hours)	1-2
<b>Total</b>	<b>7-23</b>
T1	7 to <15
T2	15 to <18
T3	18 to 23

#### Confounding and effect modification

Sociodemographic and established breast cancer risk factors identified *a priori* were included in the final Cox proportional hazard regression. Information collected at baseline

included sociodemographic data (age, race and ethnicity, education, and marital status) and reproductive and hormone history (age at menarche, age at first childbirth, number of children for parous women, oral contraceptive, age and type of menopause and menopausal hormone status). **Figure 20** shows the association of confounders in relation to the HLI score and breast cancer risk reflected in the DAG. The DAG also illustrates the relationship of effect modification by race and ethnicity.

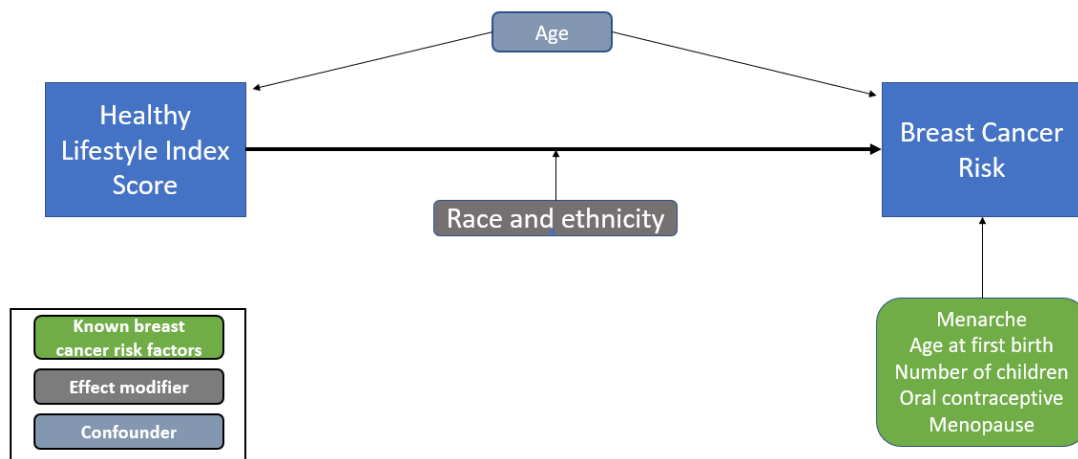


Figure 20 Direct acyclic graph of potential confounders

Bivariate associations were assessed to understand the direction and magnitude of association with the HLI score and breast cancer diagnosis. The possibility of missing values included in the analysis could lead to unbalanced differences in the analytic population by exposure or outcome. All categorical covariates with missing were retained in the model by retaining the missing values as an “unknown” category. Age at baseline was the only continuous variable included in the model and had no missing data.

Information bias: Healthy Lifestyle Index assessment

Information on each component of the HLI was collected and defined using the MEC baseline questionnaire. Several of the HLI components had comprehensive measurements

and included the intensity, frequency, and duration of exposure. However, additional information in relation to type and intensity for alcohol intake and sleep would improve the overall measurement of these HLI components. Alcohol intake was measured using the total average grams of alcohol consumed per day and did not account for the type of alcohol consumed (i.e., wine, beer, and liquor) which can vary on average by day. Although the type of alcohol consumed was not included in the alcohol intake HLI component, the inclusion of this information would have likely had minimal influence on more accurately classifying alcohol consumption among participants given 83.4% consumed less than 5 grams of alcohol per day. The HLI sleep component did not account for fluctuations in sleep patterns and additional characteristics of sleep health such as sleep difficulty, quality, and disturbances. Additional sleep information could potentially further characterize sleep health in the overall HLI.

HLI exposure data was measured at baseline only. Assessing multiple exposure timepoints would potentially strengthen assessment of the association between the HLI score and breast cancer risk by enabling analysis of the HLI score over time during the study period. However, the use of baseline exposure measures is widespread practice in large cohort studies.

*Information bias: Social desirability bias*

Social desirability bias applies to the exposure and covariate data ascertainment from the MEC questionnaires. The MEC questionnaires gathered self-reported data for each of the healthy lifestyle index components and the participant's health/disease history, behavioral, socioeconomic, and sociodemographic background. Additional information is gathered from the participant's perspective, views and opinions that would otherwise not be included in

medical records or objective measures such as clinical examinations. Social desirability bias occurs when questions are asked about private or sensitive topics such as dietary intake, lifestyle behaviors and income and the participant may report socially acceptable responses rather than an accurate representation of the individual's personal background and health history. An effective strategy used to reduce social desirability is to ensure all questionnaires remain confidential and anonymous. Additionally, the use of validated data collection instruments such the Health Eating Index 2010, based on evidence-based recommendations to focus on food and nutrients to predict chronic disease, was used to collect detailed dietary intake [305].

### *Aim III: Neighborhood socioeconomic status and biomarkers*

#### Study design and study population

The Aim III study design was a cross-sectional study using previously collected data from the MEC blood draw questionnaire and biospecimen collection at blood draw between 1998 and 2000. The blood draw questionnaire was comprised of 14 questions about demographics, medication, and medical history.

#### Inclusion and exclusion criteria

The MEC inclusion criteria was applied in the order listed in **Figure 21**. The final analytic population included n=13,818 adults.

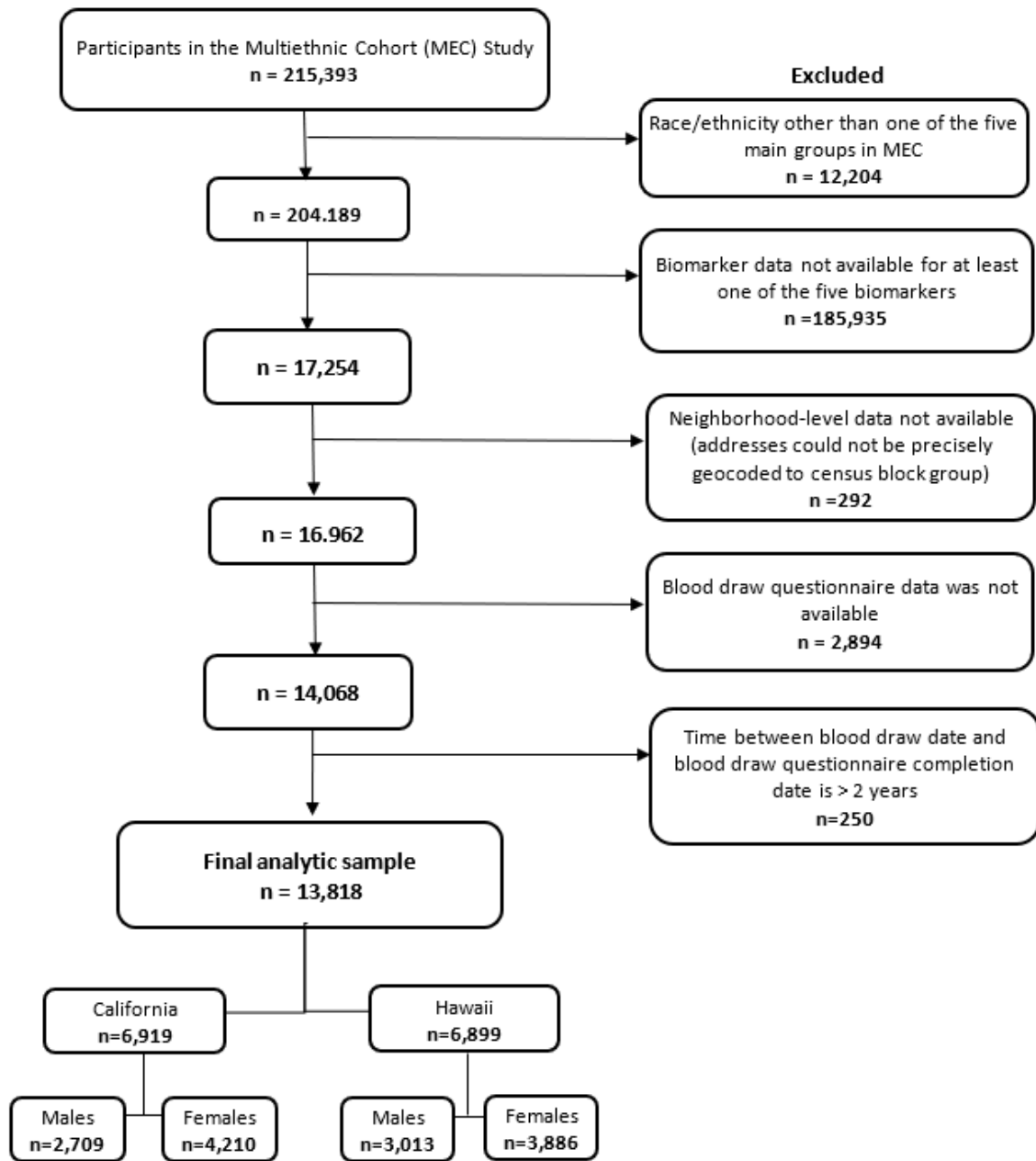


Figure 21 Derivation of the analytic sample

### Power calculations

The cross-sectional analysis using a fixed analytic sample size of adults (n= 13,818) to assess neighborhood socioeconomic status (group-level exposure) and associations with serum biomarker concentrations of C-reactive protein, leptin, and adiponectin (individual-level outcome) among men and women was sufficiently powered (power >0.99). Participants

were classified into neighborhood socioeconomic status (nSES) quintiles (Q1: low to Q5: high). The null hypothesis states equal change in serum biomarker (CRP, adiponectin and leptin) concentration levels in each nSES (Q1 to Q4) compared to high nSES (Q5). With power  $\geq 99\%$ , a difference greater than 5% between low nSES and high nSES for each biomarker is detectable. The Type I error probability is  $\alpha = 0.05$ .

Statistical hypotheses:

The central hypothesis is individuals living in low nSES neighborhoods (Quintiles 1 -3) will have increased CRP and leptin levels and decreased adiponectin levels compared to individuals living in high nSES neighborhoods (Quintile 5). The serum concentrations will vary by sex, state and race and ethnicity.

*Alternative hypotheses:*

**Adiponectin:** Individuals in low nSES (Quintiles 1-3) will have decreased adiponectin levels compared to high nSES (Quintile 5). Individuals in Quintile 4, also characterized as high nSES, will have decreased serum levels but to a lesser magnitude than individuals in quintiles characterized by low nSES (Quintiles 1-3) compared to Quintile 5. Females will have lower adiponectin levels across all Quintiles compared to males. Adiponectin levels will vary by state and race and ethnicity. **CRP:** Individuals in low nSES (Quintiles 1-3) will have increased CRP levels compared to high nSES (Quintile 5). Individuals in Quintile 4, also characterized as high nSES, will have increased serum levels but to a lesser magnitude than individuals in quintiles characterized by low nSES (Quintiles 1-3) compared to Quintile 5. Females will have higher CRP levels across all quintiles compared to males. CRP levels will vary by state and race and ethnicity.

**Leptin:** Individuals in low nSES (Quintiles 1-3) will have increased leptin levels compared to

high nSES (Quintile 5). Individuals in Quintile 4, also characterized as high nSES, will have increased serum levels but to a lesser magnitude than individuals in quintiles characterized by low nSES (Quintiles 1-3) compared to Quintile 5. Females will have higher leptin levels across all quintiles compared to males. Leptin levels will vary by state and race and ethnicity.

Statistical approach

The statistical approach for Aim 3 used the multivariable linear regression to assess the association between nSES and biomarker serum concentrations. The intraclass coefficient (ICC) was assessed to quantify the total variation in biomarker serum levels attributable to neighborhood-level pseudo census block groups. Approximately  $\leq 9\%$  of total variance in each biomarker was due to variation by pseudo census block group (neighborhood unit clustering variable). The ICC ranged from 0% to 9% suggests most or all the total variation is due to individual-level variation (Table 12).

Table 10 Quantification of total variance attributable to neighborhood pseudo census block-level variance for each biomarker

<b>Biomarker Type</b>	<b>Intraclass correlation coefficient (ICC)</b>
C-reactive protein	0.09
Adiponectin	0.02
Leptin	0.08

Exposure ascertainment

Neighborhood socioeconomic status (nSES) was measured as a composite score using principal component analysis of census block group data for education, housing, employment, occupation, income, and poverty, as described previously [317]. The composite score was operationalized by categorizing the distribution of nSES into quintiles (quintile 1 – low and quintile 5 – high).

### Confounding and effect modification

The model building strategy to achieve the final analytic model for Aim 3, included first examining the bivariate associations of each potential confounder with the exposure (neighborhood socioeconomic status) and the outcome (each biomarker). The alpha was set to 0.20 to identify significant associations between covariate and exposure and outcome. Then, the change-in-estimate strategy was conducted using the base model with adjustment for age (continuous), sex (binary: male, female), race (categorical: African American, Japanese American, Latina, Native Hawaiian and White), fasting hours (0 -7.9, 8-12, >12) and pseudo census block group.

Eight additional covariates were assessed for inclusion in the model: alcohol intake, physical activity, chronic disease status, education, marital status, smoking, menopausal hormone therapy and menopausal status. The covariates were assessed hierarchically in the model by firstly adding sociodemographic, then behavioral and lastly reproductive factors. The beta estimates were observed for changes in-estimate of absolute percentage equal to or greater than 10%. If the change equal to absolute percentage change was equal to or greater than 10%, then the factor was identified as a confounder in the model. The model building strategy and final full multivariable models are included in **Table 11**.

Table 11 Model building strategy for final multivariable linear regression models

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<b>Aim 3: Model building strategy</b>
<b>CRP</b>
Base model (Model 1): Serum CRP concentrations = $\beta_{nSES} + \beta_{AGE} + \beta_{SEX} + \beta_{RACE} + \beta_{FASTING} + \beta_{CENSUS\ BLOCK\ GROUP}$
Model 2: Serum CRP concentrations = $\beta_{nSES} + \beta_{AGE} + \beta_{SEX} + \beta_{RACE} + \beta_{FASTING} + \beta_{CENSUS\ BLOCK\ GROUP} + \beta_{BMI}$
Model 3: Serum CRP concentrations = $\beta_{nSES} + \beta_{AGE} + \beta_{SEX} + \beta_{RACE} + \beta_{FASTING} + \beta_{CENSUS\ BLOCK\ GROUP} + \beta_{BMI} + \beta_{EDUCATION} + \beta_{SMOKING} + \beta_{MENOPAUSAL\ HT}$

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## Adiponectin

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Base model (Model 1):

Serum adiponectin concentrations = nSES + AGE + SEX + RACE + FASTING+ CENSUS BLOCK GROUP

Model 2:

Serum adiponectin concentrations = nSES + AGE + SEX + RACE + FASTING+ CENSUS BLOCK GROUP + BMI

Model 3:

Serum adiponectin concentrations = nSES + AGE + SEX + RACE + FASTING+ CENSUS BLOCK GROUP + BMI +  
EDUCATION + MARITAL + ALCOHOL

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## Leptin

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Base model (Model 1):

Serum leptin concentrations = nSES + AGE + SEX + RACE + FASTING+ CENSUS BLOCK GROUP

Model 2:

Serum leptin concentrations = nSES + AGE + SEX + RACE + FASTING+ CENSUS BLOCK GROUP + BMI

Model 3:

Serum leptin concentrations = nSES + AGE + SEX + RACE + FASTING+ CENSUS BLOCK GROUP + BMI + EDUCATION  
+ MARITAL + SMOKING+ MENOPAUSAL HT

---

Adiponectin and leptin, adipose tissue derived hormonal proteins, and CRP, a hallmark indicator of inflammation, are associated with obesity, measured by BMI [318]. To assess interaction effects of 1) sex and nSES and 2) race and ethnicity and nSES, the parsimonious model (Model 2) was identified for testing multiplicative effects of these joint associations. **Figure 22** shows the relationship between neighborhood socioeconomic status and biomarkers.

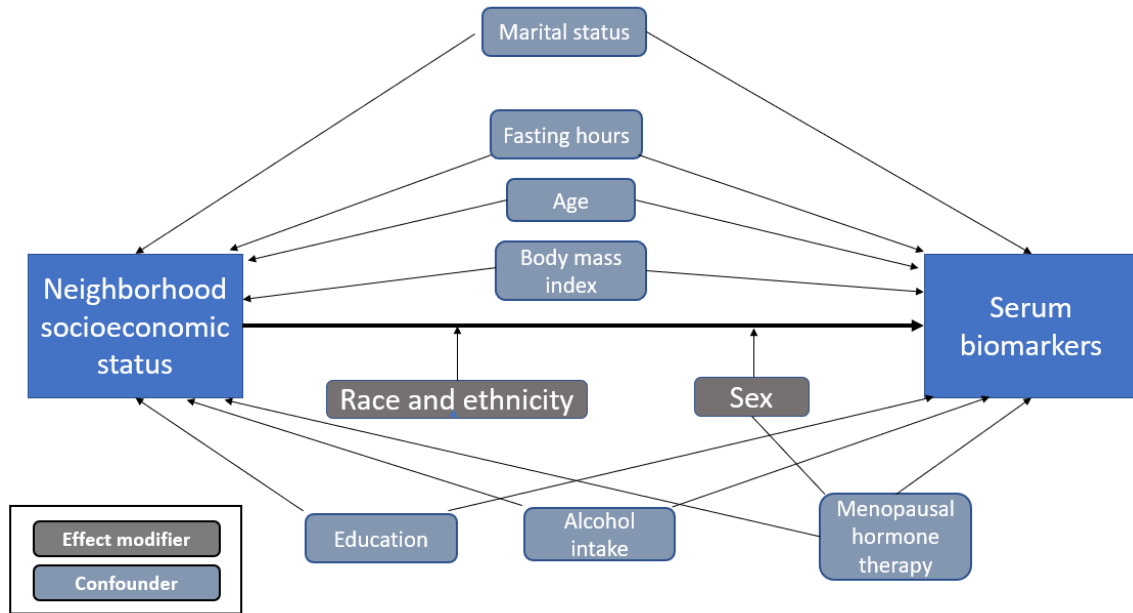


Figure 22 Direct acyclic graph

Bivariate associations were assessed to understand the direction and magnitude of association with the nSES and biomarkers. The possibility of missing values included in the analysis could lead to unbalanced differences in the analytic population by exposure or outcome. All categorical covariates with missing were retained in the model by retaining the missing values as an “unknown” category. Age at baseline was the only continuous variable included in the model and had no missing data.

### Potential biases

#### *Information bias: laboratory assays*

The serum samples from the MEC biorepository were collected and stored in liquid nitrogen. At blood collection, samples were obtained between 7am to 10am. CRP, adiponectin and leptin were analyzed using the double-antibody enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA)[271]CRP was assessed using a Cobas MiraPlus clinical chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA) and a latex

particle-enhanced immunoturbidimetry-based kit from Pointe Scientific (Lincoln Park, MI, USA)[271]. The ELISA is a standard and preferred method for determining the precise concentration of an unknown antibody [319]. In processing the ELISA, measurement error may be introduced when unintended variation in sample is prepared in the arrangement of the sample plates and handling of the biospecimen. However, studies have shown that using the 96-well ELISA reduces measurement error by introducing multiple samples for assessment to enhance the validity of results. The intra-batch coefficient of variation is a measure of variability within the samples evaluated. Generally, a high CV% > 12% may suggest a high degree of imprecision and variability within replicate samples and the scientific procedures should be repeated to produce lower more favorable CV% [320]. As reported previously [321, 322], in this dissertation study the intra-batch coefficients of variation was based on 96 blinded duplicate and 9 triplet samples for leptin, adiponectin, CRP and were 3.4–6.4%, 2.5–9.4% and 3.5–5.0%, respectively.

*Information bias: neighborhood socioeconomic status*

The cross-sectional design facilitated the assessment of associations between existing neighborhood socioeconomic status, obtained using Census data from the similar time period (1998 to 2000) as blood collection, and inflammatory biomarker data. However, the cross-sectional design has limitations including the inability to establish temporality and to assess causal associations between nSES and biomarker serum levels. While all participants had geocoded addresses during the study period, participant's residence prior to the study was not available. A prior residence could influence long term effects of the neighborhood environment that could change the types, duration, and intensity of neighborhood-level exposures such as population density, traffic patterns, violence, green space, fast food

restaurant proximity [280], which could be associated with serum biomarkers differently. However, there is minimal likelihood that the individual-level outcome could influence the neighborhood-levels such as socioeconomic status. Also, the biospecimen analyzed in this dissertation were from one available timepoint and were not available for multiple timepoints. Access to multiple biospecimen collections would enable the assessment of nSES and changes and patterns in serum biomarkers.

The participants' home address was geocoded at or around the time of the blood draw or blood draw questionnaire completion. This address represents a singular place among other locations that characterize an individual's neighborhood environment. Moreover, nSES, which is a key indicator of neighborhood characteristics, is a single indicator that does not assess changes in built, social and physical characteristics of a neighborhood during the two-year study period. In addition, unmeasured confounding could influence the association between nSES and biomarker concentrations due to the complexity of upstream factors with residual effects of structural racism, redlining impact on neighborhood socioeconomic status and the downstream factors such as individual health characterized by biological profiles of biomarkers. Despite the multifactorial influence of factors at the individual-level and neighborhood-level, the MEC data are robust and provide comprehensive information on the demographic, individual lifestyle, medication and medical history and disease history.

#### *Information bias: Individual-level adjustment factors*

The covariates assessed and included in the final models were obtained from the blood draw questionnaire and from the baseline MEC questionnaire. While education is often used as an indicator of individual-socioeconomic status, more specific data regarding the individual socioeconomic status would improve the assessment of confounding in the

multivariable linear regression assessing nSES and biomarker serum levels. Individual-level education was assessed as a proxy for individual-level SES [323], however, more detailed information to characterize the individual socioeconomic profile using employment type, employment duration, household income and number of dependents living in the household [324] would further classify participants characteristics and confounding factors thereby reducing residual confounding.

Obesity was measured using self-reported weight on the blood draw questionnaire and height from the MEC baseline questionnaire to calculate BMI. Detailed information characterizing body fat composition using visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) was unavailable at baseline. Imaging measures such as dual x-ray absorptiometry (DEXA) or the conventional measure of waist and hip circumference was not included in the baseline data collection. As a result, the variation of serum biomarker levels relative to VAT and SAT was not assessed.

Participants included in the Aim 3 study were restricted to those with two years or less between the time of their blood draw and when the blood draw questionnaire was completed. This threshold was set to reduce the effects of residual confounding in the covariate and confounding variables included in the multivariable linear regression. Ideally, measurement of covariate and confounding factors would be obtained at the same time of exposure and outcome ascertainment to minimize changes in these factors. However, the confounding effect is minimized by applying the two year or less threshold applied. Additionally, other covariates such as alcohol intake, marital status, education, and smoking status were collected at MEC baseline (1993-1996), a maximum of six years prior to the earliest blood draw date. Participants' demographic status could change during this time

leading to non-differential misclassification of covariates. However, the likelihood of misclassification among individuals in low nSES neighborhoods and individuals living in high nSES neighborhoods is expected to be similar.

## Chapter 4: Manuscript 1

Cholesterol-lowering drug use and breast cancer risk among postmenopausal women in the Multiethnic cohort (MEC) Study

Abstract

**Introduction:** Cholesterol-lowering drugs, namely statins, have been examined in relation to breast cancer risk given their proposed anticancer properties. However, prior studies have mainly been conducted among populations of White women with inconsistent associations reported. Limited studies have assessed the association between cholesterol-lowering drug use and breast cancer risk among a diverse multiethnic population of postmenopausal women.

**Methods:** Within the Multiethnic Cohort (MEC) Study, (n=41, 394 postmenopausal women), 1,681 incident invasive breast cancer cases were diagnosed during an average of 11 years of follow-up between the MEC follow-up questionnaire #3 (2003 – 2008) and end of follow-up (2017). Multivariable Cox proportional hazards regression estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between cholesterol-lowering drug use status and duration in relation to breast cancer risk overall and by race and ethnicity. Sub-group analyses by hormone receptor status were performed. Heterogeneity in associations between cholesterol-lowering drug use and breast cancer risk by race and ethnicity was assessed using multiplicative model for joint effects.

**Results:** Cholesterol-lowering drug use and duration were not associated with breast cancer risk among post-menopausal women overall, although current use  $\geq 3$  years was suggestive of a modest elevated risk (adjusted HR (aHR): 1.11 [95% CI:0.97, 1.26]). In race and ethnicity stratified analyses, there was no evidence of heterogeneity in associations by race and ethnicity ( $p$  int  $>0.05$ ), however, a statistically significant increased risk was observed among Native Hawaiian women who were current users for 3 or more years (aHR:1.61 [95% CI:1.11-2.33]) compared to never users. No statistically significant associations were

observed between cholesterol-lowering drug use and HR+ and HR- breast cancer overall and by race and ethnicity.

**Conclusions:** In analyses among all women and stratified by race and ethnicity, findings suggest a modest increase in breast cancer risk with current use of cholesterol-lowering drugs for  $\geq 3$  years. While study findings do not support a reduction in breast cancer risk with cholesterol-lowering drug use, future studies should examine the indication of cholesterol-lowering drug use to substantiate the findings among multiethnic populations of postmenopausal women.

## Introduction

Cholesterol-lowering drugs, namely statins, commonly prescribed as a pharmacologic preventative therapy to manage lipid levels and associated cardiovascular risk [325], have been examined in relation to breast cancer risk given their suggested anticancer properties. Proposed biological mechanisms for statins include the inhibition of 3-hydroxy-3-methylgluteral-Coenzyme A (HMG-CoA) reductase expression [326] in breast cancer tumors [327], induction of apoptosis [328] and inhibition of inflammation [328], key processes in breast tumorigenesis. With regards to statin efficacy, differences by race and ethnicity have been observed [329, 330]. Pharmacologic studies have shown differential response to statin therapy among African American women and women of Asian descent [331]. More specifically, at similar concentrations and dosage, women of Asian descent experience statin toxicity [330] as compared to White women [332] and a higher statin tolerance has been observed among African American women [331]. However, prior studies assessing cholesterol-lowering drug use and breast cancer risk have not examined whether associations vary among diverse racial and ethnic groups of postmenopausal women.

The majority of epidemiologic studies assessing cholesterol-lowering drug use and breast cancer risk have been conducted among predominately White and European populations [180] with primarily null associations observed. A comprehensive meta-analysis [180] included 10 prospective cohort studies conducted between 2000 and 2016 with ranging sample sizes (n= 189 to 334,754) and a pooled estimate of HR:1.0 [95% CI: 0.96, 1.05]. Prior cohort studies have observed inconsistent findings including null associations [174, 185-187, 333-336] or positive [337] or inverse associations [338] that were not statistically

significant. Majority of these studies (n=7) assessed cholesterol-lowering drug use as a binary exposure (never/ever use) and did not assess duration of use among women classified as former or current cholesterol-lowering drug users.

To expand the understanding of cholesterol-lowering drug use and breast cancer risk among multiethnic populations of postmenopausal women, the study assessed the association between cholesterol-lowering drug use and duration in relation to breast cancer risk among African American, Japanese American, Latina, Native Hawaiian, and White postmenopausal women in the Multiethnic Cohort (MEC) Study.

## Methods

### Study Design and Population

The Multiethnic Cohort (MEC) is a large prospective epidemiological study established between 1993 and 1996 to investigate cancer disparities among five racial and ethnic groups. Participants were residents of Hawaii and California, namely Los Angeles County, and were identified using driver's license records. At baseline, more than 215,000 adult participants 45 to 75 years of age completed a 26-page mailed questionnaire consisting of data on diet, lifestyle, personal and family medical history and medication use. In 2003-2008, the third MEC follow-up questionnaire was administered and included information about cholesterol-lowering drug use. Additional details on the MEC study have been described previously [339, 340]. This study was approved by the respective institutional review boards (University of Hawaii, University of Southern California, and University of Maryland).

For the present analysis, the following exclusion criteria were applied to the initial sample of women who completed the third MEC follow-up questionnaire in 2003-2008 ( $n=54,924$ ): (1) did not self-identify as one of the five racial and ethnic groups (African American, Japanese American, Latino, Native Hawaiian and White) ( $n = 3,351$ ), (2) reported breast cancer diagnosis on the third MEC follow-up questionnaire ( $n = 2,089$ ) or (3) ascertained via tumor registry ( $n = 2,588$ ), (4) had a death date that preceded the entry or diagnosis date ( $n=3$ ), (5) premenopausal ( $n=344$ ), (6) had a prior history of invasive cancer excluding non-melanoma skin cancer ( $n = 1,135$ ) or (7) were missing cholesterol-lowering drug status of use data ( $n=4,020$ ). The final analytic population comprised of 41,394 postmenopausal women (African American [13.7 %], Japanese American [31.7%], Latino [18.2%], Native Hawaiian [7.7 %], and White [28.7%]).

### Cholesterol-lowering drug exposure assessment

Participants self-reported information on cholesterol-lowering drug use and duration by responding to a series of questions: 1) “*Have you ever taken any of the following medications at least two times per week? (Lipitor, Mevacor, Zocor, Pravachol, Lopid or other)?*” and 2) “*If yes, how many years have you ever taken them?*”. Cholesterol-lowering drug use status was defined as: *never, ever/former ever/current*. Duration of cholesterol-lowering drug use was defined based on the response categories: *one year or less, 2 to 3 years, 4 to 5 years, 6 to 10 years, and 11 years or more*. Based on prior studies [186, 341] and the distribution of duration data, duration of use was operationalized as a dichotomous variable (*<3 years, ≥3 years, unknown*). Status and duration of cholesterol drug use were combined to form a variable with the following categories: *never; former, <3 years; former, ≥3 years; current, <3 years; current, ≥3 years, unknown duration of use*). The unknown category was defined as responses left blank or missing. The *never* category was used as the referent group.

### Invasive breast cancer ascertainment

Incident invasive breast cancer cases were identified through linkage with the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the statewide Hawaii Tumor Registry, all part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Information on date of diagnosis, tumor stage, hormone receptor status, age at diagnosis and hormone receptor status were also obtained from the registries. Vital status was determined by linkage to California and Hawaii death files and the National Death Index. During a mean follow-up of 11.1 years (standard deviation (SD): 3.3 years), 1,681 incident invasive breast cancer cases were diagnosed between the third MEC follow-up questionnaire (2003-2008) and the end of follow-up (December 31, 2017).

### Statistical Analyses

The distributions of sociodemographic, lifestyle and breast cancer risk factors among all women and by race and ethnicity were assessed using the mean and SD for continuous variables and frequencies and percentages for categorical variables. Differences in the distributions by race and ethnicity were evaluated using One-way ANOVA F tests for continuous variables and Chi-square tests for categorical variables.

Multivariable Cox proportional hazards regression was conducted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between cholesterol-lowering drug use and invasive breast cancer risk among postmenopausal women overall and stratified by race and ethnicity. Follow-up for postmenopausal women started at age at the third MEC follow-up questionnaire (2003-2008) and ended at the earliest of the following events: age at in situ breast cancer diagnosis, age at invasive breast cancer diagnoses, age at death or age at study completion (December 30, 2017).

Multivariable models adjusting for known breast cancer risk factors including: age at third MEC follow-up questionnaire (continuous), body mass index (< 25, 25 to <30,  $\geq 30$  kg/m<sup>2</sup>, unknown), race and ethnicity (African American, Japanese American, Latino, Native Hawaiian, White), education (high school or less, vocational school or college, graduate or professional school, unknown), marital status (married, separated/divorced, widowed, never married, unknown), Alternative Healthy Eating Index score (Q1:27-59, Q2: 60-66, Q3:67-72, Q4:73-103, unknown), alcohol intake (0-4.9, 5.0-14.9,  $\geq 15$  grams/day, unknown), smoking status (never, former, current, unknown), physical activity (0-2.9, 3-6, >6 metabolic equivalents (METs), unknown), family history of breast cancer (yes, no, unknown), age at menarche ( $\leq 12$ , 13–14, >14 years, unknown), parity: age at first birth and number of children (nulliparous, 15-20 years /1-3 children, 15-20 years /4+ children, 21-30 years/1-3 children,

21-30 years/4+ children, >30 years/1-4+ children, unknown), breastfeeding (no, breastfed for  $\leq 6$ , breastfed for 7 to 11, breastfed  $\geq 12$  months, unknown), oral contraceptive use (never, ever  $<5$ , ever  $\geq 5$  years, unknown), type of menopause: (natural, oophorectomy (includes single and double), oophorectomy (with or without hysterectomy), other surgery (including hysterectomy and endometrial ablation), unknown), menopausal hormone therapy (never estrogen use, past estrogen use with or without progestin, current estrogen use, unknown). In the overall multivariable adjusted models, heterogeneity in associations for cholesterol-lowering drug use and invasive breast cancer risk by race and ethnicity and history of cardiovascular disease was assessed using the multiplicative model for joint effects. Multivariable adjusted models for hormone receptor specific analyses estimated HRs and 95% CI of invasive hormone-receptor-positive (HR+) and hormone-receptor-negative (HR-) in separate models. HR+ was defined as estrogen-receptor positive (ER+) and progesterone-receptor positive (PR+) or negative (PR-) and HR-negative was defined as estrogen-receptor negative (ER-) and PR-.

Cox proportional hazards assumptions were assessed using log-log plots and Schoenfeld residuals for the covariates included in the multivariable models. There were no observed violations of the Cox proportional hazard assumption. A two-tailed  $p$ -value  $<0.05$  was defined as statistically significant. All statistical analyses were performed using SAS (version 9.3) (SAS Institute Inc., Cary, North Carolina).

### *Results*

Distributions of sociodemographic and breast cancer risk factors among all postmenopausal women and by race and ethnicity are summarized in **Table 1**. Women on average contributed 11.1 (SD: 3.3) years of follow-up time. The mean age at the third MEC follow-up

questionnaire was 69.3 (SD: 8.3) years ranging from 65.9 years among Native Hawaiian women to 70.4 years among African American women. Overall, the mean BMI was 26.4 (SD: 5.9) kg/m<sup>2</sup> which ranged from 23.9 (SD:4.2) kg/m<sup>2</sup> to 29.4 (SD:6.6) kg/m<sup>2</sup> by race and ethnicity with Japanese American women having a lower average BMI and African American women with a higher BMI. Overall women were more likely to be classified as light drinkers, never smokers, having no family history of breast cancer, ≤12 years old at menarche and 21 to 30 years old with 1 to 3 children. Additionally, women were more likely to never use oral contraception, have natural menopause and use estrogen and progesterone. African American women were less likely to breastfeed (compared to <37.5% in other racial and ethnic groups). Vocational school or college education were more common among African American, Japanese American, and White women whereas a high school degree or less was more common among Latina and Native Hawaiians. African American women were more likely to be separated or divorced than other racial and ethnic groups. African American and Latina women were more likely to have a low AHEI score (Q1) and White women were more likely to exert >6 METS in physical activity (40.3%).

Distributions of cholesterol-lowering drug use and duration among postmenopausal women overall and by race and ethnicity are presented in **Table 2**. Overall, 44.2% of postmenopausal women reported ever using cholesterol-lowering drugs. A higher proportion of Japanese American and Native Hawaiian women reported ever using cholesterol-lowering drugs (49.9% and 48.6%, respectively) and were more likely to be current users (43.3% and 40.1%, respectively) compared to African American, Latina and White women (< 33.3%). When considering both cholesterol-lowering drug use status and duration, Japanese American women reported the highest proportion of current cholesterol-lowering drug use

for both < 3 years (18.9%) and  $\geq$  3 years (23.2%) duration. Similarly, 18.6% of Latina women reported current use with < 3 years duration.

The distribution of select characteristics of invasive breast cancer cases are shown in **Table 3**. Overall, the mean age at diagnosis was 68.3 (SD: 7.9) years with Native Hawaiian women having the youngest age at diagnosis, 65 (SD:7.6) years compared to other racial and ethnic groups ranging from 68.2 years to 69.1 years. The proportion of women currently taking cholesterol-lowering drugs ranged from 30% among African American Women to 50% among Native Hawaiian women. Women with estrogen-receptor positive (ER+) and progesterone receptor positive (PR+) or negative (PR-) tumors ranged from 58% among African American women to 80% among Native Hawaiian women. African American women were more likely to have grade III or IV tumors whereas other groups were more likely to have grade II. Most women had localized breast cancer at diagnosis.

**Table 4** presents the multivariable adjusted estimates for the association between cholesterol-lowering drug use and duration in relation to invasive breast cancer risk overall and by race and ethnicity. Overall, no statistically significant associations were observed when cholesterol drug use was assessed as: 1) never/ever status, 2) never/former/current status, and 3) duration of use, however a modest positive association was observed by status and duration of use. In race-stratified analyses, although Native Hawaiian women who were ever users (aHR 1.38 [95% CI: 1.02,1.89]) , current users (aHR 1.47 [95% CI: 1.07, 2.01]) , users for 3 or more years (aHR 1.50 [95% CI: 1.05, 2.14]) or were current users for 3 or more years had increased risk of developing invasive breast cancer (aHR 1.61 [95% CI: 1.11, 2.33]), the interaction effects by race and ethnicity were not statistically significant ( $p\text{-int}=0.32$ ;  $p\text{-int}=0.22$ ;  $p\text{-int}=0.22$  and  $p\text{-int}=0.11$ , respectively).

Results from HR+ specific analyses are shown in **Table 5**. No statistically significant associations were observed between cholesterol-lowering use and HR+ or HR- invasive breast cancer cases (data not shown). Using the multiplicative model for joint effects, no significant interaction effects were observed between cholesterol-lowering drug use or duration of use and breast cancer risk by history of cardiovascular disease ( $P_{\text{int}} > 0.05$ ; **Supplemental table A**). Additionally, no significant interaction effects were observed between history of cardiovascular disease and breast cancer risk by race and ethnicity ( $P_{\text{int}} > 0.05$ ); **Supplemental Table B**).

### Discussion

Findings from this large, racially, and ethnically diverse prospective cohort study of postmenopausal women do not support an association between cholesterol lowering drug use and invasive breast cancer risk. Overall, no statistically significant associations were observed, although a modest positive association was observed among current users for  $\geq 3$  years. In analyses stratified by race and ethnicity, no statistically significant heterogeneity in associations was observed by race and ethnicity, however, current use  $\geq 3$  years was modestly associated with elevated risk among Native Hawaiian women. In the hormone receptor-specific analyses, no statistically significant associations were observed among HR+ and HR- breast cancer cases.

Prior studies [180] have shown primarily null associations between statin use and breast cancer risk in predominantly White and European populations. A meta-analysis conducted by Islam et al. comprehensively assessed ten prospective cohort studies examining statin use and breast cancer risk [180]. The majority of individual studies reported null associations [174, 185-187, 333-336], or positive [337] or inverse associations [338] that

were not statistically significant, and when meta-analyzed yielded a pooled estimate (HR:1.0 [95% CI: 0.96, 1.05]) suggesting null associations between statin use and breast cancer risk [180]. Of the individual studies included in this meta-analysis, seven studies defined statin use as never/ever [174, 187, 333, 334, 336-338], two studies considered duration of use ( $\leq 4$  years,  $< 4$  to  $< 8$  years, and  $\geq 8$  years or  $< 5$  and  $> 5$  years as cut points)[185, 187] and one study examined statin use and breast cancer risk by molecular subtype [335]. Although the current analysis did not have complete classification of cholesterol-lowering drugs in the third MEC follow-up questionnaire, supplemental information provided about participants cholesterol-lowering drug class suggested most cholesterol-lowering drug users were taking statins. The current analysis expands the assessment of cholesterol-lowering drug use in previous studies by evaluating both cholesterol-lowering drug use and duration data among diverse multiethnic populations of postmenopausal women.

In the present analysis, and in agreement with the findings from prior studies [180] no statistically significant associations were observed in analyses of all postmenopausal women when never/ever cholesterol-lowering drug use was assessed in relation to breast cancer risk and no associations were observed among White postmenopausal women, the most comparable racial group included in the current study. A prospective cohort study conducted by Jacobs et al. did not observe statistically significant associations in the overall estimate for former use (Risk Ratio [RR]: 0.96, 95% CI: 0.72, 1.27), current use for  $< 5$  years ([RR]: 0.98 95% CI :0.88, 1.10) and current use for  $\geq 5$  years ([RR]: 1.11 95% CI :0.98, 1.25) in relation to breast cancer risk. Another prospective cohort study using data from the Nurse's Health Study (n=77,845) conducted by Borquist et al. also did not observe statistically significant associations for former and current statin users with duration of use for  $\leq 4$  years,  $< 4$  to  $< 8$

years, and  $\geq 8$  years [185]. Although the current analysis expanded the statin use and duration exposure assessment to include a former status with duration of cholesterol-lowering drug use, no associations were observed among those with former use  $< 3$  years or  $\geq 3$  years suggesting statins are not associated with breast cancer risk irrespective of former or current use.

While prior studies have reported null associations among predominantly White populations of postmenopausal women, limited studies have assessed cholesterol-lowering drug use by race and ethnicity [342]. In the present analysis, the statistically significant positive associations between cholesterol-lowering drugs and breast cancer risk among Native Hawaiian women and modest positive association among Japanese American women did not support the study hypothesis of which cholesterol-lowering drug use would reduce breast cancer risk and vary by race and ethnicity. Despite these positive associations, the heterogeneity in associations by race and ethnicity were not statistically significant. To explore the associations observed among Native Hawaiian women, interaction effects between self-reported history of cardiovascular disease and race and ethnicity in relation to breast cancer risk were assessed given the higher prevalence of cardiovascular disease among Native Hawaiian women at the national level compared to non-Hispanic White women [343, 344]. However, no interaction effects were observed between history of cardiovascular disease and breast cancer risk by race and ethnicity. In the current study, while Native Hawaiian women have the highest prevalence of cholesterol-lowering use among breast cancer cases (49.5% compared to  $<46\%$  among other racial and ethnic groups of women), Native Hawaiians also have the smallest sample case size compared to other racial and ethnic groups of postmenopausal women that should be considered when interpreting the findings.

Moreover, high cholesterol levels are closely linked to cardiovascular disease and obesity [345] and Native Hawaiian women in MEC have a higher prevalence of obesity, a higher prevalence of dyslipidemia and diabetes [152] and increased risk of breast cancer in other studies [344, 346, 347]. Although BMI as a measure of obesity was included as an adjustment factor in the models, there is possibility of residual confounding associated with obesity. Potential explanations for the observed association in risk among Native Hawaiian women are complex and should be interpreted with caution given the relatively small sample of breast cancer cases. Future studies should focus on assessing cholesterol-lowering drug use and duration in relation to breast cancer risk by race and ethnicity.

In addition to limited studies among diverse racial and ethnic populations, associations have not been examined by hormone receptor status. A prior large retrospective population-based cohort conducted by Boudreau et al. [335] assessed the association between statin use and estrogen receptor-positive (ER+) and negative (ER-) breast cancer. Ever and current statin use was not associated with ER+ or ER- breast cancer when compared to never statin users[335]. Similarly, in the present analysis, null associations were observed between cholesterol-lowering drug use and HR+ and HR- breast cancer. The current study uses hormone receptor status categorization of HR+ as ER+/PR+, ER+/PR-, ER-/PR+ and HR- as ER-/PR- which differs slightly from the Boudreau et al. study in which ER- cases were defined as ER+/PR- *and* ER-/PR-. Despite this difference, the current study findings support the null findings from the Boudreau et al. study.

There are several limitations to consider in this study. Information on the classification of cholesterol-lowering drugs was limited and did not permit further assessment of cholesterol-lowering drug use by drug classification and breast cancer risk. In addition, the

indication for cholesterol-lowering drug prescription was not available and could not inform the disease state or condition linked to an individual's use of cholesterol-lowering drugs which could suggest the possibility of residual confounding. Although duration of cholesterol-lowering drug use was evaluated, the specific timeframe response categories were limited to  $< 3$  years and  $\geq 3$  years. Analyses examining the association between cholesterol-lowering drug use and breast cancer risk by race and ethnicity were limited by case counts less than 20 among the never/former/current and status and duration of use variables. Moreover, participants could have changed their cholesterol-lowering drug use status and duration of use during the follow-up period.

This study extends prior research by assessing cholesterol-lowering drug use and breast cancer risk among diverse racial and ethnic groups of postmenopausal women in the MEC study. The MEC questionnaire collected comprehensive sociodemographic, lifestyle behavior, medical history pertinent to assess and adjust for known potential confounders. In summary, findings from the present study corroborate the null findings suggested in prior studies [180, 185, 335] and extend understanding of the association between of cholesterol-lowering drug use and duration and breast cancer risk among multiethnic population of postmenopausal women. Future studies should examine the indication of cholesterol-lowering drug use to substantiate the findings among multiethnic populations of postmenopausal women.

*Tables and Figures for Manuscript 1*

Table 1. Distributions of breast cancer risk factors among postmenopausal women overall and by race and ethnicity at the third Multiethnic Cohort follow-up questionnaire (2003)

	Overall n = 41,394	African American n = 5,665	Japanese American n = 13,112	Latina n = 7,544	Native Hawaiian n = 3,183	White N = 11,890
Follow-up time, mean years (SD)	11.1 (3.3)	10.8 (3.6)	11.3 (3.2)	11.3 (3.2)	10.9 (3.4)	10.9 (3.3)
Age, mean years (SD)	69.3 (8.3)	70.4 (8.5)	70.3 (8.6)	69.4 (7.3)	65.9 (7.9)	68.5 (8.4)
Body mass index, kg/m <sup>2</sup> (SD)	26.4 (5.9)	29.4 (6.6)	23.9 (4.2)	28.2 (5.7)	29.2 (6.8)	26.2 (5.7)
Education, years, n (%)						
High school or less	15,212 (36.7)	1,710 (30.2)	4,400 (33.6)	4,735 (62.8)	1,539 (48.3)	2,828 (23.8)
Vocational school/college	19,349 (46.8)	3,075 (54.3)	6,391 (48.7)	2,270 (30.1)	1,343 (42.2)	6,270 (52.7)
Graduate or professional school	6,476 (15.7)	824 (14.6)	2,234 (17.0)	433 (5.7)	281 (8.8)	2,704 (22.8)
Marital status, n (%)						
Married	21,568 (52.1)	1,659 (29.3)	8,086 (61.7)	3,672 (48.7)	1,808 (56.8)	6,343 (53.4)
Separated/divorced	7,133 (17.2)	1,671 (29.5)	1,258 (9.6)	1,419 (18.8)	472 (14.8)	2,313 (19.5)
Widowed	9,587 (23.2)	1,821 (32.1)	2,849 (21.7)	1,765 (23.4)	738 (23.2)	2,414 (20.3)
Never married	2,248 (5.4)	311 (5.5)	745 (5.7)	446 (5.9)	122 (3.8)	624 (5.3)
Alternative Healthy Eating Index score, n (%)						
Q1: 27-59	9,944 (24.0)	1,786 (31.5)	1,883 (14.4)	2,946 (39.1)	652 (20.5)	2,677 (22.5)
Q2: 60-66	10,014 (24.2)	1,536 (27.1)	2,904 (22.2)	2,052 (27.2)	789 (24.8)	2,733 (23.0)
Q3: 67-72	9,078 (21.9)	1,135 (20.0)	3,300 (25.2)	1,355 (18.0)	777 (24.4)	2,511 (21.1)
Q4: 73 - 103	10,889 (26.3)	1,023 (18.1)	4,571 (34.9)	931 (12.3)	859 (27.0)	3,505 (29.5)
Alcohol intake, gram/day, n (%)						
0-4.9	33,449 (80.8)	4,825 (85.2)	11,821 (90.2)	6,571 (87.1)	2,636 (82.8)	7,596 (63.9)
5.0-14.9	3,401 (8.2)	366 (6.5)	511 (3.9)	457 (6.1)	266 (8.4)	1,801 (15.2)
≥15	3,075 (7.4)	289 (5.1)	326 (2.5)	256 (3.4)	175 (5.5)	2,029 (17.1)
Smoking status, n (%)						
Never	23,245 (56.2)	2,622 (46.3)	8,925 (68.1)	4,643 (61.6)	1,476 (46.4)	5,579 (46.9)
Former	14,709 (35.5)	2,458 (43.4)	3,439 (26.2)	2,175 (28.8)	1,321 (41.5)	5,316 (44.7)
Current	2,373 (5.7)	424 (7.5)	508 (3.9)	281 (3.7)	323 (10.2)	837 (7.0)
Physical activity, METs, n (%)						
0 - 2.9	16,918 (40.9)	2,993 (52.9)	5,447 (41.6)	3,400 (45.1)	1,228 (38.6)	3,850 (32.4)
3 - 6	9,943 (24.0)	1,167 (20.6)	3,379 (25.8)	1,708 (22.6)	819 (25.7)	2,870 (24.1)
>6	12,872 (31.1)	1,207 (21.3)	3,878 (29.6)	1,942 (25.8)	1,058 (33.3)	4,787 (40.3)
Family history of breast cancer †, n (%)						
No	34,045 (82.3)	4,666 (82.4)	10,750 (82.0)	6,418 (85.1)	2,477 (77.8)	9,734 (81.9)
Yes	7,336 (17.7)	998 (17.6)	2,361 (18.0)	1,120 (14.8)	704 (22.1)	2,153 (18.1)
Age at menarche, years, n (%)						
≤12	20,960 (50.6)	2,886 (50.9)	6,776 (51.7)	3,706 (49.1)	1,772 (55.6)	5,824 (49.0)

	Overall n = 41,394	African American n = 5,665	Japanese American n = 13,112	Latina n = 7,544	Native Hawaiian n = 3,183	White N = 11,890
13-14	15,432 (37.3)	2,049 (36.2)	4,765 (36.4)	2,807 (37.2)	1,046 (32.9)	4,765 (40.1)
>14	4,583 (11.1)	665 (11.7)	1,447 (11.0)	933 (12.4)	326 (10.3)	1,212 (10.2)
Parity, age at first birth, n (%)						
Nulliparous	5,220 (12.6)	704 (12.4)	1,690 (12.9)	591 (7.8)	223 (7.0)	2,012 (16.9)
15-20y/1-3 children	4,981 (12.0)	1,227 (21.7)	793 (6.1)	895 (11.9)	464 (14.6)	1,602 (13.5)
15-20y/4+ children	5,443 (13.2)	1,137 (20.1)	455 (3.5)	1,892 (25.1)	866 (27.2)	1,093 (9.2)
21-30y/1-3 children	15,874 (38.4)	1,558 (27.5)	6,925 (52.8)	1,951 (25.9)	865 (27.2)	4,575 (38.5)
21-30y/4+ children	5,910 (14.3)	593 (10.5)	1,770 (13.5)	1,536 (20.4)	546 (17.2)	1,465 (12.3)
>30y/1-4+ children	2,784 (6.7)	245 (4.3)	1,143 (8.7)	411 (5.5)	100 (3.1)	885 (7.4)
Breastfeeding and duration, months, n (%)						
Never breastfed	14,273 (54.8)	2,492 (50.4)	3,814 (29.1)	2,826 (37.5)	1,190 (37.4)	3,951 (33.2)
Breastfed, ≤ 6	15,480 (59.5)	1,748 (35.3)	5,772 (44.0)	2,558 (33.9)	1,321 (41.5)	4,081 (34.3)
Breastfed 7 to 11	3,707 (14.2)	440 (8.9)	1,188 (9.1)	781 (10.4)	223 (7.0)	1,075 (9.0)
Breastfed ≥ 12	1,758 (6.8)	139 (2.8)	411 (3.1)	500 (6.6)	145 (4.6)	563 (4.7)
Oral contraceptive use, n (%)						
Never	20,471 (49.4)	2,686 (47.4)	7,701 (58.7)	3,997 (53.0)	1,433 (45.0)	4,654 (39.1)
Ever user, < 5 years	12,589 (30.4)	1,673 (29.5)	3,467 (26.5)	2,212 (29.3)	1,075 (33.8)	4,162 (35.0)
Ever user, ≥ 5 years	7,508 (18.1)	1,198 (21.2)	1,752 (13.4)	984 (13.0)	629 (19.7)	2,945 (24.8)
Type of menopause, n (%)						
Natural menopause	27,289 (65.9)	3,011 (53.2)	9,400 (71.7)	4,828 (64.0)	2,042 (64.2)	8,008 (67.4)
Surgical menopause <sup>§</sup>	7,189 (17.4)	1,257 (22.2)	2,166 (16.5)	1,182 (15.7)	607 (19.0)	1,977 (16.6)
Other surgery <sup>¶</sup>	6,370 (15.4)	1,299 (22.9)	1,383 (10.5)	1,415 (18.8)	479 (15.1)	1,794 (15.1)
Unknown reason for menopause	546 (1.3)	98 (1.7)	163 (1.2)	119 (1.6)	55 (1.7)	111 (0.9)
Menopausal hormone therapy, n (%)						
Never estrogen use	12,158 (29.4)	2,169 (38.3)	3,480 (26.5)	2,343 (31.1)	1,120 (35.2)	3,046 (25.6)
Past estrogen and progesterone use	19,491 (47.1)	2,548 (45.0)	6,334 (48.3)	3,515 (46.6)	1,422 (44.7)	5,672 (47.7)
Current estrogen use only	8,085 (19.5)	670 (11.8)	2,861 (21.8)	1,132 (15.0)	536 (16.8)	2,886 (24.3)

SD – Standard deviation. Totals may not sum to 100% due to missing values. † Family history refers to immediate family members including mother, father, brother(s) and sister(s); § oophorectomy; ¶ Hysterectomy or endometrial ablation. All p-values for Chi-square tests of categorical variables and One-way ANOVA F tests for continuous variables p<0.05.

Table 2. Distribution of cholesterol-lowering drug use and duration among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (2003)

Cholesterol-lowering drug use	Overall n = 41,394	African American n = 5,665	Japanese American n = 13,112	Latina n = 7,544	Native Hawaiian n = 3,183	White n= 11,890
Never/ever, n (%)						
Never	23,093 (55.8)	3,159 (55.8)	6,566 (50.1)	4,192 (55.6)	1,635 (51.4)	7,541 (63.4)
Ever	18,301 (44.2)	2,506 (44.2)	6,546 (49.9)	3,352 (44.4)	1,548 (48.6)	4,349 (36.6)
Ever/former/current, n (%)						
Never	23,093 (55.8)	3,159 (55.8)	6,566 (50.1)	4,192 (55.6)	1,635 (51.4)	7,541 (63.4)
Former	3,261 (7.9)	614 (10.8)	865 (6.6)	835 (11.1)	271 (8.5)	676 (5.7)
Current	15,040 (36.3)	1,892 (33.4)	5,681 (43.3)	2,517 (33.3)	1,277 (40.1)	3,673 (30.9)
Duration of use, n (%)						
Never	23,093 (55.8)	3,159 (55.8)	6,566 (50.1)	4,192 (55.6)	1,635 (51.4)	7,541 (63.4)
< 3 years	9,550 (23.1)	1,443 (25.5)	3,015 (23.0)	2,018 (26.8)	790 (24.8)	2,284 (19.2)
≥ 3 years	7,972 (19.2)	895(15.7)	3,333 (25.4)	1,113 (14.7)	709 (22.2)	1,922(16.1)
Unknown	779 (1.9)	168 (3.0)	198 (1.5)	221 (2.9)	49 (1.5)	143 (1.2)
Status and duration, n (%)						
Never	23,093 (55.8)	3,159 (55.8)	6,566 (50.1)	4,192 (55.6)	1,635 (51.4)	7,541 (63.4)
Former, <3 years	2,243 (5.4)	427 (7.5)	534 (4.1)	613 (8.1)	200 (6.3)	469 (3.9)
Former, ≥ 3 years	745 (1.8)	116 (2.1)	288 (2.2)	128 (1.7)	56 (1.8)	157 (1.3)
Current, <3 years	7,307 (17.7)	1,016 (17.9)	2,481 (18.9)	1,405 (18.6)	590 (18.5)	1,815 (15.3)
Current, ≥ 3 years	7,227 (17.5)	779 (13.8)	3,045 (23.2)	985 (13.1)	653 (20.5)	1,765 (14.8)
Unknown duration	779 (1.9)	168 (3.0)	198 (1.5)	221 (2.9)	49 (1.5)	143 (1.2)

All p-values for Chi-square tests of categorical variables and One-way ANOVA F tests for continuous variables p<0.05.

Table 3. Select characteristics of invasive breast cancer cases among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (2003-2017)

	Overall n=1,681	African American n=219	Japanese American n=562	Latina n=234	Native Hawaiian n=184	White n=482
			Mean (Standard deviation)			
Age at diagnosis, years	68.3 (7.9)	69.1 (8.2)	68.7 (7.9)	69.1 (7.1)	65 (7.6)	68.2 (7.8)
Time to diagnosis, years	6.0 (3.7)	5.7 (3.4)	6.3 (3.8)	5.5 (3.6)	6.5 (3.7)	5.9 (3.7)
			n (%)			
Cholesterol-lowering drug use status						
Never	912 (54.3)	128 (58.5)	269 (47.9)	126 (53.9)	80 (43.5)	309 (64.1)
Former	118 (7.0)	25 (11.4)	34 (6.1)	29 (12.4)	13 (7.1)	17 (3.5)
Current	651 (38.7)	66 (30.1)	259 (46.1)	79 (33.8)	91 (49.5)	156 (32.4)
Hormone receptor status						
ER+ PR+/-	1,156 (68.8)	127 (58.0)	394 (70.1)	138 (59)	146 (79.4)	351 (72.8)
ER- PR+/-	440 (26.2)	75 (34.3)	151 (26.9)	70 (29.9)	32 (17.4)	112 (23.2)
Borderline/unknown	85 (5.1)	17 (7.8)	17 (3.0)	26 (11.1)	6 (3.3)	19 (3.9)
Tumor grade						
Grade I <sup>†</sup>	468 (27.8)	46 (21.0)	187 (33.2)	41 (17.5)	57 (31.0)	137 (28.4)
Grade II <sup>§</sup>	698 (41.5)	69 (31.5)	242 (43.1)	94 (40.2)	84 (45.7)	209 (43.4)
Grade III and IV <sup>¶</sup>	433 (25.8)	90 (41.1)	117 (20.9)	81 (34.6)	35 (19.0)	110 (22.8)
Disease stage at diagnosis						
Localized	1,225 (72.9)	149 (68.0)	452 (80.4)	157 (67.1)	126 (68.5)	342 (71.0)
Regional/distant	419 (24.9)	67 (30.6)	101 (18.0)	71 (30.3)	56 (30.4)	124 (25.7)

Total may not equal 100% due to missing.

All p-values for Chi-square tests of categorical variables and One-way ANOVA F tests for continuous variables p<0.05.

ER+: estrogen receptor positive; ER-: ER negative; PR+: progesterone receptor positive; PR-: PR negative

<sup>†</sup>Well differentiated;

<sup>§</sup> Moderately differentiated;

<sup>¶</sup> Poorly differentiated and Undifferentiated.

Table 4. Association between cholesterol-lowering drug use and duration and invasive breast cancer risk among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort, (2003 – 2017)

Cholesterol-lowering drug use	Overall		African American			Japanese American			Latina			Native Hawaiian			White			P int	
	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR		95% CI
Never/ever																			0.32
Never	912	1.00		128	1.00		269	1.00		126	1.00		80	1.00		309	1.00		
Ever	769	1.05	0.95, 1.16	91	0.95	0.72, 1.25	293	1.10	0.93, 1.30	108	1.09	0.84, 1.42	104	1.38	1.02, 1.89	173	0.92	0.75, 1.11	
Never/former/current																			0.22
Never	912	1.00		128	1.00		269	1.00		126	1.00		80	1.00		309	1.00		
Former	118	0.98	0.81, 1.19	25	1.10	0.71, 1.70	34	1.05	0.73, 1.50	29	1.23	0.81, 1.85	-			-			
Current	651	1.07	0.96, 1.18	66	0.90	0.67, 1.22	259	1.11	0.93, 1.32	79	1.05	0.78, 1.40	91	1.47	1.07, 2.01	156	0.97	0.80, 1.19	
Duration of use																			
Never	912	1.00		128	1.00		269	1.00		126	1.00		80	1.00		309	1.00		0.22
≤ 3 years	388	1.04	0.92, 1.17	64	1.17	0.86, 1.58	131	1.10	0.89, 1.36	60	0.98	0.72, 1.34	45	1.09	0.75, 1.58	88	0.88	0.69, 1.12	
≥ 3 years	353	1.14	1.00, 1.29	23	0.67	0.43, 1.05	159	1.18	0.97, 1.45	38	1.09	0.75, 1.56	53	1.50	1.05, 2.14	80	0.98	0.76, 1.26	
Status and duration																			0.11
Never	912	1.00		128	1.00		269	1.00		126	1.00		80	1.00		309	1.00		
Former, <3 years	84	1.01	0.81, 1.26	-			25	1.25	0.83, 1.89	-			-			-			
Former, ≥ 3 years	27	0.97	0.66, 1.42	-			-			-			-			-			
Current, <3 years	304	1.03	0.90, 1.17	45	1.13	0.80, 1.59	106	1.04	0.83, 1.31	42	1.01	0.71, 1.44	35	1.20	0.80, 1.80	76	0.94	0.73, 1.21	
Current, ≥ 3 years	326	1.11	0.97, 1.26	-			150	1.19	0.97, 1.46	31	1.03	0.69, 1.53	50	1.61	1.11, 2.33	76	1.01	0.78, 1.30	
Unknown duration	21	1.02	0.69, 1.48	-			-			-			-	2.86	1.21, 7.79	-			

(–) Indicates small case count <20. HR: Hazard ratios; CI: Confidence Intervals. Multivariable model adjusted for age, race (overall model only), body mass index, education, marital status, alcohol intake, Alternative Healthy Eating Index score, physical activity, history of breast cancer, age at menarche, parity: age at first birth, menopause type, oral contraceptive use, breastfeeding, and menopause hormone therapy. Interaction effects between cholesterol-lowering drug use and race and ethnicity were assessed using multiplicative model for joint effects.

Table 5. Association between cholesterol-lowering drug use and duration and risk of hormone receptor-positive invasive breast cancer among postmenopausal women overall in the Multiethnic Cohort, (2003 – 2017)

Cholesterol-lowering drug use	Hormone receptor-positive breast cancer		
	Cases, N=1,376	HR (95% CI)	p-value
<b>Never/ever</b>			
Never	747	1.00	
Ever	629	1.05 (0.94, 1.17)	0.37
<b>Never/former/current</b>			
Never	747	1.00	
Former	96	0.98 (0.81,1.19)	0.96
Current	533	1.07 (0.96,1.18)	0.30
<b>Duration of use</b>			
Never	747	1.00	
< 3 months	319	1.02 (0.90, 1.17)	0.67
≥ 3 months	285	1.06 (0.92, 1.22)	0.40
<b>Status and duration</b>			
Never	747	1.00	
Former, <3 years	68	1.02 (0.80, 1.31)	0.90
Former, ≥3 years	21	0.93 (0.60, 1.44)	0.78
Current, < 3 years	251	1.03 (0.90, 1.19)	0.61
Current, ≥ 3 years	264	1.08 (0.93, 1.25)	0.31
Missing duration	25	1.15 (0.77, 1.72)	0.49

(-) Indicates small case count; HR: Hazard ratios; CI: confidence interval. Multivariable model adjusted for age, race, body mass index marital status, alcohol intake, Alternative Healthy Eating Index, physical activity (metabolic equivalents), family history of breast cancer, age at menarche, age at first birth, number of live births, breastfeeding, menopause type, oral contraceptive use and menopausal hormone therapy use.

Supplemental Table A. Association between cholesterol-lowering drug use and duration and breast cancer risk among postmenopausal women by history of cardiovascular disease in the Multiethnic Cohort, (2003 – 2017)

	History of cardiovascular disease n=24,285		No history of cardiovascular disease n = 17,109		<i>P</i> int
	Cases, n=1,014	HR (95% CI)	Cases, n=667	HR (95% CI)	
<b>Cholesterol-lowering drug use</b>					
<b>Never/ever</b>					0.11
Never	444	1.00	468	1.00	
Ever	570	1.00 (0.89, 1.14)	199	1.10 (0.92, 1.30)	
<b>Never/former/current</b>					0.07
Never	444	1.00	468	1.00	
Former	91	1.05 (0.84, 1.32)	27	0.75 (0.50, 1.10)	
Current	479	1.03 (0.87, 1.14)	172	1.19 (0.99, 1.42)	
<b>Duration of use</b>					0.09
Never	444	1.00	468	1.00	
< 3 months	283	1.00 (0.86, 1.16)	105	1.01 (0.82, 1.13)	
≥ 3 months	266	1.02 (0.87, 1.18)	87	1.24 (0.98, 1.57)	
<b>Status and duration</b>					0.05
Never	444	1.00	468	1.00	
Former, <3 years	63	1.07 (0.82, 1.40)	21	0.78 (0.50, 1.21)	
Former, ≥3 years	22	1.06 (0.69, 1.63)	-		
Current, < 3 years	220	0.99 (0.85, 1.18)	84	1.08 (0.85, 1.36)	
Current, ≥ 3 years	244	1.08 (0.91, 1.25)	82	1.31 (1.03, 1.67)	
Missing duration	21	0.98 (0.63, 1.53)	-		

HR: Hazard ratios; CI: confidence interval; Multivariable model adjusted for age, race, body mass index, marital status, alcohol intake, Alternative Healthy Eating Index, physical activity (metabolic equivalents), family history of breast cancer, age at menarche, age at first birth, number of live births, breastfeeding, menopause type, oral contraceptive use and menopausal hormone therapy use. ( - ) indicates small sample size (<20). Interaction effects between cholesterol-lowering drug use and race and ethnicity were assessed using multiplicative model for joint effects.

Supplemental Table B. Association between history of cardiovascular disease and breast cancer risk among postmenopausal women by race and ethnicity in the Multiethnic Cohort, (2003 – 2017)

History of cardiovascular disease	African American Cases, n = 219		Japanese American Cases, n = 562		Latina Cases, n = 234		Native Hawaiian Cases, n = 184		White Cases, n = 482		P <sub>int</sub>
	Cases, n	HR (95% CI)	Cases, n	HR (95% CI)	Cases, n	HR (95% CI)	Cases, n	HR (95% CI)	Cases, n	HR (95% CI)	
No	50	1.00	221	1.00	90	1.00	55	1.00	251	1.00	
Yes	169	1.07 (0.77, 1.50)	341	1.17 (0.98, 1.40)	144	1.07 (0.82, 1.41)	129	1.34 (0.96, 1.88)	231	1.00 (0.82, 1.21)	0.16

HR: Hazard ratios; CI: confidence interval; Multivariable model adjusted for age, body mass index marital status, alcohol intake, Alternative Healthy Eating Index, physical activity (metabolic equivalents), family history of breast cancer, age at menarche, age at first birth, number of live births, breastfeeding, menopause type, oral contraceptive use and menopausal hormone therapy use. Interaction effects between cholesterol-lowering drug use and race and ethnicity were assessed using multiplicative model for joint effects.

## Chapter 5: Manuscript 2

Association Between a Healthy Lifestyle Index and Breast Cancer Risk among Postmenopausal Women in the Multiethnic Cohort (MEC) Study

*Abstract*

**Background:** A healthy lifestyle index (HLI), characterized by a healthy weight, engaging in physical activity, limiting alcohol consumption, eating healthy and not smoking, has been associated with a reduction in postmenopausal breast cancer risk. However, this association has not been well studied in racially and ethnically diverse populations of postmenopausal women for whom the prevalence of these lifestyle factors vary. Moreover, emerging breast cancer risk factors such as sleep duration and sedentary behavior have not been considered as HLI components.

**Methods:** Within the Multiethnic Cohort study, the association between the HLI and breast cancer risk was assessed among 65,561 eligible postmenopausal women (African American [18.7 %], Native Hawaiian [6.7 %], Japanese American [28.3%], Latina [21.1%], and White [25.3%]). During a mean follow-up of 19.2 years, 4,555 incident invasive breast cancer cases were diagnosed between baseline (1993-1996) and the end of follow-up (2017). Self-reported baseline information on seven lifestyle factors: dietary intake, physical activity, sedentary behavior, alcohol intake, smoking status and pack-years, body mass index (BMI) and sleep duration was used to create an HLI based on the sum of scores (range: 7 to 23). Multivariable and race and ethnicity stratified adjusted Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between the HLI score (tertiles) and breast cancer risk overall and by hormone receptor (HR) subtype (HR-positive, HR-negative).

**Results:** Postmenopausal women with higher HLI scores were at reduced risk of invasive breast cancer compared to women with lower HLI scores (T1) with a significant dose-response observed (adjusted hazard ratio (aHR)<sub>T2</sub>: 0.88 [95% CI:0.79-0.97]; aHR<sub>T3</sub>: 0.76

[95% CI: 0.69–0.84]; p-trend <0.01). Similar patterns were observed across all racial and ethnic groups with statistically significant inverse associations observed among Native Hawaiian and White women. Native Hawaiian women with higher HLI scores (aHR<sub>T2</sub>: 0.72 [95% CI: 0.56–0.94] and aHR<sub>T3</sub>: 0.67 [95% CI: 0.51–0.87], p-trend <0.01) and White women with HLI score in the highest tertile (aHR<sub>T3</sub>: 0.76 [95% CI: 0.64–0.91], p-trend <0.0) had a reduced risk of breast cancer. Similarly, a higher HLI score was significantly associated with a reduction in HR-positive breast cancer among all women (aHR<sub>T2</sub>: 0.89 [95% CI: 0.79–1.00]; aHR<sub>T3</sub>: 0.77 [95% CI: 0.68–0.87]) (p-trend <0.01) and specifically, among Native Hawaiian and White women; inverse associations among other women were not statistically significant. No association was observed in analyses of HR-negative breast cancer. Sensitivity analyses excluding sleep duration and sedentary behavior yielded similar findings.

**Conclusion:** Study findings suggest that postmenopausal women with higher HLI scores have a reduced risk of breast cancer, with similar inverse associations observed among racial and ethnic groups. This analysis lends further support to the American Cancer Society’s recommendation for maintaining a healthy lifestyle to reduce the risk of breast cancer among all women and expands the field of breast cancer disparities to further understand the HLI and breast cancer risk among racial and ethnic groups of postmenopausal women.

## Introduction

Recent studies have examined a healthy lifestyle index (HLI) in relation to breast cancer risk with consistent evidence supporting a risk reduction with increasing HLI composite scores (1-6). HLI components examined include body mass index (BMI), physical activity, alcohol intake, dietary intake and smoking status given observed relationships between these individual lifestyle factors and cancer [35, 348, 349]. Examining an HLI provides an opportunity to assess multiple factors in tandem given that many lifestyle factors often cluster together [350] and thus, the collective assessment or a combination of these modifiable lifestyle factors may lead to differential magnitudes of risk reduction [351].

The prevalence of healthy lifestyle factors vary across racial and ethnic groups of women [352] and may influence the association with breast cancer risk differently when assessing these factors collectively. However, prior HLI and breast cancer studies [250, 254-258] including other cancer outcomes [54, 353] have mainly examined associations among predominantly White, British or European women. Prior prospective studies have examined the HLI in relation to breast cancer with reductions in risk ranging from 17% to 26% when comparing those with the highest HLI score to the lowest HLI score [250, 254-258]. While these prior studies support inverse associations of a healthy lifestyle, measured by a higher HLI score, and breast cancer risk, it remains unclear whether the observed reductions in risk vary by race and ethnicity.

HLI studies to date have consistently assessed five factors or a combination of these factors: body mass index, BMI, physical activity, alcohol intake, smoking and diet. Obesity [354, 355] and alcohol consumption [246, 356] increase postmenopausal breast cancer risk while physical activity has been shown to be protective [35, 357]. In addition to these lifestyle factors, sedentary behavior [358] and sleep [316, 359] are emerging as cancer risk

factors. Sleep is hypothesized to influence breast cancer risk through mechanisms linked to circulating hormones and insulin involved in various chronic conditions [360] associated with insufficient sleep [361]. Although epidemiologic studies suggest no association between sleep and breast cancer risk, [362], these prior studies were examined among White and European populations. Limited studies have been conducted among diverse racial and ethnic groups despite two prior MEC study studies [48, 316] suggesting the importance of understanding the interrelationship of sleep and breast cancer etiology. Accumulating epidemiologic evidence [358] also suggests sedentary behavior increases the risk of breast cancer [358], independent of physical activity. However, prior HLI studies have not considered the addition of sleep and sedentary behavior as HLI components.

To further understand the collective effects of modifiable lifestyle factors, this study examined an expanded, seven component HLI, comprised of dietary intake, physical activity, sedentary behavior, BMI, smoking status and pack-years, alcohol intake and sleep duration, in relation to breast cancer risk among postmenopausal women in the MEC study, overall and by race and ethnicity.

## Methods

### Study Design and Population

The Multiethnic Cohort (MEC) study established between 1993 and 1996 to investigate cancer disparities among five racial and ethnic groups is comprised of more than 215,000 adult participants 45 to 75 years of age. Participants completed a 26-page mailed baseline questionnaire consisting of data on diet, lifestyle, personal and family medical history and medication use and were residents of Hawaii and California, namely Los Angeles County. Additional details of the MEC study design and recruitment methodology have been previously described [340]. This study was approved by the respective institutional review

boards (University of Hawaii, University of Southern California, and University of Maryland).

For the present study, the following exclusion criteria were applied to the initial sample of women in MEC (n=118,748): did not self-identify as one of the five racial and ethnic groups (African American, Japanese American, Latina, Native Hawaiian or White) (n=7,150), reported breast cancer diagnosis on the baseline questionnaire (n=4,894) or via tumor registry (n=179), had a death date that preceded the diagnosis or study entry date (n=7), had a follow-up time  $\leq$  zero (n=5), were pre-menopausal (n = 23,951), had a prior history of invasive cancer excluding non-melanoma skin cancer (n=2,980) or were missing data on any of the seven healthy lifestyle components (n=14,021). The final analytic sample population included 65,561 postmenopausal women (African American [18.7 %], Japanese American [28.2%], Latina [21.1%], Native Hawaiian [6.7 %] and White [25.3%]).

#### Outcome ascertainment

Information on incident invasive breast cancer cases including date of diagnosis, tumor stage, hormone receptor status, age at diagnosis and molecular subtype was ascertained through linkage data from the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the statewide Hawaii Tumor Registry, all part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Vital status was determined by linkage to California and Hawaii death files and the National Death Index. During a median follow-up of 19.2 years, 4,571 incident invasive breast cancer cases were diagnosed between baseline (1993-1996) and the end of follow-up (2017).

### Exposure and covariate ascertainment

On the MEC baseline questionnaire (1993-1996), participants provided information on health behaviors included in the HLI: dietary intake, physical activity, sedentary behavior, BMI, smoking, alcohol intake and sleep duration. Each HLI component was operationalized based on national health guidelines and cut points and modified to fit the distribution of the data. Average dietary intake was measured within the last year using the Healthy Eating Index-2010 (HEI-2010) score, composed of 12 components: total and whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, and empty calories, and categorized into quartiles based on distribution of the data [307, 308].

Moderate and vigorous physical activity were measured as total metabolic equivalents (METs) in activities involving moderate or vigorous movement per day, on average, during the last year [363] and sedentary behavior was measured by total hours in sitting activities per day, on average, during the last year [309]. Smoking status (never/former/current) and pack-years on average in the last year were combined into one variable and operationalized into quintiles based on the distribution of pack-years by status [45, 228]. Alcohol intake was defined as average alcoholic beverages (drinks per day) in the last year and categorized into tertiles based on the National Institute on Alcohol Abuse and Alcoholism defined drinking levels [364]. BMI at baseline was defined using the Quetelet Index (kg/m<sup>2</sup>) and categorized into tertiles based on National Heart, Lung and Blood Institute cut points [365]. Sleep was measured by number of hours per day spent sleeping (including naps), on average, during the last year and categorized as a dichotomous variable ( $\leq 6$  hours or  $\geq 9$  hours and 7 to 8 hours) to represent adverse effects associated with short and long sleep duration [48, 316, 366, 367].

Last year refers to the prior year the participant completed the baseline questionnaire (1993 – 1996).

The HLI score represents the total sum of each HLI component: dietary intake (1-4), moderate and vigorous physical activity (METs) (1-3), sedentary time (1-3), smoking status and pack-years (1-5), alcohol intake (1-3), BMI (1-3) and sleep duration (1-2). The HLI score ranged between 7 and 23 and was categorized into tertiles based on the distribution: T<sub>1</sub>: 7 to < 15, T<sub>2</sub>: 15 to <18, T<sub>3</sub>:18 to 23. A higher HLI score (T<sub>3</sub>) represents a healthier lifestyle: high HEI 2010 score indicating a healthy diet (Quartile 4), physical activity > 6 METs/hours (Tertile 3), 0 to < 6 hours of sedentary time (Tertile 3), never smoker (Quintile 5), minimal alcohol consumption between 0 to 4.9 grams/day (Tertile 3), a normal BMI < 25 kg/m<sup>2</sup> (Tertile 3), and adequate sleep duration between 7 and 8 hours per day. Sociodemographic, behavioral and breast cancer characteristics included in the analysis as covariates were collected at baseline (1993-1996).

### Statistical Analyses

Distributions of sociodemographic, behavioral and breast cancer risk factors, in all women and by race and ethnicity, were assessed by estimating mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. Differences in distributions of characteristics by race and ethnicity were assessed using the Chi-square test.

Stratified Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between the HLI score tertiles and invasive breast cancer risk among all postmenopausal women and stratified by race and ethnicity. Postmenopausal women were followed from age at baseline until age at invasive

breast cancer diagnosis. Censoring (non-cases) was defined as age at *in situ* breast cancer diagnosis, age at death or age at study completion (December 30, 2017). The HLI score was assessed in tertiles (T<sub>1</sub> as the referent group) with multivariable models including adjustment for age (continuous), race and ethnicity (African American; Japanese American; Latina; Native Hawaiian; White), education (high school or less; vocational school or college; graduate or professional school; unknown), marital status (married; separated/divorced/widowed/never married, unknown), family history of breast cancer (yes, no, unknown), age at menarche ( $\leq 12$ ; 13–14;  $> 14$  years, unknown), age at first childbirth (nulliparous;  $\leq 20$ ; 21–30;  $> 30$  years, unknown), number of children for parous women (nulliparous, 1; 2–3;  $\geq 4$ , unknown), oral contraceptive use (never, ever  $< 5$  years, ever  $\geq 5$  years, unknown), age at and type of menopause: (natural: age  $< 49$ , 50+ years; oophorectomy (includes single and double oophorectomy with or without hysterectomy): age  $< 45$ , 45+ years; Other surgery (including hysterectomy and endometrial ablation): age  $< 45$ , 45+ years); menopausal hormone therapy (never estrogen use; past estrogen use with or without progestin; current estrogen use without progestin; current estrogen use with past/current progestin, unknown). Missing values were retained as unknown categories in the models. Women overall and race-stratified multivariable models were performed by hormone receptor status (hormone receptor-positive (HR+) defined as estrogen-receptor positive (ER+) and progesterone-receptor positive (PR+) or negative (PR-) and hormone-receptor-negative (HR) defined as estrogen-receptor negative (ER-) and (PR-). For the multivariable models, dose-response was assessed by modeling the ordinal HLI score variable as a continuous variable.

Cox proportional hazards assumptions were evaluated using log-log plots and Schoenfeld residuals. The Cox proportional hazards assumptions were met except for

menopausal hormone use. To satisfy the Cox proportional hazards assumption, the stratified Cox proportional hazard model was used. In the overall multivariable adjusted models, interaction effects by race and ethnicity of the association between HLI score and invasive breast cancer risk were assessed using the multiplicative model for joint effects.

In sensitivity analyses, the sleep and sedentary behavior HLI components were excluded separately and together from the HLI score. The reduced HLI score consisted of five components (versus 7): dietary intake, physical activity, BMI, smoking status, and alcohol consumption similar to previous studies [54, 252, 255, 353]. The sensitivity analyses examined the modified HLI score in women overall and race and ethnicity-stratified models in the following sequence: 1) excluding sleep duration only, 2) excluding sedentary behavior only, and 3) excluding both sleep duration and sedentary behavior. Each modified HLI score was operationalized into tertiles based on the distribution of data. All statistical models were performed using SAS (version 9.3).

### Results

Distributions of sociodemographic and breast cancer risk factors among postmenopausal women, overall and race and ethnicity-stratified, are summarized in **Table 1**. The average follow-up time overall was 19.2 years (SD:6.6 years). Mean age at baseline ranged from 58.4 years among Native Hawaiian women to 63 years among Japanese American women. Women across all racial and ethnic groups were more likely to be married, have no family history of breast cancer, be 12 years or younger at menarche, be between 21 and 31 years of age at their first childbirth, use oral contraceptives for less than five years and never use menopausal hormone therapy. Japanese American, Latina and Native Hawaiian women were more likely to have a high school degree or less, whereas African American and

White women were more likely to have a college or vocational school degree. A higher BMI was most prevalent among African American women (mean BMI: 28.9 (SD: 5.7) kg/m<sup>2</sup>) followed by Native Hawaiian women (mean BMI: 28.4 (SD: 6.0) kg/m<sup>2</sup>). Latina and Native Hawaiian women were more likely to have four or more children. Natural menopause was the most prevalent cause for menopause occurring at any age among all women.

**Table 2** shows the distribution of HLI components among postmenopausal women overall and by race and ethnicity. On average, women had an HLI score of 17.4 (SD: 2.5). Japanese American, Latina and White women had on average higher HLI scores (T3: 18 ≤ to 23) and African American and Native Hawaiian women had the highest proportion (17.8% and 17.4%, respectively) of lower HLI scores (T1: 7 to <15). Across all racial and ethnic groups, most women had HEI-2010 scores in Q3 (healthier diet): 60-78.9, exerted between 0 and 2.9 METs on average a day (low physical activity), were never smokers and consumed between 0 and 4.9 grams of ethanol a day (light drinkers). Approximately 70% of Japanese American women followed by 53% of White women had a BMI < 25 kg/m<sup>2</sup>, whereas Native Hawaiian, Latina and African American women had 26% to <32% with BMI < 25 kg/m<sup>2</sup>. Native Hawaiian women reported more time sedentary (≥ 10 hours a day) while Latina women reported the least number of hours sedentary (0-6 hours a day). African American and Native Hawaiian women reported having shorter or longer sleep duration (≤6 or ≥9 hours), while Japanese American, Latina and White women reported average sleep duration (7-8 hours).

Select characteristics of breast cancer cases, overall and by race and ethnicity, are shown in (**Table 3**). Overall, 4,555 invasive breast cancer cases occurred in the follow-up period (1993 – 2017) (African American [17.0%], Japanese American [31.2%], Latina

[16.0%], Native Hawaiian [9.3%] and White [26.5%]). Japanese American women were older at diagnosis (62.1 SD: 7.4 years) whereas Native Hawaiian women were younger (57.9 SD:7.4 years). The majority of invasive breast cancer cases were ER+/PR+ (59.8%) and localized at diagnosis (71.1%). Tumor grade varied by race and ethnicity with Japanese American, Latina, Native Hawaiian and White women more likely having grade II tumors, whereas African American women were diagnosed with grade III and IV tumors.

In the multivariable-adjusted models assessing the association between HLI score and invasive breast cancer risk (**Table 4**), a statistically significant inverse association was observed among postmenopausal women with higher HLI scores in T<sub>2</sub> (adjusted hazard ratio [aHR]: 0.88, 95% confidence interval [CI]: 0.79, 0.97) and T<sub>3</sub> (aHR:0.76, 95% CI: 0.69, 0.84); *p* trend <0.01. For the race and ethnicity-stratified models, significant inverse associations among Native Hawaiian and White women and marginally significant inverse associations among African American, Japanese American and Latina women with HLI scores in the highest tertile (T<sub>3</sub>) were observed. A significant dose-response was observed in HLI scores except for marginal significance among African American postmenopausal women (*p* trend = 0.05).

In the hormone-receptor sub-group analysis (**Table 5a**), the overall multivariable-adjusted model for HR+ cases yielded similar patterns as the overall model described above. Postmenopausal women with higher HLI scores in T<sub>2</sub> (aHR: 0.89, 95% CI: 0.79, 1.00) and T<sub>3</sub> (aHR:0.77, 95% CI: 0.68, 0.87) had a reduced risk of HR+ invasive breast cancer (*p* trend <0.01). Similar reductions in risk of developing HR+ cases were observed across all racial and ethnic groups. Analogous to the overall race and ethnicity stratified models, as HLI scores increased the risk of HR+ breast cancer decreased in all racial and ethnic groups (*p*

trend ranged between 0.01 and 0.03), except among African American women ( $p$  trend = 0.14). No significant associations were observed among HR- breast cancer cases in the overall and race-stratified multivariable-adjusted models (**Table 5b**).

In the sensitivity analyses, the HLI score excluding sleep (**Supplemental 6a**), sedentary behavior (**Supplemental 6b**) or both components (**Supplemental 6c**) were inversely associated with invasive breast cancer risk overall. Significant associations among African American women with HLI scores in T<sub>2</sub> and T<sub>3</sub>, and Japanese American and Latina women with HLI scores in T<sub>3</sub> were observed. However, the association between Native Hawaiian women with HLI scores in T<sub>2</sub> and T<sub>3</sub> and invasive breast cancer risk were no longer statistically significant.

### Discussion

Findings from this diverse multiethnic prospective cohort study further supports that postmenopausal woman who engage in healthier lifestyle behaviors, characterized by a higher HLI score, have a reduced risk of invasive breast cancer, namely HR+ breast cancer risk. All postmenopausal women with a higher HLI score had a significant reduction in breast cancer risk (ranging from 5% to 18% and 17% to 33% in T<sub>2</sub> and T<sub>3</sub> of the HLI, respectively). Similar risk reductions were observed among postmenopausal women across racial and ethnic groups and specifically, statistically significant reductions were observed among Native Hawaiian and White women with HR+ breast cancer. Significant dose responses were observed in all women, women with HR+ breast cancer and across all racial and ethnic groups (Native Hawaiian, White, Latina and Japanese American), with marginal significance observed among African American women.

To date, four prospective cohort studies have shown inverse associations between the HLI and breast cancer risk [250, 254, 255, 258] in predominately White, British and European women. In the United Kingdom Biobank prospective cohort study, Arthur et al., [258] included women with BMI between 18.5 kg/m<sup>2</sup> and ≥30 kg/m<sup>2</sup> and also reported significant inverse associations among postmenopausal women with higher HLI scores and breast cancer risk using an HLI comprised of diet, alcohol consumption, physical activity, BMI and waist circumference and smoking (T<sub>2</sub>: Intermediate and T<sub>3</sub>:High; HR:0.82, 95%:0.70, 0.96; HR:0.71, 95% CI:0.59, 0.88, respectively) [258]. While the present analysis included women with BMI between <25 kg/m<sup>2</sup> and ≥30 kg/m<sup>2</sup>, risk reductions similar to the study by Arthur et al. were observed. Those with a higher HLI score (T<sub>2</sub> and T<sub>3</sub>) had a reduced risk of breast cancer by approximately 15% and 23%, respectively. Using data from the same UK Biobank and HLI measure, Peila et al. restricted analyses to postmenopausal women with normal BMI (18.5 to < 25 kg/m<sup>2</sup>) and observed significant inverse associations higher HLI scores and breast cancer risk among postmenopausal (T<sub>2</sub>: Intermediate and T<sub>3</sub>: High) (HR<sub>T<sub>2</sub></sub>: 0.84, 95% CI: 0.72,0.96 and HR<sub>T<sub>3</sub></sub>:0.76, 95% CI 0.64, 0.94, respectively) [255]. McKenzie et al. [254] assessed the collective assessment of modifiable lifestyle factors in relation to breast cancer among a prospective cohort of European postmenopausal women (n=242,918) from 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom) and reported an inverse association between higher HLI scores and breast cancer risk [adjusted HR: 0.74; 95% confidence interval (CI): 0.66–0.83].

Breast cancer risk factors associations can vary by hormone receptor status [132]. To date, only one prior study by Arthur et al. (1) has examined the HLI and breast cancer risk by

molecular subtype status. Postmenopausal women in the highest HLI quintile had 30%, 37%, and 30% lower risk for overall, ER+/PR+, and human epidermal growth factor receptor 2 (HER2) positive breast cancer, respectively compared to women with HLI scores in the lowest quintile. Data on HER2 was limited in the current study and HR-specific analyses characterized breast cancer by hormone receptor status only. Overall, women in the highest tertile (T<sub>3</sub>) had a 13% risk reduction in HR+ (ER+ and PR+/PR-) breast cancer. Although Arthur et al. observed a stronger reduction in risk, the study population (n=131,833) was comprised of predominantly White postmenopausal women. The present analyses support overall and race and ethnicity-stratified risk reduction in HR+ breast cancer; however, as expected the HLI score was not associated with HR- breast cancer risk in overall and race and ethnicity-stratified associations. These findings extend the existing understanding of the association between HLI and breast cancer risk by hormone receptor type across racial and ethnic groups.

Findings from the current study corroborate those of prior studies and expand knowledge by examining associations among racial and ethnic diverse groups of postmenopausal women and by expanding the components included in the HLI. The present analysis utilized a seven component HLI, including sleep and sedentary behavior, as compared to the five component HLI (diet, alcohol, physical activity, BMI, or waist circumference or both, smoking or breastfeeding) utilized in the prior studies [250, 254-258]. Sleep is essential for overall health [48], and has emerged as an important factor in breast cancer risk [361]. Similarly, sedentary behavior, characterized by sitting behavior, has been associated with increased breast cancer risk [368]. To assess whether sleep and/or sedentary behavior influence the observed findings, sensitivity analyses were conducted excluding

sleep only, sedentary behavior only and both factors from the HLI. The exclusion of the sleep HLI component only, sedentary HLI component only and both sleep, and sedentary behavior HLI components yielded a similar magnitude of risk reduction in all women and by race and ethnicity. This suggests sleep duration and sedentary behavior assessed collectively with other established lifestyle factors may have minimal influence beyond the other components contributing to the observed reduction in breast cancer risk. Particular lifestyle factors such as obesity [42, 106, 205, 354, 355], physical activity [369], and alcohol intake[246]) have consistent and strong associations with breast cancer risk which may be driving the observed associations with the seven component HLI.

This study has several limitations. Despite the availability of hormone receptor status for the majority of breast cancer cases, HER2 status was not available to further characterize the breast cancer cases. Information on breastfeeding history was not measured in the MEC baseline questionnaire and therefore was not included as an HLI component. Breast feeding is a recommended lifestyle practice in accordance with the healthy lifestyle guidelines for breast cancer prevention [370]. Information on HLI components was self-reported and subject to non-differential measurement error. However, this would have led to an attenuation of the observed reductions in risk. HLI components were measured at baseline only and therefore the HLI exposure does not capture potential change in lifestyle factors over time. Despite this, information for the HLI components and emerging cancer risk factors for sleep duration and sedentary time were well characterized on the baseline questionnaire and utilized in the operationalization of the HLI score. Additional strengths to this study include the inclusion of a racially and ethnically diverse group of postmenopausal women, a large breast cancer case sample across the racial and ethnic groups, and the extension of prior

research by examining analyses by race and ethnicity, HR status and accounting for many covariates and established breast cancer risk factors.

Findings from this study further support associations between higher HLI score and a reduced risk of breast cancer among postmenopausal women, namely HR+ breast cancer. Among all women and those HR+ breast cancer, higher HLI scores were inversely associated with breast cancer risk among Native Hawaiian and White women. Significant dose responses were observed; as the HLI score increased the risk of breast cancer decreased among Native Hawaiian, White, Latina and Japanese American women, and specifically HR+ breast cancer risk decreased among Native Hawaiian and Latina women. While sleep and sedentary behavior are emerging breast cancer risk factors, these factors had minimal influence as HLI components in the collective association with breast cancer risk. Future research should examine these healthy lifestyle factors among diverse racial and ethnic populations of postmenopausal women and by molecular subtype to substantiate our findings. Consistent with recommendations from the American Cancer Society, healthy lifestyle strategies to maintain a normal weight, engage in physical activity, adopt a healthy diet, avoid smoking tobacco, and limit alcohol consumption, contribute to reducing the risk of developing breast cancer in postmenopausal women across diverse racial and ethnic groups.

*Tables and Figures for Manuscript 2*

Table 1. Distributions of breast cancer risk factors among postmenopausal women overall and by race and ethnicity at baseline in the Multi-ethnic Cohort Study (1993-1996)

	Overall n = 65,561	African American n = 12,236	Japanese American n = 18,531	Latina n = 13,836	Native Hawaiian n = 4,365	White N = 16,593
Follow-up time, mean years (SD)	19.2 (6.6)	18.2 (7.4)	19.6 (6.2)	19.9 (6.1)	18.6 (6.8)	19.0 (6.6)
Age, mean years (SD)	61.3 (7.9)	61.6 (8.3)	63.0 (7.7)	60.5 (7.0)	58.4 (8.0)	60.7 (8.2)
BMI, mean kg/m <sup>2</sup> (SD)	26.3 (5.4)	28.9 (5.7)	23.5 (3.8)	27.8 (5.1)	28.4 (6.0)	25.7 (5.2)
Education, years			n (%)			
High School or less	29,927 (45.6)	4,492 (36.7)	8,303 (44.8)	9,566 (69.1)	2,476 (56.7)	5,090 (30.7)
Vocational School/College	27,548 (42.0)	6,262 (51.2)	7,834 (42.3)	3,506 (25.3)	1,552 (35.6)	8,394 (50.6)
Graduate or Professional School	7,872 (12.0)	1,449 (11.8)	2,341 (12.6)	676 (4.9)	330 (7.6)	3,076 (18.5)
Marital status						
Married	38,737 (59.1)	4,634 (37.9)	13,350 (72.0)	7,783 (56.3)	2,814 (64.5)	10,156 (61.2)
Separated/Divorced	12,464 (19.0)	3,995 (32.7)	1,550 (8.4)	2,826 (20.4)	669 (15.3)	3,424 (20.6)
Widowed	10,156 (15.5)	2,782 (22.7)	2,468 (13.3)	2,100 (15.2)	684 (15.7)	2,122 (12.8)
Never Married	3,679 (5.6)	657 (5.4)	1,087 (5.9)	986 (7.1)	173 (4.0)	776 (4.7)
Family history of breast cancer						
No	26,091 (39.8)	3,534 (28.9)	8,384 (45.2)	4,838 (35.0)	1,744 (40.0)	7,591 (45.8)
Yes	5,898 (9.0)	825 (6.7)	1,959 (10.6)	867 (6.3)	537 (12.3)	1,710 (10.3)
Age at menarche, years						
≤12	32,389 (49.4)	6,105 (49.9)	8,791 (47.4)	6,747 (48.8)	2,484 (56.9)	8,262 (49.8)
13-14	25,181 (38.4)	4,630 (37.8)	7,295 (39.4)	5,280 (38.2)	1,419 (32.5)	6,557 (39.5)
>14	7,813 (11.9)	1,467 (12.0)	2,387 (12.9)	1,779 (12.9)	451 (10.3)	1,729 (10.4)
Age at first birth, years						
Nulliparous	1,580 (12.9)	2,431 (13.1)	1,159 (8.4)	295 (6.8)	2,553 (15.4)	8,018 (12.2)
≤20	5,465 (44.7)	1,707 (9.2)	5,414 (39.1)	1,921 (44.0)	4,251 (25.6)	18,758 (28.6)
21-30	4,448 (36.4)	12,547 (67.7)	6,408 (46.3)	1,955 (44.8)	8,590 (51.8)	33,948 (51.8)
>30	519 (4.2)	1,641 (8.9)	675 (4.9)	104 (2.4)	1,017 (6.1)	3,956 (6.0)
Number of live births						
Nulliparous	7,939 (12.1)	1,572 (12.9)	2,406 (13.0)	1,134 (8.2)	288 (6.6)	2,539 (15.3)
1	7,229 (11.0)	2,000 (16.4)	2,037 (11.0)	981 (7.1)	270 (6.2)	1,941 (11.7)
2-3	28,887 (44.1)	4,474 (36.6)	10,273 (55.4)	4,640 (33.5)	1,546 (35.4)	7,954 (47.9)
4+	21,116 (32.2)	4,099 (33.5)	3,741 (20.2)	6,958 (50.3)	2,239 (51.3)	4,079 (24.6)
Oral Contraceptive Use						
Never	39,312 (60.0)	7,066 (57.8)	13,016 (70.2)	8,482 (61.3)	2,472 (56.6)	8,276 (49.9)
Ever user < 5 years	16,088 (24.5)	3,059 (25.0)	3,546 (19.1)	3,514 (25.4)	1,183 (27.1)	4,786 (28.8)
Ever user ≥ 5 years	9,528 (14.5)	2,000 (16.4)	1,831 (9.9)	1,566 (11.3)	689 (15.8)	3,442 (20.7)
Age and Type of menopause						
Natural menopause at age <49	19,181 (29.3)	3,175 (26.0)	4,881 (26.3)	4,740 (34.3)	1,380 (31.6)	5,005 (30.2)
Natural menopause at age 50+	21,409 (32.7)	2,921 (23.9)	7,904 (42.7)	4,137 (29.9)	1,241 (28.4)	5,206 (31.4)
Oophorectomy <sup>†</sup> at age <45	6,804 (10.4)	1,701 (13.9)	1,581 (8.5)	1,181 (8.5)	522 (12.0)	1,819 (11.0)
Oophorectomy <sup>†</sup> at age 45+	5,026 (7.7)	905 (7.4)	1,678 (9.1)	796 (5.8)	360 (8.3)	1,287 (7.8)
Other Surgery <sup>††</sup> at age <45	10,054 (15.3)	2,846 (23.3)	1,711 (9.2)	2,295 (16.6)	658 (15.1)	2,544 (15.3)
Other Surgery <sup>††</sup> at age 45+	3,087 (4.7)	688 (5.6)	776 (4.2)	687 (5.0)	204 (4.7)	732 (4.4)
Menopausal hormone therapy						
Never estrogen use	27,905 (42.6)	6,309 (51.6)	7,226 (39.0)	6,931 (50.1)	2,020 (46.3)	5,419 (32.7)
Past estrogen use	12,377 (18.9)	2,889 (23.6)	2,741 (14.8)	2,741 (19.8)	825 (18.9)	3,181 (19.2)
Current estrogen use	10,842 (16.5)	1,690 (13.8)	3,361 (18.1)	1,880 (13.6)	671 (15.4)	3,240 (19.5)
Current estrogen-progesterone use	13,175 (20.1)	1,074 (8.8)	4,852 (26.2)	1,922 (13.9)	776 (17.8)	4,551 (27.4)

Note: Totals may not sum to 100 due to missing values. All p-values for Chi-square tests of categorical variables and One-way ANOVA F tests for continuous variables

Table 2. Distributions of the components of the Healthy Lifestyle Index among postmenopausal women overall and by race and ethnicity at baseline in the Multiethnic Cohort study, (1993 – 1996)

	Overall n = 65,561	African American n = 12,236	Japanese American n = 18,531	Latina n = 13,836	Native Hawaiian n = 4,365	White n = 16,593
Healthy Lifestyle Index, mean (SD)	17.5 (2.4)	16.7 (2.4)	18.3 (2.1)	17.5 (2.1)	16.8 (2.5)	17.4 (2.6)
Healthy Lifestyle Index						
T1: 7 to <15	7,386 (11.3)	2,172 (17.8)	918 (5.0)	1,204 (8.7)	759 (17.4)	2,333 (14.1)
T2: ≤15 to < 18	23,457 (35.8)	5,328 (43.5)	4,979 (26.9)	5,490 (39.7)	1,840 (42.2)	5,820 (35.1)
T3: ≤18 to 23	34,718 (53.0)	4,736 (38.7)	12,634 (68.2)	7,142 (51.6)	1,766 (40.5)	8,440 (50.9)
<i>HLI Components</i>						
BMI, kg/m <sup>2</sup>						
<25.0	30,643 (46.7)	3,138 (25.7)	12,980 (70.0)	4,402 (31.8)	1,393 (31.9)	8,730 (52.6)
25.0 to <30.0	20,992 (32.0)	4,625 (37.8)	4,488 (24.2)	5,495 (39.7)	1,514 (34.7)	4,870 (29.4)
≥30.0	13,926 (21.2)	4,473 (36.6)	1,063 (5.7)	3,939 (28.5)	1,458 (33.4)	2,993 (18.0)
Dietary Intake, HEI-2010 score						
20-40.9	552 (3.3)	110 (0.9)	72 (0.4)	162 (1.2)	39 (0.9)	169 (1.0)
41-59.9	12,177 (18.6)	1,863 (15.2)	3,155 (17.0)	3,570 (25.8)	929 (21.3)	2,660 (16.0)
60-78.9	35,961 (54.9)	6,169 (50.4)	10,732 (57.9)	7,896 (57.1)	2,380 (54.5)	8,784 (52.9)
77-99.9	16,871 (25.7)	4,094 (33.5)	4,572 (24.7)	2,208 (16.0)	1,017 (23.3)	4,980 (30.0)
Physical Activity, METs						
0.0 – 2.9	35,274 (53.8)	7,801 (63.8)	10,144 (54.7)	8,551 (61.8)	1,989 (45.6)	6,789 (40.9)
3.0 – 6.0	13,343 (20.4)	2,258 (18.5)	39,17 (21.1)	2,460 (17.8)	956 (21.9)	3,752 (22.6)
> 6.0	16,944 (25.8)	2,177 (17.8)	4,470 (24.1)	2,825 (20.4)	1,420 (32.5)	6,052 (36.5)
Sedentary Behavior, hours						
0.0 to <6.0	19,050 (29.1)	3,281 (26.8)	4,851 (26.2)	5,654 (40.9)	1,149 (26.3)	4,115 (24.8)
6.0 to <10.0	25,845 (39.4)	4,662 (38.1)	7,686 (41.5)	4,782 (34.6)	1,570 (36.0)	7,145 (43.1)
≥ 10.0	20,666 (31.5)	4,293 (35.1)	5,994 (32.4)	3,400 (24.6)	1,646 (37.7)	5,333 (32.1)
Smoking Status, pack-years						
Never	36,758 (56.1)	5,481 (44.8)	12,932 (69.8)	9,055 (65.5)	1,967 (45.1)	7,323 (44.1)
Former, ≤20	15,644 (23.9)	3,523 (28.8)	3,409 (18.4)	3,029 (21.9)	1,072 (24.6)	4,611 (27.8)
Former, 20+	3,665 (5.6)	716 (5.9)	586 (3.2)	272 (2.0)	327 (7.5)	1,764 (10.6)
Current, ≤20	5,486 (8.4)	1,737 (14.2)	945 (5.1)	1,146 (8.3)	572 (13.1)	1,086 (6.5)
Current, 20+	4,008 (6.1)	779 (6.4)	659 (3.6)	334 (2.4)	427 (9.8)	1,809 (10.9)
Alcohol Intake, grams/day						
0.0-4.9	54,914 (83.8)	10,332 (84.4)	17,456 (94.2)	12,296 (88.9)	3,683 (84.4)	11,147 (67.2)
5.0 - 14.9	4,998 (7.6)	933 (7.6)	597 (3.2)	936 (6.8)	335 (7.7)	2,197 (13.2)
>15.0	5,649 (8.6)	971 (7.9)	478 (2.6)	604 (4.4)	347 (8.0)	3,249 (19.6)
Sleep duration, hours						
≤6 or ≥9	28,635 (43.7)	6,349 (51.9)	8,078 (43.6)	6,159 (44.5)	2,259 (51.8)	5,790 (34.9)
7-8	36,926 (56.3)	5,887 (48.1)	10,453 (56.4)	7,677 (55.5)	2,106 (48.3)	10,803 (65.1)

SD: Standard deviation; HEI-2010 score: Health Eating Index – 2010 score; BMI: Body mass index; METs: Metabolic equivalents

Note: P-values not shown. All p-values for Chi-square tests of categorical variables and One-way ANOVA F tests for continuous variables

Table 3. Select characteristics of invasive breast cancer cases among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (1993 – 2017)

	Overall n=4,555	African American n=774	Japanese American n=1,421	Latina n=727	Native Hawaiian n=424	White n=1,209
	Mean (Standard deviation)					
Age at diagnosis, years	61.0 (7.6)	61.6 (8.0)	62.1 (7.4)	60.4 (6.8)	57.9 (7.4)	60.8 (7.8)
Duration of Follow-up, years	10.5 (6.5)	10.6 (6.7)	10.4 (6.6)	10.7 (6.5)	11.3 (6.6)	10.0 (6.4)
BMI, kg/m <sup>2</sup>	26.6 (5.3)	29.1 (5.5)	24.3 (4.0)	28.0 (5.0)	29.4 (6.1)	25.8 (4.9)
	n (%)					
Hormone Receptor Status*						
ER+/ PR+	2,726 (59.8)	354 (45.7)	925 (65.1)	376 (51.7)	304 (71.7)	767 (63.4)
ER+/ PR-	496 (10.9)	72 (9.3)	171 (12.0)	72 (9.9)	36 (8.5)	145 (12.0)
ER-/PR+	57 (1.3)	17 (2.2)	18 (1.3)	9 (1.2)	5 (1.2)	8 (0.7)
ER-/PR-	644 (14.1)	140 (18.1)	184 (13.0)	121 (16.6)	50 (11.8)	149 (12.3)
Borderline/Unknown	632 (13.9)	191 (24.7)	123 (8.7)	149 (20.5)	29 (6.8)	140 (11.6)
Tumor Grade*						
Grade I <sup>†</sup>	1,148 (25.2)	157 (20.3)	417 (29.4)	136 (18.7)	113 (26.7)	325 (26.9)
Grade II <sup>†</sup>	1,858 (40.8)	248 (32.0)	624 (43.9)	299 (41.1)	188 (44.3)	499 (41.3)
Grade III and IV <sup>††</sup>	1,186 (26.0)	281 (36.3)	297 (20.9)	225 (31.0)	101 (23.8)	282 (23.3)
Disease stage at diagnosis*						
Localized	3,239 (71.1)	491 (63.4)	1,109 (78.0)	485 (66.7)	295 (69.6)	859 (71.1)
Regional and Distant	1,246 (27.4)	267 (34.5)	300 (21.1)	224 (30.8)	127 (30.0)	328 (27.1)

Note: Totals may not equal 100% due to missing values. All p-values for Chi-square tests of categorical variables and One-way ANOVA F tests for continuous variables ER+: estrogen receptor positive; ER-: ER negative; PR+: progesterone receptor positive; PR-: PR negative

\*Well differentiated;

† Moderately differentiated;

†† Poorly differentiated and Undifferentiated.

Table 4: Association between Healthy Lifestyle Index score and invasive breast cancer risk among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (1993 – 2017)

	Overall	African American	Japanese American	Latina	Native Hawaiian	White	<i>P</i> -int
Cases, n	4,555	774	1,421	727	424	1,209	0.72
Person-months	47,681	8,224	14,782	7,774	4,780	12,121	
HLI Scores							
T1: 7 to ≤14	1.00 0.88	1.00 0.95	1.00 0.91	1.00 0.91	1.00 0.72	1.00 0.85	
T2:15 to <18	(0.79, 0.97)	(0.78, 1.16) 0.83	(0.71, 1.17)	(0.70, 1.19)	(0.56, 0.94)	(0.71, 1.02)	
T3:18 to 23	0.76 (0.69, 0.84)	(0.67, 1.02)	0.78 (0.61, 1.00)	0.77 (0.59, 1.00)	0.67 (0.51, 0.87)	0.76 (0.64, 0.91)	
<i>P</i> -trend	<0.01	0.05	<0.01	<0.01	< 0.01	<0.01	

Note: T1: 7 to ≤14 as reference group. HR: Hazard ratios; CI: Confidence Intervals. Multivariable model adjusted for age, race (overall model only), education, marital status, history of breast cancer, age at menarche, age at first birth, number of live births, oral contraceptive use and menopause status. To satisfy the Cox proportional hazards model, menopausal hormone therapy use was added as a strata variable in the multivariable model.

Table 5a. Association between Healthy Lifestyle Index and hormone-receptor-positive Invasive breast cancer risk among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (1993 - 2017)

	Overall	African American	Japanese American	Latina	Native Hawaiian	White	<i>P</i> -int
Cases, n	3,279	443	1,114	457	345	920	
Person-months	36,547	5,322	11,980	5,354	4,051	9,839	0.52
	HR (95% CI)						
<b>HLI Scores</b>							
T1: 7 to ≤14	1.00	1.00	1.00	1.00	1.00	1.00	
	0.89	1.01	0.95	0.94	0.71	0.84	
T2:15 to <18	(0.79,1.00)	(0.77, 1.34)	(0.72, 1.27)	(0.67, 1.31)	(0.54, 0.95)	(0.68, 1.03)	
	0.77	0.85	0.81	0.77	0.67	0.78	
T3:18 to 23	(0.68, 0.87)	(0.64, 1.13)	(0.61, 1.07)	(0.55, 1.07)	(0.50, 0.90)	(0.64, 0.95)	
<i>P</i> -trend	<0.01	0.14	0.01	0.03	0.02	0.02	

Note: T1: 7 to ≤14 as reference group. Multivariable model adjusted for age, race (overall model only), education, marital status, history of breast cancer, age at menarche, age at first birth, number of live births, oral contraceptive use and menopause status. To satisfy the Cox proportional hazards model, menopausal hormone therapy use was added as a strata variable in the multivariable model. Missing hormone-receptor-positive cases not included. HR: Hazard ratios; CI: Confidence Intervals.

Table 5b. Association between Healthy Lifestyle Index and hormone-receptor-negative Invasive breast cancer risk among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (1993 - 2017)

	Overall	African American	Japanese American	Latina	Native Hawaiian	White	<i>P</i> -int
Cases, n	644	140	184	121	50	149	0.70
Person-months	6,699	1,552	1,941	1,345	522	1,339	
	HR (95% CI)						
<b>HLI Scores</b>							
T1: 7 to ≤14	1.00	1.00	1.00	1.00	1.00	1.00	
	0.92	0.99	0.70	1.16	0.71	1.09	
T2:15 to <18	(0.71, 1.20)	(0.60, 1.62)	(0.38, 1.30)	(0.55, 2.48)	(0.34, 1.48)	(0.65, 1.84)	
	0.87	1.09	0.69	1.10	0.64	0.86	
T3:18 to 23	(0.67, 1.13)	(0.66, 1.80)	(0.38, 1.25)	(0.53, 2.32)	(0.30, 1.37)	(0.51, 1.45)	
<i>P</i> -trend	0.34	0.65	0.4	0.99	0.28	0.32	

Note: T1: 7 to ≤14 as reference group. Multivariable model adjusted for age, race (overall model only), education, marital status, history of breast cancer, age at menarche, age at first birth, number of live births, oral contraceptive use and menopause status. To satisfy the Cox proportional hazards model, menopausal hormone therapy use was added as a strata variable in the multivariable model. Missing hormone-receptor-negative cases not included. HR: Hazard ratios; CI: Confidence Intervals.

Table 6a. Association between Healthy Lifestyle Index without sleep component Invasive breast cancer risk among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (1993 - 2017)

	Overall	African American	Japanese American	Latina	Native Hawaiian	White	<i>P</i> -int
Cases, n	4,555	774	1,421	727	424	1,209	0.84
Person-months	47,681	8,224	14,782	7,774	4,780	12,121	
HLI Scores							
T1: 6 ≤ to < 15	1.00	1.00	1.00	1.00	1.00	1.00	
	0.84	0.81	0.90	0.85	0.80	0.86	
T2: 15 ≤ to < 19	(0.79, 0.90)	(0.70, 0.94)	(0.76, 1.05)	(0.72, 1.02)	(0.65, 0.99)	(0.75, 0.98)	
	0.74	0.78	0.78	0.72	0.82	0.65	
T3: 19 ≤ to ≤21	(0.66, 0.82)	(0.58, 1.06)	(0.64, 0.95)	(0.53, 0.97)	(0.57, 1.19)	(0.53, 0.80)	
<i>P</i> -trend	<0.01	0.01	0.01	0.02	0.07	<0.01	

Note: T1: 7 to ≤14 as reference group. Multivariable model adjusted for age, race (overall model only), education, marital status, history of breast cancer, age at menarche, age at first birth, number of live births, oral contraceptive use and menopause status. To satisfy the Cox proportional hazards model, menopausal hormone therapy use was added as a strata variable in the multivariable model. Missing hormone-receptor-negative cases not included. HR: Hazard ratios; CI: Confidence Intervals.

Table 6b. Association between Healthy Lifestyle Index without sedentary behavior component Invasive breast cancer risk among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (1993 - 2017)

	Overall	African American	Japanese American	Latina	Native Hawaiian	White	<i>P</i> -int
Cases, n	4,555	774	1,421	727	424	1,209	0.92
Person-time	47,681	8,224	14,782	7,774	4,780	12,121	
HLI Scores							
T1: 6 ≤ to < 14	1.00	1.00	1.00	1.00	1.00	1.00	
	0.87	0.87	0.93	0.85	0.84	0.86	
T2: 15 ≤ to < 18	(0.80, 0.94)	(0.74, 1.03)	(0.76, 1.14)	(0.70, 1.04)	(0.68, 1.06)	(0.75, 1.00)	
	0.73	0.72	0.82	0.72	0.78	0.66	
T3: 18 ≤ to ≤20	(0.66, 0.81)	(0.55, 0.95)	(0.66, 1.03)	(0.54, 0.96)	(0.55, 1.09)	(0.55, 0.80)	
<i>P</i> -trend	<0.01	0.02	0.03	0.03	0.10	<0.01	

Note: T1: 7 to ≤14 as reference group. Multivariable model adjusted for age, race (overall model only), education, marital status, history of breast cancer, age at menarche, age at first birth, number of live births, oral contraceptive use and menopause status. To satisfy the Cox proportional hazards model, menopausal hormone therapy use was added as a strata variable in the multivariable model. Missing hormone-receptor-negative cases not included. HR: Hazard ratios; CI: Confidence Intervals.

Table 6c. Association between Healthy Lifestyle Index without sleep and sedentary behavior components Invasive breast cancer risk among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort study, (1993 -2017)

	Overall	African American	Japanese American	Latina	Native Hawaiian	White	<i>P</i> - int
Cases, n	4,555	774	1,421	727	424	1,209	0.99
Person-time	47,681	8,224	14,782	7,774	4,780	12,121	
HLI Scores							
T1: 5 ≤ to < 13	1.00	1.00	1.00	1.00	1.00	1.00	
T2: 13 ≤ to < 16	0.86 (0.80, 0.92)	0.84 (0.72, 0.99)	0.87 (0.73, 1.03)	0.92 (0.76, 1.09)	0.86 (0.69, 1.07)	0.85 (0.76, 0.97)	
T3: 16 ≤ to ≤18	0.74 (0.68, 0.81)	0.75 (0.59, 0.94)	0.76 (0.63, 0.92)	0.74 (0.58, 0.95)	0.76 (0.57, 1.03)	0.72 (0.61, 0.85)	
<i>P</i> - trend	<0.01	0.01	0.01	0.03	0.07	<0.01	

Note: T1: 7 to ≤14 as reference group. Multivariable model adjusted for age, race, education, marital status, history of breast cancer, age at menarche, age at first birth, number of live births, oral contraceptive use and menopause status. To satisfy the Cox proportional hazards model, menopausal hormone therapy use was added as a strata variable in the multivariable model. Missing hormone-receptor-negative cases not included. HR: Hazard ratios; CI: Confidence Intervals.

## Chapter 6: Manuscript 3

A cross-sectional analysis of neighborhood socioeconomic status and inflammatory biomarkers among adults in the Multiethnic cohort (MEC) Study

Abstract

**Introduction:** Obesity is a public health epidemic with multifactorial and complex mechanisms contributing to a steady rise in its prevalence among adults. Neighborhood socioeconomic status (nSES) has been associated with obesity, and studies have reported low nSES to be associated with higher inflammatory serum biomarker levels. However, these studies have been conducted among predominately White populations. This study examines the association between nSES and inflammatory biomarkers and adipose-derived cytokines among a racially and ethnically diverse population of adults in California and Hawaii.

**Methods:** Using data from the Multiethnic (MEC) study, baseline residential addresses of MEC participants (recruited at ages 45-75 years in 1993-1996) were geocoded and linked to census block group measures of nSES composite scores categorized into quintiles (Q1 – low and Q5 – high). Multivariable linear regression was used to examine the cross-sectional associations between nSES quintiles and circulating levels of inflammatory biomarkers (C-reactive protein (CRP), leptin and adiponectin) in state-specific models stratified by race and ethnicity. Multivariable linear regression adjusted for age, sex, race and ethnicity, body mass index and census block group. Heterogeneity in effects by race, ethnicity, and sex were examined.

**Results:** Overall among California residents, increased CRP ( $p$ -trend<0.001) and leptin ( $p$ -trend <0.001) and lower adiponectin ( $p$ -trend <0.001) levels were observed in individuals living in low nSES neighborhoods, compared to higher nSES neighborhoods ( $p$ -trend <0.05). California residents living in low nSES neighborhoods was associated with increased CRP levels in African American and Latino adults ( $p$ -trend<0.001;  $p$ -trend = 0.041), decreased adiponectin in African Americans and Japanese American adults ( $p$ -trend =0.004;  $p$ -trend =

0.037, respectively) and increased leptin levels in African American and White adults ( $p$ -trend = 0.029) compared to high nSES neighborhoods. Similar patterns overall were observed among Hawaiian residents, however,  $\beta$  estimates were lower compared to California residents, and statistically significant dose-response associations were only observed for nSES with CRP and adiponectin ( $p$ -trends <0.05) levels. Among Hawaiian residents living in low nSES neighborhoods was associated with increased CRP ( $p$ -trend = 0.041) and leptin ( $p$ -trend = 0.023) levels in Japanese American adults compared to high nSES neighborhoods. However, in models with further adjustment for BMI, the aforementioned results were attenuated and no longer statistically significant with the exception of an inverse association between nSES and leptin observed among Native Hawaiians ( $p$ -trend = 0.014). No interaction effects between nSES and race and ethnicity or sex were observed.

**Conclusion:** Residing in low nSES neighborhoods was associated with increased serum CRP, leptin and decreased adiponectin levels with dose response associations observed by race and ethnicity. Results were attenuated with adjustment for BMI. Low nSES neighborhoods may lead to unfavorable inflammatory biomarker levels.

### Introduction

Obesity, characterized by abnormal or excessive accumulation of adipose tissue, has emerged as a public health epidemic with projected estimates of prevalence increasing in adults over the next two decades [2, 3]. The inflammatory biomarker, C-reactive protein (CRP), has been studied as a hallmark indicator of acute or chronic inflammation and is positively associated with obesity [371]. Additionally, adipokines, adiponectin and leptin derived from biologically active adipose tissue, are two markers that help characterize the individual metabolic profile and unveil information about risk of disease and metabolic health [372]. Elevated CRP and leptin levels are positively associated with increased adipose tissue and associated with inflammation [373-375] whereas adiponectin is negatively associated with increased inflammation, [275] a characteristic condition of MetS and linked to obesity [11]. The development of obesity and its biological consequences are multifactorial and complex; modifiable individual level factors contribute to the development of obesity, however, interest in understanding the influence of the neighborhood environment on biological markers of inflammation has emerged [30].

Neighborhood socioeconomic status (nSES) is a key indicator of neighborhood environment and is an important predictor of individual health [14]. Epidemiologic studies have consistently shown that individuals residing in neighborhoods with low nSES have a higher risk of overweight and obesity [29, 30] and associated cardiometabolic conditions such as insulin resistance [4], hyperlipidemia [5], hypertension [6], and metabolic syndrome (MetS) [7]. Typically, neighborhoods with low nSES have been shown to have fewer health-promoting amenities, such as community centers, physical activity facilities, access to

healthy groceries and less social capital [14]. Inadequate access to these amenities adversely impacts health, in part, by limiting viable options to engage in physical activity outdoors and increasing exposure of convenient unhealthy food and minimal healthy eating options, which in turn leads to an “obesogenic environment” [33].

Systemic inflammation has emerged as a plausible physiologic pathway influenced by the neighborhood environment characterized by nSES. Previous epidemiologic studies have focused on examining the association between nSES and inflammation pathways using inflammatory biomarkers, namely C-reactive protein [156, 298-302]. However limited studies have assessed the association between nSES and serum biomarker concentrations among diverse racial and ethnic adult groups using inflammatory biomarkers *and* adipose-derived proteins which may be more strongly correlated to insulin resistance and metabolic health [373]. Prior studies have observed positive associations between nSES and CRP serum levels [156, 298-302], with three studies conducted among predominately White populations [156, 298, 302], two cross-sectional studies among racially homogenous groups: African American adults [299] and Mexican American women [300], and a longitudinal study assessing change in serum levels among a multiethnic population [301] To date, one study observed inverse associations between nSES and adiponectin serum levels among African American men (n=4,340) [303]. To our knowledge, no prior studies have assessed the association between nSES and CRP, adiponectin, and leptin among African American, Japanese American, Latino, Native Hawaiian and White adults.

To extend the understanding of the influence of nSES on biological risk profile, this study assesses the association between nSES and inflammatory serum biomarkers, CRP, adiponectin, and leptin. The central hypothesis of this study is that individuals living in low

nSES neighborhoods have increased CRP and leptin levels and decreased adiponectin levels compared to individuals living in high nSES neighborhoods. The serum concentrations of CRP, adiponectin and leptin will vary by state and race and ethnicity.

### Methods

#### Study Population and Design

This cross-sectional analysis uses data from the large prospective Multiethnic Cohort (MEC) study comprised of adult men and women ages 45-75 years who self-identify as African American, Japanese American, Latino, Native Hawaiian and White. Individuals residing primarily in Los Angeles, California and Hawaii in 1993-1996 (baseline) were identified through drivers' license files, voter registration lists and Medicare data. Adults were recruited using a self-administered, 26-page questionnaire on diet, cancer, chronic disease, and lifestyle behaviors. Details on the MEC study recruitment and design have been described previously [339]. This study was approved by the respective institutional review boards (University of Hawaii, University of Southern California, University of California, San Francisco, and University of Maryland).

In this study, the following exclusion criteria were applied to the initial sample of females and males participating (n = 215,393) in the MEC study: self-identified with a race and ethnicity other than one of the five main groups (African American, Japanese American, Latina, Native Hawaiian or White) (n=12,204), did not have data available on at least one of the five biomarkers (C-reactive protein (CRP), adiponectin, leptin, Interleukin-6 (IL-6) or tumor necrosis factors -alpha (TNF- $\alpha$ ) (n=185,935) and had no geocoded addresses to append to small area neighborhood-level data (n =292). Additionally, participants who did not complete the blood draw questionnaire (n=2,894) or had > 2 years or more between the blood

draw date and the blood draw questionnaire completion date (n=250). The final analytic sample size was n= 13,818, including 6,919 (50.1%) and 6,899 (49.9%) adults residing in California and Hawaii, respectively.

The prospective MEC biospecimen sub-cohort was established from 2001 to 2006 and was comprised of blood and urine collection of participating cohort members [321]. Blood samples were drawn and processed within 4 hours of collection by centrifugation and the components (serum, plasma, buffy coat, red cells) were aliquoted by automation into 0.5-mL cryotubes and stored in the vapor phase of liquid nitrogen ( $-186^{\circ}\text{C}$ )[271]. For approximately 95% of the participants contributing to the biorepository, fasting blood samples ( $\geq 8$  hours) were obtained. In total, 67,594 cohort members contributed to the biorepository from the sample for the present study was selected[271]. The institutional review boards of the University of Hawaii and the University of Southern California approved the study protocol.

#### Laboratory assays

The Analytical Biochemistry Shared Resource at the University of Hawaii Cancer Center performed all assays as previously described [321, 322]. In brief, serum samples from the MEC biorepository were analyzed in duplicates to quantify leptin and adiponectin using double-antibody enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA)[271]. CRP was assessed using a Cobas MiraPlus clinical chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA) and a latex particle-enhanced immunoturbidimetry-based kit from Pointe Scientific (Lincoln Park, MI, USA)[271]. As reported previously [321, 322], intra-batch coefficients of variation based on 96 blinded duplicate and 9 triplet samples for leptin, adiponectin, CRP, were 3.4–6.4%, 2.5–9.4% and 3.5–5.0%, respectively.

### Address history and geocoding

The MEC obtains up-to-date information on all participants by sending periodic mailings of newsletters and follow-up MEC questionnaires and linkages with databases such as the U.S. Postal Service. Residential addresses at blood draw of MEC participants were geocoded to latitude and longitude coordinates using parcel data and then street centerline data for those that failed to geocode to a parcel [33, 145]. Geocodes of participants' addresses (1997–2005) were linked to a total of 3,677 2000 U.S. Census block groups, of these, 3,130 2000 U.S. Census block groups comprised of 6,919 residents in Los Angeles County, California and 549 2000 U.S. Census block groups comprised of 6,899 residents in Hawaii with represented our neighborhood cluster unit.

### Neighborhood socioeconomic status exposure assessment

Neighborhood socioeconomic status (nSES) was measured as a composite score using principal component analysis of census block group data [317] for education, housing, employment, occupation, income, and poverty, as described previously [317]. The composite score was operationalized by categorizing the distribution of nSES into quintiles (quintile 1 – low and quintile 5 – high) based on the distribution in Los Angeles County and Hawaii.

### Statistical Analyses

The distribution of sociodemographic, lifestyle and sex-specific risk factors overall and by race and ethnicity were assessed by estimating the mean and standard deviation (SD) for age as a continuous variable and frequencies and percentages for categorical variables separate by state. Differences in the distributions by race and ethnicity were evaluated using One-way ANOVA F tests for continuous age and Chi-square test for categorical variables. Spearman rank correlation coefficients ( $r$ ) were calculated between each biomarker: CRP, adiponectin and leptin, and participant characteristic including race and ethnicity, sex, fasting

hours, BMI, alcohol intake, physical activity, smoking, menopausal hormonal therapy, and menopausal status to assess their linear relationships.

Multivariable linear regression models were used to examine associations between nSES quintiles and biomarkers (CRP, adiponectin, and leptin) by state (California and Hawaii) and race and ethnicity. High nSES (quintile 5) served as the referent group. Serum biomarkers were log-transformed to satisfy the linear model assumptions. Using the intra class coefficient (ICC) test, a minimal percentage of variation in the individual-level serum biomarker levels (2%, 8% and 9% for adiponectin, leptin and CRP, respectively) were explained by the cluster group, census block group, suggesting minimal variation in biomarker levels (outcome) by census block group; thus, multilevel analysis were not conducted. Multivariable linear models adjusted for age, sex, race and ethnicity, fasting hours and census block group (Model 1) with additional adjustment for body mass index (Model 2), and further adjustment for: physical activity in metabolic equivalents (METs)/day (0-2.9, 3.0-6.0, >6, unknown), education (high school or less, vocational school or college, graduate or professional school, unknown) alcohol intake grams/day (0-4.9, 5.0-14.9, >15, unknown), smoking status (never, former, current, unknown), marital status (married, separated or divorced, widowed, never married, unknown), menopausal status (premenopausal, postmenopausal, unknown) and menopausal hormone therapy (none, estrogen or progesterone only, estrogen and progesterone, unknown) (Model 3). Further adjustment (Model 3) for additional characteristics did not influence the model results and were therefore not included in the final models. Dose-response was assessed by modeling the ordinal nSES variable as a continuous variable and biomarker levels in state-specific race and ethnicity- stratified models. Tests for heterogeneity in association between nSES and

biomarker levels by race and ethnicity and sex were also assessed using the Likelihood Ratio test.

Sensitivity analyses were conducted as state-specific overall, and race and ethnicity stratified models restricted to participants with CRP serum levels < 10 mg/L to assess the association nSES and CRP serum levels among individuals who are not conventionally treated as having acute inflammation and clinically identified as having CRP measurements above 10 mg/L [376]. There were 94% participants overall (n=13,007) and among 91.7% residing in California (n=6,346) and among 96.6% residing in Hawaii (n=6,661) with CRP level <10 mg/L. In the sensitivity analyses, interaction effects between nSES and race and ethnicity were assessed, and dose-response was assessed by modeling the ordinal nSES variable as a continuous variable and biomarker levels in state-specific race and ethnicity-stratified models. All statistical models were performed using SAS (version 9.3) with a two-sided P-value of <0.05 considered as statistically significant.

### Results

The state-specific distribution of sociodemographic, lifestyle behaviors and sex-specific characteristics are summarized overall and by race and ethnicity for participants residing in California (**Table 1A**) and Hawaii (**Table 1B**).

In California (**Table 1A**), the average age was 69.1 years (standard deviation (SD): 7.7 years), with the White adults as the oldest group (70.7, SD:7.7 years) at blood draw. Overall and across racial and ethnic groups, participants in California were more likely to be female, report BMI between 25.0 – 29.9 kg/m<sup>2</sup>, consume > 15 grams of alcohol per day, exert between 0-2.9 METs/day and be married. African American, Japanese American, and White adults (ranging between 43.7% to 64%) were more likely to have vocational school or

college degree whereas Latinos were more likely to have a high school degree or less (61%). Women in California were more likely to be postmenopausal and not current users of menopausal hormone therapy.

In Hawaii (**Table 1B**), the average age at blood draw was 67.6 years (standard deviation (SD): 8.5 years), with the Japanese adults as the oldest group (68.7, SD: 8.4 years) and younger overall than participants in California. Overall and across racial and ethnic groups, participants in Hawaii were more likely to be female, report BMI between 25.0 – 29.9 kg/m<sup>2</sup>, consume > 15 grams of alcohol per day, have a vocational school or college degree and be married. Japanese Americans were less physically active (0 – 2.9 METs/day) than other adults and more likely to be never smokers. Whereas Native Hawaiian and White adults were more likely to be former smokers (ranging between 46.5% to 50%, respectively). Similarly, to women in California, women in Hawaii were more likely to be postmenopausal and not current users of menopausal hormone therapy.

**Table 2A** shows the adjusted geometric means and 95% confidence intervals CRP, adiponectin and leptin levels among adults residing in California. For model 1, higher CRP and leptin and lower adiponectin levels were observed in individuals living in low NSES neighborhoods, whereas the inverse was observed among individuals living in higher nSES neighborhoods. African American adults had higher CRP and leptin, and lower adiponectin levels similar to adiponectin levels in Japanese American adults. Females had higher mean serum levels for CRP, adiponectin and leptin compared to males. The average CRP and adiponectin serum levels were relatively similar across fasting hours. Mean serum levels for CRP and leptin increased and adiponectin levels decreased as BMI increased. With further adjustment for BMI, the mean serum levels increased.

Adjusted geometric means and 95% confidence intervals for CRP, adiponectin and leptin among adults residing Hawaii are overall lower than adults living in California (**Table 2B**). For model 1, higher CRP and leptin and lower adiponectin levels were observed in individuals living in low NSES neighborhoods, whereas the inverse was observed among individuals living in higher nSES neighborhoods following a similar pattern observed in California. White adults had higher CRP and leptin levels similar to leptin levels in Native Hawaiian adults. Japanese Americans had lower adiponectin levels similar to adiponectin levels in Japanese American adults. Females had higher mean serum levels for CRP, adiponectin and leptin compared to males. The average CRP and adiponectin serum levels were relatively similar across fasting hours. Mean serum levels for CRP and leptin increased and adiponectin levels decreased as BMI increased. With further adjustment for BMI, the mean serum levels increased.

**Table 3A** summarizes the association between nSES quintiles and the proportion of change (exponentiated  $\beta$  estimates) in serum biomarker levels and 95% confidence intervals for adults living in California. Adults living in low nSES have increased CRP (p-trend <0.0001) and leptin (p-trend <0.0001) and decreased adiponectin levels (p-trend <0.0001) compared to adult living in high nSES (Q5). With further adjustment for BMI, the dose-response attenuated and was no longer significant. For model 1, adults living in neighborhoods with low nSES (Q1 and Q2) had 16% increased CRP serum levels and 13% increase in leptin among low nSES (Q1 and Q2) and 11 % increase in leptin serum levels among low nSES (Q3) compared to adults living in neighborhoods with high nSES (Q5). With further adjustment for BMI (Model 2), these associations attenuated and were no longer statistically significant.

Neighborhood socioeconomic status quintiles and the proportion of change (exponentiated  $\beta$  estimates) in serum biomarkers and 95% confidence intervals for adults living in Hawaii are shown in **Table 3B**. Adults living in low nSES have increased CRP ( $p$ -trend = 0.02) and decreased adiponectin levels ( $p$ -trend = 0.03) as nSES decreases. With further adjustment for BMI, the dose-response is attenuated and no longer significant. In model 1, Adults living in neighborhoods with low nSES (Q1 - Q3) have 11% increased CRP serum levels, 5% decreased in adiponectin serum levels and 12% increase in leptin levels, respectively compared to adults living in neighborhoods with high nSES (Q5). Marginal associations among adults living in neighborhoods with high nSES (Q4) had an increase of 7% in CRP serum levels compared to high nSES (Q5). With further adjustment for BMI (Model 2), association was no longer observed. However, individuals living in neighborhoods with low nSES (Q1) had a 6% marginally significant decrease in leptin levels compared to individuals living in neighborhoods with high nSES (Q5).

The association between nSES quintiles and the proportion of change (exponentiated  $\beta$  estimates) in serum biomarkers and 95% confidence intervals for adults by race and ethnicity living in California is shown in **Table 4A**. In model 1, African American adults living in lower nSES neighborhoods had increased CRP ( $p$ -trend <0.001) and leptin ( $p$ -trend <0.001) serum levels and decreased adiponectin ( $p$ -trend = 0.004) serum levels compared to high nSES neighborhoods. Latino adults living in low nSES neighborhoods had increasing CRP serum levels ( $p$ -trend = 0.041) compared to high nSES neighborhoods. Japanese American adults living in low nSES neighborhoods had decreasing adiponectin serum levels ( $p$ -trend = 0.037) compared to high nSES neighborhoods. White adults living in low nSES neighborhoods had increasing leptin serum levels ( $p$ -trend = 0.029) compared to high nSES

neighborhoods. After adjustment further adjustment for BMI, the dose-response associations were no longer significant. No interaction effects between race and ethnicity and nSES and biomarkers were observed. No interaction effects were observed between sex and nSES and biomarkers in California (data not shown). Geometric means levels of CRP, adiponectin, and leptin by nSES across race and ethnicity in California is presented in **Supplemental Table A**.

**Table 4B** summarizes the association between nSES quintiles and the proportion of change (exponentiated  $\beta$  estimates) in serum biomarkers and 95% confidence intervals for adults by race and ethnicity living in Hawaii. In Model 1, Japanese American adults living in low nSES neighborhoods had increasing CRP ( $p$ -trend = 0.041) and leptin ( $p$ -trend = 0.023) serum levels compared to high nSES neighborhoods. With further adjustment for BMI, Native Hawaiian adults living in low nSES neighborhoods had increased leptin serum levels ( $p$ -trend = 0.014). No interaction effects were observed between race and ethnicity and nSES and biomarkers and no interaction effects were observed between sex and nSES and biomarkers in Hawaii (data not shown). Geometric means levels of CRP, adiponectin and leptin by nSES across race and ethnicity in Hawaii is presented in **Supplemental Table B**.

In sensitivity analyses, MEC participants with CRP serum levels > 10 mg/L were excluded (n=811) which yielded comparable results as the main race and ethnicity-stratified analysis. The association between nSES quintiles and the proportion of change (exponentiated  $\beta$  estimates) in serum biomarkers and 95% confidence intervals for adults with CRP serum levels < 10 mg/L by race and ethnicity living in California summarized in **Table 5A**. African Americans living in low nSES neighborhoods had increased CRP serum levels ( $p$ -trend = 0.023) compared to high nSES neighborhoods, however with further

adjustment for BMI, the associations were no longer significant. In **Table 5B** shows the association between nSES quintiles and the proportion of change (exponentiated  $\beta$  estimates) in serum biomarkers and 95% confidence intervals for adults with CRP levels < 10 mg/L by race and ethnicity living in Hawaii. Japanese Americans living in low nSES neighborhoods had increasing CRP serum levels ( $p$ -trend = 0.015) compared to high nSES neighborhoods. With further adjustment for BMI the association was no longer significant. Geometric means levels of CRP < 10 mg/L by nSES across race and ethnicity in California and Hawaii are presented in **Supplemental Tables C and D**. Similar results from the sensitivity analyses to the primary analysis may suggest the sample size excluded could have minimal influence on the overall effect estimates.

### Discussion

Findings from this cross-sectional study suggest nSES is associated with inflammatory biomarkers, CRP, adiponectin and leptin, important indicators of chronic disease. To our knowledge, the current study is the first to demonstrate positive associations between low nSES neighborhoods and CRP and leptin, and inverse associations between low nSES neighborhoods and adiponectin compared to high nSES neighborhoods in a multiethnic population with robust generalizability. Moreover, in both California and Hawaii, similar statistically significant dose-response patterns were observed between nSES and inflammatory biomarker levels. However, overall associations and associations by race and ethnicity were attenuated with further adjustment for BMI, with exception for an association between low nSES and leptin compared to high nSES among Native Hawaiians.

African American, Japanese American, Latino and White adult men and women living in California had higher effect estimates than Japanese American, Native Hawaiian

and White adults living in Hawaii with varying associations between nSES and biomarker serum levels by racial and ethnic groups. In California, the magnitude of effect size was greater for all biomarkers across the nSES quintiles, suggesting a 16% (0.26 mg/L) increase in CRP levels, a 13% (1.13 ng/mL) increase in leptin levels and 9% (0.63 ug/mL) decrease in adiponectin levels among adults living in low nSES neighborhoods compared to high nSES neighborhoods. However, in Hawaii, there was an 11% (0.13 mg/L) increase in CRP levels and 4% (0.28 ug/mL) decrease in adiponectin levels among adults living in low nSES neighborhoods in Hawaii compared to high nSES neighborhoods. In the overall and race and ethnicity stratified analyses, further adjustment for BMI attenuated associations between low nSES and all biomarkers compared to high nSES and were no longer statistically significant, apart from positive associations between low nSES and leptin levels compared to high nSES among Native Hawaiians living in Hawaii.

Inflammatory biomarkers are important indicators of chronic diseases associated with obesity [318] and are plausible measures reflecting the underlying biological mechanisms for increased risk of inflammation [296]. Neighborhood environment characterized by low nSES has been associated with increased risk of chronic disease [33]. Prior studies have shown inverse associations between neighborhood deprivation index and CRP, however, inflammatory biomarkers such as leptin and adiponectin have not been examined among a multiethnic population. In agreement with the findings of the current study, a cross-sectional study by Nazmi et al. observed inverse associations between neighborhood deprivation index (NDI) score and an 0.8 % decrease in CRP levels per one-unit increase in NDI score in a multiethnic population consisting of predominately White and other racial and ethnic groups (African American, Hispanic and Chinese) [301]. The deprivation score was based on 19

census tract-levels available in the 2000 US Census and six factors related to access to communication/transportation resources and income (percent vacant housing, percent with no telephone, percent with no vehicle, percent unemployed, median household income, and percent poverty) [301]. Although the present study used composite nSES index categorized into quintiles derived from six related neighborhood characteristics (education, housing, employment, occupation, income and poverty), among adults in both Hawaii and California, CRP levels also decreased as nSES increased in the overall associations ( $p$  - *trend* <0.05). More specifically, CRP serum levels increased by 11% in Hawaii and 16% in California for those residing in low nSES versus high nSES neighborhoods. Findings from the present study also align with those from Roberts et al. [302] and Chaparro et al. [298]. In a cross-sectional study of adults living in Baltimore, Maryland, Roberts et al. assessed levels of neighborhood disorder, disadvantage and deprivation and observed proportional increases in serum CRP levels with each one-unit level increase in unfavorable neighborhood characteristic [302]. Additionally, a study by Chaparro et al. conducted in Britain observed positive associations between neighborhood deprivation and serum CRP levels ( $\beta$  0.056, 95% CI: 0.044, 0.068) [298]. Similarly, the current study observed adults living in low nSES neighborhoods had increased levels of CRP compared to adults in high nSES neighborhoods overall in California and Hawaii.

The association of nSES and inflammatory biomarkers by race and ethnicity is not well understood despite observed differences in CRP, leptin and adiponectin serum levels by race and ethnicity (253, 369) and a higher concentration of racial and ethnic minorities residing in low nSES neighborhoods. This is in part due to the limited studies conducted among diverse populations. Two previous studies examined nSES and CRP serum levels in

African American [299] and Mexican American women [300] with observed inverse associations in agreement with the current study. Cozier et al. assessed cross-sectional associations between nSES quintiles and CRP among African American women in the Black Women's Health Study. Low nSES was inversely associated with serum CRP levels ( $p$ -trend = 0.004) with a mean age adjusted difference of 1.24 ug/mL between low nSES (Q1) and high nSES (Q5) among Black women. Similarly, in the present study, low nSES (Q1) was inversely associated with high nSES (Q5) with adjustment for age, sex, race and ethnicity, and fasting hours and a significant dose-response observed. Findings are similar to effect estimates by Cozier et al.; however, nSES and CRP associations with additional adjustment for BMI and sociodemographic, behavioral and reproductive factors remained statistically significant ( $p$ -trend = 0.013) in the Cozier et al. study unlike the present analyses where finds were attenuated and no longer statistically significant with additional adjustment for BMI (model 2) and further adjustment for sociodemographic, behavioral and reproductive factors (data not shown). A prior study conducted by Gallo et al. comprised of Mexican American women observed high nSES neighborhoods had lower (23.6%) serum CRP levels with adjustment for age, language, nativity, smoker status and duration of current residence [300]. However, with further adjustment for BMI and other behavioral factors, the inverse association was attenuated and no longer significant, in agreement with the current study findings. Additionally, the study population (n=284) included in the study by Gallo et al.[300] largely resided in South San Diego, California, geographically approximate to participants residing in Los Angeles, California in the current study.

Previous studies have not examined nSES and serum biomarkers among diverse multiethnic populations including Japanese American and Native Hawaiian adults.

Moreover, previous studies have not examined nSES and leptin in a multiethnic population to understand the anti-inflammatory biological pathway, despite the strong association of leptin and obesity [373]. In the current study, it is important to highlight the patterns in CRP and leptin serum biomarkers among African American, Latino, Japanese American and White adults. Low nSES neighborhoods had increased CRP and leptin serum levels compared to high nSES neighborhoods (p-trend <0.05). However, with further adjustment of BMI, the associations were attenuated and no longer statistically significant, with the exception of Native Hawaiians living in low nSES neighborhoods who had increased leptin levels compared adults living in high nSES neighborhoods.

Neighborhood socioeconomic status is inversely associated with obesity and obesity is more prevalent among African American, Latino and White adults living in low nSES versus high nSES [33], which may suggest nSES and inflammatory biomarkers are associated via the obesogenic environment theory. To this end, low nSES characterizes a neighborhood environment that may be more conducive to weight gain and promotes obesity [294]. Given CRP, adiponectin and leptin are obesity-related biomarkers, the adjustment for BMI may lead to an overadjustment. Future studies should further examine these associations and the influence of BMI.

The influence of the neighborhood socioeconomic status on sex differences in CRP, leptin and adiponectin has been observed. A cross-sectional study conducted by Lyer et al. [156] using data from the Nurse's Health Study (NHS) of women only and Health Professional Follow-Up study (HPFS) comprised of males only observed inverse associations between nSES and CRP suggesting a one-unit increase in nSES decreases CRP serum levels by 8.4% and increases adiponectin levels 2.4% in women. These associations were not

observed in men [156]. In the current study, no interaction effects were observed between nSES quintiles and biomarker serum levels ( $p$ -int >0.05) by sex suggesting there was no statistically significant heterogeneity in associations by sex in California and Hawaii.

However, overall findings from the current study support the association between low nSES and serum CRP levels compared to high nSES by Lyer et al. [156] and extends the research to diverse racial and ethnic adult populations.

Limitations to the present study include the use of the cross-sectional design which is subject to temporal ambiguity and the measurement of biomarker at one timepoint. Using multiple timepoints would enable assessment of changes or patterns in serum biomarker levels over time. Despite this, notable strengths include the assessment of neighborhood socioeconomic status in relation to multiple markers of inflammation, CRP, adiponectin, and leptin among a multiethnic population in California and Hawaii. The large-population-based data strengthens the generalizability of the study findings.

The cross-sectional findings from this multiethnic study expand the current understanding of the association between nSES and serum inflammatory biomarkers namely leptin, adiponectin and CRP. While racial and ethnic differences in serum levels were observed among adults living in neighborhoods with low nSES compared to high nSES, when adjusting for BMI the association was no longer observed. Future studies should examine the relationship between neighborhood socioeconomic status and other neighborhood-level attributes and consider additional biomarkers representing the inflammatory pathway such as interleukin-6, interleukin-8, and tumor necrosis factor – alpha among multiethnic populations.

Tables for Manuscript 3

Table 1A. Participant characteristics with at least one inflammatory biomarker sample available among adults residing in California overall and by race and ethnicity in the Multiethnic Cohort (1993 – 1996)

	Overall (n=6,919)	African American (n=2,196)	Japanese American (n=648)	Latino (n=3,988)	White (n=87)
Age, years, mean (SD)	69.1 (7.7)	68.6 (8.4)	70.5 (8.0)	69.2 (7.2)	70.7 (7.6)
Sex,			n (%)		
Male	2709 (39.1)	555 (25.3)	299 (46.1)	1821 (45.7)	34 (39.1)
Female	4210 (60.9)	1641 (74.7)	349 (53.9)	2167 (54.3)	53 (60.9)
Fasting, hours					
0 - 7.9	378 (5.5)	77 (3.5)	31 (4.8)	265 (6.6)	5 (5.7)
8 - 12	1948 (28.2)	623 (28.4)	192 (29.6)	1105 (27.7)	28 (32.2)
12 or more	4593 (66.4)	1496 (68.1)	425 (65.6)	2618 (65.7)	54 (62.1)
Body mass index, mean kg/m <sup>2</sup>					
< 24.9	2093 (30.3)	577 (26.3)	380 (58.6)	1105 (27.7)	31 (35.6)
25.0 - 29.9	2963 (42.8)	856 (39.0)	237 (36.6)	1839 (46.1)	31 (35.6)
30.0 - 34.9	1272 (18.4)	477 (21.7)	26 (4.0)	755 (18.9)	14 (16.1)
35.0 +	575 (8.3)	279 (12.7)	3 (0.5)	284 (7.1)	9 (10.3)
Alcohol intake, grams/day					
0-4.9	858 (12.4)	259 (11.8)	55 (8.5)	530 (13.3)	14 (16.1)
5.0-14.9	789 (11.4)	211 (9.6)	53 (8.2)	515 (12.9)	10 (11.5)
> 15	5087 (73.5)	1671 (76.1)	522 (80.6)	2835 (71.1)	59 (67.8)
Physical activity, METs/day					
0 - 2.9	3292 (47.6)	1100 (50.1)	262 (40.4)	1882 (47.2)	48 (55.2)
3-6	1328 (19.2)	461 (21.0)	159 (24.5)	690 (17.3)	18 (20.7)
>6	1821 (26.3)	503 (22.9)	202 (31.2)	1098 (27.5)	18 (20.7)
Education					
High school or less	3170 (45.8)	581 (26.5)	120 (18.5)	2433 (61)	36 (41.4)
Vocational school/college	3009 (43.5)	1281 (58.3)	415 (64.0)	1275 (32)	38 (43.7)
Graduate or professional school	668 (9.7)	315 (14.3)	110 (17.0)	230 (5.8)	13 (14.9)
Marital status					
Married	4492 (64.9)	1060 (48.3)	522 (80.6)	2856 (71.6)	54 (62.1)
Separated/divorced	1278 (18.5)	658 (30.0)	42 (6.5)	564 (14.1)	14 (16.1)
Widowed	671 (9.7)	309 (14.1)	40 (6.2)	311 (7.8)	11 (12.6)
Never married	415 (6.0)	145 (6.6)	40 (6.2)	223 (5.6)	7 (8.1)
Smoking status					
Never	3421 (49.4)	1017 (46.3)	335 (51.7)	2036 (51.1)	33 (37.9)
Former	3000 (43.4)	989 (45.0)	271 (41.8)	1694 (42.5)	46 (52.9)
Current	278 (4.0)	111 (5.1)	22 (3.4)	139 (3.5)	6 (6.9)
Menopausal status*					
Premenopausal	492 (7.0)	230 (10.5)	43 (6.6)	215 (5.4)	4 (4.6)
Postmenopausal	3664 (53.0)	1403 (63.9)	302 (46.6)	1910 (47.9)	49 (56.3)
Current menopausal hormone therapy*					
None	3277 (47.4)	1301 (59.2)	247 (38.1)	1689 (42.4)	40 (46.0)
Estrogen or progesterone only	657 (9.5)	263 (12.0)	78 (12.0)	307 (7.7)	9 (10.3)
Estrogen and progesterone	164 (2.4)	47 (2.1)	14 (2.2)	99 (2.5)	4 (4.6)

SD – standard deviation; METs – metabolic equivalents; Totals may not sum to 100% due to missing values not shown.;

\*Females only; P-values not presented in the table. Chi-square tests (p<0.001). One-way ANOVA F-test (p<0.05)

Table 1B. Participant characteristics with at least one inflammatory biomarker sample available among adults residing in Hawaii overall and by race and ethnicity in the Multiethnic Cohort (1993 – 1996)

	Overall (n=6,899)	Japanese American (n=3,303)	Native Hawaiian (n=2,229)	White (n=1,367)
Age, years, mean (SD)	67.6 (8.5)	68.7 (8.4)	65.4 (8.1)	68.5 (8.5)
Sex	n (%)			
Male	3013 (43.7)	1399 (42.4)	1042 (46.8)	572 (41.8)
Female	3886 (56.3)	1904 (57.6)	1187 (53.3)	795 (58.2)
Fasting hours, hours				
0 - 7.9	63 (0.9)	30 (0.9)	16 (0.7)	17 (1.2)
8 - 12	1704 (24.7)	760 (23.0)	569 (25.5)	375 (27.4)
12 or more	5132 (74.4)	2513 (76.1)	1644 (73.8)	975 (71.3)
Body mass index, mean kg/m <sup>2</sup>				
< 24.9	3103 (45.0)	1886 (57.1)	612 (27.5)	605 (44.3)
25.0 - 29.9	2508 (36.4)	1106 (33.5)	904 (40.6)	498 (36.4)
30.0 - 34.9	841 (12.2)	241 (7.3)	431 (19.3)	169 (12.4)
35.0 +	414 (6.0)	56 (1.7)	272 (12.2)	86 (6.3)
Alcohol intake, grams/day				
0-4.9	1138 (16.5)	369 (11.2)	371 (16.6)	398 (29.1)
5.0-14.9	746 (10.8)	251 (7.6)	279 (12.5)	216 (15.8)
> 15	4845 (70.2)	2591 (78.4)	1537 (69.0)	717 (52.5)
Physical activity, METs/day				
0 - 2.9	2415 (35)	1304 (39.5)	703 (31.5)	408 (29.9)
3-6	1650 (23.9)	828 (25.1)	498 (22.3)	324 (23.7)
>6	2669 (38.7)	1102 (33.4)	966 (43.3)	601 (44.0)
Education				
High school or less	2137 (31.0)	1028 (31.1)	883 (39.6)	226 (16.5)
Vocational school/college	3530 (51.2)	1701 (51.5)	1114 (50.0)	715 (52.3)
Graduate or professional school	1198 (17.4)	559 (16.9)	219 (9.8)	420 (30.7)
Marital status				
Married	5342 (77.4)	2660 (80.5)	1705 (76.5)	977 (71.5)
Separated/divorced	754 (10.9)	255 (7.7)	277 (12.4)	222 (16.2)
Widowed	410 (5.9)	183 (5.5)	133 (6.0)	94 (6.9)
Never married	373 (5.4)	197 (6)	108 (4.9)	68 (5.0)
Smoking status				
Never	3390 (49.1)	1774 (53.7)	1018 (45.7)	598 (43.8)
Former	3130 (45.4)	1409 (42.7)	1036 (46.5)	685 (50.1)
Current	247 (3.6)	82 (2.5)	117 (5.3)	48 (3.5)
Menopausal status*				
Premenopausal	794 (11.5)	384 (11.6)	269 (12.1)	141 (10.3)
Postmenopausal	3072 (44.5)	1511 (45.8)	908 (40.7)	653 (47.8)
Current menopausal hormone therapy*				
None	2901 (42.1)	1403 (42.5)	939 (42.1)	559 (40.9)
Estrogen or progesterone only	667 (9.7)	349 (10.6)	181 (8.1)	137 (10.0)
Estrogen and progesterone	306 (4.4)	147 (4.5)	63 (2.8)	96 (7.0)

SD – standard deviation; METs – metabolic equivalents; Unknown categories not listed; n does not sum to 100%

\*Females only; P-values not presented in the table. Chi-square tests (p<0.001). One-way ANOVA F-test (p<0.05)

Table 2A Adjusted geometric means and 95% confidence intervals of neighborhood socioeconomic status and inflammatory biomarkers and other factors among adults residing in California in the Multiethnic Cohort (1993 – 1996)

	C-reactive protein (mg/L) n= 6,828		Adiponectin (ug/mL) n=6,694		Leptin (ng/mL) n=6,638	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	Geometric means (95% CI)		Geometric means (95% CI)		Geometric means (95% CI)	
<b>nSES Quintiles</b>						
Q1(Low)	1.9 (1.8, 2.1)	2.3 (2.0, 2.6)	6.5 (6.2, 6.8)	6.4 (5.9, 7.0)	12.5 (11.7, 13.4)	14.7 (13.2, 16.5)
Q2	1.9 (1.8, 2.1)	2.3 (2.0, 2.6)	6.7 (6.4, 7.0)	6.6 (6.1, 7.2)	12.6 (11.8, 13.4)	15.1 (13.5, 16.9)
Q3	1.8 (1.6, 2.0)	2.2 (1.9, 2.5)	6.9 (6.6, 7.3)	6.7 (6.2, 7.3)	12.3 (11.5, 13.2)	15.4 (13.8, 17.3)
Q4	1.7 (1.6, 1.9)	2.1 (1.8, 2.4)	6.9 (6.5, 7.2)	6.6 (6.0, 7.2)	11.5 (10.7, 12.4)	15.0 (13.4, 16.7)
Q5 (High)	1.7 (1.5, 1.8)	2.2 (1.9, 2.5)	7.1 (6.7, 7.6)	6.7 (6.1, 7.4)	11.1 (10.2, 12.1)	15.4 (13.7, 17.4)
<b>Race and ethnicity</b>						
African American	2.4 (2.2, 2.5)	2.7 (2.4, 3.0)	6.0 (5.7, 6.2)	6.0 (5.5, 6.5)	16.2 (15.4, 17)	18.2 (16.4, 20.2)
Latina	2.1 (2.0, 2.2)	2.5 (2.3, 2.8)	7.8 (7.6, 8.0)	7.7 (7.1, 8.3)	13.9 (13.4, 14.5)	16.6 (15, 18.4)
Japanese American	1.0 (0.9, 1.1)	1.4 (1.2, 1.6)	6.0 (5.6, 6.3)	5.4 (4.9, 6.0)	6.8 (6.3, 7.3)	10.7 (9.5, 12.1)
White	2.1 (1.7, 2.7)	2.5 (2.0, 3.2)	7.9 (7.0, 8.8)	7.7 (6.8, 8.8)	13.6 (11.4, 16.1)	16.1 (13.7, 18.9)
<b>Sex</b>						
Male	1.5 (1.4, 1.6)	1.9 (1.6, 2.1)	5.5 (5.3, 5.7)	5.3 (4.9, 5.8)	6.7 (6.3, 7.2)	8.5 (7.6, 9.4)
Female	2.2 (2.0, 2.3)	2.6 (2.3, 2.9)	8.5 (8.1, 8.8)	8.2 (7.6, 8.9)	21.4 (20.3, 22.7)	27.0 (24.3, 30.0)
<b>Fast</b>						
0 - 7.9 hours	1.8 (1.6, 2.1)	2.3 (1.9, 2.6)	7.0 (6.5, 7.5)	6.7 (6.1, 7.4)	11.7 (10.6, 13)	14.9 (13.2, 16.9)
8 - 12 hours	1.7 (1.6, 1.9)	2.1 (1.8, 2.4)	6.9 (6.6, 7.1)	6.7 (6.2, 7.3)	12.5 (11.8, 13.3)	15.6 (14.0, 17.4)
12 or more hours	1.9 (1.7, 2.0)	2.3 (2.0, 2.6)	6.7 (6.4, 6.9)	6.5 (6.0, 7.0)	11.8 (11.2, 12.4)	14.8 (13.4, 16.5)
<b>Body mass index, kg/m<sup>2</sup></b>						
< 24.9	-	1.3 (1.2, 1.5)	-	8.0 (7.6, 8.3)	-	6.8 (6.5, 7.2)
25.0 - 29.9	-	1.8 (1.7, 2.0)	-	6.5 (6.3, 6.8)	-	13.6 (13, 14.2)
30.0 - 34.9	-	2.5 (2.3, 2.8)	-	5.8 (5.5, 6.1)	-	21.5 (20.4, 22.7)
35.0 +	-	3.6 (3.3, 4.0)	-	5.5 (5.1, 5.8)	-	30.7 (28.7, 32.9)
Unknown	-	2.3 (1.4, 3.8)	-	7.7 (5.3, 11.3)	-	12.9 (7.9, 21.1)

Quintile 1 – low; Quintile 5-high (referent group); nSES – neighborhood socioeconomic status;  
 Model 1 adjusted for age, sex, race and ethnicity, fasting hours and census block group  
 Model 2 adjusted for Model 1 + body mass index

Table 2B Adjusted Geometric means and 95% confidence intervals of neighborhood socioeconomic status and inflammatory biomarkers among adults residing in Hawaii in the Multiethnic Cohort (1993 – 1996)

	C-reactive protein (mg/L) n=6,447		Adiponectin (ug/mL) n=6,480		Leptin (ng/mL) n=6,394	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	Geometric means (95% CI)		Geometric means (95% CI)		Geometric means (95% CI)	
<b>nSES Quintiles</b>						
Q1(Low)	1.3 (1.1, 1.5)	1.6 (1.4, 1.9)	6.3 (5.8, 6.7)	5.6 (5.2, 6.1)	9.5 (8.5, 10.6)	13.1 (11.9, 14.5)
Q2	1.2 (1.1, 1.4)	1.6 (1.4, 1.8)	6.2 (5.8, 6.6)	5.6 (5.2, 6.1)	10.0 (9, 11.1)	13.5 (12.2, 15.0)
Q3	1.2 (1.1, 1.3)	1.5 (1.3, 1.7)	6.4 (6.0, 6.9)	5.9 (5.4, 6.3)	10.5 (9.6, 11.6)	14.2 (12.8, 15.6)
Q4	1.2 (1.1, 1.4)	1.6 (1.4, 1.8)	6.4 (6.0, 6.8)	5.7 (5.3, 6.1)	9.6 (8.8, 10.6)	13.7 (12.4, 15.2)
Q5 (High)	1.2 (1, 1.3)	1.5 (1.4, 1.7)	6.5 (6.2, 6.9)	5.8 (5.4, 6.2)	9.4 (8.7, 10.3)	14.1 (12.8, 15.4)
<b>Race and Ethnicity</b>						
Japanese American	0.9 (0.8, 0.9)	1.2 (1.1, 1.4)	5.5 (5.2, 5.9)	4.7 (4.4, 5.0)	7.3 (6.7, 7.9)	12.1 (11.1, 13.3)
White	1.5 (1.4, 1.7)	2.0 (1.7, 2.2)	8.2 (7.7, 8.8)	7.4 (6.9, 7.9)	11.3 (10.2, 12.4)	15.8 (14.3, 17.5)
Native Hawaiian	1.4 (1.3, 1.5)	1.6 (1.4, 1.8)	5.6 (5.3, 6.0)	5.4 (5.0, 5.8)	11.5 (10.5, 12.6)	13.4 (12.2, 14.8)
<b>Sex</b>						
Male	1.1 (1, 1.2)	1.3 (1.2, 1.5)	5.3 (5.0, 5.6)	4.8 (4.5, 5.2)	5.6 (5.2, 6.2)	7.5 (6.8, 8.2)
Female	1.4 (1.3, 1.6)	1.9 (1.7, 2.1)	7.7 (7.3, 8.1)	6.8 (6.4, 7.2)	17 (15.6, 18.6)	25.1 (22.9, 27.6)
<b>Fasting hours</b>						
0 - 7.9 hours	1.1 (0.8, 1.4)	1.4 (1.0, 1.8)	6.2 (5.3, 7.2)	5.7 (4.9, 6.6)	9.7 (7.6, 12.5)	13.1 (11, 15.5)
8 - 12 hours	1.3 (1.2, 1.3)	1.7 (1.5, 1.9)	6.6 (6.4, 6.8)	5.8 (5.6, 6.1)	9.8 (9.4, 10.3)	14.3 (13.2, 15.5)
12 or more hours	1.3 (1.3, 1.4)	1.7 (1.6, 1.9)	6.3 (6.2, 6.4)	5.7 (5.4, 5.9)	9.8 (9.5, 10.2)	13.8 (12.8, 14.9)
<b>Body mass index, kg/m<sup>2</sup></b>						
< 24.9	-	0.9 (0.8, 1.0)	-	8.1 (7.6, 8.5)	-	5.2 (4.9, 5.5)
25.0 - 29.9	-	1.3 (1.1, 1.4)	-	5.7 (5.4, 6.0)	-	11.7 (11.1, 12.5)
30.0 - 34.9	-	1.8 (1.6, 2.0)	-	5.1 (4.8, 5.5)	-	19.5 (18.2, 20.8)
35.0 +	-	2.8 (2.5, 3.2)	-	4.6 (4.3, 5.0)	-	31.6 (29.4, 33.8)
Missing	-	1.8 (1.2, 2.7)	-	5.6 (4.6, 6.8)	-	13.0 (9.0, 18.8)

Quintile 1 – low; Quintile 5-high (referent group); nSES – neighborhood socioeconomic status;  
 Model 1 adjusted for age, sex, race and ethnicity, fasting hours and census block group  
 Model 2 adjusted for Model 1 + body mass index

Table 3A. Exponentiated beta estimates and 95% confidence intervals of neighborhood socioeconomic status and inflammatory biomarkers overall among adults residing in California in the Multiethnic Cohort (1993 – 1996)

Biomarker	Neighborhood Socioeconomic Status Quintiles					P-trend
	1 (Low)	2	3	4	5 (High)	
	Exponentiated $\beta$ (95% Confidence interval)*					
C-reactive protein (mg/L)						
Model 1	<b>1.16 (1.05, 1.28)</b>	<b>1.16 (1.05, 1.28)</b>	1.08 (0.97, 1.20)	1.03 (0.92, 1.14)	1.00	<b>&lt;.0001</b>
Model 2	1.05 (0.96, 1.16)	1.06 (0.96, 1.17)	1.01 (0.92, 1.12)	0.98 (0.89, 1.09)	1.00	0.0600
Adiponectin (ug/mL)						
Model 1	0.91 (0.85, 0.97)	0.94 (0.88, 1.01)	0.97 (0.91, 1.04)	0.96 (0.90, 1.03)	1.00	<b>0.0008</b>
Model 2	0.95 (0.89, 1.01)	0.98 (0.92, 1.05)	1.00 (0.93, 1.06)	0.98 (0.92, 1.04)	1.00	0.0623
Leptin (ng/mL)						
Model 1	<b>1.13 (1.04, 1.23)</b>	<b>1.13 (1.04, 1.23)</b>	<b>1.11 (1.01, 1.21)</b>	1.04 (0.95, 1.13)	1.00	<b>0.0007</b>
Model 2	0.96 (0.89, 1.03)	0.98 (0.91, 1.05)	1.00 (0.93, 1.08)	0.97 (0.90, 1.05)	1.00	0.2157

Quintile 1 – low; Quintile 5-high (referent group); nSES – neighborhood socioeconomic status;

C-reactive protein (n=6,828); Adiponectin (n= 6,694); Leptin (n=6,638)

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1 + body mass index

Bold: p-value <0.05

Table 3B. Exponentiated beta estimates and 95% confidence intervals of neighborhood socioeconomic status and inflammatory biomarkers overall among adults residing in Hawaii in the Multiethnic Cohort (1993 – 1996)

Biomarker	Neighborhood Socioeconomic Status Quintiles					P-trend
	1 (Low)	2	3	4	5 (High)	
	Exponentiated $\beta$ (95% Confidence interval) *					
C-reactive protein (mg/L)						
Model 1	<b>1.11 (1.01, 1.23)</b>	1.08 (0.99, 1.17)	1.05 (0.97, 1.13)	<b>1.07 (1.00, 1.15)</b>	1.00	<b>0.0191</b>
Model 2	1.06 (0.96, 1.18)	1.03 (0.95, 1.11)	0.99 (0.92, 1.07)	1.05 (0.98, 1.13)	1.00	0.3415
Adiponectin (ug/mL)						
Model 1	0.96 (0.90, 1.02)	<b>0.95 (0.90, 1.00)</b>	0.98 (0.94, 1.03)	0.98 (0.94, 1.02)	1.00	<b>0.0334</b>
Model 2	0.98 (0.93, 1.03)	0.98 (0.93, 1.03)	1.02 (0.97, 1.07)	1.00 (0.96, 1.04)	1.00	0.4168
Leptin (ng/mL)						
Model 1	1.00 (0.92, 1.09)	1.06 (0.98, 1.14)	<b>1.12 (1.05, 1.19)</b>	1.02 (0.96, 1.09)	1.00	0.1075
Model 2	<b>0.94 (0.88, 0.99)</b>	0.96 (0.91, 1.02)	1.01 (0.96, 1.06)	0.98 (0.93, 1.03)	1.00	0.0683

Quintile 1 – low; Quintile 5-high (referent group); nSES – neighborhood socioeconomic status

C-reactive protein (n=6,828); Adiponectin (n= 6,694); Leptin (n=6,638)

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1+ body mass index

Bold: p-value <0.05;

Table 4A. Exponentiated Beta estimates and 95% confidence intervals of neighborhood socioeconomic status and inflammatory biomarkers among adults by race and ethnicity in California in the Multiethnic Cohort (1993 – 1996)

Neighborhood Socioeconomic status	African American		Latino		Japanese American		White		P int
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	
	Exponentiated $\beta$ (95% Confidence interval)*								0.779
C-reactive protein (mg/L)									
Quintile 1 (Low)	<b>1.29 (1.07, 1.56)</b>	1.11 (0.93, 1.34)	1.07 (0.93, 1.22)	1.00 (0.87, 1.13)	0.92 (0.61, 1.39)	0.9 (0.6, 1.3)	<b>2.16 (1.00, 4.63)</b>	1.78 (0.75, 4.25)	
Quintile 2	1.21 (0.99, 1.47)	1.06 (0.88, 1.28)	1.11 (0.96, 1.27)	1.03 (0.91, 1.18)	1.06 (0.82, 1.36)	1.0 (0.8, 1.3)	1.02 (0.57, 1.84)	1.00 (0.54, 1.85)	
Quintile 3	1.11 (0.91, 1.37)	1.02 (0.84, 1.24)	1.05 (0.91, 1.21)	1.00 (0.88, 1.15)	0.86 (0.67, 1.11)	0.8 (0.6, 1.0)	1.50 (0.87, 2.58)	1.36 (0.70, 2.65)	
Quintile 4	1.06 (0.86, 1.32)	1.02 (0.83, 1.25)	0.95 (0.82, 1.11)	0.92 (0.80, 1.07)	1.07 (0.85, 1.33)	1.0 (0.8, 1.3)	1.03 (0.52, 2.03)	1.03 (0.48, 2.20)	
Quintile 5 (High)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
p trend	<b>0.0006</b>	0.1084	0.0409	0.317	0.6976	0.4354	0.244	0.3562	
Adiponectin (ug/mL)									0.431
Quintile 1 (Low)	<b>0.88 (0.78, 0.99)</b>	0.93 (0.83, 1.05)	0.98 (0.90, 1.08)	1.01 (0.92, 1.10)	0.73 (0.52, 1.02)	0.74 (0.54, 1.03)	0.91 (0.66, 1.24)	1.14 (0.77, 1.69)	
Quintile 2	0.95 (0.84, 1.08)	1.00 (0.88, 1.13)	0.99 (0.91, 1.09)	1.02 (0.93, 1.12)	<b>0.83 (0.70, 0.98)</b>	0.85 (0.72, 1.00)	0.91 (0.67, 1.25)	0.98 (0.70, 1.36)	
Quintile 3	0.97 (0.85, 1.10)	1.00 (0.88, 1.13)	1.02 (0.93, 1.12)	1.03 (0.94, 1.13)	0.94 (0.80, 1.09)	0.96 (0.83, 1.11)	0.89 (0.62, 1.26)	1.09 (0.72, 1.64)	
Quintile 4	0.97 (0.85, 1.10)	0.98 (0.86, 1.11)	1.03 (0.94, 1.13)	1.05 (0.95, 1.15)	<b>0.83 (0.73, 0.96)</b>	<b>0.86 (0.76, 0.99)</b>	0.82 (0.58, 1.16)	0.90 (0.64, 1.27)	
Quintile 5 (High)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
p trend	<b>0.0047</b>	0.1258	0.1259	0.4569	0.0372	0.0536	0.3198	0.4355	
Leptin (ng/mL)									0.721
Quintile 1 (Low)	<b>1.21 (1.01, 1.44)</b>	0.99 (0.85, 1.15)	1.02 (0.91, 1.14)	<b>0.90 (0.82, 0.99)</b>	1.13 (0.79, 1.62)	1.04 (0.74, 1.45)	<b>2.09 (1.19, 3.65)</b>	1.28 (0.73, 2.26)	
Quintile 2	1.18 (0.98, 1.41)	0.98 (0.84, 1.15)	1.06 (0.95, 1.19)	0.94 (0.86, 1.04)	1.15 (0.94, 1.41)	1.05 (0.89, 1.25)	1.28 (0.74, 2.24)	1.07 (0.67, 1.70)	
Quintile 3	1.15 (0.96, 1.38)	1.02 (0.87, 1.19)	1.01 (0.90, 1.14)	0.94 (0.86, 1.04)	<b>1.20 (1.00, 1.44)</b>	1.08 (0.92, 1.27)	<b>2.67 (1.76, 4.05)</b>	<b>1.81 (1.21, 2.71)</b>	
Quintile 4	1.00 (0.82, 1.20)	0.95 (0.81, 1.12)	0.98 (0.87, 1.11)	0.93 (0.84, 1.03)	1.15 (0.98, 1.36)	1.05 (0.90, 1.21)	1.58 (0.96, 2.58)	1.24 (0.77, 2.01)	
Quintile 5 (High)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
p trend	<b>0.0004</b>	0.9081	0.2962	0.0776	0.1719	0.5526	0.029	0.8404	

Quintile 1 – low; Quintile 5-high (referent group); nSES – neighborhood socioeconomic status; C-reactive protein (n=6,828); Adiponectin (n= 6,694); Leptin (n=6,638)

Bold: p-value <0.05;

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1 + body mass index

Table 4B. Exponentiated Beta estimates and 95% confidence intervals of inflammatory biomarkers and adiponectin levels and neighborhood socioeconomic status among adults by race and ethnicity residing in Hawaii in the Multiethnic Cohort (1993 – 1996)

Neighborhood Socioeconomic status	Japanese American		Native Hawaiian		White		P int
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	
<b>CRP</b>	Exponentiated $\beta$ (95% Confidence interval)*						
Quintile 1 (Low)	1.10 (0.93, 1.3)	1.03 (0.87, 1.23)	1.04 (0.89, 1.21)	0.98 (0.84, 1.14)	<b>1.31 (1.03, 1.66)</b>	<b>1.28 (1.03, 1.60)</b>	0.615
Quintile 2	<b>1.13 (1.01, 1.26)</b>	1.08 (0.97, 1.2)	1.04 (0.89, 1.21)	0.97 (0.85, 1.1)	1.04 (0.86, 1.26)	1.03 (0.85, 1.24)	
Quintile 3	1.07 (0.96, 1.18)	1.00 (0.91, 1.11)	1.02 (0.91, 1.14)	0.95 (0.85, 1.05)	1.01 (0.84, 1.22)	0.98 (0.82, 1.18)	
Quintile 4	1.08 (0.98, 1.18)	1.05 (0.95, 1.15)	1.04 (0.92, 1.16)	1.01 (0.91, 1.12)	1.15 (0.94, 1.41)	1.14 (0.95, 1.37)	
Quintile 5 (High)	1.00	1.00	1.00	1.00	1.00	1.00	
<i>p</i> trend	<b>0.0405</b>	0.384	0.6141	0.5307	0.158	0.2197	
<b>Adiponectin</b>							0.340
Quintile 1 (Low)	0.94 (0.85, 1.04)	0.97 (0.88, 1.07)	0.96 (0.88, 1.04)	0.97 (0.89, 1.06)	0.93 (0.81, 1.08)	0.95 (0.84, 1.08)	
Quintile 2	0.99 (0.90, 1.08)	1.03 (0.94, 1.12)	0.88 (0.81, 0.97)	0.91 (0.83, 1.00)	0.96 (0.87, 1.06)	0.98 (0.89, 1.08)	
Quintile 3	0.99 (0.92, 1.07)	1.03 (0.95, 1.11)	0.91 (0.84, 1.00)	0.95 (0.87, 1.03)	1.07 (0.98, 1.17)	<b>1.10 (1.01, 1.20)</b>	
Quintile 4	0.98 (0.93, 1.05)	1.00 (0.94, 1.07)	0.94 (0.87, 1.01)	0.95 (0.89, 1.03)	1.04 (0.94, 1.15)	1.05 (0.96, 1.16)	
Quintile 5 (High)	1.00	1.00	1.00	1.00	1.00	1.00	
<i>p</i> trend	0.3594	0.8525	0.0511	0.1645	0.5897	0.946	
<b>Leptin</b>							0.058
Quintile 1 (Low)	1.08 (0.96, 1.21)	0.98 (0.90, 1.08)	0.94 (0.81, 1.09)	0.87 (0.79, 0.96)	0.98 (0.75, 1.29)	0.95 (0.78, 1.16)	
Quintile 2	1.10 (0.99, 1.22)	1.01 (0.93, 1.10)	1.05 (0.93, 1.19)	0.92 (0.84, 1.01)	0.97 (0.82, 1.15)	0.91 (0.79, 1.04)	
Quintile 3	<b>1.10 (1.01, 1.21)</b>	1.00 (0.92, 1.09)	1.08 (0.96, 1.20)	0.94 (0.86, 1.03)	<b>1.22 (1.04, 1.43)</b>	1.13 (0.99, 1.29)	
Quintile 4	1.04 (0.95, 1.14)	0.99 (0.92, 1.07)	0.95 (0.85, 1.06)	0.89 (0.82, 0.97)	1.12 (0.95, 1.32)	1.09 (0.95, 1.26)	
Quintile 5 (High)	1.00	1.00	1.00	1.00	1.00	1.00	
<i>p</i> trend	<b>0.0275</b>	0.9634	0.9441	<b>0.0135</b>	0.7004	0.5507	

Quintile 1 – low; Quintile 5-high (referent group); nSES – neighborhood socioeconomic status; C-reactive protein (n=6,828); Adiponectin (n= 6,694); Leptin (n=6,638) (ng/mL) Bold: p-value <0.05;

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1 + body mass index

Table 5A. Exponentiated Beta estimates and 95% confidence intervals C-reactive protein levels <10 mg/L among adults by race and ethnicity in California in the Multiethnic Cohort (1993 – 1996)

nSES Quintiles	African American		Latino		Japanese American		White		<i>P</i> int
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	
C-reactive protein (mg/L)	Exponentiated $\beta$ (95% confidence intervals)								
Quintile 1 (Low)	<b>1.22 (1.03, 1.44)</b>	1.09 (0.93, 1.28)	1.05 (0.92, 1.2)	0.98 (0.87, 1.11)	0.94 (0.64, 1.39)	0.91 (0.63, 1.31)	1.16 (0.57, 2.38)	0.98 (0.46, 2.07)	0.560
Quintile 2	<b>1.25 (1.05, 1.49)</b>	1.14 (0.96, 1.35)	1.08 (0.95, 1.23)	1.01 (0.89, 1.14)	1.08 (0.83, 1.39)	1.00 (0.78, 1.28)	0.92 (0.53, 1.59)	0.85 (0.49, 1.49)	
Quintile 3	1.13 (0.95, 1.36)	1.07 (0.90, 1.27)	1.06 (0.93, 1.21)	1.01 (0.89, 1.15)	0.90 (0.70, 1.16)	0.84 (0.66, 1.06)	1.29 (0.84, 1.97)	1.05 (0.62, 1.79)	
Quintile 4	1.13 (0.93, 1.36)	1.10 (0.91, 1.32)	0.95 (0.82, 1.10)	0.92 (0.80, 1.05)	1.10 (0.88, 1.37)	1.04 (0.83, 1.29)	0.71 (0.37, 1.36)	0.71 (0.36, 1.41)	
Quintile 5 (High)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
<i>p</i> trend	<b>0.0232</b>	0.4869	0.0813	0.5367	0.7891	0.4319	0.5551	0.6661	

Analysis sample size was based on restricting to participants with untransformed CRP levels < 10 mg/L. Beta estimates are log-transformed CRP levels and neighborhood socioeconomic status quintiles.

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1 + body mass index

Bold: *p*-value <0.05;

Table 5B. Exponentiated Beta estimates and 95% confidence intervals C-reactive protein levels <10 mg/L among adults by race and ethnicity in Hawaii in the Multiethnic Cohort (1993 – 1996)

nSES Quintiles	Japanese American		Native Hawaiian		White		<i>P</i> int
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	
C-reactive protein (mg/L)	Exponentiated $\beta$ (95% confidence intervals)						
Quintile 1 (Low)	1.11 (0.95, 1.29)	1.04 (0.89, 1.21)	0.99 (0.85, 1.15)	0.94 (0.81, 1.08)	1.18 (0.97, 1.45)	1.18 (0.98, 1.43)	0.376
Quintile 2	<b>1.14 (1.02, 1.26)</b>	1.09 (0.98, 1.21)	1.01 (0.87, 1.16)	0.94 (0.83, 1.06)	1.08 (0.91, 1.29)	1.06 (0.90, 1.25)	
Quintile 3	1.09 (0.99, 1.21)	1.03 (0.93, 1.14)	1.04 (0.93, 1.17)	0.97 (0.88, 1.08)	1.07 (0.90, 1.28)	1.05 (0.88, 1.25)	
Quintile 4	1.06 (0.97, 1.17)	1.03 (0.94, 1.14)	1.05 (0.95, 1.17)	1.02 (0.92, 1.13)	<b>1.19 (1.00, 1.43)</b>	<b>1.19 (1.01, 1.40)</b>	
Quintile 5 (High)	1.00	1.00	1.00	1.00	1.00	1.00	
<i>p</i> trend	<b>0.0149</b>	0.2296	0.8666	0.1759	0.1397	0.1783	

Analysis restricted to participants with untransformed CRP levels < 10 mg/L. Beta estimates are log-transformed CRP levels and neighborhood socioeconomic status quintiles.

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1+ body mass index

Bold: *p*-value <0.05;

*Supplemental Tables for Manuscript 3*

Supplemental Table A. Adjusted geometric means and 95% confidence intervals of inflammatory biomarkers and adiponectin levels and neighborhood socioeconomic status among adults by race and ethnicity residing in California in the Multiethnic Cohort (1993 – 1996)

Neighborhood Socioeconomic status	African American		Latina		Japanese American		White		P int
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	
Geometric mean (95% Confidence interval)									
<b>CRP</b>									0.779
Quintile 1 (Low)	2.8 (2.5, 3.1)	2.9 (2.5, 3.4)	2.2 (2.1, 2.4)	2.9 (2.6, 3.3)	0.8 (0.5, 1.2)	1.1 (0.8, 1.6)	3.0 (1.6, 5.9)	2.4 (1.1, 5.4)	
Quintile 2	2.6 (2.3, 3.0)	2.8 (2.4, 3.3)	2.3 (2.1, 2.5)	3.0 (2.6, 3.5)	0.9 (0.7, 1.1)	1.2 (1.0, 1.6)	1.4 (0.9, 2.3)	1.4 (0.7, 2.7)	
Quintile 3	2.4 (2.1, 2.7)	2.7 (2.3, 3.2)	2.2 (2.0, 2.4)	2.9 (2.5, 3.4)	0.7 (0.6, 0.9)	1.0 (0.8, 1.3)	2.1 (1.5, 3.1)	1.9 (1.1, 3.2)	
Quintile 4	2.3 (2.0, 2.7)	2.7 (2.2, 3.2)	2.0 (1.8, 2.2)	2.7 (2.3, 3.2)	0.9 (0.7, 1.1)	1.3 (1.0, 1.6)	1.5 (0.9, 2.4)	1.4 (0.8, 2.5)	
Quintile 5 (High)	2.2 (1.8, 2.6)	2.6 (2.1, 3.2)	2.1 (1.8, 2.4)	2.9 (2.5, 3.5)	0.8 (0.7, 1.0)	1.2 (1.0, 1.5)	1.4 (0.9, 2.1)	1.4 (0.6, 3.0)	
p trend	<b>0.0006</b>	0.1084	0.0409	0.317	0.6976	0.4354	0.244	0.3562	
<b>Adiponectin</b>									0.431
Quintile 1 (Low)	5.34 (5.0, 5.8)	5.39 (4.6, 6.3)	7.58 (7.3, 7.9)	7.11 (6.5, 7.8)	5.17 (3.7, 7.3)	5.98 (4.2, 8.6)	7.3 (5.9, 8.9)	7.6 (6.0, 9.7)	
Quintile 2	5.77 (5.3, 6.3)	5.78 (4.9, 6.8)	7.66 (7.3, 8.0)	7.18 (6.5, 7.9)	5.87 (5.0, 6.8)	6.81 (5.5, 8.4)	7.3 (6.0, 9.0)	6.5 (4.9, 8.7)	
Quintile 3	5.86 (5.4, 6.4)	5.77 (4.9, 6.7)	7.84 (7.5, 8.2)	7.27 (6.6, 8.0)	6.64 (5.8, 7.6)	7.72 (6.4, 9.3)	7.1 (5.7, 8.9)	7.3 (5.8, 9.1)	
Quintile 4	5.86 (5.3, 6.4)	5.64 (4.8, 6.6)	7.96 (7.6, 8.3)	7.37 (6.7, 8.1)	5.92 (5.3, 6.7)	6.94 (5.8, 8.3)	6.5 (5.2, 8.3)	6.0 (4.6, 7.8)	
Quintile 5 (High)	6.06 (5.3, 6.9)	5.78 (4.8, 7.0)	7.71 (7.1, 8.4)	7.04 (6.2, 7.9)	7.09 (6.3, 7.9)	8.04 (6.7, 9.6)	8.0 (6.2, 10.3)	6.7 (4.7, 9.5)	
p trend	<b>0.0047</b>	0.1258	0.1259	0.4569	<b>0.0372</b>	0.0536	0.3198	0.4355	
<b>Leptin</b>									0.721
Quintile 1 (Low)	17.2 (15.6, 19.0)	18.5 (16.0, 21.4)	14.2 (13.4, 15.0)	16.1 (13.7, 19.0)	6.8 (4.9, 9.6)	8.78 (5.8, 13.3)	15.8 (10.4, 24.0)	15.2 (10.4, 22.2)	
Quintile 2	16.8 (15.0, 18.8)	18.4 (15.8, 21.4)	14.7 (13.9, 15.6)	16.8 (14.3, 19.8)	7.0 (5.8, 8.4)	8.92 (6.5, 12.3)	9.7 (6.3, 15.1)	12.6 (8.4, 19.0)	
Quintile 3	16.4 (14.7, 18.3)	19.1 (16.5, 22.1)	14.0 (13.1, 15.1)	16.9 (14.3, 19.9)	7.3 (6.1, 8.6)	9.18 (6.8, 12.4)	20.2 (15.6, 26.2)	21.4 (17.5, 26.3)	
Quintile 4	14.2 (12.6, 16.0)	17.9 (15.4, 20.7)	13.6 (12.6, 14.7)	16.6 (14.0, 19.6)	7.0 (6.1, 8.0)	8.87 (6.6, 12.0)	11.9 (8.4, 17.0)	14.7 (10.7, 20.3)	
Quintile 5 (High)	14.2 (11.9, 17.1)	18.8 (15.4, 22.8)	13.9 (12.5, 15.4)	17.9 (14.9, 21.4)	6.0 (5.3, 6.9)	8.48 (6.3, 11.4)	7.6 (4.9, 11.6)	11.8 (7.7, 18.2)	
p trend	<b>0.0004</b>	0.9081	0.2962	0.0776	0.1719	0.5526	<b>0.029</b>	0.8404	

Quintile 1 – low; Quintile 5-high (referent group); nSES – neighborhood socioeconomic status; C-reactive protein (n=6,828); Adiponectin (n= 6,694); Leptin (n=6,638)

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1 + body mass index

Supplemental Table B. Adjusted geometric means and 95% confidence intervals of inflammatory biomarkers and adiponectin levels and neighborhood socioeconomic status among adults by race and ethnicity residing in Hawaii in the Multiethnic Cohort (1993 – 1996)

Neighborhood Socioeconomic status	Japanese American		Native Hawaiian		White		<i>P</i> int
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	
Geometric mean (95% Confidence interval)							
<b>CRP</b>							
Quintile 1 (Low)	0.92 (0.8, 1.1)	1.25 (1.0, 1.6)	1.32 (1.0, 1.7)	1.58 (1.2, 2.1)	1.9 (1.4, 2.4)	2.4 (1.8, 3.2)	0.615
Quintile 2	0.95 (0.8, 1.1)	1.3 (1.1, 1.6)	1.32 (1.0, 1.7)	1.57 (1.2, 2.1)	1.5 (1.2, 1.8)	1.9 (1.5, 2.4)	
Quintile 3	0.89 (0.8, 1.1)	1.21 (1.0, 1.5)	1.29 (1.0, 1.6)	1.53 (1.2, 2.0)	1.4 (1.2, 1.7)	1.8 (1.4, 2.3)	
Quintile 4	0.90 (0.8, 1.1)	1.27 (1.1, 1.5)	1.32 (1.1, 1.6)	1.63 (1.3, 2.1)	1.6 (1.3, 2.0)	2.1 (1.7, 2.7)	
Quintile 5 (High)	0.84 (0.7, 1.0)	1.21 (1.0, 1.4)	1.27 (1.0, 1.6)	1.62 (1.2, 2.1)	1.4 (1.2, 1.7)	1.9 (1.5, 2.3)	
<i>p</i> trend	<b>0.0405</b>	0.384	0.6141	0.5307	0.158	0.2197	
<b>Adiponectin</b>							
Quintile 1 (Low)	5.39 (4.8, 6.1)	4.63 (4.0, 5.3)	5.53 (4.9, 6.2)	5.38 (4.8, 6.1)	7.95 (6.7, 9.4)	6.77 (5.7, 8.0)	0.34
Quintile 2	5.67 (5.0, 6.4)	4.88 (4.3, 5.6)	5.11 (4.5, 5.7)	5.05 (4.4, 5.7)	8.17 (7.2, 9.3)	6.98 (6.0, 8.0)	
Quintile 3	5.68 (5.1, 6.3)	4.87 (4.3, 5.5)	5.29 (4.7, 5.9)	5.26 (4.7, 5.9)	9.13 (8.1, 10.3)	7.85 (6.8, 9.0)	
Quintile 4	5.65 (5.1, 6.2)	4.76 (4.2, 5.3)	5.43 (4.9, 6.0)	5.29 (4.7, 5.9)	8.83 (7.7, 10.1)	7.5 (6.5, 8.7)	
Quintile 5 (High)	5.74 (5.2, 6.3)	4.75 (4.2, 5.3)	5.78 (5.2, 6.4)	5.54 (4.9, 6.2)	8.51 (7.6, 9.5)	7.13 (6.3, 8.1)	
<i>p</i> trend	0.3594	0.8525	0.0511	0.1645	0.5897	0.946	
<b>Leptin</b>							
Quintile 1 (Low)	7.74 (6.7, 8.9)	11.38 (9.8, 13.1)	10.67 (8.6, 13.3)	13.55 (11.3, 16.2)	9.88 (7.2, 13.5)	14.98 (11.5, 19.6)	0.058
Quintile 2	7.91 (6.9, 9.0)	11.69 (10.2, 13.4)	11.94 (9.8, 14.5)	14.25 (11.9, 17.0)	9.76 (7.6, 12.5)	14.38 (11.6, 17.9)	
Quintile 3	7.94 (7.0, 9.0)	11.6 (10.1, 13.3)	12.2 (10.0, 14.9)	14.57 (12.1, 17.5)	12.23 (9.7, 15.5)	17.88 (14.4, 22.2)	
Quintile 4	7.47 (6.6, 8.4)	11.51 (10.1, 13.2)	10.8 (9.0, 13.0)	13.86 (11.6, 16.5)	11.25 (8.9, 14.3)	17.29 (13.6, 21.9)	
Quintile 5 (High)	7.19 (6.4, 8.1)	11.58 (10.2, 13.1)	11.35 (9.5, 13.5)	15.52 (13.1, 18.4)	10.04 (8.3, 12.1)	15.81 (12.9, 19.3)	
<i>p</i> trend	<b>0.0275</b>	0.9634	0.9441	0.0135	0.7004	0.5507	

Quintile 1 – low; Quintile 5-high (referent group); nSES – neighborhood socioeconomic status; C-reactive protein (n=6,828); Adiponectin (n= 6,694); Leptin (n=6,638) (ng/mL) Bold: p-value <0.05;  
 Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group  
 Model 2: Model 1 + body mass index

Supplemental Table C. Adjusted Geometric means and 95% confidence intervals C-reactive protein levels <10 mg/L among adults by race and ethnicity in California in the Multiethnic Cohort (1993 – 1996)

Neighborhood Socioeconomic status	African American		Latina		Japanese American		White		P int
	Geometric mean (95% Confidence interval)								
C-reactive protein (mg/L)	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	0.560
Quintile 1 (Low)	2.08 (1.9, 2.3)	2.28 (2, 2.6)	1.88 (1.8, 2)	2.37 (2.2, 2.5)	0.74 (0.5, 1.1)	1.07 (0.8, 1.5)	1.82 (1, 3.4)	1.6 (0.8, 3.3)	
Quintile 2	2.14 (1.9, 2.4)	2.37 (2, 2.8)	1.93 (1.8, 2.1)	2.43 (2.2, 2.6)	0.84 (0.7, 1.1)	1.18 (0.9, 1.5)	1.44 (0.9, 2.2)	1.4 (0.7, 2.6)	
Quintile 3	1.94 (1.7, 2.2)	2.23 (1.9, 2.6)	1.9 (1.8, 2)	2.44 (2.2, 2.7)	0.71 (0.6, 0.9)	0.99 (0.8, 1.2)	2.02 (1.6, 2.6)	1.73 (1, 2.9)	
Quintile 4	1.93 (1.7, 2.2)	2.28 (1.9, 2.7)	1.7 (1.5, 1.9)	2.21 (2, 2.4)	0.86 (0.7, 1)	1.22 (1, 1.5)	1.11 (0.7, 1.8)	1.17 (0.7, 2.1)	
Quintile 5 (High)	1.71 (1.4, 2)	2.08 (1.7, 2.5)	1.79 (1.6, 2)	2.41 (2.1, 2.7)	0.78 (0.6, 1)	1.18 (0.9, 1.5)	1.57 (1, 2.4)	1.64 (0.8, 3.5)	
p trend	<b>0.0232</b>	0.4869	0.0813	0.5367	0.7891	0.4319	0.5551	0.6661	

Analysis sample size was based on restricting to participants with untransformed CRP levels < 10 mg/L. Beta estimates are log-transformed CRP levels and neighborhood socioeconomic status quintiles.

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1 + Body mass index

Supplemental Table D. Adjusted Geometric means and 95% confidence intervals C-reactive protein levels <10 mg/L among adults by race and ethnicity in Hawaii in the Multiethnic Cohort (1993 – 1996)

Neighborhood Socioeconomic status	Japanese American		Native Hawaiian		White		P int
	Geometric mean (95% Confidence interval)						
C-reactive protein (mg/L)	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	0.376
Quintile 1 (Low)	0.85 (0.7, 1.0)	1.15 (0.9, 1.4)	1.10 (0.9, 1.3)	1.29 (1, 1.6)	1.49 (1.2, 1.9)	1.90 (1.5, 2.5)	
Quintile 2	0.88 (0.8, 1.0)	1.21 (1.0, 1.4)	1.12 (0.9, 1.3)	1.29 (1, 1.6)	1.37 (1.1, 1.7)	1.70 (1.4, 2.1)	
Quintile 3	0.84 (0.7, 1.0)	1.14 (1.0, 1.4)	1.16 (1.0, 1.4)	1.34 (1.1, 1.7)	1.36 (1.1, 1.7)	1.68 (1.3, 2.1)	
Quintile 4	0.82 (0.7, 0.9)	1.15 (1.0, 1.3)	1.17 (1.0, 1.4)	1.41 (1.1, 1.8)	1.51 (1.2, 1.9)	1.91 (1.5, 2.4)	
Quintile 5 (High)	0.77 (0.7, 0.9)	1.11 (0.9, 1.3)	1.11 (0.9, 1.3)	1.38 (1.1, 1.7)	1.26 (1.1, 1.5)	1.60 (1.3, 1.9)	
p trend	<b>0.0149</b>	0.2296	0.8666	0.1759	0.1397	0.1783	

Analysis sample size was based on restricting to participants with untransformed CRP levels < 10 mg/L. Beta estimates are log-transformed CRP levels and neighborhood socioeconomic status quintiles.

Model 1 for all biomarkers: age, sex, race and ethnicity, fasting hours and census block group

Model 2: Model 1 + Body mass index

## Chapter 7: Public Health Significance

### Conclusions

The findings from this dissertation extend the field of racial and ethnic disparities by highlighting associations between individual factors related to breast cancer risk and neighborhood-level factors in relation to inflammatory biomarkers among diverse, multiethnic populations that have otherwise not been examined. For Aim 1, cholesterol-lowering drugs were not associated with breast cancer risk overall or by hormone receptor status. Although significant associations were observed among Native Hawaiian women who were current users and current users for  $\geq 3$  years and White women who were former users, the interaction effects by race and ethnicity were not statistically significant suggesting no differences by race and ethnicity. The dissertation findings did not support cholesterol-lowering drug use as a protective factor in breast cancer risk. For Aim 2, the collective influence of seven healthy lifestyle behaviors: dietary intake, physical activity, sedentary behavior, BMI, alcohol consumption, smoking and sleep measured as an HLI was inversely associated with breast cancer risk, specifically among postmenopausal women with HR+ breast cancer. Risk reductions were observed in all women and across all racial and ethnic groups of postmenopausal women. While sleep duration and sedentary behavior are emerging as breast cancer risk factors, these factors had minimal influence on breast cancer risk after accounting for other behavioral factors. Findings from this analysis confirm those of prior HLI studies also provides evidence that the breast cancer risk reduction observed with a higher HLI extends to postmenopausal women of diverse racial and ethnic backgrounds. For Aim 3, neighborhood socioeconomic status was not associated with inflammatory biomarkers: CRP and adiponectin independent of BMI, however significant

dose-response associations between nSES and leptin were observed among Native Hawaiian adults. Residing in a low nSES neighborhood was inversely associated with CRP and leptin and positively associated with adiponectin compared to residing in high nSES neighborhoods. Racial and ethnic differences in serum levels of all inflammatory biomarkers were observed among adults living in neighborhoods with low nSES compared to high nSES. Examining individual and neighborhood-level factors in relation to breast cancer is complex and continued focus on understanding these factors and their relationships with breast cancer can help inform and educate women to live more healthily and make changes to improve their health.

#### Public health implications

The prospective MEC data are robust and contain invaluable information on chronic disease among underrepresented and under-researched ethnic and racial minorities. The three aims of this dissertation utilize multiethnic diverse data to expand the knowledge and understanding of cardiometabolic factors in relation to breast cancer in a field that has historically researched primarily White, homogenous racial groups. This dissertation underscores the need for research among racial and ethnic groups that have a high prevalence of chronic disease risk factors such as obesity, smoking, alcohol intake, physical inactivity and unhealthy dietary intake. Findings from this dissertation contribute to breast cancer and chronic disease disparities research by assessing potentially modifiable individual and neighborhood-level factors and improving knowledge and understanding of mechanisms that contribute to breast cancer risk among racially diverse populations of women.

### Future directions

The dissertation assessed individual and neighborhood-level factors in relation to breast cancer risk and biomarkers of inflammation, a key pathway in carcinogenesis. Future breast cancer research on cholesterol lowering medications as potential chemopreventive agents should consider the indication for the prescription and adherence to cholesterol-lowering drug use to enhance the current knowledge. To extend breast cancer research, future studies should also focus on the assessment of the collective modifiable factors measured using the HLI in relation to premenopausal breast cancer to help inform preventative strategies for breast cancer risk. Additional research should focus on evaluating sleep health more accurately and evaluating BMI and other obesity metrics as an effect modifier. To expand the work in neighborhood environment and inflammatory biomarkers, additional biomarkers including IL-6 and IL-8 and additional neighborhood-level factors such as urban environment, unhealthy food, mixed-land development and nature parks should be examined to characterize the neighborhood environment. The use of multiple timepoints for each exposure assessed would strengthen the understanding of the outcome by demonstrating patterns over time, changes in exposures and the association with breast cancer risk and obesity. Examining individual and neighborhood-level factors in relation to breast cancer is complex and continued focus on understanding these factors and their relationships with breast cancer can help inform and educate women to live more healthily and make changes to improve their health.

## Appendices

## Appendix A: Additional background

Appendix Table A-1 Prospective randomized statin trials for cardiovascular disease

Study	Type of Statin	Study Population description	Outcome
AFCAPS/ TexCAPS	Lovastatin, 20– 40 mg/d vs placebo	6,605 men and women	40% reduction in fatal and nonfatal MI; 37% reduction in first ACS; 33% reduction in coronary revascularizations; 32% reduction in unstable angina
ASCOT	Atorvastatin 10 mg/d vs placebo	10,305 hypertensive men (n = 8,463) and women (n = 1,942) with treated high BP and no previous CAD	36% reduction in total CHD/nonfatal MI; 27% reduction in fatal and nonfatal stroke; total coronary event reduced by 29%; fatal and nonfatal stroke reduced by 27%
CARDS	Atorvastatin 10 mg/d vs placebo	2,838 patients with type 2 diabetes mellitus and 1 CHD risk factor	37% reduction in major cardiovascular events; 27% reduction in total mortality; 13.4% reduction in acute CVD events; 36% reduction in acute coronary events; 48% reduction in stroke
Heart Protection Study	Simvastatin 40 mg/d vs placebo	20,536 high-risk patients (previous CHD, other vascular disease, hypertension among men aged > 65 y, or diabetes)	25% reduction in all-cause and coronary death rates and in strokes; need for revascularization reduced by 24%; fatal and nonfatal stroke reduced by 25%; nonfatal MI reduced by 38%; coronary mortality reduced by 18%; all-cause mortality reduced by 13%; cardiovascular event rate reduced by 24%
PROSPER	Pravastatin 40 mg/d vs placebo	5,804 men (n = 2,804) and women (n = 3,000) aged 70–82 y	15% reduction in combined end point (fatal/nonfatal MI or stroke); 19% reduction in total/nonfatal CHD; no effect on stroke (but 25% reduction in TIA)
JUPITER	Pravachol therapy 40 mg/d vs placebo  Rosuvastatin 20 mg/d vs placebo	6,595 men  17,802 men (> 50 y) and women (> 60 y) with no history of CAD or DM, entry LDL < 130 mg/dL, and CRP > 2.0 mg/L	CHD death in nonfatal MI reduced by 31%; CVD death reduced by 32%; total mortality reduced by 22%  44% reduction in primary end point in major coronary events; 65% reduction in nonfatal MI; 48% reduction in nonfatal stroke; 46% reduction in need for revascularization; 20% reduction in all-cause mortality
4S	Simvastatin 20 mg/d vs placebo	4,444 patients with angina pectoris or history of MI	Coronary mortality reduced by 42%; myocardial revascularization reduced by 37%; all-cause mortality reduced by 30%; nonfatal major coronary event reduced by 34%; fatal and nonfatal stroke reduced by 30%
AVERT	Atorvastatin 80 mg/d vs angioplasty and usual care	341 patients with stable CAD	36% reduction in ischemic event; delayed time to first ischemic event reduced by 36%

CARE	Pravastatin 40 mg/d vs placebo	3,583 men and 576 women with history of MI	Death from CHD or nonfatal MI reduced by 24%; death from CHD reduced by 20%; nonfatal MI reduced by 23%; fatal MI reduced by 37%; CABG or PTCA reduced by 27%
IDEAL	Atorvastatin 80 mg/d vs simvastatin 20–40 mg/day	8,888 men and women with CHD	Major cardiac events reduced by 13%, nonfatal MI reduced by 17%, revascularization reduced by 23%, peripheral arterial disease reduced by 24%
LIPID	Pravachol 40 mg/d vs placebo	9,014 patients	Coronary mortality reduced by 24%; stroke reduced by 19%; fatal CHD or nonfatal MI reduced by 24%; fatal or nonfatal MI reduced by 29%
LIPS	Fluvastatin 40 mg/d vs placebo	1,667 men and women aged 18–80 y post-angioplasty for CAD	22% lower rate in major coronary events (e.g., cardiac deaths, nonfatal MI, or reintervention procedure)
MIRACL	Atorvastatin 80 mg/d vs placebo	3,086 patients with ACS	Reduction in composite end point by 16%; ischemia reduced by 26%; stroke reduced by 50%
PROVE IT	Atorvastatin 80 mg/d vs pravastatin 40 mg/day	4,162 patients with ACS	16% reduction in composite end point; 14% reduction in CHD death, MI, or revascularization; revascularizations reduced by 14%; unstable angina reduced by 29%
REVERSAL	Atorvastatin 80 mg/d vs pravastatin 40 mg/day	654 patients with CAD	Atheroma: atorvastatin 0.4%, pravastatin 2.7%, difference of –3.1%, $P = .02$
TNT	Atorvastatin 10 mg/d vs 80 mg/day	10,003 patients with CHD and LDL cholesterol 130–250 mg/dL	22% reduction in composite end point; MI reduced by 22%; stroke reduced by 25%

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Appendix Table A-2: Summary of prior studies examining neighborhood attributes and the obesogenic environment

Author, Year	Study Population	Exposure/ Outcome	Participant Characteristics	Race/Ethnicity (Nationality)	Outcomes/ (Findings)
[280] Sallis,2020	International Physical Activity and Environment Network (IPEN)  Cross-sectional  N= 14,000  13 countries (17 cities)	<b>Neighborhood environment attributes</b> (GIS-based built environment measure: neighborhood buffers, net residential density, land-use mix, intersection density, transit, Park access, and walkability)  <b>Neighborhood environment walkability scale (NEWS)</b> self-report: residential density, land-use mix diversity, land-use mix access, street connectivity, Infrastructure and safety, Park proximity, transit proximity, Aesthetics, safety from traffic and safety from crime.  <b>Physical activity and obesity</b>	18-66 years old  Men and women	Adelaide, Australia; Ghent, Belgium; Curitiba, Brazil; Bogotá, Colombia; Olomouc and Hradec Králové, Czech Republic; Aarhus, Denmark; Hong Kong, China; Cuernavaca, Mexico; North Shore, Waitakere, Wellington, and Christchurch, New Zealand; Pamplona, Spain; Stoke-on-Trent, the United Kingdom; and Baltimore and Seattle regions in the United States.	Neighborhood environment attributes were strongly related to all physical activity outcomes and meaningfully related to overweight/obesity. Activity-supportive built environments should be a higher international health priority. GIS measured and self-reported built environment variables were consistently related to physical activity, particularly residential density and intersection density. GIS-measured park density and reported park proximity were significantly associated with all three physical activity measures. Self-reported mixed land use was related to all physical activity variables, but the GIS measure was related to none.
[377] Davillas, 2020	The Multiethnic Cohort (MEC) study 1993 and 2010  n= 95,472 Los Angeles, CA, participants 2295 invasive CRC cases	<b>Neighborhood environment attributes</b> (Socioeconomic status, population density, restaurant and retail food environments, numbers of recreational facilities and businesses, commute patterns, traffic density, and street connectivity)  <b>Colorectal cancer risk</b>	45 to 75 years old; Men (n = 40, 870) and women (n = 54,602)	African American, Japanese American, Latino, and White	Changes over time in neighborhood attributes influence the risk of colorectal cancer, which is separate from the baseline levels of the same attributes and individual-level risk factors, and differs between sexes, movers and non-movers and across racial and ethnic groups.
[33] Conroy, 2018	The MEC Study 1993 through 1996  n=107,635	<b>Neighborhood obesogenic environment</b> (Neighborhood socioeconomic status and built environment attributes (i.e., population density, % commute by car/motorcycle,	45 to 75 years old; from Hawaii and California.	African American, Japanese Americans, Latinos and Whites	The strongest association observed was between nSES and overweight or obesity, independent of individual-level education, diet, physical activity and other individual- and neighborhood-level factors. In sex and racial and ethnic specific analysis, African

Author, Year	Study Population	Exposure/ Outcome	Participant Characteristics	Race/Ethnicity (Nationality)	Outcomes/ (Findings)
		Restaurant Environment Index (REI), Retail Food Environment Index (RFEI), number of businesses, number of parks, traffic density, number or recreational facilities, and street connectivity)  <b>Overweight or obesity</b> (measured self-reported BMI $\geq 30$ kg/m <sup>2</sup> )			American, Latino, and white men and women living in low- versus high-SES neighborhoods had statistically significant higher odds of obesity (p-trends 0.02 for all; OR ranging from 1.45–2.50 for the lowest vs. highest nSES quintile), with a larger magnitude of effect among women than men.
[378] Hobbs, 2018	Yorkshire Health Study Yorkshire and Humber region, England.  n= 27,806	<b>Physical activity (PA) environment</b> (Unfavorable PA, moderately favorable PA, favorable PA)  <b>Overweight or obesity</b> (measured self-reported BM)	18 to 86 years men and women	White, non-White	Favorable PA environments were associated with lower odds of obesity, once stratified by education-level, this relationship was present for the higher education category. Furthermore, there was no difference in odds of obesity by 151 PA environment within educational groups.
[292] Wong, 2018	2011 – 2013 California Health Interview Survey (CHIS)  n = 62,396	<b>Sociodemographic environment</b> (Census-tract level measures of neighborhood SES (median household income, and educational attainment (percent with a high school degree or less)) and racial and ethnic composition (percent Hispanic, Black, and Asian).  <b>Soda consumption and weight status</b>	18 years and older	Non-Hispanic White, Hispanic, Non-Hispanic African American and Non-Hispanic Asian	Greater number of neighborhood sociodemographic, social, and built environment characteristics were associated with soda consumption and weight status
[379] Canchola, 2017	MEC Study between 1993 and 2010	<b>Obesogenic neighborhood attributes</b> (Socioeconomic status, population density, restaurant and retail food environments,	Adults from California (men: 35,397 and women:45,800),	Non-Hispanic White, Hispanic, Non-Hispanic African American and Non-Hispanic Asian	Neighborhood obesogenic characteristics are not strongly associated with the risk of colorectal cancer.

Author, Year	Study Population	Exposure/ Outcome	Participant Characteristics	Race/Ethnicity (Nationality)	Outcomes/ (Findings)
	n = 81,197  1973 incident cases (981 males and 992 females) identified between 1993 and 2010	numbers of recreational facilities and businesses, commute patterns, traffic density, and street connectivity  <b>Colorectal cancer risk</b>			
[380]  Conroy, 2017	MEC Study  n=48,247  n = 2,341 cases	<b>Obesogenic environment</b> (Neighborhood socioeconomic status (nSES), urban, mixed-land development, unhealthy food environment, parks)  <b>Postmenopausal breast cancer risk</b>	Postmenopausal women residing in Los Angeles County	Non-Hispanic White, Hispanic, Non-Hispanic African American and Non-Hispanic Asian	Obesogenic neighborhood environment factors, especially nSES, urbanicity, and mixed-land development, were differentially and independently associated with breast cancer risk in this multiethnic population
[381]  Wen, 2012	National Health Nutrition Examination Survey (NHANES) between 2003 – 2008  2000 Census and GIS-based data	<b>Neighborhood-level variables Built environment</b> (Population density, median age of neighborhood buildings, and percentage of residents walking to work)  <b>Obesity risk</b>	20 – 64 excluding pregnant women.	Non-Hispanic White, Hispanic, Non-Hispanic African American and Others	Results indicate that whites are at lower risks of obesity than African Americans and Hispanics and the magnitude of disparity is greater in women than in men. These patterns are consistent with previously published prevalence studies.
[382]  Vella, 2017	Multi-Ethnic Study of Atherosclerosis (MESA) (recruitment between July 2000 to August 2002).  N=6814  United States (six regions)	<b>Physical activity</b>  <b>Adipokines</b> (adiponectin, leptin, resistin, TNF- $\alpha$ , IL-6) and assessed association of abdominal visceral and subcutaneous fat as confounders.	45-84 years old Men and women	African American, Chinese American, Hispanic and non-Hispanic white	Higher levels of moderate-to-vigorous physical activity were associated with significantly higher levels of adiponectin and lower levels of leptin, IL-6, and resistin. The associations of moderate-to-vigorous physical activity with leptin, IL-6, and resistin were independent of relevant covariates including measures of total and central adiposity, whereas the association with adiponectin was attenuated by central adiposity. Notably, the magnitude of the associations did not vary by race/ethnic group or sex. These results suggest that physical activity may positively influence

Author, Year	Study Population	Exposure/ Outcome	Participant Characteristics	Race/Ethnicity (Nationality)	Outcomes/ (Findings)
					levels of selected adiposity-associated inflammatory markers, irrespective of total and/or central adiposity.
[383] Morimoto, 2014	Multiethnic Cohort (MEC) Baseline (1993) to Questionnaire #2 F/U (2003) Biospecimen (2001 – 2006)  Cross-sectional  n=1,251  Los Angeles, California and Hawaii	<b>Race/ethnicity</b>  <b>Serum biomarkers:</b> leptin, adiponectin, CRP, IL-6 and TNF- $\alpha$  Body fat distribution independent of weight status.	45 to 75 years old; men (n=321) and women (n= 930)	African American, Japanese American, Latino, and White, and Native Hawaiians (NH)	Within the multiethnic study population, comprised of older men and women with a wide range of BMI levels, ethnic differences in serum adipokine and CRP levels were detected in men and women. As compared to whites, leptin levels were lower in Japanese American (JA) men and women and higher in African American (AA) women, adiponectin levels were lower in AA men and women and in JA and Native Hawaiians (NH) women, CRP was lower in JA men and women as well as in NH women and higher in AA men and women after considering BMI. Differences in biomarker levels across ethnicity/races may be due to other causes such as relative proportions of VAT vs SAT, genetics, or lifestyle factors, although BMI explains a substantial proportion of the ethnic differences in biomarker levels.
[300] Gallo, 2012	South San Diego neighborhoods (2006 and 2009)  Cross-sectional  n=321  San Diego, California	<b>Individual socioeconomic status (SES) from SES-diverse communities</b>  <b>Inflammatory markers (CRP, IL-6, sICAM)</b>	40 to 65 years old	Mexican American	Individual SES was inversely associated with all inflammatory markers, although the relationship with IL-6 was least robust. The observed inverse association between SES and sICAM-1 in Latinos supports several study findings that have identified an association in other sociodemographic groups. Neighborhood SES was associated with lower CRP and sICAM-1 only. However, control for individual SES attenuated all neighborhood effects to non-significance.

Appendix B-1 Distributions of breast cancer risk factors among postmenopausal women overall and by race and ethnicity at baseline in the Multiethnic Cohort Study (2003)

	<b>Overall</b> n = 41,394	<b>African American</b> n = 5,665	<b>Japanese American</b> n = 13,112	<b>Latina</b> n = 7,544	<b>Native Hawaiian</b> n = 3,183	<b>White</b> n = 11,890
<b>Waist circumference, inches (SD)</b>	35.4 (5.8)	37.5 (6.0)	32.9 (4.6)	37.3 (5.6)	37.7 (6.4)	35.4 (5.8)
<b>Cardiovascular disease risk, n (%)</b>						
No history of cardiovascular disease	17,109 (0.4)	1,261 (22.3)	5,562 (42.5)	3,010 (39.9)	1,116 (35.1)	6,160 (51.8)
History of cardiovascular disease	24,285 (0.6)	4,404 (77.7)	7,550 (57.6)	4,534 (60.1)	2,067 (64.9)	5,730 (48.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Diabetes status, n (%)</b>						
Not diabetic	34,303 (0.8)	4,360 (77)	11,016 (84)	5,783 (76.7)	2,398 (75.4)	10,746 (90.4)
Diabetic	7,091 (0.2)	1,305 (23.1)	2,096 (16)	1,761 (23.3)	785 (24.6)	1,144 (9.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Family history* of cardiovascular disease, n (%)</b>						
No	16,209 (39.2)	2,077 (36.7)	5,357 (40.9)	3,390 (44.9)	1,141 (35.8)	4,244 (35.7)
Yes	25,173 (60.8)	3,587 (63.3)	7,753 (59.1)	4,149 (55)	2,040 (64.1)	7,644 (64.3)
Missing	12 (0.0)	1 (0.0)	2 (0.0)	5 (0.1)	2 (0.1)	2 (0.0)
<b>Family history* of diabetes, n (%)</b>						
No	24,530 (59.3)	3,024 (53.4)	7,754 (59.1)	3,776 (50.1)	1,560 (49.0)	8,416 (70.8)
Yes	16,854 (40.7)	2,641 (46.6)	5,357 (40.9)	3,763 (49.9)	1,621 (50.9)	3,472 (29.2)
Missing	10 (0.0)	0 (0.0)	1 (0.0)	5 (0.1)	2 (0.1)	2 (0.0)
<b>Co-medications†, n (%)</b>						
NSAIDs	8,873 (21.4)	1,125 (19.9)	3,116 (23.8)	1,461 (19.4)	853 (26.8)	2,318 (19.5)
Acetaminophen	1,782 (4.3)	130 (2.3)	762 (5.8)	131 (1.7)	206 (6.5)	553 (4.7)
Antihypertension	11,331 (27.4)	1,899 (33.5)	4,316 (32.9)	2,090 (27.7)	1,129 (35.5)	1,897 (16.0)
Alpha blocker	404 (1.0)	99 (1.8)	142 (1.1)	71 (0.9)	41 (1.3)	51 (0.4)
Angiotensin II receptor blocker	2,829 (6.8)	264 (4.7)	1,452 (11.1)	319 (4.2)	342 (10.7)	452 (3.8)
Ace inhibitor	3,638 (8.8)	704 (12.4)	1,029 (7.9)	929 (12.3)	408 (12.8)	568 (4.8)
Beta blocker	3,981 (9.6)	710 (12.5)	1,392 (10.6)	796 (10.6)	353 (11.1)	730 (6.1)
Calcium channel blocker	3,624 (8.8)	760 (13.4)	1,446 (11.0)	569 (7.5)	376 (11.8)	473 (4.0)

SD: Standard deviation; NSAIDs: Non-steroidal anti-inflammatory drugs

Appendix B-2 Association between cholesterol-lowering drug use and duration and risk of hormone receptor-positive invasive breast cancer among postmenopausal women overall and by race and ethnicity in the Multiethnic Cohort, (2003 – 2017)

	Overall Cases, n= 1,376		African American Cases, n = 153		Japanese American Cases, n = 479		Latina Cases, n = 166		Native Hawaiian Cases, n = 165		White Cases, n = 413	
	HR+ cases, n	HR (95% CI)	HR+ Cases, n	HR (95% CI)	HR+ Cases, n	HR (95% CI)	HR+ Cases, n	HR (95% CI)	HR+ Cases, n	HR (95% CI)	HR+ Cases, n	HR (95% CI)
<b>Never/ever, n (%)</b>												
Never	747	1.00	93	1.00	231	1.00	91	1.00	70	1.00	262	1.00
Ever	629	1.10(0.99,1.23)	60	0.85 (0.61,1.19)	248	1.10 (0.91,1.32)	75	1.07 (0.78,1.45)	95	<b>1.48</b> <b>(1.07,2.04)</b>	151	0.97 (0.79,1.2)
<b>Ever/former/current, n (%)</b>												
Never	747	1.00	93	1.00	231	1.00	91	1.00	70	1.00	262	1.00
Former	96	0.993 (0.8,1.23)	-	-	27	0.98 (0.66,1.47)	24	1.41 (0.9,2.22)	-	-	-	-
Current	533	1.123 (1,1.26)	43	0.80 (0.56,1.16)	221	1.11 (0.92,1.34)	51	0.95 (0.67,1.35)	83	<b>1.56</b> <b>(1.12,2.17)</b>	135	1.02 (0.82,1.27)
<b>Duration of use, n (%)</b>												
Never	747	1.00	93	1.00	231	1.00	91	1.00	70	1.00	262	1.00
< 3 years	319	1.053 (0.92,1.2)	42	1.04 (0.72,1.5)	113	1.11 (0.89,1.39)	43	0.97 (0.68,1.39)	40	1.11 (0.75,1.64)	81	0.98 (0.76,1.26)
≥ 3 years	285	1.145(1,1.32)			132	1.15 (0.92,1.43)	23	0.91(0.57,1.43)	49	<b>1.59</b> <b>(1.1,2.31)</b>	66	0.99 (0.75,1.31)
Missing												
<b>Status and duration, n (%)</b>												
Never	747	1.00	93	1.00	231	1.00	91	1.00	70	1.00	262	1.00
Former, <3 years	68	1.01 (0.79,1.3)	-	-	22	1.31 (0.84,2.03)	-	-	-	-	-	-
Former, ≥ 3 years	21	0.98 (0.63,1.51)	-	-	-	-	-	-	-	-	-	-
Current, <3 years	251	1.072 (0.93,1.24)	30	1.03 (0.68,1.56)	91	1.05 (0.82,1.34)	29	0.98 (0.64,1.5)	31	1.22 (0.79,1.87)	70	1.04 (0.8,1.37)
Current, ≥ 3 years	264	<b>1.17(1.01,1.35)</b>	12	0.55 (0.3,1)	127	1.18 (0.95,1.48)	17	0.80 (0.47,1.34)	46	<b>1.75</b> <b>(1.19,2.57)</b>	62	1.00(0.75,1.33)
Current, ≥ 3 years	25	1.13 (0.75,1.68)	-	-	-	-	-	-	-	-	-	-

Multivariable model adjusted for age, body mass index marital status, alcohol intake, Alternative Healthy Eating Index, physical activity (metabolic equivalents), cardiovascular disease history, cardiovascular disease, family history of breast cancer, age at menarche, age at first birth, number of live births, breastfeeding, menopause type, oral contraceptive use and menopausal hormone therapy use.

Appendix B-3 Association between cholesterol-lowering drug use and risk invasive breast cancer among postmenopausal women by body mass index and waist circumference cut points in the Multiethnic Cohort, (2003 – 2017)

Cholesterol-lowering drug use status	BMI < 25 kg/m <sup>2</sup>				BMI 25 to <30 kg/m <sup>2</sup>				BMI ≥30 kg/m <sup>2</sup>			
	WC < 35 inches		WC ≥35 inches		WC < 35 inches		WC ≥35 inches		WC < 35 inches		WC ≥35 inches	
	Cases, n= 504	HR (95% CI)	Cases, n= 119	HR (95% CI)	Cases, n=144	HR (95% CI)	Cases, n=378	HR (95% CI)	Cases, n=13	HR (95% CI)	Cases, n=396	HR (95% CI)
Never	326	1.00	58	1.00	81	1.00	191	1.00	-	-	-	-
Former	22	0.80 (0.52,1.24)					34	1.16 (0.8,1.67)	-	-	30	0.96 (0.65,1.42)
Current	156	1.03 (0.85,1.26)	51	1.28 (0.87,1.88)	54	1.13 (0.79,1.6)	153	1.00 (0.8,1.24)	-	-	181	1.16 (0.94,1.42)
<i>P-value</i>		0.80		0.21		0.52		0.98				0.17

Multivariable models adjusted for age, body mass index marital status, alcohol intake, smoking status, Alternative Healthy Eating Index, physical activity (metabolic equivalents), family history of breast cancer, age at menarche, age at first birth, number of live births, breastfeeding, menopause type, oral contraceptive use and menopausal hormone therapy use.

Appendix B-4 Association between cholesterol-lowering drug use and risk invasive breast cancer among postmenopausal women by body mass index cut points in the Multiethnic Cohort, (2003 – 2017)

Cholesterol-lowering drug use status	BMI < 25 kg/m <sup>2</sup>		BMI 25 to <30 kg/m <sup>2</sup>		BMI ≥30 kg/m <sup>2</sup>	
	Cases, n= 623	HR (95% CI)	Cases, n=522	HR (95% CI)	Cases, n=409	HR (95% CI)
Never	384	1.00	272	1.00	191	1.00
Former	32	0.89 (0.63, 1.26)	43	1.06 (0.76, 1.46)	31	0.98 (0.69, 1.41)
Current	207	1.10 (0.92, 1.30)	207	1.02 (0.85, 1.23)	187	1.17 (0.96, 1.42)
<i>P-value</i>		0.32		0.80		0.13

Multivariable models adjusted for age, body mass index marital status, alcohol intake, smoking status, Alternative Healthy Eating Index, physical activity (metabolic equivalents), family history of breast cancer, age at menarche, age at first birth, number of live births, breastfeeding, menopause type, oral contraceptive use and menopausal hormone therapy use.

Appendix B-5 Association between cholesterol-lowering drug use and risk invasive breast cancer among postmenopausal women by cardiovascular history in the Multiethnic Cohort, (2003 – 2017)

Cholesterol-lowering drug use status	History of CVD		No History of CVD	
	Cases, n=1,014	HR (95% CI)	Cases, n= 667	HR (95% CI)
Never		1.00		1.00
Former		1.03 (0.82, 1.29)		0.74 (0.50, 1.09)
Current		1.03 (0.90, 1.17)		1.20 (1.00, 1.43)

Multivariable models adjusted for age, body mass index marital status, alcohol intake, smoking status, Alternative Healthy Eating Index, physical activity (metabolic equivalents), family history of breast cancer, age at menarche, age at first birth, number of live births, breastfeeding, menopause type, oral contraceptive use and menopausal hormone therapy use.

Appendix C-1. Association between individual HLI components and risk of invasive breast cancer overall and by race and ethnicity among postmenopausal women in MEC, 1993 - 2017

	Overall		African American		Japanese American		Latina		Native Hawaiians		White	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
<b>BMI, kg/m<sup>2</sup></b>												
<25.0	2018	Referent	183	Referent	896	Referent	213	Referent	106	Referent	620	Referent
25.0 to <30.0	1531	1.15 (1.07,1.24)	307	1.08 (0.9,1.3)	415	1.52 (1.25,1.86)	291	1.22 (1.01,1.48)	150	1.57 (1.23,2.01)	368	1.08 (0.93,1.26)
≥30.0	1006	1.12 (1.04,1.19)	284	1.08 (0.9,1.3)	110	1.35 (1.2,1.51)	223	1.1 (0.93,1.32)	168	1.31 (1.02,1.67)	221	1.06 (0.93,1.21)
<i>P</i> trend		<0.01		0.5		<0.01		0.04		<0.01		0.3
<b>Dietary Intake, HEI-2010 score</b>												
20-40.9	31	Referent		Referent		Referent		Referent		Referent		Referent
41-59.9	755	1.01 (1.01,1.02)	118	0.83 (0.41,1.7)	223	2.66 (0.66,10.68)	169	0.83 (0.43,1.63)	83	0.6 (0.26,1.38)	162	1.57 (0.70,3.55)
60-78.9	2577	1.05 (0.74,1.51)	382	0.77 (0.38,1.55)	865	3.1 (0.78,12.40)	418	0.92 (0.48,1.79)	240	0.67 (0.3,1.51)	672	1.87 (0.84,4.18)
77-99.9	1192	1.2 (0.84,1.71)	266	0.76 (0.38,1.54)	331	2.85 (0.71,11.44)	131	1.03 (0.52,2.02)	95	0.64 (0.28,1.47)	369	1.73 (0.77,3.88)
<i>P</i> trend		0.04		0.4		0.4		0.1		0.9		0.4
<b>Physical Activity, METs</b>												
0.0 – 2.9	2364	Referent	481	Referent	761	Referent	455	Referent	203	Referent	464	Referent
3.0 – 6.0	974	1.05 (0.97,1.13)	149	1.01 (0.84,1.21)	319	1.05 (0.92,1.19)	121	0.9 (0.74,1.1)	84	0.79 (0.61,1.02)	301	1.14 (0.98,1.32)
> 6.0	1217	1.02 (0.96,1.1)	144	1 (0.83,1.2)	341	0.98 (0.86,1.11)	151	0.97 (0.81,1.17)	137	0.86 (0.69,1.07)	444	1.03 (0.9,1.17)
<i>P</i> trend		0.40		0.99		0.99		0.6		0.14		0.65
<b>Sedentary Behavior, hours</b>												
0.0 to <6.0	1189	Referent	228	Referent	296	Referent	272	Referent	100	Referent	293	Referent
6.0 to <10.0	1876	1 (0.93,1.07)	288	1 (0.85,1.19)	649	1.11 (0.99,1.26)	265	0.97 (0.81,1.17)	140	0.8 (0.64,1)	534	1.01 (0.89,1.16)
≥ 10.0	1490	0.85 (0.78,0.91)	258	1.12 (0.93,1.34)	476	0.8 (0.69,0.92)	190	0.84 (0.7,1.01)	184	0.79 (0.62,1.01)	382	0.95 (0.81,1.1)
<i>P</i> trend		<0.01		0.25		<0.01		0.05		0.04		0.52
<b>Smoking Status, pack-years</b>												
Never	2526	Referent	356	Referent	986	Referent	465	Referent	185	Referent	534	Referent
Former, ≤20	1119	1.19 (1.05,1.35)	214	1.23 (0.91,1.66)	279	0.89 (0.65,1.21)	164	1.42 (0.92,2.2)	111	1.21 (0.87,1.7)	351	1.09 (0.89,1.33)
Former, 20+	293	1 (0.89,1.12)	53	1.05 (0.84,1.31)	56	0.78 (0.6,1.02)	-	-	39	0.91 (0.66,1.27)	126	1.13 (0.89,1.43)
Current, ≤20	273	1.33 (1.18,1.5)	49	1.34 (1.01,1.79)	42	1.31 (1,1.72)	21	1.5 (0.95,2.38)	43	1.48 (1.05,2.09)	118	1.09 (0.9,1.32)
Current, 20+	344	1.07 (1,1.15)	102	0.99 (0.84,1.17)	58	1.05 (0.92,1.2)	58	1.07 (0.9,1.28)	46	1.13 (0.89,1.43)	80	1.08 (0.94,1.23)
<i>P</i> trend		<0.01		0.14		0.4		0.12		0.4		0.22
<b>Alcohol Intake, grams/day</b>												
0.0-4.9	3666	Referent	636	Referent	1318	Referent	638	Referent	359	Referent	715	Referent
5.0 - 14.9	399	1.35 (1.23,1.48)	60	1.37 (1.08,1.73)	53	1.34 (1.01,1.77)	56	1.06 (0.75,1.5)	35	0.87 (0.6,1.27)	195	1.46 (1.28,1.67)
>15.0	490	1.19 (1.07,1.31)	78	1.03 (0.79,1.35)	50	1.13 (0.86,1.48)	33	1.12 (0.85,1.47)	30	1.06 (0.75,1.51)	299	1.36 (1.16,1.59)
<i>P</i> trend		<0.01		0.02		0.03		0.5		0.62		<0.01
<b>Sleep duration, hours</b>												
≤6 or ≥9	1952	0.99 (0.93,1.05)	396	0.99 (0.86,1.14)	619	1.02 (0.91,1.13)	322	1.01 (0.87,1.16)	214	0.97 (0.8,1.18)	401	0.95 (0.84,1.07)
7-8	2603	Referent	378	Referent	802	Referent	405	Referent	210	Referent	808	Referent
<i>P</i> trend		0.71		0.92		0.78		0.94		0.76		0.38

Appendix D-1 Unadjusted geometric means and descriptive statistic for California and Hawaii overall and by race and ethnicity (1998-2000)

	California					Hawaii			
	Overall	African American	Japanese American	Latino	White	Overall	Japanese American	Native Hawaiian	White
C-reactive protein (mg/L)									
Geometric Mean	2.2	2.7	1.0	2.2	2.2	1.2	0.9	1.5	1.6
Standard deviation	3.0	3.0	3.1	2.9	3.1	3.2	3.1	3.0	3.2
Median	2.3	2.9	1.0	2.3	2.1	1.2	1.0	1.5	1.7
10 <sup>th</sup> Percentile	0.5	0.7	0.2	0.6	0.7	0.3	0.2	0.4	0.4
90 <sup>th</sup> Percentile	9.0	10.8	3.7	8.7	11.9	5.0	3.6	5.9	7.1
Adiponectin (ug/mL)									
Geometric Mean	7.2	6.4	6.2	7.8	8.4	6.3	5.9	5.6	8.9
Standard deviation	2.0	2.0	2.1	1.9	1.8	2.1	2.1	2.0	2.0
Median	7.4	6.6	6.4	7.8	8.8	6.4	6.0	5.6	9.2
10 <sup>th</sup> Percentile	3.0	2.6	2.5	3.5	3.6	2.5	2.4	2.3	3.7
90 <sup>th</sup> Percentile	17.0	15.8	15.8	17.5	19.6	16.1	15.3	13.4	22.2
Leptin (ng/mL)									
Geometric Mean	16.1	22.4	7.1	15.2	15.4	10.2	8.2	12.2	13.1
Standard deviation	2.9	2.7	2.6	2.8	2.7	3.0	2.8	3.0	3.1
Median	18.2	25.7	7.8	16.8	16.8	11.2	9.2	13.7	14.8
10 <sup>th</sup> Percentile	4.1	6.2	1.8	4.1	4.6	2.4	1.9	3.1	2.9
90 <sup>th</sup> Percentile	56.3	69.7	22.3	50.8	53.1	36.7	27.3	42.3	49.6

C-reactive protein (n=6,828); Adiponectin (n= 6,694); Leptin (n=6,638) (ng/mL)

Appendix D-2 Likelihood Ratio test interaction effects of neighborhood socioeconomic status and sex and each biomarker

Interaction Sex and nSES	CRP	Adiponectin	Leptin
California	0.3111	0.6250	0.2970
Hawaii	0.7535	0.1231	0.0817

Interaction assessed using model 2 including adjustment for age, sex, race, fasting hours census block group and BMI Type 3 p-value

## Bibliography

1. Schneider, A.P., 2nd, et al., *The breast cancer epidemic: 10 facts*. Linacre Q, 2014. **81**(3): p. 244-77.
2. Zavala, V.A., et al., *Cancer health disparities in racial/ethnic minorities in the United States*. Br J Cancer, 2021. **124**(2): p. 315-332.
3. Gomez, S.L., et al., *Hidden breast cancer disparities in Asian women: disaggregating incidence rates by ethnicity and migrant status*. Am J Public Health, 2010. **100 Suppl 1**(Suppl 1): p. S125-31.
4. Harvie, M., L. Hooper, and A.H. Howell, *Central obesity and breast cancer risk: a systematic review*. Obes Rev, 2003. **4**(3): p. 157-73.
5. Del Giudice, M.E., et al., *Insulin and related factors in premenopausal breast cancer risk*. Breast Cancer Res Treat, 1998. **47**(2): p. 111-20.
6. Eketunde, A.O., *Diabetes as a Risk Factor for Breast Cancer*. Cureus, 2020. **12**(5): p. e8010.
7. Hardefeldt, P.J., S. Edirimanne, and G.D. Eslick, *Diabetes increases the risk of breast cancer: a meta-analysis*. Endocr Relat Cancer, 2012. **19**(6): p. 793-803.
8. Schairer, C., et al., *Lipid-lowering drugs, dyslipidemia, and breast cancer risk in a Medicare population*. Breast Cancer Res Treat, 2018. **169**(3): p. 607-614.
9. Klop, B., J.W. Elte, and M.C. Cabezas, *Dyslipidemia in obesity: mechanisms and potential targets*. Nutrients, 2013. **5**(4): p. 1218-40.
10. Han, H., et al., *Hypertension and breast cancer risk: a systematic review and meta-analysis*. Sci Rep, 2017. **7**: p. 44877.
11. Silva Meneguelli, T., et al., *Food consumption by degree of processing and cardiometabolic risk: a systematic review*. Int J Food Sci Nutr, 2020. **71**(6): p. 678-692.
12. Gill, J.M., C.A. Celis-Morales, and N. Ghouri, *Physical activity, ethnicity and cardio-metabolic health: does one size fit all?* Atherosclerosis, 2014. **232**(2): p. 319-33.
13. Same, R.V., et al., *Relationship Between Sedentary Behavior and Cardiovascular Risk*. Current Cardiology Reports, 2015. **18**(1): p. 6.
14. Mohammadian Khonsari, N., et al., *Normal Weight Obesity and Cardiometabolic Risk Factors: A Systematic Review and Meta-Analysis*. Front Endocrinol (Lausanne), 2022. **13**: p. 857930.
15. Drozd, D., et al., *Obesity and Cardiometabolic Risk Factors: From Childhood to Adulthood*. Nutrients, 2021. **13**(11).
16. Gallucci, G., et al., *Cardiovascular risk of smoking and benefits of smoking cessation*. J Thorac Dis, 2020. **12**(7): p. 3866-3876.
17. Lankester, J., et al., *Alcohol use and cardiometabolic risk in the UK Biobank: A Mendelian randomization study*. PLoS One, 2021. **16**(8): p. e0255801.
18. Dejenie, T.A., et al., *Impact of objectively-measured sleep duration on cardiometabolic health: A systematic review of recent evidence*. Front Endocrinol (Lausanne), 2022. **13**: p. 1064969.
19. Guo, M., et al., *Association Between Metabolic Syndrome and Breast Cancer Risk: An Updated Meta-Analysis of Follow-Up Studies*. Front Oncol, 2019. **9**: p. 1290.

20. Moore, J.X., N. Chaudhary, and T. Akinyemiju, *Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012*. *Prev Chronic Dis*, 2017. **14**: p. E24.
21. Hirode, G. and R.J. Wong, *Trends in the Prevalence of Metabolic Syndrome in the United States, 2011-2016*. *Jama*, 2020. **323**(24): p. 2526-2528.
22. Lopez-Neyman, S.M., et al., *Racial disparities and prevalence of cardiovascular disease risk factors, cardiometabolic risk factors, and cardiovascular health metrics among US adults: NHANES 2011-2018*. *Sci Rep*, 2022. **12**(1): p. 19475.
23. Meloni, A., et al., *Gender Differences and Cardiometabolic Risk: The Importance of the Risk Factors*. *Int J Mol Sci*, 2023. **24**(2).
24. Hsu, H.Y., et al., *Efficacy of more intensive lipid-lowering therapy on cardiovascular diseases: a systematic review and meta-analysis*. *BMC Cardiovasc Disord*, 2020. **20**(1): p. 334.
25. Javed, Z., et al., *Race and Ethnicity and Cardiometabolic Risk Profile: Disparities Across Income and Health Insurance in a National Sample of US Adults*. *J Public Health Manag Pract*, 2022. **28**(Suppl 1): p. S91-s100.
26. Whitfield, J.B., *Genetic insights into cardiometabolic risk factors*. *Clin Biochem Rev*, 2014. **35**(1): p. 15-36.
27. Zhao, P., et al., *The Metabolic Syndrome Is a Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis*. *Obes Facts*, 2020. **13**(4): p. 384-396.
28. Organization., W.H. *Social determinants of health*. 2022 [cited 2023 January 30]; Available from: [https://www.who.int/health-topics/social-determinants-of-health#tab=tab\\_1](https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1).
29. Mohammed, S.H., et al., *What does my neighbourhood have to do with my weight? A protocol for systematic review and meta-analysis of the association between neighbourhood socioeconomic status and body weight*. *BMJ Open*, 2017. **7**(9): p. e017567.
30. Mohammed, S.H., et al., *Neighbourhood socioeconomic status and overweight/obesity: a systematic review and meta-analysis of epidemiological studies*. *BMJ Open*, 2019. **9**(11): p. e028238.
31. Ribeiro, A.I., et al., *Neighborhood Socioeconomic Deprivation and Allostatic Load: A Scoping Review*. *Int J Environ Res Public Health*, 2018. **15**(6).
32. Townshend, T. and A. Lake, *Obesogenic environments: current evidence of the built and food environments*. *Perspect Public Health*, 2017. **137**(1): p. 38-44.
33. Conroy, S.M., et al., *Characterizing the neighborhood obesogenic environment in the Multiethnic Cohort: a multi-level infrastructure for cancer health disparities research*. *Cancer Causes Control*, 2018. **29**(1): p. 167-183.
34. Lv, H., et al., *Association Between Statin Use and Prognosis of Breast Cancer: A Meta-Analysis of Cohort Studies*. *Front Oncol*, 2020. **10**: p. 556243.
35. Chen, X., et al., *Physical Activity and Risk of Breast Cancer: A Meta-Analysis of 38 Cohort Studies in 45 Study Reports*. *Value Health*, 2019. **22**(1): p. 104-128.
36. Michaels, E.K., et al., *Everyday Racial Discrimination and Hypertension among Midlife African American Women: Disentangling the Role of Active Coping Dispositions versus Active Coping Behaviors*. *Int J Environ Res Public Health*, 2019. **16**(23).

37. Wang, K., et al., *Smoking increases risks of all-cause and breast cancer specific mortality in breast cancer individuals: a dose-response meta-analysis of prospective cohort studies involving 39725 breast cancer cases*. *Oncotarget*, 2016. **7**(50): p. 83134-83147.
38. Freisling, H., et al., *Lifestyle factors and risk of multimorbidity of cancer and cardiometabolic diseases: a multinational cohort study*. *BMC Med*, 2020. **18**(1): p. 5.
39. Matthews, C.E., et al., *Physical activity, sedentary behavior, and cause-specific mortality in black and white adults in the Southern Community Cohort Study*. *Am J Epidemiol*, 2014. **180**(4): p. 394-405.
40. Buchowski, M.S., et al., *Physical activity and obesity gap between black and white women in the southeastern U.S*. *Am J Prev Med*, 2010. **39**(2): p. 140-7.
41. Nomura, S.J., et al., *Sedentary time and breast cancer incidence in African American women*. *Cancer Causes Control*, 2016. **27**(10): p. 1239-52.
42. Fortner, R.T., et al., *Obesity and Breast Cancer*. *Recent Results Cancer Res*, 2016. **208**: p. 43-65.
43. Gaudet, M.M., et al., *Active smoking and breast cancer risk: original cohort data and meta-analysis*. *J Natl Cancer Inst*, 2013. **105**(8): p. 515-25.
44. Gram, I.T., et al., *Smoking and Risk of Breast Cancer in a Racially/Ethnically Diverse Population of Mainly Women Who Do Not Drink Alcohol: The MEC Study*. *Am J Epidemiol*, 2015. **182**(11): p. 917-25.
45. Gram, I.T., et al., *Smoking and breast cancer risk by race/ethnicity and oestrogen and progesterone receptor status: the Multiethnic Cohort (MEC) study*. *Int J Epidemiol*, 2019. **48**(2): p. 501-511.
46. Rosenberg, L., et al., *Patterns and correlates of alcohol consumption among African-American women*. *Ethn Dis*, 2002. **12**(4): p. 548-54.
47. Xue, F., et al., *Cigarette smoking and the incidence of breast cancer*. *Arch Intern Med*, 2011. **171**(2): p. 125-33.
48. Maskarinec, G., et al., *Sleep duration and incidence of type 2 diabetes: the Multiethnic Cohort*. *Sleep Health*, 2018. **4**(1): p. 27-32.
49. Rácz, B., et al., *Links between the circadian rhythm, obesity and the microbiome*. *Physiol Res*, 2018. **67**(Suppl 3): p. S409-s420.
50. Johnson, D.A., et al., *The Contribution of Psychosocial Stressors to Sleep among African Americans in the Jackson Heart Study*. *Sleep*, 2016. **39**(7): p. 1411-9.
51. Matthews, K.A., et al., *Do reports of sleep disturbance relate to coronary and aortic calcification in healthy middle-aged women?: Study of women's health across the nation*. *Sleep Med*, 2013. **14**(3): p. 282-7.
52. Wang, D., et al., *Sleep duration and risk of coronary heart disease: A systematic review and meta-analysis of prospective cohort studies*. *Int J Cardiol*, 2016. **219**: p. 231-9.
53. Sorice, K.A., et al., *Systematic review of neighborhood socioeconomic indices studied across the cancer control continuum*. *Cancer Med*, 2022. **11**(10): p. 2125-2144.
54. Arthur, R., et al., *A healthy lifestyle index and its association with risk of breast, endometrial, and ovarian cancer among Canadian women*. *Cancer Causes Control*, 2018. **29**(6): p. 485-493.

55. Tabung, F.K., et al., *An Empirical Dietary Inflammatory Pattern Score Is Associated with Circulating Inflammatory Biomarkers in a Multi-Ethnic Population of Postmenopausal Women in the United States*. J Nutr, 2018. **148**(5): p. 771-780.
56. Drewnowski, A., et al., *Obesity and the Built Environment: A Reappraisal*. Obesity (Silver Spring), 2020. **28**(1): p. 22-30.
57. Tahergorabi, Z. and M. Khazaei, *The relationship between inflammatory markers, angiogenesis, and obesity*. ARYA Atheroscler, 2013. **9**(4): p. 247-53.
58. Cozier, Y.C., et al., *Neighborhood Socioeconomic Status in Relation to Serum Biomarkers in the Black Women's Health Study*. J Urban Health, 2016. **93**(2): p. 279-91.
59. Schootman, M., et al., *Adverse housing and neighborhood conditions and inflammatory markers among middle-aged African Americans*. J Urban Health, 2010. **87**(2): p. 199-210.
60. Society, A.C. *Cancer Facts and Figures 2021*. American Cancer Society 2021 2021.
61. Cowell, C.F., et al., *Progression from ductal carcinoma in situ to invasive breast cancer: revisited*. Mol Oncol, 2013. **7**(5): p. 859-69.
62. Sleightholm, R., et al., *Percentage of Hormone Receptor Positivity in Breast Cancer Provides Prognostic Value: A Single-Institute Study*. J Clin Med Res, 2021. **13**(1): p. 9-19.
63. Yedjou, C.G., et al., *Health and Racial Disparity in Breast Cancer*. Adv Exp Med Biol, 2019. **1152**: p. 31-49.
64. Dunnwald, L.K., M.A. Rossing, and C.I. Li, *Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients*. Breast Cancer Res, 2007. **9**(1): p. R6.
65. Loo, L.W.M., M. Williams, and B.Y. Hernandez, *The high and heterogeneous burden of breast cancer in Hawaii: A unique multiethnic U.S. Population*. Cancer Epidemiol, 2019. **58**: p. 71-76.
66. Sloane, J.P., et al., *Consistency achieved by 23 European pathologists from 12 countries in diagnosing breast disease and reporting prognostic features of carcinomas*. European Commission Working Group on Breast Screening Pathology. Virchows Arch, 1999. **434**(1): p. 3-10.
67. Rakha, E.A., et al., *Breast cancer prognostic classification in the molecular era: the role of histological grade*. Breast Cancer Res, 2010. **12**(4): p. 207.
68. Ogbenna, B.T., *Molecular Subtypes of breast cancer 2023*.
69. Howlader, N., et al., *Differences in Breast Cancer Survival by Molecular Subtypes in the United States*. Cancer Epidemiol Biomarkers Prev, 2018. **27**(6): p. 619-626.
70. Parise, C.A. and V. Caggiano, *Risk of mortality of node-negative, ER/PR/HER2 breast cancer subtypes in T1, T2, and T3 tumors*. Breast Cancer Res Treat, 2017. **165**(3): p. 743-750.
71. Prat, A., et al., *Molecular characterization of basal-like and non-basal-like triple-negative breast cancer*. Oncologist, 2013. **18**(2): p. 123-33.
72. Ahmad, A., *Breast Cancer Statistics: Recent Trends*. Adv Exp Med Biol, 2019. **1152**: p. 1-7.
73. Curtis, E., et al., *Racial and ethnic differences in breast cancer survival: how much is explained by screening, tumor severity, biology, treatment, comorbidities, and demographics?* Cancer, 2008. **112**(1): p. 171-80.

74. Iqbal, J., et al., *Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States*. *Jama*, 2015. **313**(2): p. 165-73.
75. Jatoi, I., et al., *Breast cancer trends among black and white women in the United States*. *J Clin Oncol*, 2005. **23**(31): p. 7836-41.
76. Li, C.I., K.E. Malone, and J.R. Daling, *Differences in breast cancer stage, treatment, and survival by race and ethnicity*. *Arch Intern Med*, 2003. **163**(1): p. 49-56.
77. DeSantis, C.E., et al., *Breast cancer statistics, 2019*. *CA Cancer J Clin*, 2019. **69**(6): p. 438-451.
78. Group, U.S.C.S.W. *U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019)*. 2022 [cited 2023 January 30]; Available from: <https://www.cdc.gov/cancer/dataviz>.
79. Newman, L.A., *Breast Cancer Disparities: Socioeconomic Factors versus Biology*. *Ann Surg Oncol*, 2017. **24**(10): p. 2869-2875.
80. Foy, K.C., et al., *Disparities in breast cancer tumor characteristics, treatment, time to treatment, and survival probability among African American and white women*. *NPJ Breast Cancer*, 2018. **4**: p. 7.
81. Rojas, K. and A. Stuckey, *Breast Cancer Epidemiology and Risk Factors*. *Clin Obstet Gynecol*, 2016. **59**(4): p. 651-672.
82. Jung, S.Y., et al., *Risk profiles for weight gain among postmenopausal women: a classification and regression tree analysis approach*. *PLoS One*, 2015. **10**(3): p. e0121430.
83. Henderson, B.E., R. Ross, and L. Bernstein, *Estrogens as a cause of human cancer: the Richard and Hinda Rosenthal Foundation award lecture*. *Cancer Res*, 1988. **48**(2): p. 246-53.
84. Marchant, D.J., *Epidemiology of breast cancer*. *Clin Obstet Gynecol*, 1982. **25**(2): p. 387-92.
85. Kapil, U., et al., *Reproductive factors and risk of breast cancer: A Review*. *Indian J Cancer*, 2014. **51**(4): p. 571-6.
86. Vatten, L.J. and S. Kvinnsland, *Prospective study of height, body mass index and risk of breast cancer*. *Acta Oncol*, 1992. **31**(2): p. 195-200.
87. Baretta, Z., et al., *Effect of BRCA germline mutations on breast cancer prognosis: A systematic review and meta-analysis*. *Medicine (Baltimore)*, 2016. **95**(40): p. e4975.
88. Soguel, L., et al., *Adiposity, breast density, and breast cancer risk: epidemiological and biological considerations*. *Eur J Cancer Prev*, 2017. **26**(6): p. 511-520.
89. Song, J.L., et al., *The association between prognosis of breast cancer and first-degree family history of breast or ovarian cancer: a systematic review and meta-analysis*. *Fam Cancer*, 2017. **16**(3): p. 339-349.
90. Dyrstad, S.W., et al., *Breast cancer risk associated with benign breast disease: systematic review and meta-analysis*. *Breast Cancer Res Treat*, 2015. **149**(3): p. 569-75.
91. Yanes, T., et al., *Clinical applications of polygenic breast cancer risk: a critical review and perspectives of an emerging field*. *Breast Cancer Research*, 2020. **22**(1): p. 21.
92. Fioretti, F., et al., *Risk factors for breast cancer in nulliparous women*. *Br J Cancer*, 1999. **79**(11-12): p. 1923-8.

93. Troisi, R., et al., *The role of pregnancy, perinatal factors and hormones in maternal cancer risk: a review of the evidence*. J Intern Med, 2018. **283**(5): p. 430-445.
94. Ruiz, R., et al., *Epidemiology and pathophysiology of pregnancy-associated breast cancer: A review*. Breast, 2017. **35**: p. 136-141.
95. de Menezes, R.F., A. Bergmann, and L.C. Thuler, *Alcohol consumption and risk of cancer: a systematic literature review*. Asian Pac J Cancer Prev, 2013. **14**(9): p. 4965-72.
96. Munsell, M.F., et al., *Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status*. Epidemiol Rev, 2014. **36**(1): p. 114-36.
97. Pizot, C., et al., *Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies*. Eur J Cancer, 2016. **52**: p. 138-54.
98. de Boer, M.C., et al., *The Mechanisms and Effects of Physical Activity on Breast Cancer*. Clin Breast Cancer, 2017. **17**(4): p. 272-278.
99. DANDAMUDI, A., et al., *Dietary Patterns and Breast Cancer Risk: A Systematic Review*. 2018. **38**(6): p. 3209-3222.
100. Kinney, A.Y., et al., *Alcohol consumption and breast cancer among black and white women in North Carolina (United States)*. Cancer Causes Control, 2000. **11**(4): p. 345-57.
101. Liu, Y., N. Nguyen, and G.A. Colditz, *Links between alcohol consumption and breast cancer: a look at the evidence*. Womens Health (Lond), 2015. **11**(1): p. 65-77.
102. Park, S.Y., et al., *Alcohol consumption and breast cancer risk among women from five ethnic groups with light to moderate intakes: the Multiethnic Cohort Study*. Int J Cancer, 2014. **134**(6): p. 1504-10.
103. Shield, K.D., I. Soerjomataram, and J. Rehm, *Alcohol Use and Breast Cancer: A Critical Review*. Alcohol Clin Exp Res, 2016. **40**(6): p. 1166-81.
104. Williams, L.A., et al., *Alcohol Intake and Breast Cancer Risk in African American Women from the AMBER Consortium*. Cancer Epidemiol Biomarkers Prev, 2017. **26**(5): p. 787-794.
105. Williams, L.A., et al., *Alcohol intake and invasive breast cancer risk by molecular subtype and race in the Carolina Breast Cancer Study*. Cancer Causes Control, 2016. **27**(2): p. 259-69.
106. Iyengar, N.M., et al., *Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study*. JAMA Oncol, 2019. **5**(2): p. 155-163.
107. Schoemaker, M.J., et al., *Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women*. JAMA Oncol, 2018. **4**(11): p. e181771.
108. Inumaru, L.E., E.A. Silveira, and M.M. Naves, *[Risk and protective factors for breast cancer: a systematic review]*. Cad Saude Publica, 2011. **27**(7): p. 1259-70.
109. Le Marchand, L., et al., *Estrogen metabolism-related genes and breast cancer risk: the multiethnic cohort study*. Cancer Epidemiol Biomarkers Prev, 2005. **14**(8): p. 1998-2003.
110. Weiss, L.K., et al., *Hormone replacement therapy regimens and breast cancer risk(1)*. Obstet Gynecol, 2002. **100**(6): p. 1148-58.

111. Samavat, H. and M.S. Kurzer, *Estrogen metabolism and breast cancer*. *Cancer Lett*, 2015. **356**(2 Pt A): p. 231-43.
112. Coughlin, S.S., *Social determinants of breast cancer risk, stage, and survival*. *Breast Cancer Res Treat*, 2019. **177**(3): p. 537-548.
113. Ambrosone, C.B., et al., *Important Role of Menarche in Development of Estrogen Receptor-Negative Breast Cancer in African American Women*. *J Natl Cancer Inst*, 2015. **107**(9).
114. Quan, L., et al., *Variants of estrogen-related genes and breast cancer risk in European and African American women*. *Endocr Relat Cancer*, 2014. **21**(6): p. 853-64.
115. Winters, S., et al., *Breast Cancer Epidemiology, Prevention, and Screening*. *Prog Mol Biol Transl Sci*, 2017. **151**: p. 1-32.
116. Masala, G., et al., *Mammographic breast density and breast cancer risk in a Mediterranean population: a nested case-control study in the EPIC Florence cohort*. *Breast Cancer Res Treat*, 2017. **164**(2): p. 467-473.
117. Maskarinec, G., et al., *Involution of breast tissue and mammographic density*. *Breast Cancer Res*, 2016. **18**(1): p. 128.
118. Maskarinec, G., et al., *Mammographic density and breast cancer risk: the multiethnic cohort study*. *Am J Epidemiol*, 2005. **162**(8): p. 743-52.
119. Palmer, J.R., et al., *Family history of cancer and risk of breast cancer in the Black Women's Health Study*. *Cancer Causes Control*, 2009. **20**(9): p. 1733-7.
120. Hodgson, M.E., B. Newman, and R.C. Millikan, *Birthweight, parental age, birth order and breast cancer risk in African-American and white women: a population-based case-control study*. *Breast Cancer Res*, 2004. **6**(6): p. R656-67.
121. Key, T.J., et al., *Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies*. *Br J Cancer*, 2011. **105**(5): p. 709-22.
122. Nahleh, Z., J. Arenas, and A.J.J.o.C.T. Tfayli, *Sex Steroids and Breast Cancer: An Overview*. 2013. **04**: p. 851-856.
123. Key, T., et al., *Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies*. *J Natl Cancer Inst*, 2002. **94**(8): p. 606-16.
124. James, R.E., et al., *Postmenopausal serum sex steroids and risk of hormone receptor-positive and -negative breast cancer: a nested case-control study*. *Cancer Prev Res (Phila)*, 2011. **4**(10): p. 1626-35.
125. Althuis, M.D., et al., *Etiology of hormone receptor-defined breast cancer: a systematic review of the literature*. *Cancer Epidemiol Biomarkers Prev*, 2004. **13**(10): p. 1558-68.
126. Cui, J., Y. Shen, and R. Li, *Estrogen synthesis and signaling pathways during aging: from periphery to brain*. *Trends Mol Med*, 2013. **19**(3): p. 197-209.
127. Anderson, S.E., G.E. Dallal, and A. Must, *Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart*. *Pediatrics*, 2003. **111**(4 Pt 1): p. 844-50.
128. Biro, F.M., et al., *Age of Menarche in a Longitudinal US Cohort*. *J Pediatr Adolesc Gynecol*, 2018. **31**(4): p. 339-345.

129. Chlebowski, R.T., et al., *Ethnicity and breast cancer: factors influencing differences in incidence and outcome*. J Natl Cancer Inst, 2005. **97**(6): p. 439-48.
130. Haiman, C.A., et al., *Ethnic differences in ovulatory function in nulliparous women*. Br J Cancer, 2002. **86**(3): p. 367-71.
131. John, E.M., et al., *Menstrual and reproductive characteristics and breast cancer risk by hormone receptor status and ethnicity: The Breast Cancer Etiology in Minorities study*. Int J Cancer, 2020. **147**(7): p. 1808-1822.
132. Sarink, D., et al., *Racial/ethnic differences in postmenopausal breast cancer risk by hormone receptor status: The multiethnic cohort study*. Int J Cancer, 2022. **150**(2): p. 221-231.
133. Warner, E.T., et al., *Estrogen receptor positive tumors: do reproductive factors explain differences in incidence between black and white women?* Cancer Causes Control, 2013. **24**(4): p. 731-9.
134. Xiang, A.H., et al., *Breastfeeding Persistence at 6 Months: Trends and Disparities from 2008 to 2015*. J Pediatr, 2019. **208**: p. 169-175.e2.
135. Bandera, E.V., et al., *Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium*. Breast Cancer Res Treat, 2015. **150**(3): p. 655-66.
136. Ambrosone, C.B., et al., *Parity and breastfeeding among African-American women: differential effects on breast cancer risk by estrogen receptor status in the Women's Circle of Health Study*. Cancer Causes Control, 2014. **25**(2): p. 259-65.
137. Kim, S., et al., *Menopausal hormone therapy and the risk of breast cancer by histological type and race: a meta-analysis of randomized controlled trials and cohort studies*. Breast Cancer Research and Treatment, 2018. **170**(3): p. 667-675.
138. Christmas, M., et al., *Menopause hormone therapy and complementary alternative medicine, quality of life, and racial/ethnic differences: the Study of Women's Health Across the Nation (SWAN)*. Menopause, 2022. **29**(12): p. 1357-1364.
139. Brewer, H.R., et al., *Family history and risk of breast cancer: an analysis accounting for family structure*. Breast Cancer Res Treat, 2017. **165**(1): p. 193-200.
140. John, E.M., et al., *Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups*. Jama, 2007. **298**(24): p. 2869-76.
141. Peeters, P.H., et al., *Age at menarche and breast cancer risk in nulliparous women*. Breast Cancer Res Treat, 1995. **33**(1): p. 55-61.
142. Chakravarthi, B.V. and S. Varambally, *Targeting the link between late pregnancy and breast cancer*. Elife, 2013. **2**: p. e01926.
143. Simon, M.S., et al., *Breast cancer risk estimates for relatives of white and African American women with breast cancer in the Women's Contraceptive and Reproductive Experiences Study*. J Clin Oncol, 2006. **24**(16): p. 2498-504.
144. DeBono, N.L., et al., *Race, Menopausal Hormone Therapy, and Invasive Breast Cancer in the Carolina Breast Cancer Study*. J Womens Health (Larchmt), 2018. **27**(3): p. 377-386.
145. Conroy, S.M., et al., *Racial/Ethnic Differences in the Impact of Neighborhood Social and Built Environment on Breast Cancer Risk: The Neighborhoods and Breast Cancer Study*. Cancer Epidemiol Biomarkers Prev, 2017. **26**(4): p. 541-552.
146. Cannon, C.P., *Cardiovascular disease and modifiable cardiometabolic risk factors*. Clin Cornerstone, 2007. **8**(3): p. 11-28.

147. Grundy, S.M., et al., *Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition*. *Circulation*, 2004. **109**(3): p. 433-8.
  148. Huang, P.L., *A comprehensive definition for metabolic syndrome*. *Dis Model Mech*, 2009. **2**(5-6): p. 231-7.
  149. Han, T.S. and M.E. Lean, *A clinical perspective of obesity, metabolic syndrome and cardiovascular disease*. *JRSM Cardiovasc Dis*, 2016. **5**: p. 2048004016633371.
  150. DeFronzo, R.A., R.C. Bonadonna, and E. Ferrannini, *Pathogenesis of NIDDM. A balanced overview*. *Diabetes Care*, 1992. **15**(3): p. 318-68.
  151. Virani, S.S., et al., *Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association*. *Circulation*, 2021. **143**(8): p. e254-e743.
  152. Watanabe, L.M. and L.A. Seale, *Challenging Aspects to Precise Health Strategies in Native Hawaiian and Other Pacific Islanders Using Statins*. *Front Public Health*, 2022. **10**: p. 799731.
  153. Hales, C.M., et al., *Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018*. *NCHS Data Brief*, 2020(360): p. 1-8.
  154. Prevention, C.f.D.C.a., *National Diabetes Statistics report, 2020*. Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services: Atlanta, GA., 2020.
  155. Sampson, R.J. and P. Sharkey, *Neighborhood selection and the social reproduction of concentrated racial inequality*. *Demography*, 2008. **45**(1): p. 1-29.
  156. Iyer, H.S., et al., *Impact of neighborhood socioeconomic status, income segregation, and greenness on blood biomarkers of inflammation*. 2022. **162**: p. 107164.
  157. Cheraghi, Z., et al., *Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis*. *PLoS One*, 2012. **7**(12): p. e51446.
  158. Feingold, K.R., *Cholesterol Lowering Drugs*, in *Endotext*, K.R. Feingold, et al., Editors. 2000, MDText.com, Inc.
- Copyright © 2000-2021, MDText.com, Inc.: South Dartmouth (MA).
159. Hebert, P.R., et al., *Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials*. *Jama*, 1997. **278**(4): p. 313-21.
  160. Fan, J. and I.A. de Lannoy, *Pharmacokinetics*. *Biochem Pharmacol*, 2014. **87**(1): p. 93-120.
  161. Ahern, T.P., et al., *Statins and breast cancer prognosis: evidence and opportunities*. *Lancet Oncol*, 2014. **15**(10): p. e461-8.
  162. Goldstein, J.L. and M.S. Brown, *A century of cholesterol and coronaries: from plaques to genes to statins*. *Cell*, 2015. **161**(1): p. 161-172.
  163. Stancu, C. and A. Sima, *Statins: mechanism of action and effects*. *J Cell Mol Med*, 2001. **5**(4): p. 378-87.
  164. Kapur, N.K. and K. Musunuru, *Clinical efficacy and safety of statins in managing cardiovascular risk*. *Vasc Health Risk Manag*, 2008. **4**(2): p. 341-53.
  165. Wierzbicki, A.S., R. Poston, and A. Ferro, *The lipid and non-lipid effects of statins*. *Pharmacol Ther*, 2003. **99**(1): p. 95-112.
  166. Harper, C.R. and T.A. Jacobson, *Using apolipoprotein B to manage dyslipidemic patients: time for a change?* *Mayo Clin Proc*, 2010. **85**(5): p. 440-5.
  167. Toth, P.P. and M. Banach, *Statins: Then and Now*. *Methodist DeBakey Cardiovasc J*, 2019. **15**(1): p. 23-31.

168. Mercado, C., et al., *Prevalence of Cholesterol Treatment Eligibility and Medication Use Among Adults--United States, 2005-2012*. MMWR Morb Mortal Wkly Rep, 2015. **64**(47): p. 1305-11.
169. Potluri, R., et al., *The interplay between cholesterol and breast cancer: is there a potential role for statin therapy?* Future Oncol, 2018. **14**(19): p. 1885-1888.
170. Neuhouser, M.L., et al., *Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials*. JAMA Oncol, 2015. **1**(5): p. 611-21.
171. Cedó, L., et al., *HDL and LDL: Potential New Players in Breast Cancer Development*. J Clin Med, 2019. **8**(6).
172. Ni, H., H. Liu, and R. Gao, *Serum Lipids and Breast Cancer Risk: A Meta-Analysis of Prospective Cohort Studies*. PLoS One, 2015. **10**(11): p. e0142669.
173. Bosco, J.L., et al., *Cardiometabolic factors and breast cancer risk in U.S. black women*. Breast Cancer Res Treat, 2012. **134**(3): p. 1247-56.
174. Eliassen, A.H., et al., *Serum lipids, lipid-lowering drugs, and the risk of breast cancer*. Arch Intern Med, 2005. **165**(19): p. 2264-71.
175. His, M., et al., *Prospective associations between serum biomarkers of lipid metabolism and overall, breast and prostate cancer risk*. Eur J Epidemiol, 2014. **29**(2): p. 119-32.
176. Zhang, Y., et al., *Associations of Blood Pressure and Cholesterol Levels During Young Adulthood With Later Cardiovascular Events*. J Am Coll Cardiol, 2019. **74**(3): p. 330-341.
177. Padhi, S., A.K. Nayak, and A. Behera, *Type II diabetes mellitus: a review on recent drug based therapeutics*. Biomed Pharmacother, 2020. **131**: p. 110708.
178. Ward, N.C., G.F. Watts, and R.H. Eckel, *Statin Toxicity*. Circ Res, 2019. **124**(2): p. 328-350.
179. Islam, M.M., Yang, HC., Nguyen, PA. et al., *Exploring association between statin use and breast cancer risk: an updated meta-analysis*. Arch Gynecol Obstet, 2017. **296**.
180. Islam, M.M., et al., *Exploring association between statin use and breast cancer risk: an updated meta-analysis*. Arch Gynecol Obstet, 2017. **296**(6): p. 1043-1053.
181. Browning, D.R. and R.M. Martin, *Statins and risk of cancer: a systematic review and metaanalysis*. Int J Cancer, 2007. **120**(4): p. 833-43.
182. Wu, Q.J., et al., *Statin use and breast cancer survival and risk: a systematic review and meta-analysis*. Oncotarget, 2015. **6**(40): p. 42988-3004.
183. Eaton, M., et al., *Statins and breast cancer in postmenopausal women without hormone therapy*. Anticancer Res, 2009. **29**(12): p. 5143-8.
184. Harborg, S., et al., *Statin use and breast cancer recurrence in postmenopausal women treated with adjuvant aromatase inhibitors: a Danish population-based cohort study*. Breast Cancer Res Treat, 2020. **183**(1): p. 153-160.
185. Borgquist, S., et al., *Statin Use and Breast Cancer Risk in the Nurses' Health Study*. Cancer Epidemiol Biomarkers Prev, 2016. **25**(1): p. 201-6.
186. Desai, P., et al., *Prospective analysis of association between statin use and breast cancer risk in the women's health initiative*. Cancer Epidemiol Biomarkers Prev, 2013. **22**(10): p. 1868-76.

187. Jacobs, E.J., et al., *Long-term use of cholesterol-lowering drugs and cancer incidence in a large United States cohort*. *Cancer Res*, 2011. **71**(5): p. 1763-71.
188. Cauley, J.A., et al., *Statin use and breast cancer: prospective results from the Women's Health Initiative*. *J Natl Cancer Inst*, 2006. **98**(10): p. 700-7.
189. De Cicco, P., et al., *Nutrition and Breast Cancer: A Literature Review on Prevention, Treatment and Recurrence*. *Nutrients*, 2019. **11**(7).
190. Skouroliakou, M., et al., *Serum antioxidant capacity, biochemical profile and body composition of breast cancer survivors in a randomized Mediterranean dietary intervention study*. *Eur J Nutr*, 2018. **57**(6): p. 2133-2145.
191. Aune, D., et al., *Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies*. *Breast Cancer Res Treat*, 2012. **134**(2): p. 479-93.
192. Masala, G., et al., *Fruit and vegetables consumption and breast cancer risk: the EPIC Italy study*. *Breast Cancer Res Treat*, 2012. **132**(3): p. 1127-36.
193. Fung, T.T., et al., *Intake of specific fruits and vegetables in relation to risk of estrogen receptor-negative breast cancer among postmenopausal women*. *Breast Cancer Res Treat*, 2013. **138**(3): p. 925-30.
194. Farvid, M.S., et al., *Consumption of red and processed meat and breast cancer incidence: A systematic review and meta-analysis of prospective studies*. *Int J Cancer*, 2018. **143**(11): p. 2787-2799.
195. Anderson, J.J., et al., *Red and processed meat consumption and breast cancer: UK Biobank cohort study and meta-analysis*. *Eur J Cancer*, 2018. **90**: p. 73-82.
196. Prentice, R.L., et al., *Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial*. *Jama*, 2006. **295**(6): p. 629-42.
197. Turner, L.B., *A meta-analysis of fat intake, reproduction, and breast cancer risk: an evolutionary perspective*. *Am J Hum Biol*, 2011. **23**(5): p. 601-8.
198. Schlesinger, S., et al., *Carbohydrates, glycemic index, glycemic load, and breast cancer risk: a systematic review and dose-response meta-analysis of prospective studies*. *Nutr Rev*, 2017. **75**(6): p. 420-441.
199. Moradi, S., et al., *Associations between dietary inflammatory index and incidence of breast and prostate cancer: a systematic review and meta-analysis*. *Nutrition*, 2018. **55-56**: p. 168-178.
200. Petimar, J., et al., *Dietary index scores and invasive breast cancer risk among women with a family history of breast cancer*. *Am J Clin Nutr*, 2019. **109**(5): p. 1393-1401.
201. Friedenreich, C.M., *Physical activity and breast cancer: review of the epidemiologic evidence and biologic mechanisms*. *Recent Results Cancer Res*, 2011. **188**: p. 125-39.
202. Loprinzi, P.D., et al., *Physical activity and the risk of breast cancer recurrence: a literature review*. *Oncol Nurs Forum*, 2012. **39**(3): p. 269-74.
203. Johnsson, A., et al., *Physical activity and survival following breast cancer*. *Eur J Cancer Care (Engl)*, 2019. **28**(4): p. e13037.
204. Renehan, A.G., et al., *Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies*. *Lancet*, 2008. **371**(9612): p. 569-78.
205. Yung, R.L. and J.A. Ligibel, *Obesity and breast cancer: risk, outcomes, and future considerations*. *Clin Adv Hematol Oncol*, 2016. **14**(10): p. 790-797.

206. Picon-Ruiz, M., et al., *Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention*. CA Cancer J Clin, 2017. **67**(5): p. 378-397.
207. Chollet-Hinton, L., et al., *Biology and Etiology of Young-Onset Breast Cancers among Premenopausal African American Women: Results from the AMBER Consortium*. Cancer Epidemiol Biomarkers Prev, 2017. **26**(12): p. 1722-1729.
208. Robinson, W.R., et al., *Body size across the life course and risk of premenopausal and postmenopausal breast cancer in Black women, the Carolina Breast Cancer Study, 1993-2001*. Cancer Causes Control, 2014. **25**(9): p. 1101-17.
209. Devericks, E.N., et al., *The obesity-breast cancer link: a multidisciplinary perspective*. Cancer Metastasis Rev, 2022. **41**(3): p. 607-625.
210. Cornelius, M.E., et al., *Tobacco Product Use Among Adults - United States, 2019*. MMWR Morb Mortal Wkly Rep, 2020. **69**(46): p. 1736-1742.
211. Creamer, M.R., et al., *Tobacco Product Use and Cessation Indicators Among Adults - United States, 2018*. MMWR Morb Mortal Wkly Rep, 2019. **68**(45): p. 1013-1019.
212. National Center for Chronic Disease, P., S. Health Promotion Office on, and Health, *Publications and Reports of the Surgeon General, in E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General*. 2016, Centers for Disease Control and Prevention (US): Atlanta (GA).
213. Mueller, N.B., et al., *The best practices: use of the guidelines by ten state tobacco control programs*. Am J Prev Med, 2006. **31**(4): p. 300-6.
214. Hecht, S.S., *Tobacco smoke carcinogens and breast cancer*. Environ Mol Mutagen, 2002. **39**(2-3): p. 119-26.
215. Kim, K.H., et al., *A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects*. Environ Int, 2013. **60**: p. 71-80.
216. Hecht, S.S., *Tobacco carcinogens, their biomarkers and tobacco-induced cancer*. Nat Rev Cancer, 2003. **3**(10): p. 733-44.
217. Carreras, G., et al., *Burden of disease from breast cancer attributable to smoking and second-hand smoke exposure in Europe*. Int J Cancer, 2020. **147**(9): p. 2387-2393.
218. Conway, K., et al., *Prevalence and spectrum of p53 mutations associated with smoking in breast cancer*. Cancer Res, 2002. **62**(7): p. 1987-95.
219. Ernster, V.L., *Female lung cancer*. Annu Rev Public Health, 1996. **17**: p. 97-114.
220. Perry, B.J., et al., *Sites of origin of oral cavity cancer in nonsmokers vs smokers: possible evidence of dental trauma carcinogenesis and its importance compared with human papillomavirus*. JAMA Otolaryngol Head Neck Surg, 2015. **141**(1): p. 5-11.
221. Cumberbatch, M.G.K., et al., *Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018*. Eur Urol, 2018. **74**(6): p. 784-795.
222. Jones, M.E., et al., *Smoking and risk of breast cancer in the Generations Study cohort*. Breast Cancer Res, 2017. **19**(1): p. 118.
223. Goldvaser, H., et al., *The association between smoking and breast cancer characteristics and outcome*. BMC Cancer, 2017. **17**(1): p. 624.
224. Catsburg, C., A.B. Miller, and T.E. Rohan, *Active cigarette smoking and risk of breast cancer*. Int J Cancer, 2015. **136**(9): p. 2204-9.

225. Chen, C., et al., *Active and passive smoking with breast cancer risk for Chinese females: a systematic review and meta-analysis*. Chin J Cancer, 2014. **33**(6): p. 306-16.
226. Glantz, S.A. and W.W. Parmley, *Passive and active smoking. A problem for adults*. Circulation, 1996. **94**(4): p. 596-8.
227. Macacu, A., et al., *Active and passive smoking and risk of breast cancer: a meta-analysis*. Breast Cancer Res Treat, 2015. **154**(2): p. 213-24.
228. Luo, J., et al., *Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study*. Bmj, 2011. **342**: p. d1016.
229. Johnson, K.C., et al., *Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009)*. Tob Control, 2011. **20**(1): p. e2.
230. Phillips, J.A., *Dietary Guidelines for Americans, 2020-2025*. Workplace Health Saf, 2021. **69**(8): p. 395.
231. Rehm, J., et al., *The relation between different dimensions of alcohol consumption and burden of disease: an overview*. Addiction, 2010. **105**(5): p. 817-43.
232. Boffetta, P. and M. Hashibe, *Alcohol and cancer*. Lancet Oncol, 2006. **7**(2): p. 149-56.
233. Pöschl, G. and H.K. Seitz, *Alcohol and cancer*. Alcohol Alcohol, 2004. **39**(3): p. 155-65.
234. Seitz, H.K., et al., *Alcohol and cancer*. Alcohol Clin Exp Res, 2001. **25**(5 Suppl ISBRA): p. 137s-143s.
235. Barr, T., et al., *Opposing effects of alcohol on the immune system*. Prog Neuropsychopharmacol Biol Psychiatry, 2016. **65**: p. 242-51.
236. Molina, P.E., et al., *Focus on: Alcohol and the immune system*. Alcohol Res Health, 2010. **33**(1-2): p. 97-108.
237. Romeo, J., et al., *Moderate alcohol consumption and the immune system: a review*. Br J Nutr, 2007. **98 Suppl 1**: p. S111-5.
238. Bode, C. and J.C. Bode, *Effect of alcohol consumption on the gut*. Best Pract Res Clin Gastroenterol, 2003. **17**(4): p. 575-92.
239. Ning, K., et al., *The association between early life mental health and alcohol use behaviours in adulthood: A systematic review*. PLoS One, 2020. **15**(2): p. e0228667.
240. Roerecke, M. and J. Rehm, *Alcohol consumption, drinking patterns, and ischemic heart disease: a narrative review of meta-analyses and a systematic review and meta-analysis of the impact of heavy drinking occasions on risk for moderate drinkers*. BMC Med, 2014. **12**: p. 182.
241. Di Sarno, R., et al., *Critical review on the use and abuse of alcohol. When the dose makes the difference*. Minerva Med, 2020. **111**(4): p. 344-353.
242. Barnett, R., *Alcohol use disorders*. Lancet, 2017. **389**(10064): p. 25.
243. Sivolap, Y.P., *[Alcohol use disorders: current approaches to diagnosis and treatment]*. Zh Nevrol Psikhiatr Im S S Korsakova, 2015. **115**(9): p. 23-27.
244. Wang, J., et al., *Alcohol consumption and breast tumor gene expression*. Breast Cancer Res, 2017. **19**(1): p. 108.

245. Schrieke, I.C., et al., *The effect of alcohol consumption on insulin sensitivity and glycemic status: a systematic review and meta-analysis of intervention studies*. Diabetes Care, 2015. **38**(4): p. 723-32.
246. Sun, Q., et al., *Alcohol Consumption by Beverage Type and Risk of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies*. Alcohol Alcohol, 2020. **55**(3): p. 246-253.
247. Chu, L., et al., *Vibration of effects in epidemiologic studies of alcohol consumption and breast cancer risk*. Int J Epidemiol, 2020. **49**(2): p. 608-618.
248. Howlader N, N.A., Krapcho M *SEER Cancer Statistics Review, 1975-2017. Table 4.17. Cancer of the female breast (invasive)-Lifetime risk of being diagnosed with cancer given alive and cancer-free at current age*. 2017.
249. Ogbenna, B.T., *Individual-level lifestyle factors related to breast cancer*. Created with BioRender, 2023.
250. Arthur, R., et al., *The Combined Association of Modifiable Risk Factors with Breast Cancer Risk in the Women's Health Initiative*. Cancer Prev Res (Phila), 2018. **11**(6): p. 317-326.
251. Ghosn, B., et al., *Association between healthy lifestyle score and breast cancer*. Nutr J, 2020. **19**(1): p. 4.
252. Khalis, M., et al., *Healthy lifestyle and breast cancer risk: A case-control study in Morocco*. Cancer Epidemiol, 2019. **58**: p. 160-166.
253. McClain, K.M., et al., *Age-Specific Indicators of a Healthy Lifestyle and Postmenopausal Breast Cancer*. J Womens Health (Larchmt), 2017. **26**(11): p. 1176-1184.
254. McKenzie, F., et al., *Healthy lifestyle and risk of breast cancer among postmenopausal women in the European Prospective Investigation into Cancer and Nutrition cohort study*. Int J Cancer, 2015. **136**(11): p. 2640-8.
255. Peila, R., et al., *Association of a Healthy Lifestyle Index with Risk of Breast Cancer among Women with Normal Body Mass Index in the UK Biobank*. Cancer Epidemiol Biomarkers Prev, 2022. **31**(3): p. 554-560.
256. Li, Q., et al., *The associations of healthy lifestyle index with breast cancer incidence and mortality in a population-based study*. Breast Cancer, 2022.
257. McKenzie, F., et al., *Healthy lifestyle and risk of breast cancer for indigenous and non-indigenous women in New Zealand: a case control study*. BMC Cancer, 2014. **14**: p. 12.
258. Arthur, R.S., et al., *Genetic Factors, Adherence to Healthy Lifestyle Behavior, and Risk of Invasive Breast Cancer Among Women in the UK Biobank*. J Natl Cancer Inst, 2020. **112**(9): p. 893-901.
259. Sánchez-Zamorano, L.M., et al., *Healthy lifestyle on the risk of breast cancer*. Cancer Epidemiol Biomarkers Prev, 2011. **20**(5): p. 912-22.
260. Field, A.E., et al., *Impact of Overweight on the Risk of Developing Common Chronic Diseases During a 10-Year Period*. Archives of Internal Medicine, 2001. **161**(13): p. 1581-1586.
261. Kaluza, J., et al., *Adherence to the WCRF/AICR 2018 recommendations for cancer prevention and risk of cancer: prospective cohort studies of men and women*. Br J Cancer, 2020. **122**(10): p. 1562-1570.

262. Calle, E.E., et al., *Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults*. N Engl J Med, 2003. **348**(17): p. 1625-38.
263. Nehring, S.M., A. Goyal, and B.C. Patel, *C Reactive Protein*, in *StatPearls*. 2022, StatPearls Publishing
- Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL).
264. Albert, M.A., *Inflammatory biomarkers, race/ethnicity and cardiovascular disease*. Nutr Rev, 2007. **65**(12 Pt 2): p. S234-8.
265. Liu, C., et al., *Adiponectin, TNF- $\alpha$  and inflammatory cytokines and risk of type 2 diabetes: A systematic review and meta-analysis*. Cytokine, 2016. **86**: p. 100-109.
266. Khaodhjar, L., et al., *Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity*. JPEN J Parenter Enteral Nutr, 2004. **28**(6): p. 410-5.
267. Hart, P.C., et al., *C-Reactive Protein and Cancer-Diagnostic and Therapeutic Insights*. Front Immunol, 2020. **11**: p. 595835.
268. Tang, Y., et al., *C-reactive protein and ageing*. Clin Exp Pharmacol Physiol, 2017. **44 Suppl 1**: p. 9-14.
269. Milan-Mattos, J.C., et al., *Effects of natural aging and gender on pro-inflammatory markers*. Braz J Med Biol Res, 2019. **52**(9): p. e8392.
270. Barbi, W., et al., *Reliability of C-reactive Protein as a Biomarker for Cardiovascular and Oral Diseases in Young and Old Subjects*. J Pharm Bioallied Sci, 2021. **13**(Suppl 2): p. S1458-s1461.
271. Morimoto, Y., et al., *Ethnic differences in serum adipokine and C-reactive protein levels: the multiethnic cohort*. Int J Obes (Lond), 2014. **38**(11): p. 1416-22.
272. Conroy, S.M., et al., *Leptin, adiponectin, and obesity among Caucasian and Asian women*. Mediators Inflamm, 2011. **2011**: p. 253580.
273. Plaisance, E.P. and P.W. Grandjean, *Physical activity and high-sensitivity C-reactive protein*. Sports Med, 2006. **36**(5): p. 443-58.
274. Achari, A.E. and S.K. Jain, *Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction*. Int J Mol Sci, 2017. **18**(6).
275. Carbone, F., C. La Rocca, and G. Matarese, *Immunological functions of leptin and adiponectin*. Biochimie, 2012. **94**(10): p. 2082-8.
276. Schautz, B., et al., *Impact of age on leptin and adiponectin independent of adiposity*. Br J Nutr, 2012. **108**(2): p. 363-70.
277. Farr, O.M., A. Gavrieli, and C.S. Mantzoros, *Leptin applications in 2015: what have we learned about leptin and obesity?* Curr Opin Endocrinol Diabetes Obes, 2015. **22**(5): p. 353-9.
278. Isidori, A.M., et al., *Leptin and aging: correlation with endocrine changes in male and female healthy adult populations of different body weights*. J Clin Endocrinol Metab, 2000. **85**(5): p. 1954-62.
279. Suglia, S.F., et al., *Why the Neighborhood Social Environment Is Critical in Obesity Prevention*. J Urban Health, 2016. **93**(1): p. 206-12.
280. Sallis, J.F., et al., *Built Environment, Physical Activity, and Obesity: Findings from the International Physical Activity and Environment Network (IPEN) Adult Study*. Annu Rev Public Health, 2020. **41**: p. 119-139.
281. Yang, T.C. and S.J. South, *Neighborhood Poverty and Physical Health at Midlife: The Role of Life-Course Exposure*. J Urban Health, 2020. **97**(4): p. 486-501.

282. Gordon-Larsen, P., et al., *Inequality in the built environment underlies key health disparities in physical activity and obesity*. Pediatrics, 2006. **117**(2): p. 417-24.
283. Lee, C.J., C.L. Sears, and N. Maruthur, *Gut microbiome and its role in obesity and insulin resistance*. Ann N Y Acad Sci, 2020. **1461**(1): p. 37-52.
284. Chen, X. and S. Devaraj, *Gut Microbiome in Obesity, Metabolic Syndrome, and Diabetes*. Curr Diab Rep, 2018. **18**(12): p. 129.
285. John, G.K. and G.E. Mullin, *The Gut Microbiome and Obesity*. Curr Oncol Rep, 2016. **18**(7): p. 45.
286. Mayne, S.L., et al., *Neighborhood Disorder and Obesity-Related Outcomes among Women in Chicago*. Int J Environ Res Public Health, 2018. **15**(7).
287. Kwarteng, J.L., et al., *Independent Effects of Neighborhood Poverty and Psychosocial Stress on Obesity Over Time*. J Urban Health, 2017. **94**(6): p. 791-802.
288. Powell-Wiley, T.M., et al., *Relationship between perceptions about neighborhood environment and prevalent obesity: data from the Dallas Heart Study*. Obesity (Silver Spring), 2013. **21**(1): p. E14-21.
289. Serin, Y. and N. Acar Tek, *Effect of Circadian Rhythm on Metabolic Processes and the Regulation of Energy Balance*. Ann Nutr Metab, 2019. **74**(4): p. 322-330.
290. Engin, A., *Circadian Rhythms in Diet-Induced Obesity*. Adv Exp Med Biol, 2017. **960**: p. 19-52.
291. Ribeiro, A.I., et al., *Neighbourhood socioeconomic deprivation and allostatic load: a multi-cohort study*. Sci Rep, 2019. **9**(1): p. 8790.
292. Wong, M.S., et al., *The neighborhood environment and obesity: Understanding variation by race/ethnicity*. Prev Med, 2018. **111**: p. 371-377.
293. Lee, M., *Obesity among U.S. rural adults: Assessing selection and causation with prospective cohort data*. Health Place, 2020. **61**: p. 102260.
294. Lake, A. and T. Townshend, *Obesogenic environments: exploring the built and food environments*. J R Soc Promot Health, 2006. **126**(6): p. 262-7.
295. Saini, G., et al., *Disadvantaged neighborhoods and racial disparity in breast cancer outcomes: the biological link*. Cancer Causes Control, 2019. **30**(7): p. 677-686.
296. Nimptsch, K., S. Konigorski, and T. Pischon, *Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine*. Metabolism, 2019. **92**: p. 61-70.
297. Krivo, L.J., R.D. Peterson, and D.C. Kuhl, *Segregation, racial structure, and neighborhood violent crime*. Ajs, 2009. **114**(6): p. 1765-802.
298. Chaparro, M.P., et al., *Neighborhood deprivation and biomarkers of health in Britain: the mediating role of the physical environment*. 2018. **18**: p. 1-13.
299. Cozier, Y.C., et al., *Neighborhood socioeconomic status in relation to serum biomarkers in the Black Women's Health Study*. 2016. **93**: p. 279-291.
300. Gallo, L.C., et al., *Individual and neighborhood socioeconomic status and inflammation in Mexican American women: what is the role of obesity?* Psychosom Med, 2012. **74**(5): p. 535-42.
301. Nazmi, A., et al., *Cross-sectional and longitudinal associations of neighborhood characteristics with inflammatory markers: findings from the multi-ethnic study of atherosclerosis*. 2010. **16**(6): p. 1104-1112.
302. Roberts, L.C., B.S. Schwartz, and L.J. Samuel, *Neighborhood Characteristics and Cardiovascular Biomarkers in Middle-Aged and Older Adults: the Baltimore Memory Study*. J Urban Health, 2021. **98**(1): p. 130-142.

303. Davis, S.K., et al., *Association of adiponectin and socioeconomic status in African American men and women: the Jackson heart study*. BMC Public Health, 2016. **16**(1): p. 511.
304. Guindon, G.E., et al., *A systematic umbrella review of the association of prescription drug insurance and cost-sharing with drug use, health services use, and health*. BMC Health Services Research, 2022. **22**(1): p. 297.
305. Al-Ibrahim, A.A. and R.T. Jackson, *Healthy eating index versus alternate healthy index in relation to diabetes status and health markers in U.S. adults: NHANES 2007–2010*. Nutrition Journal, 2019. **18**(1): p. 26.
306. Bradley, C.K., et al., *Patient-Reported Reasons for Declining or Discontinuing Statin Therapy: Insights From the PALM Registry*. J Am Heart Assoc, 2019. **8**(7): p. e011765.
307. Dela Cruz, R., et al., *Diet Quality and Breast Cancer Incidence in the Multiethnic Cohort*. Eur J Clin Nutr, 2020. **74**(12): p. 1743-1747.
308. Park, S.Y., et al., *Diet quality and all-cause and cancer-specific mortality in cancer survivors and non-cancer individuals: the Multiethnic Cohort Study*. Eur J Nutr, 2022. **61**(2): p. 925-933.
309. Kim, Y., et al., *Association between various sedentary behaviours and all-cause, cardiovascular disease and cancer mortality: the Multiethnic Cohort Study*. Int J Epidemiol, 2013. **42**(4): p. 1040-56.
310. Park, S.Y., et al., *Physical Activity and Colorectal Cancer Risk by Sex, Race/Ethnicity, and Subsite: The Multiethnic Cohort Study*. Cancer Prev Res (Phila), 2019. **12**(5): p. 315-326.
311. Mansoubi, M., et al., *Energy expenditure during common sitting and standing tasks: examining the 1.5 MET definition of sedentary behaviour*. BMC Public Health, 2015. **15**: p. 516.
312. Luo, S.J., et al., *Smoking Cessation After Lung Cancer Diagnosis and the Risk of Second Primary Lung Cancer: The Multiethnic Cohort Study*. JNCI Cancer Spectr, 2021. **5**(5).
313. Setiawan, V.W., et al., *Sex and Ethnic Differences in the Association of Obesity With Risk of Hepatocellular Carcinoma*. Clin Gastroenterol Hepatol, 2016. **14**(2): p. 309-16.
314. Maskarinec, G., et al., *Excess body weight and colorectal cancer survival: the multiethnic cohort*. Cancer Causes Control, 2015. **26**(12): p. 1709-18.
315. Setiawan, V.W., et al., *Alcohol consumption and endometrial cancer risk: the multiethnic cohort*. Int J Cancer, 2008. **122**(3): p. 634-8.
316. Shigesato, M., et al., *Association between sleep duration and breast cancer incidence: The multiethnic cohort*. Int J Cancer, 2020. **146**(3): p. 664-670.
317. Yost, K., et al., *Socioeconomic status and breast cancer incidence in California for different race/ethnic groups*. Cancer Causes Control, 2001. **12**(8): p. 703-11.
318. Rasmussen-Torvik, L.J., et al., *Associations of body mass index and insulin resistance with leptin, adiponectin, and the leptin-to-adiponectin ratio across ethnic groups: the Multi-Ethnic Study of Atherosclerosis (MESA)*. Ann Epidemiol, 2012. **22**(10): p. 705-9.

319. Kohl, T.O. and C.A. Ascoli, *Immunometric Double-Antibody Sandwich Enzyme-Linked Immunosorbent Assay*. Cold Spring Harb Protoc, 2017. **2017**(6): p. pdb.prot093724.
320. Aziz, N., et al., *Biological variation of immunological blood biomarkers in healthy individuals and quality goals for biomarker tests*. BMC Immunology, 2019. **20**(1): p. 33.
321. Ollberding, N.J., et al., *Prediagnostic leptin, adiponectin, C-reactive protein, and the risk of postmenopausal breast cancer*. Cancer Prev Res (Phila), 2013. **6**(3): p. 188-95.
322. Conroy, S.M., et al., *Non-hodgkin lymphoma and circulating markers of inflammation and adiposity in a nested case-control study: the multiethnic cohort*. Cancer Epidemiol Biomarkers Prev, 2013. **22**(3): p. 337-47.
323. Galobardes, B., J. Lynch, and G.D. Smith, *Measuring socioeconomic position in health research*. Br Med Bull, 2007. **81-82**: p. 21-37.
324. Conway, D.I., et al., *IARC Scientific Publications Measuring socioeconomic status and inequalities*, in *Reducing social inequalities in cancer: evidence and priorities for research*, S. Vaccarella, et al., Editors. 2019, International Agency for Research on Cancer
- © International Agency for Research on Cancer, 2019. For more information contact publications@iarc.fr.: Lyon (FR).
325. Garcia-Estevez, L. and G. Moreno-Bueno, *Updating the role of obesity and cholesterol in breast cancer*. Breast Cancer Research, 2019. **21**(1): p. 35.
326. Willey, J.Z. and M.S.V. Elkind, *3-Hydroxy-3-methylglutaryl-Coenzyme A Reductase Inhibitors in the Treatment of Central Nervous System Diseases*. Archives of Neurology, 2010. **67**(9): p. 1062-1067.
327. Göbel, A., et al., *Induction of 3-hydroxy-3-methylglutaryl-CoA reductase mediates statin resistance in breast cancer cells*. Cell Death & Disease, 2019. **10**(2): p. 91.
328. Jain, M.K. and P.M. Ridker, *Anti-inflammatory effects of statins: clinical evidence and basic mechanisms*. Nat Rev Drug Discov, 2005. **4**(12): p. 977-87.
329. Kalra, D.K., *Bridging the Racial Disparity Gap in Lipid-Lowering Therapy*. J Am Heart Assoc, 2021. **10**(1): p. e019533.
330. Naito, R., K. Miyauchi, and H. Daida, *Racial Differences in the Cholesterol-Lowering Effect of Statin*. J Atheroscler Thromb, 2017. **24**(1): p. 19-25.
331. Morris, A. and K. Ferdinand, *Hyperlipidemia in racial/ethnic minorities: differences in lipid profiles and the impact of statin therapy*. Clinical Lipidology, 2009. **4**(6): p. 741-754.
332. Simon, J.A., et al., *Phenotypic predictors of response to simvastatin therapy among African-Americans and Caucasians: the Cholesterol and Pharmacogenetics (CAP) Study*. Am J Cardiol, 2006. **97**(6): p. 843-50.
333. Setoguchi, S., et al., *Statins and the risk of lung, breast, and colorectal cancer in the elderly*. Circulation, 2007. **115**(1): p. 27-33.
334. Kaye, J.A., et al., *Statin use, hyperlipidaemia, and the risk of breast cancer*. Br J Cancer, 2002. **86**(9): p. 1436-9.
335. Boudreau, D.M., et al., *Statin use and breast cancer risk in a large population-based setting*. Cancer Epidemiol Biomarkers Prev, 2007. **16**(3): p. 416-21.
336. Beck, P., et al., *Statin use and the risk of breast cancer*. J Clin Epidemiol, 2003. **56**(3): p. 280-5.

337. Strandberg, T.E., et al., *Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S)*. *Lancet*, 2004. **364**(9436): p. 771-7.
338. Cauley, J.A., et al., *Lipid-lowering drug use and breast cancer in older women: a prospective study*. *J Womens Health (Larchmt)*, 2003. **12**(8): p. 749-56.
339. Kolonel, L.N., D. Altshuler, and B.E. Henderson, *The multiethnic cohort study: exploring genes, lifestyle and cancer risk*. *Nat Rev Cancer*, 2004. **4**(7): p. 519-27.
340. Kolonel, L.N., et al., *A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics*. *Am J Epidemiol*, 2000. **151**(4): p. 346-57.
341. Moksud, N., et al., *Cholesterol lowering drug use and breast cancer survival: the Multiethnic Cohort Study*. *Breast Cancer Res Treat*, 2021. **190**(1): p. 165-173.
342. Adedinsewo, D., et al., *Prevalence and Factors Associated With Statin Use Among a Nationally Representative Sample of US Adults: National Health and Nutrition Examination Survey, 2011-2012*. *Clin Cardiol*, 2016. **39**(9): p. 491-6.
343. Ing, C.T., et al., *Ethnic and Gender Differences in 10-Year Coronary Heart Disease Risk: a Cross-Sectional Study in Hawai'i*. *J Racial Ethn Health Disparities*, 2021. **8**(4): p. 943-952.
344. Mau, M.K., et al., *Cardiometabolic health disparities in native Hawaiians and other Pacific Islanders*. *Epidemiol Rev*, 2009. **31**: p. 113-29.
345. Piché, M.E., A. Tchernof, and J.P. Després, *Obesity Phenotypes, Diabetes, and Cardiovascular Diseases*. *Circ Res*, 2020. **126**(11): p. 1477-1500.
346. Torre, L.A., et al., *Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016: Converging incidence in males and females*. *CA Cancer J Clin*, 2016. **66**(3): p. 182-202.
347. Aluli, N.E., et al., *Diabetes and cardiovascular risk factors in Native Hawaiians*. *Hawaii Med J*, 2009. **68**(7): p. 152-7.
348. Sedaghat, F., et al., *Healthy Eating Index 2010 and Breast Cancer Risk*. *Nutr Cancer*, 2018. **70**(6): p. 860-866.
349. Grosso, G., et al., *Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk*. *Nutr Rev*, 2017. **75**(6): p. 405-419.
350. Anderson, A.R., et al., *Exploring the longitudinal clustering of lifestyle behaviors, social determinants of health, and depression*. *J Health Psychol*, 2022. **27**(13): p. 2922-2935.
351. Linardakis, M., et al., *Prevalence of multiple behavioral risk factors for chronic diseases in adults aged 50+, from eleven European countries - the SHARE study (2004)*. *Prev Med*, 2013. **57**(3): p. 168-72.
352. Smith, B.P., et al., *Racial differences in lifestyle, demographic, and health factors associated with quality of life (QoL) in midlife women*. *Women's Midlife Health*, 2021. **7**(1): p. 2.
353. Arthur, R., et al., *Associations of a Healthy Lifestyle Index With the Risks of Endometrial and Ovarian Cancer Among Women in the Women's Health Initiative Study*. *Am J Epidemiol*, 2019. **188**(2): p. 261-273.
354. Mohanty, S.S. and P.K. Mohanty, *Obesity as potential breast cancer risk factor for postmenopausal women*. *Genes Dis*, 2021. **8**(2): p. 117-123.

355. Kolb, R. and W. Zhang, *Obesity and Breast Cancer: A Case of Inflamed Adipose Tissue*. *Cancers* (Basel), 2020. **12**(6).
356. Zhu, J., X. Jiang, and Z. Niu, *Alcohol consumption and risk of breast and ovarian cancer: A Mendelian randomization study*. *Cancer Genet*, 2020. **245**: p. 35-41.
357. Guo, W., et al., *Physical activity and breast cancer risk: results from the UK Biobank prospective cohort*. *Br J Cancer*, 2020. **122**(5): p. 726-732.
358. Lee, J., et al., *Sedentary work and breast cancer risk: A systematic review and meta-analysis*. *J Occup Health*, 2021. **63**(1): p. e12239.
359. Hurley, S., et al., *Sleep deficiency and breast cancer risk among postmenopausal women in the California teachers study (CTS)*. *Cancer Causes Control*, 2020. **31**(12): p. 1115-1128.
360. Morris, C.J., D. Aeschbach, and F.A. Scheer, *Circadian system, sleep and endocrinology*. *Mol Cell Endocrinol*, 2012. **349**(1): p. 91-104.
361. Qin, Y., et al., *Sleep duration and breast cancer risk: a meta-analysis of observational studies*. *Int J Cancer*, 2014. **134**(5): p. 1166-73.
362. Wong, A.T.Y., et al., *Sleep duration and breast cancer incidence: results from the Million Women Study and meta-analysis of published prospective studies*. *Sleep*, 2021. **44**(2).
363. U.S. Department of Health and Human Services, P.H.S., Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition and Physical Activity. , *Promoting physical activity: a guide for community action*. . Human Kinetics, 1999.
364. Alcoholism, N.I.o.A.A.a., *Drinking Levels Defined*. 2020.
365. National Heart, L., and Blood Institute (NHLBI), *Assessing your weight and health risk* U.S. Department of Health & Human Services, 2023.
366. Cao, J., et al., *Sleep duration and risk of breast cancer: The JACC Study*. *Breast Cancer Res Treat*, 2019. **174**(1): p. 219-225.
367. Xiao, Q., et al., *Sleep duration and breast cancer risk among black and white women*. *Sleep Med*, 2016. **20**: p. 25-9.
368. Dixon-Suen, S.C., et al., *Physical activity, sedentary time and breast cancer risk: a Mendelian randomisation study*. *Br J Sports Med*, 2022. **56**(20): p. 1157-1170.
369. Monninkhof, E.M., et al., *Physical activity and breast cancer: a systematic review*. *Epidemiology*, 2007. **18**(1): p. 137-57.
370. Hashemi, S.H., S. Karimi, and H. Mahboobi, *Lifestyle changes for prevention of breast cancer*. *Electron Physician*, 2014. **6**(3): p. 894-905.
371. Choi, J., L. Joseph, and L. Pilote, *Obesity and C-reactive protein in various populations: a systematic review and meta-analysis*. *Obes Rev*, 2013. **14**(3): p. 232-44.
372. Khanna, D., et al., *Obesity: A Chronic Low-Grade Inflammation and Its Markers*. *Cureus*, 2022. **14**(2): p. e22711.
373. Izquierdo, A.G., et al., *Leptin, Obesity, and Leptin Resistance: Where Are We 25 Years Later?* *Nutrients*, 2019. **11**(11).
374. Landecho, M.F., et al., *Relevance of Leptin and Other Adipokines in Obesity-Associated Cardiovascular Risk*. *Nutrients*, 2019. **11**(11).
375. Obradovic, M., et al., *Leptin and Obesity: Role and Clinical Implication*. *Front Endocrinol (Lausanne)*, 2021. **12**: p. 585887.

376. Ishii, S., et al., *Gender, obesity and repeated elevation of C-reactive protein: data from the CARDIA cohort*. PLoS One, 2012. **7**(4): p. e36062.
377. Davillas, A. and A.M. Jones, *Regional inequalities in adiposity in England: distributional analysis of the contribution of individual-level characteristics and the small area obesogenic environment*. Econ Hum Biol, 2020. **38**: p. 100887.
378. Hobbs, M., et al., *Associations between the combined physical activity environment, socioeconomic status, and obesity: a cross-sectional study*. Perspect Public Health, 2018. **138**(3): p. 169-172.
379. Canchola, A.J., et al., *Association between the neighborhood obesogenic environment and colorectal cancer risk in the Multiethnic Cohort*. Cancer Epidemiol, 2017. **50**(Pt A): p. 99-106.
380. Conroy, S.M., et al., *Contextual Impact of Neighborhood Obesogenic Factors on Postmenopausal Breast Cancer: The Multiethnic Cohort*. Cancer Epidemiol Biomarkers Prev, 2017. **26**(4): p. 480-489.
381. Wen, M. and L. Kowaleski-Jones, *The built environment and risk of obesity in the United States: racial-ethnic disparities*. Health Place, 2012. **18**(6): p. 1314-22.
382. Vella, C.A., et al., *Physical Activity and Adiposity-related Inflammation: The MESA*. Med Sci Sports Exerc, 2017. **49**(5): p. 915-921.
383. Morimoto, Y., et al., *Ethnic differences in weight gain and diabetes risk: the Multiethnic Cohort Study*. Diabetes Metab, 2011. **37**(3): p. 230-6.