POST-DIAGNOSIS CHANGES IN POLYCYCLIC AROMATIC HYDROCARBON SOURCES OF EXPOSURE AND SURVIVAL FOLLOWING BREAST CANCER

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ABSTRACT

Humberto Parada, Jr.: Post-diagnosis Changes in Polycyclic Aromatic Hydrocarbon Sources of Exposure and Survival Following Breast Cancer
(Under the direction of Marilie D. Gammon)

In 2016, an estimated 246,000 women will be diagnosed with, and 40,000 deaths will be attributed to, breast cancer. Polycyclic Aromatic Hydrocarbons (PAHs), a group of over 100 different chemicals formed during the incomplete combustion of organic substances, may influence survival after breast cancer. This dissertation examined whether the primary sources of PAH exposure, tobacco smoke and intake of grilled/smoked meat, and changes in exposure after diagnosis were associated with mortality after breast cancer. To address the dissertation aims, I utilized resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based cohort study of 1,508 women who were diagnosed with first primary breast cancer in 1996/1997. Women were interviewed at baseline, shortly after diagnosis, and again five years later and have been followed for 18^{+} years using the National Death Index.

Results of Aim 1A showed that smoking in the year before diagnosis was associated with a 69% increased risk of long-term all-cause mortality, but not breast cancer-specific mortality. Among women who continued smoking after breast cancer, risk of all-cause mortality was elevated by 130%, but this was attenuated by approximately 20% among women who quit smoking after diagnosis. Results of Aim 1B examining environmental tobacco smoke exposure were largely null, a finding that is in agreement with few studies conducted to date examining at-diagnosis ETS exposure.

Results of Aim 2 showed that at-diagnosis high intake of total grilled/barbecued and smoked meat was associated with a 23% increased risk of all-cause mortality. At-diagnosis intake of smoked beef/lamb/pork was positively associated with all-cause and breast cancer mortality, while intake of smoked poultry/fish was inversely associated with mortality. Women with continued high post-diagnosis intake of grilled/barbecued and smoked meat had a further elevated risk of all-cause mortality; risk increased from 23% to 31%. Consistent with the associations observed for at-diagnosis intake, risk of breast cancer-specific mortality was inversely associated with high post-diagnosis intake of smoked poultry/fish.

The results of this dissertation help strengthen smoking cessation efforts and inform the limited dietary intake guidelines currently available for the more than 3 million women who are survivors of breast cancer.

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LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body Mass Index
CC	Complete-Case
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COX-2	Cyclooxygenase-2
CYP	Cytrochrome P450
DCIS	Ductal Carcinoma *In Situ*
DNA	Deoxyribonucleic Acid
E1	Estrone
E2	Estradiol
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen Receptor
ETS	Environmental Tobacco Smoke
FCS	Fully Conditional Specification
FFQ	Food Frequency Questionnaire
HCAs	Heterocyclic Amines
HER-1	Human Epidermal Growth Factor Receptor 1
HER-2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
HRT	Hormone-Replacement Therapy
IARC	International Agency for Research on Cancer
ICD	International Statistical Classification of Diseases
LCIS	Lobular Carcinoma *in Situ*
LIBCSP	Long Island Breast Cancer Study Project
LOD	Limits of Detection

MAR	Missing At Random
MCAR	Missing Completely At Random
MNAR	Missing Not At Random
NDI	National Death Index
NHANES	National Health and Nutrition Examination Survey
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OCs	Oral Contraceptives
OH-PAHs	Monohydroxy-PAHs
OR	Odds Ratio
PA	Physical Activity
PAHs	Polycyclic Aromatic Hydrocarbons
$PM_{2.5}$	Particulate matter <2.5 μm in diameter
PM_{10}	Particulate matter <10 μm in diameter
PR	Progesterone Receptor
RR	Risk Ratio
SEER	Surveillance, Epidemiology, and End Results
SHBG	Sex Hormone-Binding Globulin
US	United States
US EPA	United States Environmental Protection Agency
WHI	Women's Health Initiative
WHR	Waist-to-hip Ratio

CHAPTER I: BACKGROUND

This dissertation examined the role polycyclic aromatic hydrocarbon (PAH) sources of exposure before and after diagnosis in relation to breast cancer survival. The first aim examined the associations between active cigarette smoking and environmental tobacco smoke and changes in cigarette smoke exposure and all-cause and breast cancer mortality after diagnosis. Similarly, the second aim examined the associations between intake of grilled and smoked meats and changes in intake of grilled and smoked meats and all-cause and breast cancer mortality after diagnosis. This background section first summarizes the epidemiology of breast cancer incidence, which has been extensively studied, along with breast cancer survival, focusing on non-PAH factors. I first discuss these established risk and prognostic factors as they provide insight into the potential underlying biological mechanisms driving the hypothesized associations with PAH exposures. The discussion of risk and prognostic factors is followed by a discussion focused on the epidemiology of PAHs in relation to breast cancer incidence and survival, summarizes the literature on the studies conducted to date, and highlights the existing gaps in research that this dissertation addressed.

Epidemiology of Breast Cancer

Breast cancer definitions

Female breast cancer represents a group of diseases in which malignant tumors arise from

the cells of the breast, are able to grow and invade surrounding tissues, and are able to metastasize to distant areas of the body (American Cancer Society 2015b). The normal structures of the breasts include lobules – the milk-producing glands; ducts – which carry the milk from the lobules to the nipples; and stroma – the fatty and connective tissues that surround the lobules, ducts, and blood and lymphatic vessels of the breasts (American Cancer Society 2015b). Approximately 80% of invasive breast cancers arise from the ductal epithelial cells and are referred to as invasive ductal carcinomas (The Johns Hopkins University 2015b). Invasive lobular carcinomas arise from the epithelial cells that line the lobules and are the second most common invasive breast cancer diagnosed (10%-15%) (The Johns Hopkins University 2015c). A small number of breast cancers originate in other tissues of the breast. Ductal and lobular carcinomas *in situ* (DCIS and LCIS, respectively) are considered non-invasive breast tumors contained within the duct or lobular basement membranes (Ellis et al. 1992; The Johns Hopkins University 2015a).

Breast cancer prevalence, incidence, and mortality

Aside from non-melanoma skin cancer, breast cancer is the second most common cancer diagnosed in the United States (US) and the most common cancer diagnosed among women (National Cancer Institute 2015, 2016; Siegel et al. 2016). It is estimated that more than 246,000 women will be newly diagnosed in the United States in the year 2016 contributing to the 3.1 million women who are survivors of breast cancer (American Cancer Society 2015a; National Cancer Institute 2016). By the year 2030, the total number of new invasive and *in situ* tumors diagnosed per year is expected to increase to 441,000 (Rosenberg et al. 2015). Using data from the Surveillance, Epidemiology, and End Results (SEER) Program, which documents data on

cancer statistics across population-based registries since 1973, an increase in the rate of new breast cancer cases diagnosed in the 1980's is evident (**Figure I-1**) (National Cancer Institute 2016). This increase is attributed to the adoption and use of mammography screening as evidenced by the increase in the number and the proportion of localized and small tumors and *in situ* tumors and the decrease in the incidence of large tumors diagnosed during this time period (Chu et al. 1996; White et al. 1990). From 1988 to 2002 the breast cancer incidence rate stabilized until it declined in the year 2003. The decline is thought to be temporally related to the first report of the Women's Health Initiative, which confirmed the findings of prior studies reporting an increased risk of coronary heart disease and breast cancer associated with the use of estrogen-progestin combination therapy (Writing Group for the Women's Health Initiative Investigators 2002) that resulted in a decrease in the use of hormone-replacement therapy among postmenopausal women in the United States (Ravdin et al. 2007). Incidence rates have since once again stabilized with the most recent data indicating that the age-adjusted incidence rate is currently 125.0 per 100,000 women per year across women of all races (National Cancer Institute 2016).

In the US, breast cancer ranks as the second cause of death from cancer among women with approximately 40,000 deaths attributed to breast cancer annually (Siegel et al. 2016). Mortality rates have steadily declined since the 1990's (**Figure I-1**) and today approximately 90% of women survive at least five years after being diagnosed with breast cancer (National Cancer Institute 2016). The age-adjusted mortality rate is 21.5 per 100,000 women per year (National Cancer Institute 2016). Regular screening and available treatments contribute to this high survival rate (Berry et al. 2005); as discussed in detail in the following section, patient and disease characteristics also play a significant role in prognosis (Soerjomataram et al. 2008).

Established risk and prognostic factors

Estrogens are a group of compounds that promote the development and maintenance of the female reproductive system. The physiologic functions of estrogens in women include development of secondary sexual characteristics, regulation of gonadotropin secretion for ovulation, preparation of tissues for progesterone response, maintenance of bone mass, regulation of lipoprotein synthesis, and regulation of insulin responsiveness (Nelson and Bulun 2001). The two major endogenous estrogens include estrone (E1), estradiol (E2) and are synthesized from androgens by the aromatase enzyme primarily in the ovaries and secondarily in adipose and skin tissues (Nelson and Bulun 2001). As outlined in a review by Yager and Davidson (Yager and Davidson 2006), estrogens are hypothesized to be mammary gland carcinogens via nuclear, mitochondrial, and plasma membrane estrogen receptor (ER)-mediated pathways. Through these pathways, in estrogen responsive tissues such as the ovaries and the mammary gland, the presence of estrogen results in altered gene expression leading to increased cell proliferation and decreased cell apoptosis (Katzenellenbogen 1996). By promoting the proliferation of cells with existing mutations or by increasing the opportunity for novel mutations, estrogens contribute to breast carcinogenesis (Pike et al. 1993). Independent of ER-mediated pathways, estrogens also undergo extensive metabolism which leads to the production of genotoxic, mutagenic, and carcinogenic metabolites (Mueck and Seeger 2007).

Epidemiologic studies conducted since as early as the 1920's (Lane-Claypon 1926) have implicated reproductive factors in the development of breast cancer. Based on accumulating evidence, it was hypothesized that exposure to endogenous hormones influenced breast cancer etiology; however, early studies conducted during the 1960's and 1970's examining the direct role of hormone levels on breast cancer risk yielded mixed results (Cole and MacMahon 1969).

This may be due to limitations of early studies that had small sample sizes, utilized timed urine samples (rather than 24-hour collection) – a less sensitive method of steroid hormone assessment than the use of serum samples (Riad-Fahmy et al. 1982), and employed a case-control study design in which samples were collected after the initiation of disease in cases (Toniolo 1997). Because disease, treatment, or behavioral changes after diagnosis may influence hormone levels, the biomarkers collected after diagnosis may not have been reflective of the etiologically relevant time-period, thus leading to mixed results (Toniolo 1997). It was not until the 1990's during which results of several prospective nested case-control studies (Berrino et al. 1996; Helzlsouer et al. 1994; Toniolo et al. 1991, 1995) specifically designed to address the role of endogenous hormones in breast cancer were published that the hypothesis regained momentum. Studies have since continued to further examine both hormones and these and other epidemiologic risk factors, and prognostic factors, in relation to breast cancer. These include age at menarche, age at menopause, parity, and age at first and multiple pregnancies (Mcpherson et al. 2000; The Endogenous Hormones and Breast Cancer Collaborative Group 2002). Additionally, exposure to exogenous sources of estrogens through exposure to oral contraceptives among premenopausal women (Collaborative Group on Hormonal Factors in Breast Cancer 1996) and hormone-replacement therapy among peri-menopausal women (Collaborative Group on Hormonal Factors in Breast Cancer 1997) have also been shown to contribute to an increased risk of developing breast cancer. These risk factors, in addition to genetics (family history and race) and other lifestyle and behavioral factors (alcohol use, non-steroidal anti-inflammatory use, obesity, and physical activity) are reviewed in the following sections and summarized in **Table I-1**.

Age

Aging and the molecular, cellular, and physiologic processes that accompany it including increased genomic instability, increased oxidative stress, increased DNA damage, and decreased DNA repair capacity, are important in the etiology of all cancers, including breast cancers (Anisimov 2007). The incidence rate of breast cancer rises rapidly with age, is highest during the reproductive years, and increases more slowly until menopause when the rate slows (Clemmesen 1948; Pike et al. 1983b). In the United States, the median age at diagnosis of breast cancer is 62 years (National Cancer Institute 2016).

Particularly poor survival has been observed among women diagnosed at a younger age, especially those diagnosed younger than 35 years of age (RR=2.18; 95% CI=1.64-2.89), and women diagnosed over the age of 80 (RR=1.80; 95% CI=1.45-2.25) compared to women diagnosed between the ages of 40 and 49 (Brandt et al. 2015; Kroman et al. 2000; Reeves et al. 2000). Although only approximately 2% of all breast cancers are diagnosed in women under the age of 35 (National Cancer Institute 2016), it is the most common cancer in women under 35 and young women generally present with more advanced and aggressive disease at diagnosis including larger tumors, axillary lymph node involvement, high tumor stage and grade, and estrogen receptor-negative tumors (Fredholm et al. 2009; Gonzalez-Angulo et al. 2005). On the other hand, 20% of all breast cancer patients are diagnosed among women over the age of 75 years (National Cancer Institute 2016) yet the clinical guidelines for the management and treatment of breast cancer in older women, are not well established and so less use of mammographic screening, lower diagnostic activity, and lower treatment activity in older women lead to a lower relative survival (Eaker et al. 2006). Among older women age-related increases in aromatase expression, and thus estrogen synthesis, in peripheral tissues (adipose and

skin) may also play an important role in survival, especially among women with hormone-sensitive tumors (Hemsell et al. 1974).

Reproductive factors

Menarche and menopause. Epidemiologic studies show that breast cancer incidence increases by 5% for each year younger at menarche and by 3% for each year older at menopause (Collaborative Group on Hormonal Factors in Breast Cancer 2012). An earlier initiation of menarche results in earlier exposure to hormones and regular menstrual cycles (Kelsey et al. 1993) and older age at menopause results in continued hormonal exposure. Because most (approximately 60-70%) breast cancers are estrogen-sensitive (Dunnwald et al. 2007), increased lifetime exposure to these hormones may raise a woman's risk of developing breast cancer. Further evidence is provided by the observation of an inverse association between bilateral oophorectomy, or surgical removal of the ovaries, and breast cancer progression, which was recognized even before the importance of estrogens was understood (Love and Philips 2002). Recent studies show that when performed before the age of 40, bilateral oophorectomy reduces the risk of breast cancer by 20% to 50% (Nichols et al. 2011).

Age at menarche and menopausal status at diagnosis, however, do not appear to be independently associated with breast cancer mortality (Barnett et al. 2008; Giordano et al. 2004). Because chemotherapy can often lead to amenorrhea, an abnormal absence of menstruation, and premature initiation of menopause in pre- and peri-menopausal women (Ganz 2005; Goodwin et al. 1999; Morgan et al. 2012) post-treatment menopausal status may be more relevant. Nonetheless, the impact of chemotherapy-induced amenorrhea on breast cancer survival remains controversial (Berliere, F.P. Duhoux, Ch. Galant, F. Dalenc, J.F. Baurain, I. Leconte, L. Fellah,

L. Dellvigne 2011). Several studies report longer disease free survival for patients who developed drug-induced amenorrhea as compared with non-amenorrheic women (Aebi et al. 2000; Bianco et al. 1991; Del Mastro et al. 1997; Pagani et al. 1998), though not all studies are in agreement (Collichio and Pandya 1994; Del Mastro et al. 1997; Vanhuyse et al. 2005).

Parity and age at first and multiple pregnancies. Numerous epidemiologic studies have reported an increased risk of developing breast cancer among nulliparous women and a long-term reduced risk of breast cancer for increasing number of full-term births and early age at first birth (Kelsey et al. 1993). In a meta-analysis (Ma et al. 2006) of ten case-control and cohort studies, each additional birth was associated with a reduced the risk of developing ER^+/PR^+ breast cancer by 11% (RR=0.89, 95% CI=0.84-0.94) and women in the oldest age group at first birth had a 27% increased (RR=1.27, 95% CI=1.07-1.50) risk of ER^+/PR^+ breast cancer than women in the youngest age group. Each pregnancy; however, is also associated with a transient increased risk of developing breast cancer for 5, but up to 15, years after childbirth (Lambe et al. 1994; Liu et al. 2002). Subsequently, women who are diagnosed with breast cancer at or shortly after a pregnancy experience particularly poor survival. These tumors are more likely to be hormone receptor-negative, high histologic grade, node positive, and have higher mitotic count, and higher stage compared to tumors of nulliparous women (Alsaker et al. 2011; Daling et al. 2002). Few studies have examined whether parity is associated with survival after breast cancer, but recent studies indicate that higher parity is associated with worse survival (Butt et al. 2009; Trivers et al. 2007a), which may be due to enhanced initiation or progression of malignant cells or delayed diagnosis and thus worse prognosis, among women with high parity (Butt et al. 2009).

Breastfeeding. Breastfeeding is hypothesized to reduce the risk of breast cancer incidence by reducing a woman's lifetime number of menstrual cycles, thereby reducing a woman's

exposure to endogenous hormones, and by increasing the differentiation of ductal cells, making them less susceptible to carcinogenic insult (Lipworth et al. 2000; Russo et al. 2001; Visvader and Stingl 2014). Breastfeeding also provides a route of excretion of many lipophilic and potentially carcinogenic chemicals as there is rapid assimilation of lipid-soluble chemicals during milk production (Sim and McNeil 1992). Before these underlying mechanisms were fully understood, animal studies, followed by epidemiologic studies, generated these hypotheses documenting an inverse association between breastfeeding and risk of breast cancer. The results of epidemiology studies show that for every 12 months of breastfeeding the risk of developing breast cancer decreases by 4%-5%, compared to no breastfeeding (Collaborative Group on Hormonal Factors in Breast Cancer 2002; Ma et al. 2006).

Studies examining whether breastfeeding influences prognosis after a breast cancer diagnosis have been limited and results have been mixed. One study (Phillips et al. 2009) reported no association between breastfeeding and mortality and two studies (Alsaker et al. 2011; Trivers et al. 2007a) reported an inverse association between a short, but not long, duration of breast feeding and mortality. In the Long Island Breast Cancer Study (LIBCSP) on which this dissertation was based, the hazard ratio of breast cancer-specific mortality was 0.76 (95% CI=0.57-1.01) among women who breastfed for ≤6 months compared to women who never breast fed (Trivers et al. 2007a). A recent study that examined the association between history of breast feeding (ever/never) and lifetime duration of breast feeding (never, <6 months, ≥6months) and mortality after breast cancer stratified by breast cancer intrinsic subtype found that women with basal-like tumors, which often lack ER, PR, or HER2 expression (Badve et al. 2011), were less likely to have breastfed before diagnosis and that any prior breastfeeding and long-term duration of breastfeeding were associated with decreased risk of breast cancer-specific mortality

(Kwan et al. 2015). The inverse associations between a history of breast feeding and breast cancer mortality were more pronounced among hormonally-sensitive (ER^+ or PR^+) Luminal A and Luminal B tumors (HR=0.52, 95% CI=0.31-0.89 and HR=0.60, 95% CI=0.26-1.41), but also among non-hormonally sensitive (ER^- and PR^-) basal-like tumors (HR=0.64, 95% CI=0.24-1.72). The authors hypothesized that the transformation of breast cells during pregnancy could lead to the development of more differentiated (ER^+ and PR^+) breast cancers which are better prognostic tumor subtypes.

Exogenous hormone use

Oral contraceptive (OC) use. Use of oral contraceptives (OCs) is highly prevalent in the US with approximately 10.7 million women reporting current use (Mosher 2010). OC pills were first introduced in the US in 1960 and since the early 1970's there has been an interest in understanding the impact of OC use on breast cancer incidence. Results of very early studies reported no increased risk of breast cancer (Arthes et al. 1971; Fasal and Paffenbarger, Ralph S. 1975; Henderson et al. 1974; Ory et al. 1976), likely due to an insufficient amount of time between the introduction of oral contraceptives and development of breast cancer and the relative rarity of breast cancer among young women, which were underpowered to detect an association. Subsequent studies reported an increased risk of breast cancer particularly among very young women associated with oral contraceptive use before first full-term pregnancy or before age 25 (Chilvers and Deacon 1990; Paffenbarger et al. 1977; Pike et al. 1981, 1983a). While changes in oral contraceptive formulations, hormonal constituents, dosages, and schedules of administration and changes in patterns and of usage have led conflicting epidemiologic results (Marchbanks et al. 2012), since the 1980's studies have reported an elevated risk of premenopausal breast cancer in both parous (OR=1.29, 95% CI=1.20-1.40) and nulliparous (OR=1.24, 95% CI=0.92-1.67)

women who ever used oral contraceptives (Hunter et al. 2010; Kahlenborn et al. 2006). This risk is further elevated among women who use OCs before their first full-term pregnancy (OR=1.44, 95% CI=1.28-1.62) compared to women who use OCs after their first full-term pregnancy (OR=1.15, 95% CI=1.06-1.26), which is consistent with observations of inverse associations between pregnancy and breast cancer incidence (Kahlenborn et al. 2006).

The use of oral contraceptives after a diagnosis of breast cancer in considered contraindicated (World Health Organization. 4th ed. 2001) due to the proliferative effects of estrogens on cancerous breast cells. Although most studies have failed to find an association between OC use and mortality (Ewertz et al. 1991; Greenberg et al. 1985; Holmberg et al. 1994; Lees et al. 1989; Millard et al. 1987; Mohle-Boetani et al. 1988; Rosner and Lane 1986; Sauerbrei et al. 1998), these studies focused on ever/never use of oral contraceptives and all-cause mortality. In contrast to these studies, three studies have examined current OC use at breast cancer diagnosis (Lu et al. 2011; Trivers et al. 2007b; Wingo et al. 2007). In the first study, among women in the LIBCSP, Trivers and colleagues reported an increased HR of all cause-mortality (HR=1.97, 95% CI=1.15-3.38) among women who currently used OCs or who used OCs within 1 year of breast cancer diagnosis (Trivers et al. 2007b). Additionally, risk of breast cancer mortality was further elevated (HR=3.03, 95% CI=1.61-5.69) among women who used high-dose estrogen formulations (Trivers et al. 2007b). In the second study published in 2007 and in the third study published in 2011, both failed to reach the same conclusions finding no association between current OC use or recent high-dose estrogen OC use and breast cancer-specific mortality (Lu et al. 2011; Wingo et al. 2007). Additional studies examining recent and post-diagnosis use of oral contraceptives are needed to help clarify these associations.

Hormone replacement therapy (HRT) use. Hormone replacement therapy (HRT) is

effective for the treatment of menopausal symptoms. Therapies include estrogen alone ("estrogen therapy") or estrogen plus progestin ("combined hormone therapy") and are administered as pills, and more recently as skin patches, gels and sprays that are applied to the skin. These hormones can act systemically or locally. While effective in managing menopausal symptoms, HRT use also has health risks. In 2002, after a follow-up of 5 years, the Women's Health Initiative (WHI) trial of estrogen plus progestin (1 daily tablet containing 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate) versus placebo was terminated early due to an observed increased risk of developing breast cancer (HR=1.26, 95% CI=1.00-1.59), heart disease (HR=1.29, 95% CI=1.02-1.63), and stroke (HR=1.41, 95% CI=1.07-1.85) among women assigned to the intervention (Writing Group for the Women's Health Initiative Investigators 2002). Similar effect estimates had been previously reported in a meta-analysis of 51 case-control studies that included 52,705 women with invasive breast cancer and 108,411 women without breast cancer; a 35% increased risk of breast cancer incidence (RR=1.35, 95% CI=1.21-1.49) among women who had used HRT for 5 years or longer (Collaborative Group on Hormonal Factors in Breast Cancer 1997). The meta-analysis also showed that the risk of developing breast cancer increased with increasing duration of use (≥15 years of use versus never-use, RR=1.58, SE=0.121) with an apparent attenuation in risk after cessation of use of HRT, which largely disappeared after 5 years of cessation (current use versus never use, RR=1.21, SE=0.04; last use 1-4 years versus never use, RR=1.10, SE=0.06; last use 5-9 years versus never use, RR=1.01, SE=0.07) (Collaborative Group on Hormonal Factors in Breast Cancer 1997).

The use of hormone replacement therapy after a diagnosis of breast cancer, which could result in an increased risk of recurrence (Pritchard 2001), is also contraindicated. Epidemiologic

evidence supporting this hypothesis, however, has been mixed. In a meta-analysis (Col et al. 2001) of 11 studies published through May 1999 of post-diagnosis HRT use and breast cancer recurrence, a statistically non-significant inverse association (RR=0.82, 95% CI=0.58-1.15) was found between HRT use and breast cancer recurrence. In one study published shortly after the meta-analysis, the rate of recurrence was significantly lower (RR=0.50, 95% CI=0.30-0.85) among women who used HRT after diagnosis compared to nonusers (O'Meara et al. 2001). Similarly, reduced rates were also observed for breast cancer mortality (RR=0.34, 95% CI=0.13-0.91) and all-cause mortality (RR=0.48, 95% CI=0.29-0.78) (O'Meara et al. 2001) among women who used HRT after diagnosis. In the Stockholm trial of HRT use (n=188 women randomized HRT and n=190 randomized to no HRT) and breast cancer recurrence, after 10.8 years of follow-up a 30% increased (HR=1.3, 95% CI=0.9-1.9) risk was observed among HRT-users compared to non-users (Fahlén et al. 2013). Several possible explanations for these contradictory findings include unmeasured confounding, including confounding by indication, and more aggressive screening among breast cancer survivors who use HRT. In contrast to these findings, a randomized clinical trial (Holmberg and Anderson 2004) that investigated the safety of a 2-year HRT treatment in women who were previously treated for breast cancer was terminated early because women with a history of breast cancer allocated to receive HRT for menopausal symptoms experienced an unacceptably high rate of breast cancer compared with breast-cancer survivors allocated to best symptomatic treatment without hormones (HR=3.5, 95% CI=1.5-8.1). These conflicting results may require additional studies to help elucidate the true association between HRT use and breast cancer recurrence and mortality, though another clinical trial may not be feasible since it is unethical to prescribe HRT to breast cancer patients given the known proliferative effects of estrogens.

Genetics

Race. From 2009-2013, the age-adjusted incidence rate of breast cancer was 125.0 per 100,000 women across all races (National Cancer Institute 2016). White women and Black women experience the highest, but similar incidence rates of breast cancer (128.0 per 100,000 women and 125.2 per 100,000 women, respectively). In contrast, Asian/Pacific Islander and Hispanic women have lower incidence rates of breast cancer (97.3 per 100,000 women and 92.4 per 100,000 women, respectively) and American Indian/Alaska Native women have the lowest incidence rate of breast cancer (81.2 per 100,000 women). Mortality rates, however, are highest among Black women (29.6 per 100,000 women) followed by White women (21.0 per 100,000), American Indian/Alaska Native (14.7 per 100,000), Hispanic (14.5 per 100,000), and Asian American/Pacific Islander women (11.2 per 100,000) (National Cancer Institute 2016; Siegel et al. 2016). Biological variability, such as differences in tumor subtype, response to therapy, and comorbidities are often cited as contributors to the disparities in survival between white and black women (Roseland et al. 2015). For example, Black women, are more likely to be diagnosed with more aggressive disease including ER^-/PR^- (Roseland et al. 2015) and higher stage and histologic grade tumors (Cunningham and Butler 2004; Henson et al. 2003), which contribute to poor prognosis. Premenopausal Black women are also more likely to be diagnosed with basal-like breast cancers, which are negative for ER, PR, and HER-2, and overexpress cytokeratins 5/6 and HER-1/epidermal growth factor receptor (EGFR), have high proliferation rates (Bauer et al. 2007), and have lymph node and distant metastases (Iqbal et al. 2015; Satariano et al. 1986). However, recent studies suggest that socioeconomic status leading to differences in access to care, treatment, and presentation characteristics (Li et al. 2003; Silber et al. 2013) could account for most, but not all, racial differences in breast cancer mortality

(O'Brien et al. 2010).

Family history. A positive family history of breast cancer is well recognized to increase the risk of developing breast cancer with risk varying according to the type of relative affected, the age at which the relative developed breast cancer, and the number of relatives affected. While the total number of breast cancer genes is unknown, at least two tumor suppressor genes BRCA1 and BRCA2, which are located on the long arms of chromosomes 17 and 13, respectively, are believed to account for a substantial proportion of high risk families (Mcpherson et al. 2000), though, only about 5~10% of breast cancer cases can be attributed to the presence of an inherited deleterious mutation in a gene that predisposes to the development of breast cancer (Ganz 2005). A systematic review and meta-analysis (Pharoah et al. 1997) of 52 case-control studies and 22 cohort studies published through 1995 examined various family history patterns and showed that the risk of breast cancer incidence was elevated among women with a history of breast cancer diagnosis in any relative (RR=1.9, 95% CI=1.7-2.0), a first-degree relative (RR=2.1, 95% CI=2.0-2.2), a mother (RR=2.0, 95% CI=1.8-2.1), a sister (RR=2.3, 95% CI=2.1-2.4), a daughter (RR=1.8, 95% CI=1.6-2.0), a mother and a sister (RR=3.6, 95% CI=2.5-5.0), and a second-degree relative (RR=1.5, 95% CI=1.4-1.6). These risks are further elevated when the family member develops breast cancer at an earlier age. *BRCA1*-mutation associated breast cancers are more likely to be ER^-/PR^- and $HER\text{-}2^-$ (Lakhani 2002) and high grade (Eccles et al. 2015), therefore it is hypothesized that women with *BRCA1* and *BRCA2* mutations might have a worse prognosis. However, despite the numerous published studies, the association between *BRCA1* or *BRCA2* mutation carriership and breast cancer prognosis is inconclusive and current evidence does not support worse breast cancer survival of *BRCA1/2* mutation carriers (van den Broek et al. 2015).

Diet

Although the relationship between diet and breast cancer incidence has received considerable scientific attention, few consistent associations are observed (Vera-Ramirez et al. 2013). This is possibly due to methodological issues including differences in measurement of dietary intake, potential misclassification of exposures, high correlations among nutrients, and insufficient time for follow-up (Moorman and Terry 2004; Vera-Ramirez et al. 2013). As reviewed below, of the dietary exposures that have been examined, only alcohol intake is consistently associated with increased risk of breast cancer incidence and inconsistently with mortality (Rock 2002; Vera-Ramirez et al. 2013). Several studies, including randomized trials, report an inverse association between fruit and vegetable intake and breast cancer incidence or mortality and a positive association between fat intake and breast cancer incidence and mortality, but results are inconsistent.

Alcohol intake. Alcohol use is a well-established risk factor for breast cancer incidence (Bagnardi et al. 2001; Corrao et al. 2004; Key et al. 2006; Longnecker 1994; Smith-Warner et al. 1998). A daily intake of 100g of alcohol is associated with a relative risk of breast cancer of 2.71 (95% CI=2.33-3.08) compared to no intake (Bagnardi et al. 2001). The mechanisms of ethanol-induced carcinogenesis are closely related to the metabolism of ethanol. As Seitz and Stickel review, acetaldehyde, the first metabolite produced during alcohol degradation, interferes with DNA synthesis and repair, causes point mutations, induces sister chromatid exchanges and chromosomal aberrations, and binds to proteins resulting in structural and functional alterations, which can lead to cancer (Seitz and Stickel 2007). In addition to being carcinogenic, increased alcohol intake (>20g/d alcohol) is also associated with increased levels of endogenous sex hormones and decreased levels of sex hormone-binding globulin (SHBG), which bind and

transport estrogens as biologically inactive forms, in premenopausal and postmenopausal women (Key et al. 2011; Rinaldi et al. 2006). Through these mechanisms, it is hypothesized that alcohol intake may also affect survival after breast cancer diagnosis. While several studies have found a positive association between the highest levels of intake of alcohol and breast cancer-specific mortality (HRs ranging from 1.51 to 4.32) when exposed before, at, and after diagnosis (Allemani et al. 2011; Fuchs et al. 1995; Hebert et al. 1998; Kwan et al. 2010; McDonald et al. 2002; Vrieling et al. 2012) and an inverse association between moderate intake of alcohol and all-cause mortality (Barnett et al. 2008; Flatt et al. 2010; Reding et al. 2008; Saxe et al. 1999), results of most studies have been null as summarized in a meta-analysis of 25 follow-up studies of alcohol use (14 studies of pre-diagnosis drinking, 10 studies of post-diagnosis drinking, and 1 study of both pre- and post-diagnosis drinking) and breast cancer mortality published in 2013 (Gou et al. 2013). In the meta-analysis (Gou et al. 2013), neither pre- nor post-diagnosis alcohol consumption were associated with breast cancer mortality (HR=1.05, 95% CI=0.93-1.19 and HR=1.08, 95% CI=0.94-1.25); however drinking >20g/d of alcohol was associated a 14% (95% CI=2%-27%) increased hazard of breast cancer-specific mortality.

Fruit and vegetable intake. Intake of fruits and vegetables – sources of vitamins, anti-oxidants, and fiber which can mitigate the damaging effects of oxidative stress and free radical damage (Block et al. 1992) – has been studied in relation to breast cancer incidence in more than 25 case-control studies. The case-control studies report a 25% reduced (RR=0.75, 95% CI=0.66-0.85) risk of breast cancer incidence among women with high intake of fruits and vegetables compared to women with low intake (Block et al. 1992; Gandini et al. 2000; Howe et al. 1990). On the other hand, prospective studies report a much smaller magnitude of association; in a meta-analysis (Smith-Warner et al. 2001) of eight cohort studies including the Nurse's Health

Study, the New York State Cohort, and the Netherlands Cohort Study, the highest quartile of total intake of fruits and vegetables was associated with only a 7% reduction (RR=0.93, 95% CI=0.86-1.00, P_{Trend} = 0.12) in breast cancer risk.

In the few observational studies that have examined fruit and vegetable intake and breast cancer-specific mortality, higher intake of fruits and vegetables and intake of micronutrients such as beta carotene, calcium, vitamin A, vitamin C, vitamin E have been shown to be inversely associated with breast cancer mortality (Fink et al. 2006; Jain et al. 1994; Patterson et al. 2010). In the Long Island Breast Cancer Study Project, among post-menopausal women, intake of any fruits and vegetables at diagnosis was associated with a reduced (HR=0.68, 95% CI=0.42-1.09) risk of all-cause mortality; the association was reported to be similar for breast cancer-specific mortality although the estimates were not provided (Fink et al. 2006). In the survival cohort study within National Breast Screening Study in Canada, the HR of breast cancer mortality among women with the highest quartiles of intake of beta carotene was 0.48 (95% CI=0.23-0.99) and vitamin C was 0.43, (95% CI=0.21-0.86) relative to women with intake in the lowest quartiles (Jain et al. 1994). Higher intake of fruits and vegetables is also inversely associated with all-cause mortality (Dal Maso et al. 2008; McEligot et al. 2006). In randomized clinical trials, fruit and vegetable intake has also been shown to be inversely associated with breast cancer mortality when combined with high physical activity (Pierce et al. 2007b), although modification of fruits and vegetable intake alone does not appear to reduced mortality from breast cancer (Pierce et al. 2007a, 2013). Given these suggestive findings, current guidelines recommend that women be encouraged to adopt a diet high in fruits and vegetables after breast cancer diagnosis (Runowicz et al. 2016).

Fat intake. Intake of dietary fat from meat and dairy products – which are high in

saturated fat, can concentrate lipophilic carcinogenic chemicals including pesticides, and may contain growth factors such as insulin-like growth factor I – has also been extensively studied in relation to breast cancer incidence. Results, however, are inconclusive and the data available do not support they hypothesis that dietary fat increases the risk of breast cancer incidence (Moorman and Terry 2004).

Studies have examined dietary fat intake in relation to breast cancer survival since the 1980's. A recently published review by Makarem and colleagues summarized 18 studies that were published since 1986 (Makarem et al. 2013). Of the 18 studies reported in the review, 5 examined the association between pre-diagnosis total dietary fat and breast cancer-specific survival. Among the 5 studies, the Iowa Women's Health Study reported a more than 2-fold increased hazard of breast cancer specific mortality among women with the highest tertiles of intake of total fat (HR=2.5, 95% CI=1.2-5.3), saturated fat (HR=2.4, 95% CI=1.1-4.9), and monounsaturated fat (HR=2.3, 95% CI=1.1-4.7) relative to women with intake in the lowest tertiles (Zhang et al. 1995). Of the 18 studies, 9 examined post-diagnosis total fat intake and breast cancer mortality, two of which reported an increased risk of breast cancer mortality. The first, a study of Japanese and Caucasian women living on the Hawaiian island of Oahu who were diagnosed with breast cancer between 1975 and 1980, reported a more than three-fold increased (HR=3.2, 95% CI=1.2-8.6) risk of breast cancer mortality (Nomura et al. 1991). The second study, the Nurse's Health Study, reported a 44% increased (HR=1.44, 95% CI=1.01-2.04) risk of breast cancer mortality for the highest versus lowest quintile of total fat intake (Holmes et al. 1999). Lastly, as summarized in the review (Makarem et al. 2013), two randomized clinical trials that have been conducted examining post-diagnosis fat intake and breast cancer recurrence; the Women's Intervention Nutrition Study, observed a 24% reduced risk of recurrence among

women assigned to a low-fat diet intervention compared to controls (Chlebowski et al. 2006), while the Women's Healthy Eating and Living Trial found no association between the intervention designed to reduce fat intake and the control groups and recurrence (Pierce et al. 2007a). Despite these mixed findings, current guidelines for breast cancer survivors recommend that women limit intake of saturated fats (Runowicz et al. 2016).

Other lifestyle factors

NSAID use. Non-steroidal anti-inflammatory drugs (NSAIDs) such as Aspirin, Acetaminophen, and Ibuprofen are chemically distinct compounds that share a common therapeutic action; they inhibit the cyclooxygenase-2 (COX-2) enzyme, which catalyzes the synthesis of prostaglandins from dietary arachidonic acid (Vane 1971). Prostaglandins increase aromatase gene expression in breast cells and in surrounding tissue resulting in estrogen biosynthesis (Brueggemeier and Díaz-Cruz 2006). Prostaglandins also stimulate the EP receptor resulting in enhancement of cellular proliferation, promotion of angiogenesis, inhibition of apoptosis, and suppression of immune responses (Wang and Dubois 2006). Given the role of prostaglandins in carcinogenesis and the observations that COX enzymes and prostaglandins are abnormally upregulated in breast cancer (Bennett et al. 1977; Parrett et al. 1997), NSAIDS have the potential to lower risk of breast and other cancers via COX-2 inhibition. While epidemiologic studies examining the association between NSAID use and breast cancer risk have provided conflicting results (Kirsh et al. 2007; Marshall et al. 2005), a meta-analysis (Khuder and Mutgi 2001) that included 16 prospective studies of NSAID use and breast cancer incidence yielded a relative risk of 0.82 (95% CI=0.75-0.89). A more recent meta-analysis (Luo et al. 2012) found a similar reduced risk of breast cancer (OR=0.86; 95% CI=0.81-0.92). The potential benefits of NSAIDs as chemopreventive agents, however, must be examined in light of the potential side

effects from treatment with NSAIDs, such as gastrointestinal bleeding and perforation (Agrawal and Fentiman 2008).

After breast cancer initiation, the primary prostaglandin produced by COX-2, PGE2, can transactivate EGFR leading to stimulation of migration of tumor cells (Wang and Dubois 2006). Intratumoral aromatase may also be an important source of estrogens available for tumor growth (Esteban et al. 1992). Therefore, inhibiting COX-2 and EGFR tyrosine kinase could block the spread of metastatic disease. Several observational studies have explored whether aspirin use is associated with survival after breast cancer. At least three have reported a reduced risk of breast cancer mortality among women who used aspirin at- (Holmes et al. 2010) and post- (Blair et al. 2007; Fraser et al. 2014) diagnosis with hazard ratios ranging from 0.53 to 0.57 for all cause-mortality and from 0.36 to 0.53 for breast cancer mortality; however, not all have results have been in agreement (Holmes et al. 2014; Kwan et al. 2007; Li et al. 2012; Wernli et al. 2011). Additionally, three studies examining *de novo* post-diagnosis use of aspirin found no association with breast cancer mortality suggesting that the benefits of aspirin use may be attributable to pre-diagnosis use (Zhang et al. 2012).

Obesity. In postmenopausal women, with cessation of estrogen synthesis in the ovaries, the major pathway of estrogen production becomes the conversion of androstenedione into estrone in adipose tissue and skin (Grodin et al. 1973; Lønning et al. 1990). Additionally, postmenopausal obese women may have a higher proportion of bioavailable estrogen due to lower levels of SHBG (Key et al. 2011; Zhang et al. 1984). Adipose tissues also secrete inflammatory factors and are associated with hyperinsulinemia and insulin resistance, which are also hypothesized to increase breast cancer risk (Goodwin and Stambolic 2011; Morris et al. 2011). Long before these mechanisms were understood, observational studies reported an

increased risk of breast cancer incidence among postmenopausal women with increased height and weight (de Waard and Baanders-Van Halewijn 1974; Valaoras et al. 1969). More recently, body mass index (BMI) – a surrogate for adiposity that incorporates both height and weight – and waist-to-hip ratio (WHR) are more consistently used measures of obesity. A recently published secondary analysis of the Women's Health Initiative (WHI) randomized clinical trial reported that women in the highest categories of obesity (BMI ≥35 kg/m^2) had a 58% increased (HR=1.58, 95% CI=1.40-1.79) risk of breast cancer incidence compared to normal weight women and obesity was associated with more advanced disease, including larger tumors, lymph node involvement, and regional or distant stage at diagnosis (Neuhouser et al. 2015). These observations were consistent with most previous studies and meta-analyses of breast cancer incidence (Cheraghi et al. 2012; Endogenous Hormones Breast Cancer Collaborative Group 2003; Munsell et al. 2014), but not all (Cecchini et al. 2012). In contrast, among premenopausal women increased obesity is associated with a small reduced risk of developing breast cancer (Amadou et al. 2013; Munsell et al. 2014; Renehan et al. 2008; Ursin et al. 1995) possibly due to anovulation and lower levels of circulating estrogen levels (Potischman et al. 1996).

The association between obesity at diagnosis and survival has been extensively studied; a meta-analysis by Protani and colleagues identified 45 studies published from 1963-2005 and reported an increased risk of all-cause (HR=1.33, 95% CI=1.21-1.47) and breast cancer-specific (HR=1.33, 95% CI=1.19-1.50) mortality among women who were obese compared to women who were not obese at diagnosis (Protani et al. 2010). When stratified by menopausal status the magnitude of the association was larger among premenopausal (HR=1.47, 95% CI=1.19-1.83) than among postmenopausal (HR=1.22, 95% CI=0.95-1.57) women, but the interaction was not statistically significant (P=0.25) possibly due to insufficient power (Protani et al. 2010). In

addition to the studies examining pre- and at-diagnosis weight and breast cancer survival, several studies have also shown that post-diagnosis weight gain after breast cancer, a common occurrence after chemotherapy treatment (Demark-Wahnefried et al. 1997), negatively impacts survival. In the LIBCSP, Bradshaw and colleagues reported an increased (HR=2.84, 95% CI=1.15-6.65) hazard of breast cancer-specific mortality among women who had more than 10% weight gain after diagnosis compared to women who maintained their weight within 5% (Bradshaw et al. 2012), consistent with findings of several prior studies (Kroenke et al. 2005; Nichols et al. 2009), but not all (Caan et al. 2008, 2012; Chen et al. 2010). While the causal mechanism remains unresolved, the authors posit two hypotheses that could explain the poorer survival observed among obese women. The first is that obese patients may have more biologically aggressive tumors thought to be a result of increased leptin production in adipose tissue which, among many functions, stimulates tumor cell mitogenesis, tumor cell migration and invasion, induces angiogenesis, and induces aromatase activity (Rose et al. 2002). The second is that obese women may be undertreated with regards to chemotherapy since doses of most chemotherapy drugs are based on body surface area and physicians may have concerns that obese women will experience toxic effects at high doses, thus, reducing doses (Griggs et al. 2005).

Physical activity (PA). Physical activity (PA) is hypothesized to lower the risk of breast cancer through several mechanisms including altered menstrual characteristics (Malina et al. 1978; Moisan et al. 1991), reduced lifetime exposure to sex steroid hormones (Bertone-Johnson et al. 2009; Rinaldi et al. 2014; van Gils et al. 2009), reduced exposure to insulin and insulin-like growth factors (Schmitz et al. 2002; Wieczorek-Baranowska et al. 2011), prevention of obesity or induction of weight loss (Haskell et al. 2007), and improved immune function and reduced

levels of inflammation (Gleeson 2007).

Epidemiologic studies examining the associations between physical activity and breast cancer incidence have been complicated by methodological issues in assessing PA including the potential for misclassification of exercise due to variation in sources of physical activity (e.g. recreational PA, occupational PA, and activities of daily living), use of varying definitions of physical activity (e.g. frequency, duration, and intensity), and inaccurate assessment of physical activity during etiologically relevant time period(s), which are unknown (Gammon et al. 1998), but studies have consistently observed an inverse association between increased levels of physical activity and breast cancer incidence. A systematic review (Monninkhof et al. 2007) of 19 cohort studies and 29 case-control studies published through February 2006 provides strong evidence for an inverse association between physical activity and incidence of breast cancer (15%-20% reduced risk) though the evidence was stronger for postmenopausal breast cancer (20%-80% reduced risk) than premenopausal breast cancer.

Physical activity is thought to influence the progression of breast cancer through the same mechanisms by which it is believed to influence incidence. Indeed, observational studies report an inverse association between PA and breast cancer survival. In a meta-analysis (Lahart et al. 2015) of 22 prospective cohort studies, inverse associations were observed between breast cancer-specific mortality and lifetime pre-diagnosis (HR=0.73, 95% CI=0.54-0.98), recent pre-diagnosis (HR=0.84, 95% CI=0.73-0.97), and post-diagnosis recreational PA (HR=0.59, 95% CI=0.45-0.78). In addition, meeting recommended PA guidelines post-diagnosis was associated with a HR of breast cancer mortality of 0.67 (95% CI=0.50-0.90) (Lahart et al. 2015). Substantial heterogeneity was found in several of the comparisons, but results were in agreement with previous reviews and meta-analyses (Ellsworth et al. 2012; Ibrahim and Al-Homaidh 2011).

Several issues regarding the benefits of physical activity in relation to breast cancer prognosis remain unresolved including understanding the optimal frequency and duration of physical activity.

Disease characteristics and treatment

Disease characteristics at the time of breast cancer diagnosis including higher stage (Reeves et al. 2000), larger tumor size (Anderson et al. 2001; Narod 2012), lymph node involvement (Carter et al. 1989; Lethaby et al. 1996; Reeves et al. 2000), negative hormone receptor status (Aaltomaa et al. 1991; Crowe et al. 1991; Dunnwald et al. 2007; Fisher et al. 1988; Parl et al. 1984), high histological grade (Elston and Ellis 1991), and histological type (Ellis et al. 1992) are known to impact treatment and, thus, survival. For example, chemotherapy may be given to patients with high grade larger tumors before surgery (neoadjuvant treatment) to reduce the size of the tumor (National Cancer Institute 2009) whereas it is not recommended for the treatment of *in situ* cancers (Breastcancer.org 2015). Chemotherapy can also be given after surgery (adjuvant treatment) to women who have no measurable metastases, but who are at risk of recurrence (National Cancer Institute 2009). Women diagnosed with hormone receptor-positive tumors can be treated with hormone therapies such as tamoxifen – a selective estrogen-receptor modulator that is an antagonist of the estrogen receptor in the breast – and letrozole – an aromatase inhibitor that blocks aromatase activity – which have high efficacy for the treatment of breast cancer (Robert 1997).

Epidemiology of Polycyclic Aromatic Hydrocarbons (PAHs) and Breast Cancer

PAH Definition

Polycyclic Aromatic Hydrocarbons (PAHs) include over 100 different chemicals that are formed during the incomplete combustion of coal, oil and gas, and other organic substances like tobacco and charbroiled/smoked meats (Agency for Toxic Substances and Disease Registry (ATSDR) 1995a). These molecules consist of two or more fused aromatic rings and are, by definition, composed of hydrogen and carbon (see **Figure I-2** for the structures and nomenclatures of the 16 PAHs on the US Environmental Protection Agency (EPA) priority pollutant list (Yan et al. 2004)). PAHs are generally lipophilic and this property increases with increasing complexity of the compounds (Boström et al. 2002). As pure chemicals PAHs are solid and range in appearance from colorless to white or pale yellow-green (US Environmental Protection Agency, 2008). The sources of exposure and metabolism, measurement of PAH exposure, PAH exposure prevalence and how PAH and PAH sources of exposure relate to breast cancer incidence and survival as reviewed in the following sections.

Sources of Exposure and Metabolism

Non-occupational PAH sources of exposure in the US include, primarily, cigarette smoking and, among non-smokers, diet; and, secondarily, outdoor and indoor air pollution (Skupińska et al. 2004). Among non-smokers, dietary sources account for up to 70% of exposure, but in urban areas with high air pollution, air can be a significant contributor to PAH exposure (Hemminki et al. 1990; Menzie et al. 1992; Phillips 1999; Skupińska et al. 2004). Given the varied and complex sources of PAH exposure, PAHs occur as complex mixtures (Agency for Toxic Substances and Disease Registry (ATSDR) 1995a). In addition to the more

than 100 possible different PAHs that can be originate within a single source, PAHs can also co-occur with other chemicals some of which are known carcinogens. For example, in vehicular traffic air pollution, PAHs, including the estrogenic PAH fluoranthene (see **Table I-2** adapted from White, 2015), are found as a mixture with ozone, carbon monoxide, nitrogen oxides, heavy metals, and other particulate matter (Wu et al. 2012). Synthetic logs can contain PAHs such as chrysene/triphenylene as well as polychlorinated biphenyls which show estrogenic and anti-estrogenic effects *in vitro* (Gullett et al. 2003; Wolff et al. 1997) (**Table I-2**). In cigarette smoke, PAHs, including benzo[*a*]pyrene which has been documented to exert both estrogenic and anti-estrogenic effects *in vitro* and naphthalene (**Table I-2**), are found with the carcinogens benzene, arsenic, heavy metals, formaldehyde, vinyl chloride, and *N*-Nitrosamines (IARC 2004). In meats and high-fat foods, PAHs can bioaccumulate along with dioxins and other persistent lipophilic pollutants such as organochlorine pesticides and polychlorinated biphenyls (Loomis et al. 2015). In high temperature-cooked foods, PAHs including benzo[*a*]pyrene, fluoranthene, pyrene, and phenanthrene (**Table I-2**), are formed along with heterocyclic amines (HCAs) depending on the method of food preparation – HCAs are formed when amino acids pyrolyze in meat juice, though pan-frying foods produces more HCAs than grilling and smoking foods (Knize et al. 1999). Although PAHs co-occur with many chemicals, PAHs are common across all sources and only PAHs and PAH sources of exposure have been consistently associated with breast cancer incidence. Although dioxin has been found to be associated with breast cancer incidence, results have been mixed; in a study of the 1976 Seveso, Italy industrial disaster, dioxin exposure measured in serum was associated with a RR of breast cancer incidence of 2.1 (95% CI=1.0-4.6) (Warner et al. 2002), but in a French study examining dioxin exposure from diet sources, no increased (0.4 pg/kg BW/d RR=1.00, 95% CI=0.96-1.05) risk of breast cancer was observed and

a decreased (quartile 4 versus quartile 1 RR=0.65, 95% CI=0.45-0.96) risk of ER^-/PR^- breast cancer was found (Danjou et al. 2015). In addition to PAHs being the most common contaminant across these sources of exposure, there is a plausible biologically mechanism linking PAHs and breast cancer (Gammon and Santella 2008).

Inhalation, ingestion, and dermal contact are the possible routes by which PAHs can enter the body. Once in the body, PAHs induce expression of Phase I and Phase II metabolizing enzymes; the most important being CYPs 1A1, 1A2, 1B1, and 3A4 – the cytochrome P450 (CYP) superfamily of enzymes – and epoxide hydrolase (Luckert et al. 2013). During Phase I metabolism, PAH parent compounds are activated to potentially estrogenic reactive dihydrodiol intermediates by cytochrome p540 enzymes (Kummer et al. 2008; Luckert et al. 2013; Menzie et al. 1992). The dihydrodiols are further oxidized into diol epoxides, which are able to covalently bond to exocyclic amino groups of guanine and adenine, forming stable adducts on DNA (Lin et al. 2001). The metabolites of the PAHs benzo[*j*]fluoranthene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene and dibenzo[*a,h*]anthracene are known carcinogens able to form adducts in laboratory studies (Cavalieri et al. 1991; IARC 2010). The DNA adducts can cause mismatch in DNA replication and may alter promoter methylation or promoter binding, leading to inheritable DNA mutations or abnormal gene expression (Moorthy et al. 2015). Phase II metabolism includes conjugation of metabolites from Phase I – the hydroxyl-PAH metabolites – with small molecules catalyzed by specific enzymes such as sulfotransferases, UDP-glucoronyl transferases, and glutathione S-transferases. Sulfation and glucoronidation produces polar conjugates that are readily eliminated from the body through urine or feces.

Measurement of PAH exposure

Measures of exposure

Exposure to PAHs can be measured indirectly by questionnaire by querying study participants about exposures to the primary sources of PAH exposure. Questionnaires have the advantage of being able to elicit information about the lifetime while being relatively inexpensive.

- Self-reported active smoking, including history, duration, and intensity of smoking, and exposure to environmental tobacco smoke are widely accepted and reliable measures of exposure (Krall et al. 1989). Smoking and ETS exposure can further be confirmed by measuring serum, hair, salivary, or urinary cotinine – the predominant metabolite of nicotine (Binnie et al. 2004).
- Intake of grilled and smoked foods and methods of food preparation via questionnaire can be used to estimate the dietary contribution of PAHs (Gammon et al. 2002b; Steck et al. 2007).
- Indoor air pollution can also be measured by questionnaire as a proxy for PAH exposure. In the LIBCSP, White and colleagues estimated exposure to PAHs by asking participants about their use of indoor stoves and fireplaces, which included the frequency of use, the type of material burned and the ages of participants during the time they lived in residences (White et al. 2014).

Because PAHs are also found in ambient air, predominantly in particulate form, measures of exposure of PAHs also include those related to the measurement of air pollution (Agency for Toxic Substances and Disease Registry (ATSDR) 1995b). In particular, ambient air monitors

specifically designed to measure particulate matter combined with meteorological data and participant residential information can be useful for predicting a person's exposure to particulate matter, and thus PAHs (Hu et al. 2013). Personal air monitors can also provide information about personal exposure to particulate matter/PAHs (Binková et al. 1995).

Measures of internal dose

PAHs can be measured in body tissues and blood, but the high cost of measuring PAH parent compounds in these media makes their use in epidemiologic studies challenging (Agency for Toxic Substances and Disease Registry (ATSDR) 1995a). Instead, urinary monohydroxy PAHs (OH-PAHs) are a less expensive biomarker alternative for assessing exposure to PAHs which show high correlations with PAH exposures. For example, feeding studies report significantly increased concentrations of urinary 1-hydroxypyrene levels after consumption of charbroiled meat (Kang et al. 1995; van Maanen et al. 1994). Urinary metabolites have the advantage of being able to account for PAH exposures from all sources and all routes of exposure, but concentrations will be reflective of recent exposures unless there is chronic exposure with little variation (Agency for Toxic Substances and Disease Registry (ATSDR) 1995b). In the feeding studies, urinary metabolite concentrations returned to baseline within 24-72 hours of cessation of exposure (Kang et al. 1995). Often, one or several PAH metabolites can be used as a surrogate for assessing exposure to several PAHs. For example, 1-hydroxypyrene, the urinary metabolite of pyrene, is often measured since levels show strong positive correlations with several environmental PAHs (Binnie et al. 2004; Ciarrocca et al. 2014).

Measures of biologically effective dose

The adducts formed between PAHs and deoxyribonucleic acid (DNA) and proteins (hemoglobin and albumin) can also be measured in various tissues to assess exposure to PAHs

(Agency for Toxic Substances and Disease Registry (ATSDR) 1995b); however, in population studies it is often too invasive or infeasible to sample specific tissues, for example breast tissue. Therefore, adducts measured in blood are often used as a surrogate for tissue adduct levels (Santella 1999). These measures have the disadvantage that adduct levels measured in blood may not accurately reflect those of the tissue of interest, but studies show strong correlations between formation of PAH-DNA adducts in peripheral white blood cells and exposures such as charcoal-broiled beef consumption (Rothman et al. 1990; van Maanen et al. 1994) and ambient air pollution in occupational settings (Santella et al. 1993). Also, like the urinary metabolites, DNA-adducts and protein-adducts reflect of short term exposures (Binková et al. 1995). These biomarkers of biologically effective dose, however, are objective measures not subject to participant recall of past exposures, unlike self-reported questionnaire data, and they represent a biologically relevant end-point associated with carcinogenesis.

PAH Exposure Prevalence

PAHs are highly ubiquitous exposures that occur in mixtures; human exposure to PAHs occurs on a daily basis (Agency for Toxic Substances and Disease Registry (ATSDR) 1995a). The National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC) conducts biomonitoring of several urinary PAH metabolites. These measurements provide estimates of PAH exposure prevalence in a population based sample of the US. In one study (Xu et al. 2010) examining the associations between eight OH-PAHs (urinary metabolites of naphthalene, fluorene, phenanthrene, and pyrene) and prevalent cardiovascular disease among US adults (age ≥20 years) and utilizing two waves of NHANES data (2001-2002 and 2003-2004 data cycles) all eight OH-PAHs were above the limits

of detection (LOD) for >95% of participants. Median levels were lowest for the phenanthrene metabolite 2-hydroxyphenanthrene (61 ng/L in 2001-2002, 63.6 ng/L in 2003-2004) and highest for the naphthalene metabolite 2-hydroxynaphthalene (2,646 ng/L in 2001-2001 and 3,118.5 ng/L in 2003-2004) (Xu et al. 2010). Median concentrations of 1-hydroxypyrene measured 46 ng/L in 2001-2002 and 80.8 ng/L in 2003-2004 (Xu et al. 2010). For comparison, in (**Table I-3**), I provide the concentrations for adults (age ≥20 years) of the 10 measured OH-PAHs in National Health and Nutrition Examination Survey (NHANES) 2011-2012 (Centers for Disease Control and Prevention 2014a), the most recently available NHANES data, by smoking status. From these data, it is evident that all OH-PAH concentrations are elevated for smokers and those exposed to ETS compared to non-smokers/never-smokers. For 10 measured OH-PAHs, proportions above the LOD were at least 98% for all participants. Patterns of exposure are similar in 2011-2012 as compared to those reported by Xu and colleagues (Xu et al. 2010).

PAH adducts and breast cancer

Epidemiologic studies evaluating the association between DNA damage (adducts) and breast cancer incidence have been limited, but modest associations are observed. In the LIBCSP, the first large-scale case-control study designed to examine these associations among a large number of participants (n cases = 576 and n controls = 427), women with the highest levels of PAH-DNA adducts measured in peripheral blood samples collected shortly after breast cancer diagnosis were observed to have a 50% increased (>21.9357 adducts per 10^8 nucleotides versus non-detects OR=1.49, 95% CI=1.00-2.21) risk of breast cancer incidence (Gammon et al. 2002b). These results were consistent with several previously reported, but much smaller, hospital-based studies. In the smaller studies, DNA adduct levels in the normal adjacent breast

tissue of breast cancer patients were higher than in the samples of the reduction mammoplasty controls (Li et al. 1996; Perera et al. 1995; Rundle et al. 2000). In the LIBCSP, after a second round of assays, the pooled (n cases = 873 and n controls = 941) OR for the association between detectable PAH-DNA adduct levels and breast cancer incidence was 1.29 (95% CI=1.05-1.58); the association was more pronounced among premenopausal (OR=1.56, 95% CI=1.09-2.23) than among postmenopausal (OR=1.14, 95% CI=0.88-1.47) women (Gammon et al. 2010).

The LIBSCP has also been the first (and only) study to examine the associations between PAH-DNA adducts measured in peripheral blood and survival after breast cancer (Sagiv et al. 2009) (see **Table I-4**). The hazard ratio for breast cancer specific mortality was elevated (HR=1.26, 95% CI=0.56-2.86) in relation to the highest quintile of PAH-DNA adduct levels, but estimates were imprecise and included the null (Sagiv et al. 2009). The magnitude of the association between PAH-DNA adducts and survival is suggestive of an association. As it is possible that the LIBCSP was underpowered to adequately address this issue, additional studies with a larger sample sizes or longer follow-up are needed to help clarify this association.

Outdoor/Indoor Air pollution and breast cancer

Several studies have suggested an association between outdoor, as well as indoor, air pollution and risk of breast cancer incidence. In an ecological study utilizing SEER data for estimates of breast cancer incidence and emission data from the US EPA for estimates of air pollution at the US national level from 1973-2007, similar trends were observed for breast cancer incidence and for nitrogen dioxides with an offset of 20 years (Chen and Bina 2012). In a second US ecological study published in the same year, emissions of nitrogen oxides, carbon monoxide, sulfur dioxide, and volatile organic compounds – PAH correlates (Tham et al. 2008) – were

found to be positively associated with breast cancer incidence (r=0.89, 0.82, 0.71, and 0.68, respectively) (Wei et al. 2012). In the LIBCSP, using a historical geographic exposure model, Mordukhovich and colleagues estimated the association between long-term, individualized residential traffic benzo[*a*]pyrene exposure estimates, as a proxy for exposure to particulate traffic PAHs, and breast cancer incidence. Consistent with prior studies of traffic-related air pollution (Crouse et al. 2010) including a study conducted on Long Island, NY (Lewis-Michl et al. 1996) and a study using similar methodology (Nie et al. 2007), in the LIBCSP women with vehicular traffic estimates in the top 5% had a 44% increased (OR=1.44, 95% CI=0.78-2.68) odds of breast cancer incidence and the magnitude of the association was more pronounced (OR=1.67, 95% CI=0.91-3.05) among women with ER-/PR- tumors (Mordukhovich et al. 2016).

The LIBCSP has been the first study to examine the association between use of indoor stoves/fireplaces, an indicator of indoor air pollution and breast cancer incidence (White et al. 2014). In their study, White and colleagues reported a 42% increased (OR=1.42, 95% CI=1.11-1.84) risk of breast cancer incidence among women who reported ever burning synthetic logs, but not among women who reported ever burning wood alone (White et al. 2014).

Only one study has examined the associations between outdoor air pollution and breast cancer survival (Hu et al. 2013) and no studies have examined the association between indoor air pollution in relation to survival (see **Table I-4**). In their study, using SEER and US EPA data from 1999-2009, Hu and colleagues observed an increased risk of breast cancer-specific mortality among women exposed to high levels of particulate matter less than 10 μm in diameter (PM_{10}) (PM_{10} ≥28.82 μg/m^3 versus <23.09 μg/m^3 HR=1.44, 95% CI=1.18-1.76) and high levels of $PM_{2.5}$ ($PM_{2.5}$ ≥15.04 μg/m^3 versus <11.64 μg/m^3 HR=1.76, 95% CI=1.24-2.49) (Hu et al. 2013). Additional studies are needed examining outdoor or indoor air pollution in relation to

both breast cancer incidence and survival.

Post-diagnosis changes in outdoor/indoor air pollution and breast cancer

No studies have examined whether post-diagnosis changes in exposure to outdoor or indoor air pollution are associated with survival after breast cancer diagnosis. However, outdoor and indoor air pollution exposures, which account for a relatively smaller proportion of PAH exposure (Skupińska et al. 2004), are unlikely to change drastically after diagnosis. Additionally, in the LIBCSP, on which this dissertation is based, the prevalence of the outdoor measures that were most strongly associated with breast cancer incidence were comparatively low (<5% for outdoor air pollution) (White, 2015).

Smoking-related PAH exposures and breast cancer

Active smoking

Tobacco smoke is known to contain over 7,000 chemicals including 69 known carcinogens such as benzene, arsenic and heavy metals, formaldehyde, vinyl chloride, N-Nitrosamines, and PAHs (IARC 2004); at least 539 PAHs and PAH-derivatives have been identified in tobacco smoke including the highly carcinogenic PAHs benzo[*a*]pyrene and dibenzo[*a,l*]pyrene (Rodgman et al. 2000). Therefore, it is not surprising that the association between active cigarette smoking and breast cancer incidence has been extensively studied; at least 130 epidemiologic studies have examined smoking in relation to breast cancer incidence, yet there is no scientific consensus (Gaudet et al. 2013). In addition to differences in study design and differences in measurement assessment of smoking throughout the lifetime, the conflicting results of active smoking may in part be explained both the carcinogenic and estrogenic effects

of cigarette smoke constituents on breast epithelial cells (Meek and Finch 1999; Rodgman et al. 2000) and the anti-estrogenic effects of smoking on menstrual function which can result in an earlier initiation of menopause (Baron et al. 1990; Windham et al. 1999). In their meta-analysis (Gaudet et al. 2013) of 15 cohort studies totaling 991,100 women of which 31,198 developed breast cancer, however, Gaudet and colleagues showed that active cigarette smoking was associated with a 1.12 (95% CI=1.08, 1.16) increase in breast cancer incidence. Additionally, the association was stronger among women who initiated smoking before a first birth (HR=1.21, 95% CI=1.14-1.28) and among women who developed ER^+ tumors (HR=1.20, 95%: 1.00-1.45 (Gaudet et al. 2013).

Examining active cigarette smoking in relation to survival after breast cancer has received much less scientific attention (**Table I-4**), despite the potential of smoking to adversely affect health outcomes by increasing the risk of treatment complications (Zhan et al. 2007), recurrence (Bishop et al. 2014), and second primary cancers (Neugut et al. 1994) via suppression of the immune system (Sopori 2002), increasing oxidative stress (Danielsen et al. 2011), and disrupting the endocrine system (Bekki et al. 2013; Fertuck et al. 2001; Sievers et al. 2013). Most studies of survival after breast cancer conducted to date show that active smoking at diagnosis is associated with an increased risk of all-cause and breast cancer-specific mortality; hazard ratios range from 1.16 to 2.63 and from 1.73 to 2.08, for all-cause and breast cancer-specific mortality, respectively (Bérubé et al. 2014; Braithwaite et al. 2012; Calle et al. 1994; Dal Maso et al. 2008; Hellmann et al. 2010; Holmes et al. 1999, 2007; Manjer 2000; Passarelli et al. 2016; Pierce et al. 2014; Tominaga et al. 1998; Warren et al. 2012; Yu et al. 1997).

Environmental Tobacco Smoke (ETS)

Exposure to environmental tobacco smoke (ETS) (U.S. Department of Health and Human Services 2006)– which has a nearly identical qualitative composition, but a total PAH content lower than sidestream (released by the cigarette) smoke (Lodovici et al. 2004; U.S. Department of Health and Human Services 2006). – has also been extensively examined in relation to breast cancer (Rodgman et al. 2000). In a meta-analysis (Khuder and Simon 2000) of three cohort studies and eight case-control studies published from 1984-2000, a relative risk of breast cancer incidence of 1.41 (95% CI=1.14-1.75) was observed among women who reported ever exposure to environmental tobacco smoke, although there was significant heterogeneity between studies. In the LIBCSP, an increased OR (OR=2.10, 95% CI=1.47-3.02) of developing breast cancer was found among nonsmokers who lived with a smoking spouse for more than 27 years (Gammon et al. 2004). Additionally, among women who developed ER^+/PR^+ tumors, the OR of breast cancer incidence was 1.42 (95% CI=1.00-2.00) for women who reported ever exposure to both active and passive smoke compared to those who were never exposed. Bing ever exposed to passive smoke only was slightly, but not significantly associated with ER^+/PR^+ breast cancer incidence (OR=1.15, 95% CI=0.80-1.65) (Gammon et al. 2004). In a more recently published meta-analysis of 24 studies published through January 2008 and the Million Women Study, in the eight prospective studies, the relative risk of breast cancer incidence was not elevated (RR=0.99, 95% CI=0.93-1.05) in relation to ever exposure to passive smoke, but the 17 case-control studies showed a 21% (RR=1.21, 95% CI=1.11-1.32) elevated risk in breast cancer incidence suggesting that there could be systematic differences in the reporting of past exposures between cases and controls (Pirie et al. 2008).

To date, few studies (Boone et al. 2015; Kakugawa et al. 2015; Sagiv et al. 2007;

Wartenberg et al. 2000) have examined whether exposure to ETS is associated with survival after breast cancer (**Table I-4**) and most (Kakugawa et al. 2015; Sagiv et al. 2007; Wartenberg et al. 2000) have found no increased risk of mortality. One group of collaborators (Boone et al. 2015) reported a two-fold (HR=2.12, 95% CI=1.24-3.63) increased risk of breast cancer-specific mortality among women with at-diagnosis moderate and/or high (>10 hours per week) recent ETS exposure among never smokers.

The paradoxical results of a no-to-weak association between active smoking and the stronger association between passive smoking and breast cancer incidence may be explained by the differences in routes of exposure. It is hypothesized that most of the breast carcinogenic damage of cigarettes may be coming from vapor phase constituents in cigarette smoke (Wells 1991). Because up to 70% of tar, a source of PAHs, in ETS is in the vapor phase, whereas all of the tar in direct smoking is in the particulate phase, ETS may be a more important source of exposure to carcinogens since particulate smoke is cleared into the mouth and swallowed, but vapor phase constituents are inhaled and absorbed into the bloodstream and into the lymph system (Wells 1991).

Post-diagnosis changes in smoking and breast cancer survival

To date, only one recently published study (Passarelli et al. 2016) has examined whether changes in active smoking after breast cancer are associated with survival. This is of particular importance since it is estimated that approximately 70% of smokers diagnosed with breast cancer continue smoking after diagnosis (Westmaas et al. 2015), and hormone withdrawal can rapidly influence the growth of hormone-sensitive tumors (Powles and Hickish 1995; Prasad et al. 2003). In their study, Passarelli and colleagues report elevated hazard ratios for women who continued smoking after breast cancer for all-cause (HR=2.57, 95% CI=2.06-3.21, versus 2.30,

95% CI=1.56-3.39, respectively) and breast cancer (HR=1.73, 95% CI=1.13-2.60, versus HR=1.60, 95% CI=0.79-3.23, respectively) mortality. No studies have examined whether ETS and changes in ETS are associated with survival following breast cancer.

Diet-related PAH exposures and breast cancer

Up to 70% of PAH exposure for a non-smoking person can be attributed to diet (Phillips 1999; Skupińska et al. 2004). PAH-containing foods include barbecued, grilled, broiled, and smoked meats; roasted, baked, or fried foods; and breads, cereals, and grains, and vegetables (IARC 2010). Thus, PAHs in food arise from two sources, food-preparation and environmental contamination – although food preparation methods such as charring or barbecuing meat over charcoal, wood, or an open flame introduces far more PAHs than contamination (Larsson et al. 1983). During grilling and barbecuing, PAHs are generated through pyrolysis of meat products when fat drips from the meat onto a heated surface and produces smoke that coats the food with the compounds (Larsson 1986). The type of cooking, cooking temperature, time, amounts of fat, and oil, and proximity to the flame influence the formation of PAHs (Larsson et al. 1983; Perez 2002). Drying techniques used for cereal preservation such as combustion gas heating and smoking leads to an increase in the concentration of PAHs (Ramesh et al. 2004). Environmental contamination of plant foods occurs through deposition on leafy plants with high surface area; contamination of livestock occurs through the consumption of contaminated pastures and vegetation; contamination of fish and shellfish occurs through contamination of fresh and coastal waters.

Because of the importance of diet as a primary source of exposure to PAHs, several epidemiologic studies have investigated the association between intake of high-temperature

cooked meat and cancer incidence, including breast cancer. Studies have consistently shown an increased risk of breast cancer incidence among women who consume the largest quantities of well-done meat (Dai et al. 2002; De Stefani et al. 1997; Iscovich et al. 1989; Knekt et al. 1994; Sinha et al. 2000; Steck et al. 2007; Zheng et al. 1998). For example, in the Iowa Women's Health Study of more than 40,000 women aged 55-69 who completed a mailed questionnaire in 1986, women who consumed well-done hamburger, beef steak and bacon had a 4.62 increased risk of breast cancer incidence compared to women who consumed the meat rare or medium done (Zheng et al. 1998). In a study conducted in China, a 92% increased (OR=1.92, 95% CI=1.30-2.83) risk of breast cancer was observed among women with high intake of well-done red meat and a 52% increased (OR=1.52, 95% CI=1.05-2.22) risk for high intake of well-done freshwater fish (Dai et al. 2002). In hospital-based case-control study of Uruguayan women – a population exposed to a diet with large amounts of red beef – the OR of breast cancer incidence was 2.26 (95% CI=1.24-4.12) among women with meat intake in the highest quartile relative to women with meat intake in the lowest quartile (De Stefani et al. 1997).

Several studies have specifically examined whether the intake of grilled and smoked meat is associated with increased risk of breast cancer incidence (Han et al. 2004; Lee et al. 2012; Mourouti et al. 2015; Steck et al. 2007). Most studies report an elevated odds of breast cancer (ORs ranging from 1.47-2.58) among women who consume the highest levels of grilled and smoked meats compared to women who consume the lowest levels (Han et al. 2004; Lee et al. 2012; Steck et al. 2007). In the LIBCSP a modest increased risk of breast cancer was observed among postmenopausal, but not premenopausal, women consuming the most grilled or barbecued and smoked meats over the life course (OR=1.47; 95CI: 1.12-1.92), which was similar for ER^+/PR^+ and ER^-/PR^- tumors (Steck et al. 2007). Although no significant association was

observed in the study by Mourouti and colleagues and the ORs for the association between intake of grilled and smoked meats and breast cancer incidence were not reported, cases were more likely to consume grilled meat at least once per week (26% versus 21%). In their study, adjustment for BMI may have resulted in over-adjustment since BMI could be a potential mediator: grilling and smoking meats results in lower fat intake compared to other cooking methods such as pan-frying and deep-frying which often use hydrogenated cooking oils – one of the major sources of *trans*-fatty acids (WC et al. 1993). Additionally, intake of grilled and smoked meats could also result in increased fat intake depending on the fat content of the meat (Rock et al. 2012).

To date, no studies have examined whether food sources of PAH-containing foods, particularly those that have been grilled or smoked, influence survival after breast cancer.

Post-diagnosis changes in dietary intake of PAH-containing foods

Observational studies suggest that women with a prior diagnosis of breast cancer report more healthful diets including diets high in fruits and vegetables and fiber and low in high-fat foods after diagnosis (Salminen et al. 2000; Thomson et al. 2002). In the Women's Healthy Eating and Living Study of 3,084 breast cancer survivors (women diagnosed, on average, in the past 24 months before study enrollment), 91% of women reported consuming grilled foods in the 12 months before diagnosis. Approximately 23% reported decreasing and 11% reported increasing their intake of grilled foods since diagnosis (Thomson et al. 2002). How dietary changes related to grilled and smoked foods after breast cancer diagnosis influence survival, however, has not been examined in any epidemiologic study.

Summary

Many of the established epidemiologic risk factors for breast cancer incidence are closely related to lifetime hormone exposures and in particular, estrogen exposure. These risk factors include, primarily, endogenous (reproductive factors such as parity, breastfeeding, menarche and menopause and obesity) as well as exogenous (oral contraceptive and hormone therapy use) sources of hormone exposure, which highlight the central role of estrogens and other hormones in directly and indirectly influencing the development of breast cancer. Other established factors such as age, family history, and genetics highlight the molecular, cellular, and biological processes that lead to the development of cancer. Other factors such as obesity, physical activity, alcohol use and NSAID use underscore the importance of endogenous estrogen exposure, but also highlight other hypothesized mechanisms of carcinogenesis, including insulin resistance, oxidative stress and inflammation.

Several of these risk factors have also received considerable scientific attention in relation to survival after breast cancer diagnosis, though most have only received limited attention. Existing survival studies, however, provide support that exposure to estrogens and estrogen-like compounds shortly before diagnosis and after diagnosis also have the ability to influence prognosis since they have the potential to induce cell proliferation in hormone-sensitive tissues. For example, ever using oral contraceptives is not associated with breast cancer mortality, but current or recent use of OCs is associated with an increased risk of breast cancer mortality; obesity, which leads to increased levels of circulating estrogens in postmenopausal women, at diagnosis and post-diagnosis are also associated with an increased risk of breast cancer mortality. Physical activity, which contributes to a reduced lifetime exposure to sex steroid hormones, is inversely associated with breast cancer mortality with increasing magnitude

of association with recreational PA closer to diagnosis and the highest benefit among women who meet PA guidelines post-diagnosis. Therefore, it is plausible that environmental chemicals, particularly those with the ability to mimic estrogens and thus promote tumor growth and metastases, such as polycyclic aromatic hydrocarbons, may also influence prognosis. By examining the two primary non-occupational sources of exposure to PAHs, active smoking and diet, results of these studies of this dissertation we can better understand whether these and other similar chemicals influence survival. Additionally, documenting the relationships between changes in these smoking and diet-related behaviors and survival would strengthen smoking cessation efforts and help inform dietary intake guidelines among breast cancer patients. Given the high burden of breast cancer in the United States, this study has the potential to affect more than 3.1 million women living with breast cancer (American Cancer Society 2015a; National Cancer Institute 2016).

Table I-1. Summary of breast cancer risk and prognostic factors.

Risk/Prognostic Factor	Breast Cancer Incidence	Breast Cancer Survival
Age	Incidence rate is highest during the reproductive years until menopause when the rate slows, but continues to increase.	There is poor survival among women with diagnosis at a younger age (<35 years) and older age (>80 years) compared to women aged 40-49 years at diagnosis.
Reproductive factors		
Menarche and Menopause	Incidence increased by 5% for each year younger at menarche and the risk increases by 3% for each year older at menopause.	Menopausal status at diagnosis does not appear to be associated with mortality; however, studies report survival benefits among women who develop drug-induced amenorrhea.
Parity, age at first and multiple pregnancies	There is an increased risk among nulliparous women and a long-term reduced risk among parous women, which decreases with increasing number of full-term births.	Higher parity has been associated with worse survival, but few studies have examined this association.
Breastfeeding	The risk of breast cancer decreases by 4%-5% for every 12 month of breastfeeding compared to no breastfeeding.	Results of studies examining breastfeeding and breast cancer mortality have been mixed, but few have examined this association.
Exogenous hormone use		
Oral contraceptive (OC) use	The risk of premenopausal breast cancer is increased by 29% among parous and by 24% among nulliparous women who ever used OCs. Risk is further increased (44%) among women who used OCs before their first full-term pregnancy compared to women who use OCs after their first full-term pregnancy.	OC use is contraindicated in women with a history of breast cancer, but epidemiologic evidence supporting this is lacking. Ever using OCs is not associated with an increased risk of breast cancer mortality. However, current or recent use of OCs appears to increase the risk of breast cancer mortality.
Hormone replacement therapy (HRT) use	HRT use is associated with a 35% increased risk of breast cancer incidence for up to 5 years after cessation of use. Longer duration (≥15 years) is associated with a 58% increased risk in breast cancer incidence.	HRT use is contraindicated in women with a history of breast cancer, but epidemiologic evidence supporting this is lacking; studies report an inverse association between HRT use at diagnosis and breast cancer mortality.
Genetics		
Race	White women experience the highest, but similar rates of breast cancer incidence.	Mortality rates are highest among Black women.
Family history	Women with a family history of breast cancer diagnosed in any relative have a 90% increased risk of developing breast cancer.	Inconclusive and current evidence does not support worse breast cancer survival of BRCA1/2 mutation carriers
Diet	A daily intake of 100g of alcohol is associated with a RR of 2.71 (95% CI=2.33-3.08). No consistent associations between fruit and vegetable intake or fat intake and risk of breast cancer.	More than 20g/d of alcohol is associated with a 14% increased risk of breast cancer mortality. There is accumulating evidence of an association between pre-, at-, and post-diagnosis dietary fat intake and breast cancer survival.
Other lifestyle factors		

Risk/Prognostic Factor	Breast Cancer Incidence	Breast Cancer Survival
NSAID use	NSAID use is inversely associated (OR=0.85, 95% CI=0.75-0.89) with breast cancer incidence.	At- and post-diagnosis NSAID use is associated with a reduced risk (HRs range: 0.36-0.53) of breast cancer mortality. *De novo* post-diagnosis use of aspirin does not appear to be associated with breast cancer mortality.
Obesity	Postmenopausal women have a 58% increased risk while premenopausal women have a slight reduced risk of breast cancer incidence.	Women who are obese at diagnosis have a 33% increased risk of breast cancer mortality as compared to non-obese women.
Physical activity (PA)	PA is associated with a 15%-20% reduced risk of breast cancer incidence. Evidence is strong for postmenopausal breast cancer.	Lifetime and recent pre-diagnosis and post-diagnosis recreational PA are inversely associated with breast cancer mortality.

Table I-2. Evidence of estrogenic and anti-estrogenic activity of selected PAH compounds by PAH exposure source.

PAH Exposure Source	Relevant PAH Compounds	Estrogenic[a]	Anti-estrogenic[a]
Synthetic Log Burning	Chrysene/triphenylene	+	+
	Benzo[e]pyrene	-	+
	Retene	no evidence	no evidence
Vehicular traffic	Benzo[g,h,i]perylene	-	-
	Pyrene	-	-
	Fluoranthene	+	-
	Phenanthrene	-	-
Tobacco smoke	Benzo[a]pyrene	+	+
	Naphthalene	no evidence	no evidence
	Pyrene	-	-
	Fluoranthene	+	-
Grilled/smoked meat	Benzo[a]pyrene	+	+
	Phenanthrene	-	-
	Pyrene	-	-
	Fluoranthene	+	-

Note: Table is adapted from White 2016.

[a]Evidence from Arcaro 1999; Chaloupka 1992; Fertuck 2001; Gozgit 2004; Kummer 2008; van Lipzig 2004; Vondracek 2002.

Table I-3. Median Percentiles of OH-PAHs in NHANES 2011-2012 among participants aged 20 years and older, by smoking status (N=1,703).

		Non-smokers (n=1310)		ETS only (n=61)		Active Smoking (n=332)	
ng/L	**LOD**	**n**	**P50**	**n**	**P50**	**n**	**P50**
Naphthalene metabolites							
1-hydroxynaphthalene (ng/L)	42	1310	1186.00	61	1588.00	332	9879.00
2-hydroxynaphthalene (ng/L)	44	1310	3750.50	61	4495.00	332	13478.00
Fluorene metabolites							
2-hydroxyfluorene (ng/L)	10	1310	177.00	61	310.00	332	1249.00
3-hydroxyfluorene (ng/L)	10	1306	61.00	61	117.00	332	665.50
9-hydroxyfluorene (ng/L)	10	1310	208.50	61	409.00	332	666.50
Phenanthrene metabolites							
1-hydroxyphenanthrene (ng/L)	10	1310	113.00	61	127.00	332	200.50
2-hydroxyphenanthrene (ng/L)	10	1307	56.00	61	75.00	332	128.50
3-hydroxyphenanthrene (ng/L)	10	1309	54.00	61	81.00	332	159.50
4-phenanthrene (ng/L)	10	1307	18.00	60	21.00	331	42.00
Pyrene metabolite							
1-hydroxypyrene (ng/L)	10	1307	87.00	61	108.00	332	242.50

		Non-smokers (n=1310)		ETS only (n=61)		Active Smoking (n=332)	
ng/g creatinine	**LOD**	**n**	**P50**	**n**	**P50**	**n**	**P50**
Naphthalene metabolites							
1-hydroxynaphthalene (ng/L)	42	1309	1160.98	61	1600.00	332	10015.21
2-hydroxynaphthalene (ng/L)	44	1309	3788.71	61	4408.68	332	13060.87
Fluorene metabolites							
2-hydroxyfluorene (ng/L)	10	1309	183.33	61	243.37	332	1257.26
3-hydroxyfluorene (ng/L)	10	1305	62.50	61	101.56	332	657.50
9-hydroxyfluorene (ng/L)	10	1309	222.69	61	369.32	332	671.20
Phenanthrene metabolites							
1-hydroxyphenanthrene (ng/L)	10	1309	119.21	61	117.31	332	197.81
2-hydroxyphenanthrene (ng/L)	10	1306	59.00	61	69.34	332	121.68
3-hydroxyphenanthrene (ng/L)	10	1308	54.55	61	88.15	332	156.63
4-phenanthrene (ng/L)	10	1306	20.22	60	20.36	331	38.64
Pyrene metabolite							
1-hydroxypyrene (ng/L)	10	1306	94.12	61	111.43	332	247.36

Table I-4. Studies examining the associations between PAH sources of exposure and survival after breast cancer.

Citation				
Year	**N**	**Population**	**Exposure Assessment/Follow-up**	**Covariate-Adjusted Results**
PAH-DNA Adducts				
Sagiv SK, Gaudet MM, Eng SM, et al. Polycyclic aromatic hydrocarbon-DNA adducts and survival among women with breast cancer. *Environ Res*. 2009;109:287–91.				
2009	722	Population-based study of women residing in Long Island, NY diagnosed with invasive disease in 1996-1997	PAH-DNA adducts assayed from non-fasting blood samples using competitive ELISA 97 deaths (54 brca) determined from the NDI. Median follow-up of 5.8 yrs. (range: 0.4-7.4 yrs.)	<u>All-cause mortality</u> Quintile 1: Ref Quintile 5: HR=0.82 (95% CI=0.44-1.52) <u>Breast cancer-specific mortality</u> Quintile 1: Ref Quintile 5: HR=1.26 (95% CI=0.56-2.86)
Outdoor/Indoor air pollution				
Hu H, Dailey AB, Kan H, Xu X. The effect of atmospheric particulate matter on survival of breast cancer among US females. *Breast Cancer Res Treat*. 2013;139(1):217–26.				
2013	255,128	Female breast cancer cases from 1999-2009 SEER	EPA-linked county estimates of PM_{10} and $PM_{2.5}$ Number of deaths not reported. From the KM survival curves ~10% of cases died. Median follow-up time not reported (range: 0-10^{+} yrs.)	<u>Breast cancer-specific mortality</u> <u>*PM_{10}*</u> Tertile 1: Ref Tertile 2: HR=0.96 (95% CI=0.64-1.44) Tertile 3: HR=1.44 (95% CI=1.18-1.76) <u>*$PM_{2.5}$*</u> Tertile 1: Ref Tertile 2: HR=1.24 (95% CI=0.79-1.94) Tertile 3: HR=1.76 (95% CI=1.24-2.49)
Grilled and smoked foods				
[No studies]				
Active smoking and environmental tobacco smoke exposure				
Passarelli MN, Newcomb PA, Hampton JM, et al. Cigarette smoking before and after breast cancer diagnosis: mortality from breast cancer and smoking-related diseases. J Clin Oncol. 2016;34:1-8.				
2016	4,562	Participants of the Collaborative Breast Cancer and Women's Longevity Study, a population-based prospective observational study conducted in Wisconsin, New Hampshire, and Massachusetts	Smoking assessed by self-report by mailed questionnaire 6,778 deaths (2,894 brca) determined by linkage to the NDI. Median follow-up of 12 years.	<u>All-cause mortality</u> Never smoker: Ref. Former smoker: HR=1.11 (95% CI=1.05-1.17) Current smoker: HR=1.67 (95% CI=1.57-1.79) Never/Never smoker: Ref. Former/Former smoker: HR=1.45 (95% CI=1.24-1.69) Current/Former smoker: HR=2.34 (95% CI=1.85-2.96) Current/Current smoker: HR=2.57 (95% CI=2.06-3.21) <u>Breast cancer-specific mortality</u> Never smoker: Ref. Former smoker: HR=0.93 (95% CI=0.85-1.02) Current smoker: HR=1.25 (95% CI=1.13-1.37) Never/Never smoker: Ref. Former/Former smoker: HR=0.98 (95% CI=0.72-1.34) Current/Former smoker: HR=1.15 (95% CI=0.70-1.90) Current/Current smoker: HR=1.72 (95% CI=1.13-2.60)
Boone SD, Baumgartner KB, Baumgartner RN, et al. Active and passive cigarette smoking and mortality among Hispanic and non-Hispanic white women diagnosed with invasive breast cancer. *Ann Epidemiol*. 2015;25(11):824-831.				
2015	2,218	Participants of the Breast Cancer Health Disparities Study (BCHDS)	Smoking assessed by self-report by interviewer-administered questionnaire	<u>All-cause mortality</u> Never smoker: Ref. Ever smoker: HR=1.21 (95% CI=0.99-1.47) Former smoker: HR=1.00 (95% CI=0.79-1.26)

Year	N	Population	Exposure Assessment/Follow-up	Covariate-Adjusted Results
			445 deaths (243 brca) determined by linkage to statewide cancer registries. Median follow-up of 10.6 years.	Current smoker: HR=1.68 (95% CI=1.30-2.17) *Among recent passive smoke exposed non-smokers* No ETS: Ref. Low: HR=1.29 (95% CI=0.86-1.93) Moderate/High: HR=1.83 (95% CI=1.17-2.88) Breast cancer-specific mortality Never smoker: Ref. Current smoker: HR=1.55 (95% CI=1.11-2.16) *Among recent passive smoke exposed non-smokers* No ETS: Ref. Low: HR=1.43 (95% CI=0.89-2.31) Moderate/High: HR=2.12 (95% CI=1.24-3.63)
Izano M, Satariano WA, Hiatt RA, Braithwaite D. Smoking and mortality after breast cancer diagnosis: the health and functioning in women study. *Cancer Med*. 2015;4(2):315–24.				
2015	975	Participants of the US Health and Functioning in Women (HFW) Study	Smoking assessed by self-report by questionnaire once 2-4 months after breast cancer diagnosis 436 deaths (317 brca) determined by vital status follow-up from the Metropolitan Detroit Cancer Surveillance System at the Michigan Cancer Foundation. Median follow-up of 11.0 yrs. (IQ range: 4.5-22.4 yrs.)	All-cause mortality Never smoker: Ref. Current smoker: HR=2.45 (95% CI=1.81-3.32) Former smoker: HR=1.47 (95% CI=1.13-1.90) Breast cancer-specific mortality Never smoker: Ref. Current smoker: HR=1.38 (95% CI=0.99-1.91) Former smoker: HR=0.94 (95% CI=0.70-1.26)
Kakugawa Y, Kawai M, Nishino Y, et al. Smoking and survival after breast cancer diagnosis in Japanese women: A prospective cohort study. *Cancer Sci*. 2015.				
2015	871	Female patients aged 21 years or over at the Miyagi Cancer Center Hospital (MCCH)	Smoking assessed by self-administered questionnaire completed at admission 170 deaths (132 brca) determined by reference to the MCCH Cancer Registry and active follow up. Median follow-up of 6.7 yrs. (range: 0-13 yrs.)	All-cause mortality *Premenopausal women* Never smoker: Ref. ≤21.5 years duration: HR=0.95 (95% CI=0.35-2.63) >21.5 years duration: HR=3.09 (95% CI=1.17-8.20) *Postmenopausal women* Never smoker: Ref. ≤21.5 years duration: HR=0.72 (95% CI=0.22-2.35) >21.5 years duration: HR=0.53 (95% CI=0.20-1.36) Breast cancer-specific mortality *Premenopausal women* Never smoker: Ref. ≤21.5 years duration: HR=1.10 (95% CI=0.39-3.15) >21.5 years duration: HR=3.35 (95% CI=1.22-9.23) *Postmenopausal women* Never smoker: Ref. ≤21.5 years duration: HR=0.72 (95% CI=0.22-2.35) >21.5 years duration: HR=0.53 (95% CI=0.20-1.36)
Padron-Monedero A, Tannenbaum SL, Koru-Sengul T, et al. Smoking and survival in female breast cancer patients. *Breast Cancer Res Treat*. 2015;150(2):395–403.				

Year	N	Population	Exposure Assessment/Follow-up	Covariate-Adjusted Results
Citation				
2015	127,754	Data were obtained from the linkage of two population-based databases, the Florida cancer data system (FCDS) and the Agency for Health Care Administration (AHCA) with the U.S. census to form a dataset of Floridian women diagnosed and treated for breast cancer from 1996–2007	Smoking assessed by self-report 38,054 deaths defined as the time from diagnosis to death or last treatment encounter. Mean follow-up 4.9 yrs. (range: 0-15.0 yrs.)	<u>All-cause mortality</u> Never smoker: Ref. Current smoker: HR=1.33 (95% CI=1.28-1.38) Former smoker: HR=1.09 (95% CI=1.06-1.13)
Bérubé S, Lemieux J, Moore L, Maunsell E, Brisson J. Smoking at time of diagnosis and breast cancer-specific survival: new findings and systematic review with meta-analysis. *Breast cancer Res*. 2014;16(2):R42.				
2014	5,892	Women with invasive breast cancer treated in one Canadian center (1987 to 2008).	Smoking assessed by review of hospital records 1,408 deaths were documented, of which 953 (67.7%) were from breast cancer, 441 (31.3%) from other causes and 14 (1.0%) from unknown causes. 41,255 person-years of follow-up (maximum: 22 years)	<u>All-cause mortality</u> Never smoker: Ref. Current smoker: HR=1.38 (95% CI=1.20-1.60) Former smoker: HR=1.17 (95% CI=1.01-1.34) <u>Breast cancer-specific mortality</u> Never smoker: Ref. Current smoker: HR=1.15 (95% CI=0.97-1.37) Former smoker: HR=1.04 (95% CI=0.88-1.24) <u>Breast cancer-specific mortality (meta-analysis)</u> Never smoker: Ref. Current smoker: HR=1.33 (95% CI=1.12-1.58)
Pierce JP, Patterson RE, Senger CM, et al. Lifetime cigarette smoking and breast cancer prognosis in the After Breast Cancer Pooling Project. *J Natl Cancer Inst*. 2014;106(1):1–8.				
2014	9,975	three US cohorts included in the ABCPP were the Women's Healthy Eating and Living (WHEL) Study, the Life After Cancer Epidemiology (LACE) Study, and the Nurses' Health Study (NHS)	Smoking assessed by self-report on average 2 years after breast cancer diagnosis. 1,803 deaths (1,059 brca) assessed by periodic reviews of the Social Security Death Index and the National Death Index for NHS and WHEL and by Kaiser Permanente North California electronic data sources for LACE. Median follow-up of 11.1 yrs.	<u>All-cause mortality</u> Never smoker: Ref. Current smoker: HR=2.17 (95% CI=1.85-2.54) Former smoker ≥35pack-yrs: HR=1.68 (95% CI=1.44-1.96) <u>Breast cancer-specific mortality</u> Never smoker: Ref. Current smoker: HR=1.61 (95% CI=1.28-2.03) Former smoker ≥35pack-yrs: HR=1.54 (95% CI=1.24-1.91)
Braithwaite D, Izano M, Moore DH, et al. Smoking and survival after breast cancer diagnosis: a prospective observational study and systematic review. *Breast Cancer Res Treat*. 2012;136(2):521–533.				
2012	2,258	LACE Cohort of women diagnosed with stage I, II, IIIa, breast cancer from 1997-2000 in the Kaiser and Utah Cancer registries or in the WHEL Study	Smoking assessed by self-report on average 23 (range: 11-39) mos. after breast cancer diagnosis. 485 deaths (244 brca) determined by Kaiser HER, mailed questionnaires, or by telephone. Median follow-up of 12.3 yrs. (range: 1.5-15.5 yrs.).	<u>All-cause mortality</u> Never smoker: Ref Current smoker: HR=2.63 (95% CI=1.93-3.58) Former smoker: HR=1.28 (95% CI=1.05-1.56) <u>Breast cancer-specific mortality</u> Never smoker: Ref Current smoker: HR=2.01 (95% CI=1.27-3.18) Former smoker: HR=1.24 (95% CI=0.94-1.64)
Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. *Int J cancer*. 2012;132(2):401–10.				
2012	882	Patients who received diagnosis, consultation or treatment at Roswell Park Cancer Institute (RPCI) between 1982 and 1998	Smoking assessed by self-report within 1 month of diagnosis Number of deaths not reported. Median follow-up not reported (range: 0-27.7 yrs.).	<u>Breast cancer-specific mortality</u> Never smoker: Ref Current smoker: HR=1.73 (95% CI=1.28-2.33) <u>*Premenopausal women*</u> Never smoker: Ref Current smoker: HR=2.10 (95% CI=1.36-2.99) <u>*Postmenopausal women*</u> Never smoker: Ref Current smoker: HR=1.40 (95% CI=0.88-2.25)
Hellmann SS, Thygesen LC, Tolstrup JS, Grønbæk M. Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. *Eur J Cancer Prev*. 2010;19(5):366–373.				
2010	528	Women participating in the Copenhagen City Heart Study	Smoking assessed by self-administered questionnaire	<u>All-cause mortality</u> Never smoker: Ref

Year	N	Population	Exposure Assessment/Follow-up	Covariate-Adjusted Results
Citation				
		(CCHS)	323 deaths (174 of 300 brca) determined by linkage to the National Danish Central Personal Registry and the Danish Causes of Death Registry. Median follow-up of 7.8 yrs. (range: 0.04-29.2 yrs.)	Current smoker: HR=1.16 (95% CI=1.05-1.29) Former smoker: HR=1.04 (95% CI=0.88-1.23) Breast cancer-specific mortality Never smoker: Ref Current smoker: HR=1.07 (95% CI=0.94-1.23) Former smoker: HR=0.98 (95% CI=0.77-1.24)
Dal Maso L, Zucchetto A, Talamini R, et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *Int J Cancer*. 2008;123(9):2188–94.				
2008	1,453	Women with incident invasive breast cancer, diagnosed between 1991 and 1994 and interviewed within the framework of an Italian multicenter case-control study	Smoking assessed by questionnaire 503 deaths (398 brca) determined by linkage to regional health system databases	All-cause mortality Never smoker: Ref Current smoker: HR=1.42 (95% CI=1.17-1.71) Breast cancer-specific mortality Never smoker: Ref Current smoker: HR=1.30 (95% CI=1.05-1.61)
Barnett GC, Shah M, Redman K, Easton DF, Ponder BAJ, Pharoah PDP. Risk factors for the incidence of breast cancer: do they affect survival from the disease? *J Clin Oncol*. 2008;26(20):3310–6.				
2008	4,560	3,312 incident and 1,248 prevalent breast cancer cases of the Studies of Epidemiology and Risk Factors in Cancer Heredity breast cancer study.	Smoking assessed by self-administered questionnaire 620 deaths identified from the East Anglian Cancer Registry. Median follow-up of: 5.05 yrs. (range: 0.03-8.92 yrs.)	All-cause mortality Never smoker: Ref Current smoker: HR=1.11 (95% CI=0.89-1.41) Former smoker: HR=1.01 (95% CI=0.83-1.23)
Sagiv SK, Gaudet MM, Eng SM, et al. Active and passive cigarette smoke and breast cancer survival. *Ann Epidemiol*. 2007;17(5):385–93.				
2007	1,273	Population-based study of women residing in Long Island, NY diagnosed with invasive disease in 1996-1997	Smoking assessed by interviewer-administered questionnaire at diagnosis. 188 deaths (111 brca) determined from the NDI. Median follow-up of 5.8 yrs. (range: 0.2-7.4 yrs.)	All-cause mortality Never smoker: Ref Current smoker: HR=1.23 (95% CI=0.83-1.84) Former smoker: HR=1.19 (95% CI=0.85-1.66) Breast cancer-specific mortality Never smoker: Ref Current smoker: HR=1.04 (95% CI=0.63-1.71) Former smoker: HR=0.89 (95% CI=0.57-1.40)
Holmes MD, Murin S, Chen WY, Kroenke CH, Spiegelman D, Colditz GA. Smoking and survival after breast cancer diagnosis. *Int J cancer*. 2007;120(12):2672–7.				
2007	5,056	Nurse's Health Study women diagnosed with stage I, II, or III breast cancer from 1978-2002	Smoking assessed by self-report in 1976. 1,275 deaths (828 brca) determined from reporting by family or postal authorities and from the NDI. Median follow-up of 8.25 years	All-cause mortality Never smoker: Ref Current smoker: HR=1.48 (95% CI=1.27-1.74) Former smoker: HR=1.07 (95% CI=0.94-1.21) Breast cancer-specific mortality Never smoker: Ref Current smoker: HR=1.02 (95% CI=0.83-1.24) Former smoker: HR=0.92 (95% CI=0.79-1.08)
Fentiman IS, Allen DS, Hamed H. Smoking and prognosis in women with breast cancer. *Int J Clin Pract*. 2005;59(9):1051–1054.				
2005	166	Women who completed a lifestyle questionnaire with confirmed operable invasive ductal or lobular breast cancer (stages I and II)	Smoking assessed by self-administered questionnaire 67 brca determined by clinic attendance or annual letter to GP. Mean follow-up was 11 years (range: 0-20yrs)	All-cause mortality Never smoker: Ref Current smoker: HR=1.41 (95% CI=0.84-2.37) Former smoker: HR=0.70 (95% CI=0.42-1.15) Breast cancer-specific mortality Never smoker: Ref Current smoker: HR=1.41 (95% CI=0.77-2.59) Former smoker: HR=0.62 (95% CI=0.34-1.14)
Wartenberg D, Calle EE, Thun MJ, Heath, Clark W. J, Lally C, Woodruff T. Passive Smoking Exposure and Female Breast Cancer Mortality. *J Natl Cancer Inst*. 2000;92(20):1666-1673.				
2000	676,306	Female participants in Cancer Prevention Study (CPS-II)	Exposure to ETS assessed by questionnaire with spouse 669 breast cancer deaths among analytic cohort determined by personal contact and by linkage to the National Death Index. Mean follow-up of 12 years	Breast cancer-specific mortality Never ETS: Ref Current ETS: HR=1.0 (95% CI=0.8-1.2) Former ETS: HR=1.0 (95% CI=0.8-1.2)
Manjer J. Survival of Women with Breast Cancer in Relation to Smoking. *Eur J Surg*. 2000;166(11):852–858.				

Citation				
Year	**N**	**Population**	**Exposure Assessment/Follow-up**	**Covariate-Adjusted Results**
2000	792	Women with breast cancer diagnosed in the Malmo mammographic screening trial between 1977 and 1986	Smoking assessed by review of hospital records 347 deaths (145 brca) determined by linkage with the Swedish Cause of Death Register. Mean follow-up 12.1 years	<u>All-cause mortality</u> Never smoker: Ref Current smoker: HR=2.14 (95% CI=1.47-3.10) Former smoker: HR=1.05 (95% CI=0.60-1.83)
Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. *Cancer*. 1999;86(5):826–35.				
1999	1,982	Women included were Nurse's Health Study participants with invasive breast carcinoma diagnosed between 1976 and 1990. Women were followed until death or June 1994, whichever came first.	Smoking assessed by self-administered questionnaire 378 deaths (326 brca) ascertained from death certificates, supplemented as needed with medical records.	<u>All-cause mortality</u> Never smoker: Ref Current smoker: HR=1.29 (95% CI=0.99-1.68) Former smoker: HR=0.92 (95% CI=0.72-1.17)
Tominaga K, Andow J, Koyama Y, et al. Family environment, hobbies and habits as psychosocial predictors of survival for surgically treated patients with breast cancer. *Jpn J Clin Oncol*. 1998;28(1):36–41.				
1998	398	Female patients who had undergone surgery for primary breast cancer between September 1, 1986 and January 31, 1995 at the Tochigi Cancer Center Hospital, Utsunomiya	Smoking status at first admission abstracted from the medical records 48 deaths identified by follow-up of outpatients. Median follow-up not reported (range: 0-9 yrs.)	<u>Breast cancer-specific mortality</u> "No habit of smoking": Ref "Habit of smoking": HR=2.08 (95% CI=1.02-4.26)
Yu GP, Ostroff JS, Zhang ZF, Tang J, Schantz SP. Smoking history and cancer patient survival: a hospital cancer registry study. *Cancer Detect Prev*. 1997;21(6):497–509.				
1997	5,471	All incident cases of cancer at Memorial Sloan-Kettering Cancer Center registered between Jan 1, 1990 and Dec 31, 1995	Smoking at diagnosis was abstracted from the clinical records. Number of breast cancer deaths not reported. Maximum follow-up of 6 years.	<u>All-cause mortality</u> <u>*White*</u> Never smoker: Ref Ever smoker: HR=1.21 (95% CI=0.9-1.6) <u>*Black*</u> Never smoker: Ref Ever smoker: HR=1.73 (95% CI=1.0-2.9) <u>*Other*</u> Never smoker: Ref Ever smoker: HR=1.68 (95% CI=0.3-9.7) <u>*Local*</u> Never smoker: Ref Ever smoker: HR=1.22 (95% CI=0.8-1.9) <u>*Regional*</u> Never smoker: Ref Ever smoker: HR=1.21 (95% CI=0.9-1.6) <u>*Distant*</u> Never smoker: Ref Ever smoker: HR=2.22 (95% CI=1.3-3.9)
Calle EE, Miracle-McMahill HL, Thun MJ, Heath, Clark W. J. Cigarette Smoking and Risk of Fatal Breast Cancer. *Am J Epidemiol*. 1994;139(10):1001–1007.				
1994	604,412	Female participants of the Cancer Prevention Study II	Smoking assessed by questionnaire 880 deaths identified by personal inquiry. Mean follow-up of 6 years	<u>All-cause mortality</u> Never smoker: Ref Current smoker: HR=1.26 (95% CI=1.05-1.50) Former smoker: HR=0.85 (95% CI=0.70-1.03) Ever smoker: HR=1.02 (95% CI=0.88-1.19) <u>*Years smoked*</u> Never smoker: Ref ≥40 years smoked: HR=1.74 (95% CI=1.05-1.83) <u>*Age of initiation*</u> Never smoker: Ref <16 yrs. old at start: HR=1.59 (95% CI=1.17-2.15) 17-19 yrs. old at start: HR=1.41 (95% CI=1.08-1.85) ≥20 yrs. old at start: HR=1.00 (95% CI=0.77-

Citation				
Year	**N**	**Population**	**Exposure Assessment/Follow-up**	**Covariate-Adjusted Results**
				1.30)
Ewertz M, Gillanders S, Meyer L, Zedeler K. Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. *Int J cancer*. 1991;49(4):526–30.				
1991	2,568	Breast cancer patients below the age of 70 diagnosed between March 1, 1983 and August 31, 1984 in Denmark identified through the Danish Breast Cancer Co-operative Group (DBCG) and the Danish Cancer Registry	Smoking at diagnosis assessed by self-administered questionnaire mailed to patients 1 year after diagnosis. 805 deaths identified by record linkage to the Central Population Registry. Median follow-up not reported (range: 0-7 yrs.).	All-cause mortality Never smoker: Ref Ever smoker: HR=1.05 (95% CI=0.87-1.26)

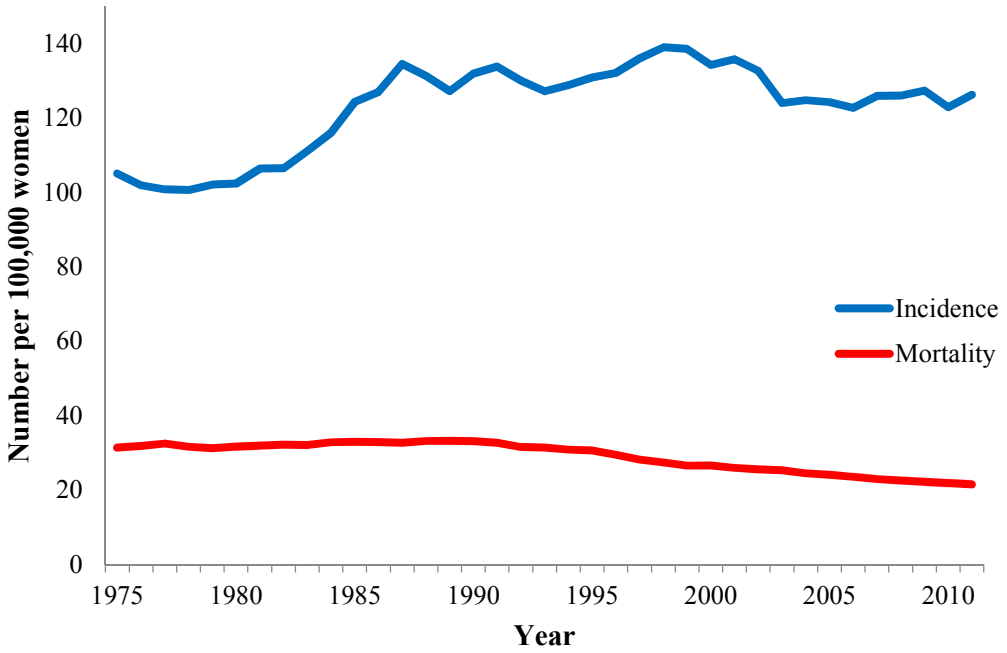

Figure I-1. Breast Cancer Incidence and Mortality Rates among Women of All-Races, United States, 1975-2011. (National Cancer Institute 2016)

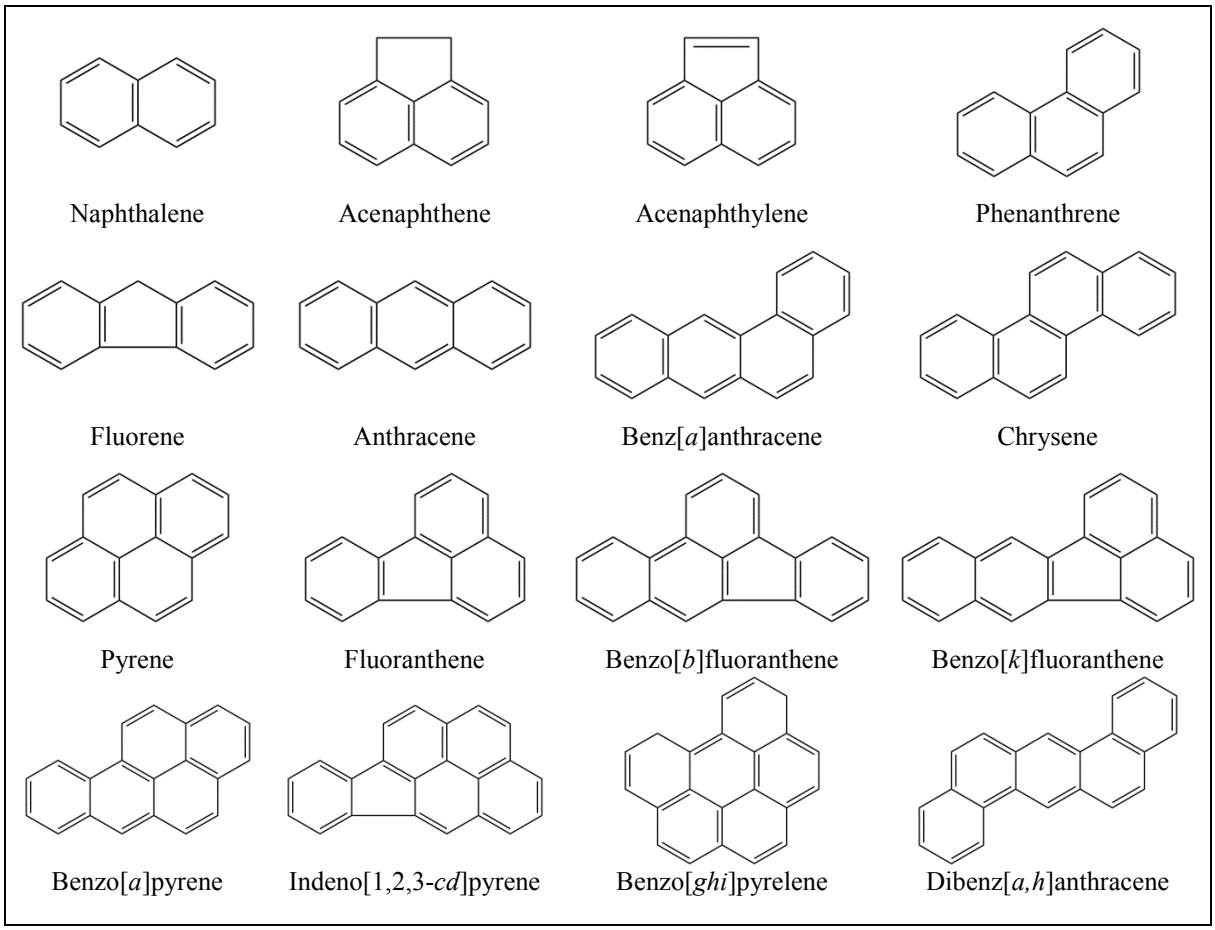

Figure I-2. Structures and nomenclatures of the 16 PAHs on the EPA priority pollutant list. Adapted from Yan J, Wang L, Fu PP, Yu H. Photomutagenicity of 16 polycyclic aromatic hydrocarbons from the US EPA priority pollutant list. *Mutat Res* 2004;557:99–108.

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CHAPTER II: RESEARCH METHODS

This dissertation examined whether PAH exposure from tobacco smoke and food sources, before and after diagnosis, was associated with an increase in mortality after breast cancer. This dissertation utilized resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study of adult female residents of Nassau and Suffolk counties of New York (Gammon et al. 2002a). Specifically, I drew upon the follow-up component of the LIBCSP that included a second post-diagnosis interview that occurred about five years after diagnosis, along with subsequent determination of vital status, of the women diagnosed with breast cancer (n=1,508) in 1996 and 1997. In the LIBCSP, PAH exposure from tobacco smoke and grilled/smoked meat was assessed before and up to five years after diagnosis, and women have been followed for vital status for 18^{+} years using the National Death Index, which provides high quality ascertainment of vital status (Cowper et al. 2002).

This dissertation addressed the following Specific Aims (Figure II-1).

Aim 1. Determine whether active cigarette smoking and ETS exposure among a population-based sample of women diagnosed with first primary breast cancer is associated with all-cause and breast cancer-specific mortality.

Aim 1A:

- Determine whether at-diagnosis active smoking among women with breast cancer is associated with all-cause and breast cancer-specific mortality.

- Among women with breast cancer, determine whether changes in active smoking within five years after breast cancer (i.e., cessation of active smoking after diagnosis, time since smoking cessation after diagnosis, and cumulative pack-years (calculated as pre-diagnosis + post-diagnosis pack-years)) are associated with subsequent all-cause and breast cancer-specific mortality.

Aim 1B:

- Determine whether pre-diagnosis ETS exposure among women with breast cancer is associated with all-cause and breast cancer-specific mortality.
- Among women with breast cancer, determine whether changes in ETS exposure within five years after breast cancer diagnosis (i.e., cessation of ETS exposure) are associated with subsequent all-cause and breast cancer-specific mortality.

Aim 2. Determine whether intake of grilled, barbecued, and smoked meat among a population-based sample of women diagnosed with first primary breast cancer is associated with all-cause and breast cancer-specific mortality after breast cancer diagnosis.

- Determine whether at-diagnosis intake of grilled, barbecued, and smoked meat among women with breast cancer is associated with all-cause and breast cancer-specific mortality.
- Among women with breast cancer, determine whether changes intake of grilled and smoked meats within 5 years after breast cancer diagnosis (i.e., change in intake categorized at the median) is associated with all-cause and breast cancer-specific mortality.

Rationale

Significance

Breast cancer is the most common cancer and the second leading cause of death from cancer among women in the United States (US) (Siegel et al. 2016). In 2016, it is estimated that more than 246,000 US women will be diagnosed with breast cancer, contributing to the 3.1 million breast cancer survivors (National Cancer Institute 2016). By 2030, it is projected that the number of breast cancer survivors will increase by as much as 50%, driven predominantly by hormonally sensitive (estrogen receptor (ER)- or progesterone receptor (PR)-positive) tumors (AACR 2015). Survival following a diagnosis of breast cancer is high with nearly 90% of women surviving at least five years (National Cancer Institute 2016), yet approximately 40,000 deaths continue to be attributed to breast cancer annually (Siegel et al. 2016). Early breast cancer detection through routine gynecological and general physical examination and the use of mammography and access to high quality surgery and adjuvant and anti-estrogen therapies contribute to this high survival rate (Shulman et al. 2010). As reviewed in **CHAPTER I: BACKGROUND** of this dissertation, survival is adversely impacted by tumor characteristics (including larger tumor size, higher grade, lymph node involvement, and ER and PR-negative status), as well as patient characteristics (such as younger (<35 years) and older age (>80 years), lower socio-economic status, a recent pregnancy, recent oral contraceptive use, and comorbidities present at diagnosis (including obesity and diabetes) (Brandt et al. 2015; Cleveland et al. 2012; Fredholm et al. 2009; Kroman et al. 2000; Soerjomataram et al. 2008; Trivers et al. 2007b). A better understanding of the contribution of environmental exposures, especially exogenous compounds with the potential to influence estrogen, estrogen receptors, or biologically relevant pathways involved in breast cancer progression, on survival – among the

largest group of cancer survivors in the US – can help us to substantially reduce the burden of breast cancer.

Polycyclic Aromatic Hydrocarbons (PAHs) are ubiquitous environmental contaminants to which most people are exposed on a regular basis (Agency for Toxic Substances and Disease Registry (ATSDR) 1995b; IARC 2010)**.** PAHs include over 100 different chemicals, including benzo[a]pyrene, and are common byproducts formed during the incomplete combustion of coal, oil and gas, and other organic substances like tobacco and charbroiled/smoked meats (Agency for Toxic Substances and Disease Registry (ATSDR) 1995b). The term PAH generally refers to a large class of compounds that contain only carbon and hydrogen and are comprised of two or more fused aromatic rings. Sources of non-occupational PAH exposure in the US include, primarily, cigarette smoking and, among non-smokers, diet; and, secondarily, outdoor and indoor air pollution (Skupińska et al. 2004). Smoking increases personal daily PAH exposure by 30-fold on average (Woodard and Snedeker 2001); one cigarette yields an intake of B[a]P of 20-40 ng (Phillips 1996). PAH levels from charring meat can be as high as 10-20 μg/kg (Skupińska et al. 2004). This gradient of exposure due to differences in behavioral practices can help to guide the development of an optimal research strategy to clarify the association between PAH exposures and breast cancer survival.

In laboratory studies, PAHs have been shown to induce tumors through mechanisms involving PAH-DNA adducts (Baird et al. 2005) and oxidative stress and inflammation (Danielsen et al. 2011). Given this evidence, IARC recognizes benzo[a]pyrene and benz[*a*]anthracene as a probable and benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, and indeno[1,2,3-*c,d*]pyrene as possible carcinogens to humans, particularly to the lung (Agency for Toxic Substances and Disease Registry (ATSDR) 1995b).

PAHs are demonstrated mammary carcinogens (Cavalieri et al. 1991), but their role in breast carcinogenesis, particularly progression after diagnosis in humans, is less well understood. PAHs and PAH metabolites, including hydroxylated PAHs and PAH quinones, may influence breast carcinogenesis and progression by acting as endocrine disruptors by directly binding to estrogen receptors (Bekki et al. 2013; Fertuck et al. 2001; Sievers et al. 2013). Of importance is that PAHs and metabolites are lipophilic (Ferreira 2001) and known to be stored in adipose tissues, including the breast (Li et al. 1999; Perera et al. 1995). These characteristics of PAHs highlight the need to better understand how these exposures influence survival after breast cancer, an understudied area of research.

A diagnosis of breast cancer is a "teachable moment" during which patients may be especially motivated to make changes and direct their priorities to restoration and maintenance of good health (McBride and Ostroff 2003)**.** A healthful lifestyle including nutritional care and exercise may help mitigate the effects of treatment, prevent new diseases, and reduce the impact of existing conditions (Rock et al. 2012). Therefore women, particularly those with newly diagnosed breast cancer, may seek out information on lifestyle modifications (Galloway et al. 1997). Post-diagnosis changes in two possible modifiable behaviors and the predominant sources of exposure to PAHs, smoking and diet, may have the maximal impact on survival among breast cancer patients because changes are likely to be sustained (Demark-Wahnefried et al. 2005). This teachable moment may also extend to family members of breast cancer patients who may also adopt more healthful behaviors such as smoking cessation (Mazanec et al. 2015). Documenting the relationships between changes in these behaviors and survival would strengthen smoking cessation efforts and help inform diet guidelines for breast cancer patients.

Innovation

This dissertation examined the associations between changes in cigarette smoking and environmental tobacco smoke (ETS) and survival following breast cancer diagnosis. Tobacco smoke contains more than 4,000 chemicals, at least 20 of which are known mammary carcinogens in rodents (IARC 2004; Johnson et al. 2011) including polycyclic aromatic hydrocarbons (PAHs) (Rodgman et al. 2000). Cigarette smoking may be weakly associated with breast cancer incidence; a recent meta-analysis of 15 cohort studies showed that active cigarette smoking was associated with a 1.12-fold (95% CI=1.08-1.16) increase (Gaudet et al. 2013). ETS and breast cancer incidence associations are consistent with a modest magnitude of 1.20 (95% CI=1.08-1.35) (Johnson et al. 2011; U.S. Department of Health and Human Services 2006). Examining cigarette smoking in relation to survival after breast cancer has received much less scientific attention, despite the potential of smoking to adversely affect health outcomes by increasing the risk of treatment complications (Zhan et al. 2007), recurrence (Bishop et al. 2014), and second primary cancers (Neugut et al. 1994) via suppression of the immune system (Sopori 2002), increasing oxidative stress (Danielsen et al. 2011), and disrupting the endocrine system (Bekki et al. 2013; Fertuck et al. 2001; Sievers et al. 2013). Most studies of survival conducted to date show that active smoking at the time of diagnosis is associated with an increased risk of all-cause and breast cancer-specific mortality; hazard ratios range from 1.16 to 2.63 and from 1.73 to 2.08, for all-cause and breast cancer-specific mortality, respectively (Braithwaite et al. 2012; Calle et al. 1994; Hellmann et al. 2010; Holmes et al. 1999, 2007; Manjer 2000; Tominaga et al. 1998; Warren et al. 2012; Yu et al. 1997). However, only one prior study has examined whether changes in smoking after breast cancer are associated with survival. This is of particular importance since it is estimated that ~30% of women quit smoking after being diagnosed with

breast cancer (Westmaas et al. 2015) and hormone withdrawal can rapidly influence the growth of hormone-sensitive tumors (Powles and Hickish 1995; Prasad et al. 2003). Additionally, no studies have examined whether post-diagnosis changes in ETS exposure are associated with survival following breast cancer.

This dissertation is the first to examine the association between dietary sources of exposure to PAHs and survival following breast cancer diagnosis. Up to 70% of PAH exposure for a non-smoking person can be attributed to diet (Phillips 1999; Skupińska et al. 2004). PAH-containing foods include barbecued, grilled, broiled, and smoked meats; roasted, baked, or fried foods; and breads, cereals, and grains, and vegetables (IARC 2010). PAHs in food arise from two sources, food-preparation and environmental contamination. For example, during grilling and barbecuing, PAHs are generated through pyrolysis of meat products when fat drips from the meat onto a heated surface and produces smoke that coats the food with the compounds (Larsson 1986). Environmental contamination of plant foods occurs through deposition on leafy plants with high surface area; contamination of livestock occurs through the consumption of contaminated pastures and vegetation; contamination of fish and shellfish occurs through contamination of fresh and coastal waters. Because of the importance of diet as a principal source of exposure to PAHs, epidemiologic studies have investigated the association between dietary PAH sources and cancer incidence, including breast cancer. One study conducted in China, showed a 92% (OR=1.92, 95% CI=1.30-2.83) increased breast cancer incidence for high intake of well-done red meat and a 52% (OR=1.52, 95% CI=1.05-2.22) increased risk for high intake of well-done freshwater fish (Dai et al. 2002). In a previous study with this sample a modest elevation in breast cancer incidence was observed among postmenopausal, but not premenopausal, women consuming the most grilled or barbecued and

smoked meats over the life course (OR=1.47; 95% CI=1.12-1.92 for the highest tertile vs. the lowest) (Steck et al. 2007). However, no studies have examined whether food sources of PAH-containing foods influence survival after breast cancer and whether dietary changes related to grilled and smoked foods after diagnosis influence survival.

Approach

Research Strategy

To address my study aims, I utilized resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study of women diagnosed with first primary breast cancer, who were interviewed shortly after diagnosis and again about five years later and who have been followed for vital status for 18^{+} years (Bradshaw et al. 2012; Gammon et al. 2002a). This prospective study represented an optimal approach in which to examine my hypotheses – that post-diagnosis changes in the primary sources of PAH-exposure, tobacco smoke and diet, are associated with all-cause and breast cancer-specific mortality – because these exposures ex estimated for before and at diagnosis (i.e., at-diagnosis exposure) and approximately 5 years after diagnosis (i.e., post-diagnosis exposure) (**Figure II-1**). Additionally, I applied the use of methods to address missing data, which is important to consider since a complete-case analysis, in addition to being inefficient, may also lead to biased estimates (Ibrahim et al. 2012). The proposed study is much more time efficient and cost-effective than a *de novo* study; and another study design such as a clinical trial could never be conducted on whether changes in smoking after diagnosis is associated with mortality following breast cancer, because it would be considered unethical to withhold smoking cessation programs to anyone, including breast cancer survivors. Similarly, it is next to impossible to blind participants in a dietary intervention trial.

Thus, an existing observational study focused on a cohort of incident breast cancer patients with long-term follow-up, as conducted in this dissertation, was the best alternative.

Study Population

LIBCSP identification and recruitment of women with a newly diagnosed first primary breast cancer was conducted in 1996-1997 in the counties of Nassau and Suffolk on Long Island, New York. Details of the study and participants have been previously published (Bradshaw et al. 2012; Gammon et al. 2002a; Sagiv et al. 2009; Steck et al. 2007). Women with a first diagnosis of *in situ* or invasive breast cancer were identified for inclusion using rapid-case ascertainment via active daily or weekly contact with local hospitals confirmed by a physician and medical records. Additional eligibility criteria included being over the age of 20, residing in Nassau or Suffolk counties of New York, and being diagnosed during August 1, 1996, through July 31, 1997. This dissertation used data from the 1,508 women who were interviewed at baseline, on average within three months of diagnosis (mean=3.19 months) and who provided signed informed consent. These women were primarily white (94%) and black (5%), with a mean age of 59 years (range: 25-98 years), and postmenopausal (59%) at baseline. The demographic characteristics of the women in the LIBCSP reflect those of the underlying geographic area, and include those at highest risk of breast cancer (American Cancer Society 2012). Many established risk factors for breast cancer, including parity, late age at first birth and a family history of breast cancer were confirmed among the LIBCSP participants (Gammon et al. 2002a).

Of the 1,508 women with breast cancer who completed the 100-minute, in-home, interviewer-administered, structured baseline questionnaire and a self-administered Food Frequency Questionnaire (Block FFQ; (Block et al. 1986)) that assessed diet in the year previous

to diagnosis, 1,414 initially agreed to participate in the follow-up component of the study. Approximately five years after the initial diagnosis of breast cancer, the 1,414 women, or a proxy identified at the time of diagnosis (usually a mother or sister), who expressed interest in participating in the follow-up study were contacted to obtain informed consent for participation. Proxy interviews comprised <8% of all follow-up interviews. Informed consent was obtained by telephone from 1,120 of the 1,414 women (i.e., 60 refused by mail, 83 refused by telephone, no proxy was identified for 96 women who were not alive at follow-up, and 55 could not be located). A 45-minute interviewer-administered, structured questionnaire that assessed information similar to that obtained at the time of diagnosis, but regarding the time period since the initial diagnosis of breast cancer (i.e., post-diagnosis exposures), was completed by telephone with the consenting 1,033 (68.5%) of the 1,508 women with breast cancer completed the follow-up questionnaire (Bradshaw et al. 2012).

Exposure Assessment

Tobacco Smoke Exposure. At baseline, approximately on average within 3 months of breast cancer diagnosis, participants were asked about their active smoking and exposure to environmental tobacco smoke (ETS) prior to baseline interview via interviewer-administered questionnaire (Gammon et al. 2004) (**APPENDIX: EXCERPTS FROM THE LIBSCP BASELINE QUESTIONNAIRE**). The variables from the smoking section of the baseline questionnaire were used to define the following at-diagnosis exposures:

- Smoking status. Never, former, and current smoker.
- Intensity of smoking. Number of cigarettes smoked per day, which was categorized as <20 cigarettes per day versus ≥20 cigarettes per day.

- Duration of smoking. Number of years of smoking, which was categorized as <15 years, ≥15 years to <30 years, and ≥30 years.
- Pack-years of smoking. Calculated as intensity times duration and categorized as <15 pack-years, ≥15 pack-years to <30 pack-years, and ≥30 pack-years.
- Smoking cessation recency. Number of years since smoking cessation, which was categorized as <5 years, ≥5 years to <10 years, and ≥10 years.

At the 5-year follow-up assessment participants were asked the same questions, but regarding the time-period since the baseline questionnaire. At both time-points, current active cigarette smokers were defined as women who smoked within the past 12 months prior to the questionnaires and former smokers were defined as women who reported quitting more than 12 months prior to the questionnaires. In Aim 1A, which examined post-diagnosis tobacco smoke exposure, changes in exposures included:

- Change in smoking status. At-diagnosis never smoker and post-diagnosis never smoker (i.e., never/never smoker); at-diagnosis former smoker and post-diagnosis former smoker (i.e., former/former smoker); at-diagnosis current smokers and post-diagnosis former smoker (i.e., current/former smoker); and at-diagnosis current smoker and post-diagnosis current smoker (i.e., current/current smoker).
- Cumulative duration of smoking. Former/former smokers <30 years versus ≥30 years, current/former smokers <30 years versus ≥30 years; and current/current smokers <30 years versus ≥30 years.
- Cumulative pack-years of smoking. Former/former smokers <30 pack-years versus ≥30 pack-years, current/former smokers <30 pack-years versus ≥30 pack-years; and current/current smokers <30 pack-years versus ≥30 pack-years.

Similarly, in Aim 1B, at-diagnosis ETS exposures and post-diagnosis changes in exposures included:

- ETS exposure status. Never, former, and current ETS exposure.
- Change in ETS exposure status. At-diagnosis never ETS exposed and post-diagnosis never ETS exposed (i.e., never/never ETS exposed); at-diagnosis former ETS exposed and post-diagnosis never ETS exposed (i.e., former/never ETS exposed); at-diagnosis former ETS exposed and post-diagnosis former ETS exposed (i.e., former/former ETS exposed); at-diagnosis former ETS exposed and post-diagnosis current ETS exposed (i.e., former/current ETS exposed); at-diagnosis current ETS exposed and post-diagnosis never ETS exposed (i.e., current/never ETS exposed); at-diagnosis current ETS exposed and post-diagnosis former ETS exposed (i.e., current/former ETS exposed); and at-diagnosis current ETS exposed and post-diagnosis current ETS exposed (i.e., current/current ETS exposed).

Intake of grilled, barbecued, and smoked meat. At baseline, approximately on average within 3 months of breast cancer diagnosis, participants were asked about their intake (number of times per week, month, or year) of four categories of grilled, barbecued, and smoked meat (smoked beef, lamb, and pork; grilled/barbecued beef, lamb, and pork; smoked poultry or fish; and grilled/barbecued poultry or fish) to estimate consumption of grilled, barbecued, and smoked foods during the decade before their diagnosis of breast cancer (Gammon et al. 2002b; Steck et al. 2007) (**APPENDIX: EXCERPTS FROM THE LIBSCP BASELINE QUESTIONNAIRE**). At the 5-year follow-up participants who completed the questionnaire responded to the same questions, but regarding the time-period since baseline to determine whether any changes in intake of grilled, barbecued, and smoked meat had occurred. In the

analysis of pre-diagnosis intake of grilled, barbecued, and smoked meat in the decade prior to diagnosis exposure variables included:

- Lifetime intake of grilled, barbecued, and smoked meat. The sum of all intake of grilled and smoked meat.
- Total annual intake of grilled, barbecued, and smoked meat. The sum of annual intake of the four types of meat, categorized at the median.
- Annual intake of grilled/barbecued beef, lamb, and pork. Annual intake of grilled/barbecued beef, lamb, and pork was categorized at the median.
- Annual intake of smoked beef, lamb, and pork. Annual intake of smoked beef, lamb, and pork was categorized at the median.
- Annual intake of grilled/barbecued poultry and fish. Annual intake of grilled poultry and fish was categorized at the median.
- Annual intake of smoked poultry and fish. Annual intake of smoked poultry and fish was categorized at the median.

In the analysis of post-diagnosis intake of grilled and smoked meat, changes in intake included:

- Change in annual intake of grilled, barbecued, and smoked meat. Pre-diagnosis low intake and post-diagnosis low intake of grilled, barbecued, and smoked meat (i.e., low/low intake), pre-diagnosis low intake and post-diagnosis high intake of grilled, barbecued, and smoked meat (i.e., low/high intake), pre-diagnosis high intake and post-diagnosis low intake of grilled, barbecued, and smoked meat (i.e., high/low intake), and pre-diagnosis high intake and post-diagnosis high intake of grilled, barbecued, and

smoked meat (i.e., high/high intake).

- Change in annual intake of grilled/barbecued beef, lamb, and pork. Pre-diagnosis low intake and post-diagnosis low intake of grilled/barbecued beef, lamb, and pork (i.e., low/low intake), pre-diagnosis low intake and post-diagnosis high intake of grilled/barbecued beef, lamb, and pork (i.e., low/high intake), pre-diagnosis high intake and post-diagnosis low intake of grilled/barbecued beef, lamb, and pork (i.e., high/low intake), and pre-diagnosis high intake and post-diagnosis high intake of grilled/barbecued beef, lamb, and pork (i.e., high/high intake).
- Change in annual intake of smoked beef, lamb, and pork. Pre-diagnosis low intake and post-diagnosis low intake of smoked beef, lamb, and pork (i.e., low/low intake), pre-diagnosis low intake and post-diagnosis high intake of smoked beef, lamb, and pork (i.e., low/high intake), pre-diagnosis high intake and post-diagnosis low intake of smoked beef, lamb, and pork (i.e., high/low intake), and pre-diagnosis high intake and post-diagnosis high intake of smoked beef, lamb, and pork (i.e., high/high intake).
- Change in annual intake of grilled/barbecued poultry and fish. Pre-diagnosis low intake and post-diagnosis low intake of grilled/barbecued poultry and fish (i.e., low/low intake), pre-diagnosis low intake and post-diagnosis high intake of grilled/barbecued poultry and fish (i.e., low/high intake), pre-diagnosis high intake and post-diagnosis low intake of grilled/barbecued poultry and fish (i.e., high/low intake), and pre-diagnosis high intake and post-diagnosis high intake of grilled/barbecued poultry and fish (i.e., high/high intake).
- Change in annual intake of smoked poultry and fish. Pre-diagnosis low intake and post-diagnosis low intake of smoked poultry and fish (i.e., low/low intake), pre-diagnosis low

intake and post-diagnosis high intake of smoked poultry and fish (i.e., low/high intake), pre-diagnosis high intake and post-diagnosis low intake of smoked poultry and fish (i.e., high/low intake), and pre-diagnosis high intake and post-diagnosis high intake of smoked poultry and fish (i.e., high/high intake).

Covariate Assessment

Fixed and time-varying covariates for consideration as potential moderators and confounders were collected at baseline by interviewer-administered questionnaire and by medical record review and at follow-up by interview. Possible moderators include, from the baseline questionnaire:

- Pre-diagnosis BMI (kg/m^2) – calculated as self-reported weight in kilograms ("One year prior to (REFERENCE DATE), how much did you weigh?") divided by the square of self-reported height in meters ("One year prior to (REFERENCE DATE), how tall were you?") (Centers for Disease Control and Prevention 2015).
- ER/PR status (ER^+ versus ER^-)

Possible confounders were selected based on prior research of breast cancer incidence and survival and using directed acyclic graphs (**Figure II-2**, **Figure II-3**, and **Figure II-4**) (Greenland et al. 1999). Given the dearth of literature examining factors associated with changes in active smoking, exposure to ETS, and grilled and smoked meat intake, I empirically examined whether each covariate confounded the associations with all-cause and breast cancer-specific mortality. From the baseline questionnaire, potential confounders included:

- Age (years) – Age at reference date (date of diagnosis).

- Education (<high school – high school graduate, some college – college graduate, post-college) – "What was the highest grade or year of school that you completed before (REFERENCE DATE)?" with response options: "none or kindergarten, first grade, second grade, third grade, fourth grade, fifth grade, sixth grade, seventh grade, eighth grade, ninth grade, tenth grade, eleventh grade, high school graduate or GED, post high school training or other than college, some college, associate degree, graduated from college, post graduate".
- Annual income (categorical).
- Physical activity (recreational physical activity in which participants engaged for at least 1 hour per week for 3 months or more in the year before diagnosis and in the year before the follow-up assessment (Bernstein et al. 1994; McCullough et al. 2012)) –
    - At baseline: "In what activity did you participate on a regular basis? Looking at the calendar, at what age did you start (ACTIVITY) regularly? At what age did you stop (ACTIVITY)? For how many years did you (ACTIVITY) regularly? For how many months each year did you do this? On average, about how many hours per week did you actually (ACTIVITY)?"
- Energy intake – estimated from the baseline frequency questionnaires (Block FFQ; (Block et al. 1986)).

For women who provided signed medical record release at baseline (97.7%), tumor stage, and ER/PR status were abstracted from the medical records. At the follow-up, the medical records were again abstracted for 598 women who again provided signed medical record release to obtain information on tumor size, nodal status, and complete course treatment for the primary breast cancer diagnosis. These data were also assessed by interview which showed high

agreement (radiation therapy $\kappa = 0.97$; chemotherapy $\kappa = 0.96$; hormone therapy $\kappa = 0.92$ (Cleveland et al. 2007)) with the medical record data. Therefore, the following disease and treatment characteristics were examined as potential confounders.

- From the baseline medical records abstraction:
  - Stage (*in situ* versus invasive)
  - Tumor size (≥2cm versus <2cm)
  - Lymph node involvement (yes/no)
- Self-reported at the follow-up interview:
  - Chemotherapy (yes/no) - "Did you have…Chemotherapy…to treat your breast cancer diagnosed in REFERNCE DATE?"
  - Radiation therapy (yes/no) – "Did you have…Radiation therapy… to treat your breast cancer diagnosed in REFERENCE DATE?"
  - Hormone therapy (yes/no) – "Since (REFERENCE DATE) were you prescribed any hormones, such as Tamoxifen (also called Nolvadex), for treatment of the breast cancer or the prevention of cancer recurrence?"

Missing Data

As indicated above, 1,033 (68.5%) of the 1,508 women with breast cancer completed the follow-up questionnaire. The high proportion of missing data could potentially influence the validity of these results since valid statistical inference in the presence of missing data requires assumptions about the missing data mechanism the generated the missing data. As stated by Ibrahim (2012), data are said to be:

- "Missing completely at random (MCAR) if the failure to observe a value does not

depend on any observed or unobserved data,

- Missing at random (MAR), if, give then observed data, the failure to observe a value does not depend on the data that are unobserved, and
- Missing not at random (MNAR) if the failure to observe a value depends on the value that would have been observed or other missing values in the dataset."

When data are MCAR, a complete-case (CC) analysis in which data from participants with any missing data are omitted while resulting in larger standard errors in the model parameter estimates does not result in biased parameter estimates (Ibrahim et al. 2012). In the case of data that are MAR, if missingness depends only on the fully observed covariates and not on the response, then a CC analysis will lead to unbiased estimates. However, if the missingness depends on the response variable, then a CC analysis when data are MAR will result in biased parameter estimates (Ibrahim et al. 2012). Lastly, when data are MNAR, a CC analysis leads to biased and inefficient parameter estimates and will require specifying the correct model for the missing data mechanism, distributional assumptions for the response, or both (Ibrahim et al. 2012). In the LIBCSP, prior analyses have not indicated that data are MNAR. Therefore, to account for the large proportion of data at the 5-year follow-up assessment, the analyses of post-diagnosis changes in exposure were first imputed using multiple followed as described below.

Outcome Assessment

All-cause and breast cancer-specific mortality. The National Death Index (NDI), a centralized database of death record information maintained by the National Center for Health Statistics (Centers for Disease Control and Prevention 2014c), has been used to ascertain date and cause of death from diagnosis in 1996-1997 until December 31, 2014. International

Statistical Classification of Diseases (ICD) codes 174.9 and C-50.9 listed anywhere on the death certificate were used to identify breast cancer-related deaths. The median duration of follow-up was 17.61 years (range: 0.23-18.41). Among the 1,508 women, 597 deaths occurred by the end of follow-up at 18 years. Of the deaths that occurred within 18 years of diagnosis, 237 were due to breast cancer. For the analyses, outcomes included time to death, or censoring if alive through December 21, 2014 (years), an indicator of all-cause mortality, and an indicator of breast cancer-specific mortality (**Table II-1**).

Data Analysis

To address my dissertation aims, I used multivariable Cox proportional hazards models (Collett 2003) to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between at-diagnosis as well as at-/post-diagnosis cigarette smoking, environmental tobacco smoke exposure, and grilled/barbecued, and smoked meat intake and all-cause and breast cancer mortality. The outcome and exposure variables used in all analyses are described in **Table II-1**. All analyses were done using the Cox Regression function in IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY). In the analyses of at-diagnosis exposures, survival time began at the date of breast cancer diagnosis to the date of death or December 31, 2014, if alive. Age-adjusted and multivariable-adjusted models were fit for each of the exposures and for all-cause and breast cancer-specific mortality.

The analyses examining post-diagnosis changes were restricted to women who survived at least 5 years after diagnosis (n=1,339). Accordingly, survival time began at the date of completion of the follow-up questionnaire to the date of death or December 31, 2014, if alive. Because a complete-case analysis when data are not missing completely at random is inefficient

and can potentially lead to biased results (Ibrahim et al. 2012), I first used multiple imputation to account for the missing data. Missing values were imputed using SPSS, which employs a fully conditional specification (FCS) algorithm (van Buuren 2007). The FCS method is an iterative Markov Chain Monte Carlo procedure that sequentially imputes missing values starting from the first variable with missing values by specifying a linear regression or logistic regression model for each continuous or categorical variable, respectively. I used 25 imputations with 1,000 iterations and included demographics (age at diagnosis, menopausal status, income, education, marital status, BMI, physical activity, and alcohol intake), post-diagnosis exposures, disease characteristics (stage, tumor size, nodal status, estrogen receptor status), treatment (radiation therapy, chemotherapy, and hormone therapy), and the outcome (the event indicator and the Nelson-Aalen estimator of the cumulative hazard (White and Royston 2009)).

Study Statistical Power

Analyses for aims 1 and 2 of this dissertation consisted of Cox proportional hazards regression. Power calculations were conducted for the analyses that examined post-diagnosis changes in exposures as those are the primary analyses of interest. Given the categorization of several of the change variables (e.g., changes in smoking status are categorized as never/never, former/former, current/former, and current/current smokers), power analyses were conducted for specific comparisons (e.g., never/never versus current/former smokers) using PROC POWER with the TWOSAMPLESURVIVAL statement on SAS version 9.4 (SAS Institute, Cary, NC). Specific details of the power analyses and results for each aim are detailed below.

Aim 1 power calculations were based on a comparison of survival rates between women who were never smokers and those who quit after diagnosis. Using 80% as the observed

proportion of women who were never smokers and 20% as the proportion of women who quit smoking after diagnosis, under a full-case analysis, 601 are never/never smokers and 153 are current/former smokers and under a complete-case analysis, 601 women are never/never smokers and 73 women are current/former smokers, at follow-up. Using the 2014 all-cause mortality rate of 27.69 deaths per 1,000 person-years (i.e., 597 death from any cause per 21,561.00 person-years), a survival probability of 0.61 [i.e., S(18 years)=EXP(-18 x 27.69 deaths per 1,000 person-years], and a significance level of 5% based on the two-sided log-rank test yields 80% power to detect a HR of all cause-mortality between 1.4 and 1.6 (**Figure II-5, Panel A**). Using the observed breast cancer-specific mortality rate of 10.99 deaths per 1,000 person-years (i.e., 237 breast cancer deaths per 21,561.00 person-years), a survival probability of 0.82 [i.e., S(18 years)=EXP(-18 x 10.99 deaths per 1,000 person-years], and a significance level of 5% based on the two- sided log-rank test yields 80% power to detect a HR of breast cancer-specific mortality between 1.7 and 1.9 (**Figure II-5, Panel A).**

Aim 2 power calculations were based on a comparison of survival rates between women who had low pre-diagnosis and post-diagnosis intake of grilled, barbecued, and smoked meat and women who had high at-diagnosis intake and high post-diagnosis intake of grilled, barbecued, and smoked meat. Using 50% as the observed proportion of women who were had low/low intake and 50% as the proportion of women who had high/high intake, under a full-case analysis, 455 had low/low intake and 409 had high/high intake and under a complete-case analysis, 281 had low/low intake and 297 had high/high intake, at follow-up. Using the mortality rate of 27.69 deaths per 1,000 person-years, survival probability of 0.61, and a significance level of 5% based on the two-sided log-rank test yields 80% power to detect a HR of all cause-mortality between 1.3 and 1.4 (**Figure II-5, Panel B**) and 80% power to detect a HR of breast cancer-specific

mortality between 1.5 and 1.6 (**Figure II-5, Panel B**).

Summary

The burden of breast cancer in United States is high and breast cancer survivors account for the majority of survivors (Siegel et al. 2016) yet breast cancer survivorship is an understudied area of research as compared to breast cancer incidence. In addition, how epidemiologic factors impact survival after breast cancer has received little scientific attention. While at least 10 studies s have examined active smoking in relation to survival after breast cancer (Bérubé et al. 2014), this number is small compared to the more than 100 studies of smoking and breast cancer incidence (Gaudet et al. 2013). Few (less than 5) studies have examined environmental tobacco smoke exposure in relation to survival and no studies have examined intake of grilled, barbecued, and smoked meat in relation to survival.

This chapter outlined the research methods used to address the dissertation aims including: the **study population** – a population-based cohort of women diagnosed with first primary invasive or *in situ* breast cancer; **assessment of outcomes** – date of death and cause of death including death from any cause and from breast cancer as identified using data from the National Death Index; **assessment of exposures** – smoking status, intensity of smoking, years of smoking, pack-years of smoking, post-diagnosis changes in smoking, ETS exposure status, post-diagnosis changes in ETS exposure status; and assessment of covariates – potential confounders of the associations between PAH sources of exposure and survival; and the **analytic approach** – multiple imputation followed by Cox proportional hazards regression to estimate hazard ratios and 95% confidence intervals of the associations between the exposures of interest and survival. A special emphasis was made in describing epidemiologic issues related to missing data, which

are common in longitudinal studies and the potential biases that may arise from a complete-case analysis when there is high missingness.

Table II-1. Coding of outcome and exposure variables for Aims 1 and 2.

Variable	Variable label	Value	Value label
	OUTCOME VARIABLES		
TIME	Time-to-event variable (continuous) defined as time to death (all cause) if NDI_2014=1 (or deceased) based on NDI records updated through 2014 or time to censor December 31, 2014 if NDI_2011=0 (or alive)	[0-18]	[none]
NDIACM	Vital status (based on all-cause mortality) for all 1508 LIBCSP cases. Vital status determined from National Death Index (NDI) records updated through December 31, 2014	0	Alive
		1	Death from any cause
NDIBCM	Indicator variable for breast cancer-related death (any mention of breast cancer on death certificate) based on NDI records updated through December 31, 2014	0	Alive/Censored
		1	Death from breast cancer
	AIM 1		
	EXPOSURE VARIABLES		
SMOKSTAT_T1	At-diagnosis smoking status: Never, Former >12 months, and Current ≤12 months	0	Never smoker
		1	Former smoker
		2	Current smoker
INTENSITY_T1	At-diagnosis smoking intensity (cigs per day)	0	Never smoker
		1	Former smoker, <20 cigs per day
		2	Former smoker, ≥20 cigs per day
		3	Current smoker, <20 cigs per day
		4	Current smoker, ≥20 cigs per day
DURATION_T1	At-diagnosis smoking duration (years)	0	Never smoker
		1	Former smoker, <15 yrs
		2	Former smoker, ≥15-<30 yrs
		3	Former smoker, ≥30 yrs
		4	Current smoker, <15 yrs
		5	Current smoker, ≥15-<30 yrs
		6	Current smoker, ≥30 yrs
PACKYEARS_T1	At-diagnosis smoking intensity and duration (pack-years)	0	Never smoker
		1	Former smoker, <15 pack-yrs
		2	Former smoker, ≥15-<30 pack-yrs
		3	Former smoker, ≥30 pack-yrs
		4	Current smoker, <15 pack-yrs
		5	Current smoker, ≥15-<30 pack-yrs
		6	Current smoker, ≥30 pack-yrs
RECENCY_T1	At-diagnosis recency (years) of smoking cessation	0	Never smoker
		1	Former smoker, <5 yrs
		2	Former smoker, ≥5–<10 yrs
		3	Former smoker, ≥10 yrs
		4	Current smoker
ippSMOKSTAT	At-/Post-diagnosis smoking status, missing values imputed	0	Never/Never smoker
		1	Former/Former smoker
		2	Current/Former smoker
		3	Current/Current smoker
ippINTENSITY_	At-/Post-diagnosis smoking intensity (cigs per day), missing values imputed	0	Never/Never smoker
		1	Former/Former smoker, <20 cigs per day
		2	Former/Former smoker, ≥20 cigs per day
		3	Current/Former smoker, <20 cigs per day
		4	Current/Former smoker, ≥20 cigs per day
		5	Current/Current smoker, <20 cigs per day
		6	Current/Current smoker, ≥20 cigs per day
ippDURATION	At-/Post-diagnosis smoking duration (years), missing values imputed	0	Never/Never smoker

Variable	Variable label	Value	Value label
		1	Former/Former smoker, <30 yrs
		2	Former/Former smoker, ≥30 yrs
		3	Current/Former smoker, <30 yrs
		4	Current/Former smoker, ≥30 yrs
		5	Current/Current smoker, <30 yrs
		6	Current/Current smoker, ≥30 yrs
ippPACKYEARS	At-/Post-diagnosis smoking intensity and duration (pack-years), missing values imputed	0	Never/Never smoker
		1	Former/Former smoker, <30 pack-yrs
		2	Former/Former smoker, ≥30 pack-yrs
		3	Current/Former smoker, <30 pack-yrs
		4	Current/Former smoker, ≥30 pack-yrs
		5	Current/Current smoker, <30 pack-yrs
		6	Current/Current smoker, ≥30 pack-yrs
ETSSTAT_T1	At-diagnosis ETS exposure status	0	Never ETS exposure
		1	Former ETS exposure
		2	Current ETS exposure
ETSDURATION_T1	At-diagnosis ETS exposure duration (years)	0	Never ETS exposure
		1	Former ETS exposure, <15 yrs
		2	Former ETS exposure, ≥15-<30 yrs
		3	Former ETS exposure, ≥30 yrs
		4	Current ETS exposure, <15 yrs
		5	Current ETS exposure, ≥15-<30 yrs
		6	Current ETS exposure, ≥30 yrs
ETSRECENCY_T1	At-diagnosis recency (years) of ETS exposure cessation	0	Never ETS exposure
		1	Former ETS exposure, <5 yrs
		2	Former ETS exposure, ≥5–<10 yrs
		3	Former ETS exposure, ≥10 yrs
		4	Current ETS exposure
ippETSSTAT	At-/Post-diagnosis ETS exposure status	0	Never/Never ETS exposure
		1	Former/Never ETS exposure
		2	Former/Former ETS exposure
		3	Former/Current ETS exposure
		4	Current/Never ETS exposure
		5	Current/Former ETS exposure
		6	Current/Current ETS exposure
	AIM 2		
	EXPOSURE VARIABLES		
LIFEGSM_MED_T1	Lifetime intake of grilled, barbecued, and smoked meat intake	0	Low
		1	High
GSM_MED_T1	Pre-diagnosis annual grilled, barbecued, and smoked meat intake	0	Low
		1	High
GBBLP_MED_T1	Pre-diagnosis annual grilled/barbecued beef/lamb/pork intake	0	Low
		1	High
GBPOF_MED_T1	Pre-diagnosis annual grilled/barbecued poultry/fish intake	0	Low
		1	High
SMBLP_MED_T1	Pre-diagnosis annual smoked beef/lamb/pork intake	0	Low
		1	High
SMPOF_MED_T1	Pre-diagnosis annual smoked poultry/fish intake	0	None
		1	Low-High
ippGSM_MED_T1	Pre-/Post-diagnosis annual grilled, barbecued, and smoked meat intake, missing values imputed	0	Low/Low
		1	Low/High
		2	High/Low
		3	High/High

Variable	Variable label	Value	Value label
ippGBBLP_MED_T1	Pre-/Post-diagnosis annual grilled/barbecued beef/lamb/pork intake, missing values imputed	0	Low/Low
		1	Low/High
		2	High/Low
		3	High/High
ippGBPOF_MED_T1	Pre-/Post-diagnosis annual grilled/barbecued poultry/fish intake, missing values imputed	0	Low/Low
		1	Low/High
		2	High/Low
		3	High/High
ippSMBLP_MED_T1	Pre-/Post-diagnosis annual smoked beef/lamb/pork intake, missing values imputed	0	Low/Low
		1	Low/High
		2	High/Low
		3	High/High
ippSMPOF_MED_T1	Pre-/Post-diagnosis annual smoked poultry/fish intake, missing values imputed	0	None/None
		1	None/Low-High
		2	Low-High/None
		3	Low-High/Low-High

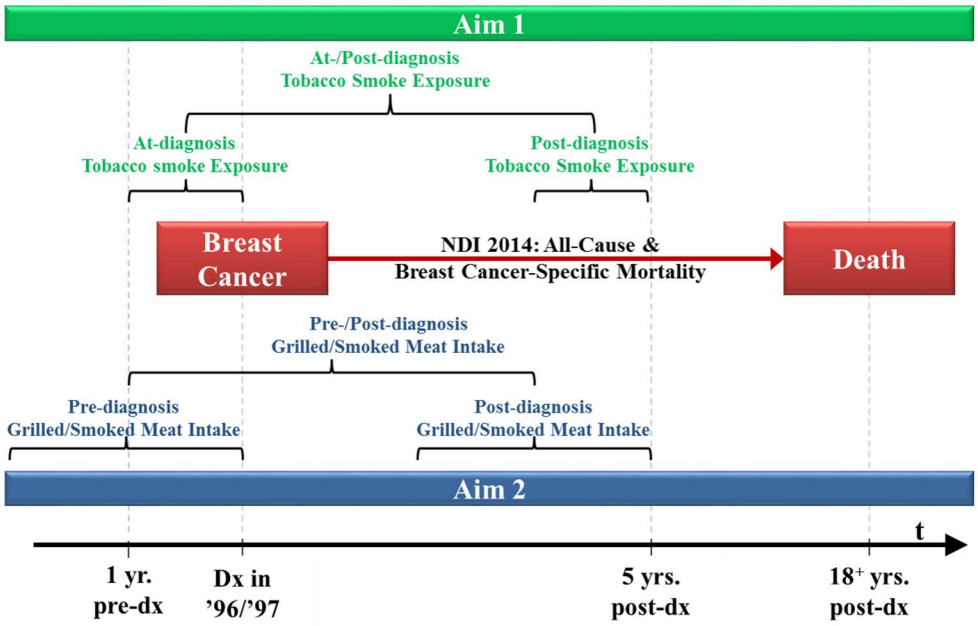
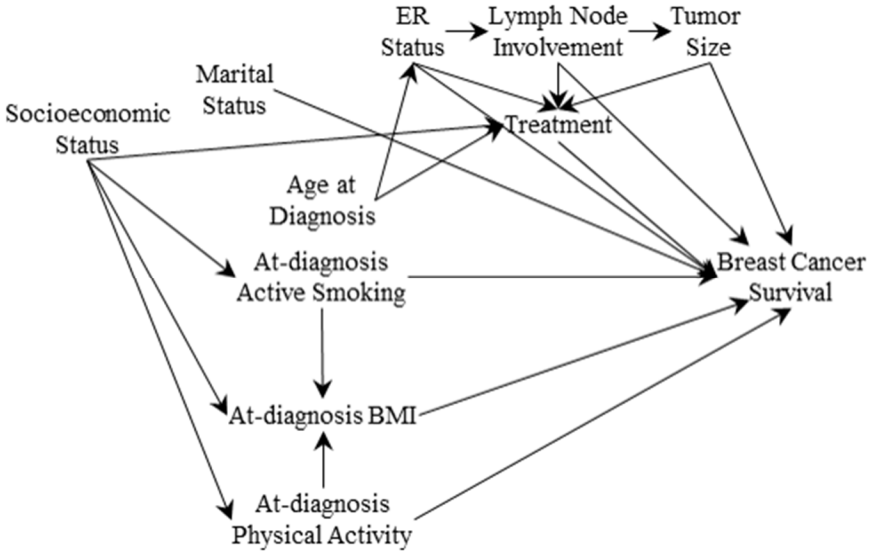


Figure II-1. Pre/At-diagnosis and Post-diagnosis PAH Exposures and Survival Following Breast Cancer in the LIBCSP.

A)



B)

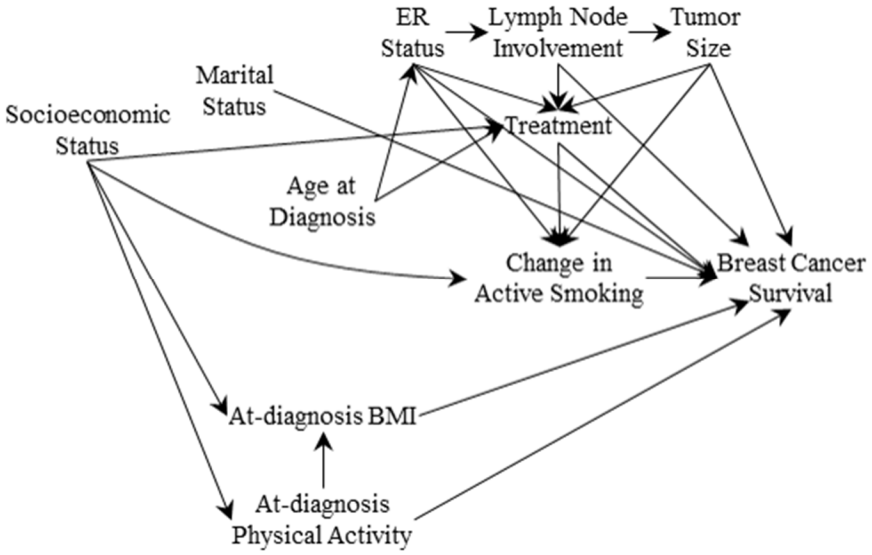
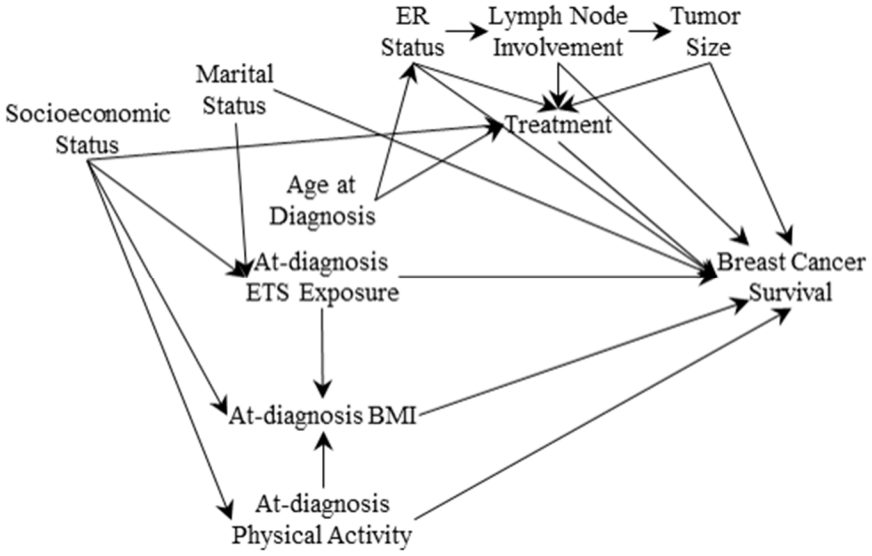


Figure II-2. Directed Acyclic Graphs of the association between breast cancer survival and at-diagnosis active smoking (A) and post-diagnosis changes smoking (B).

A)



B)

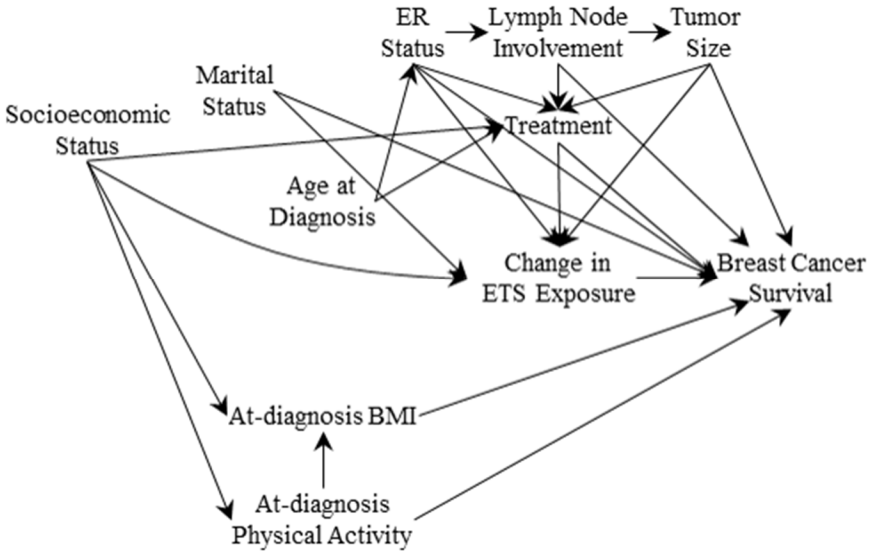
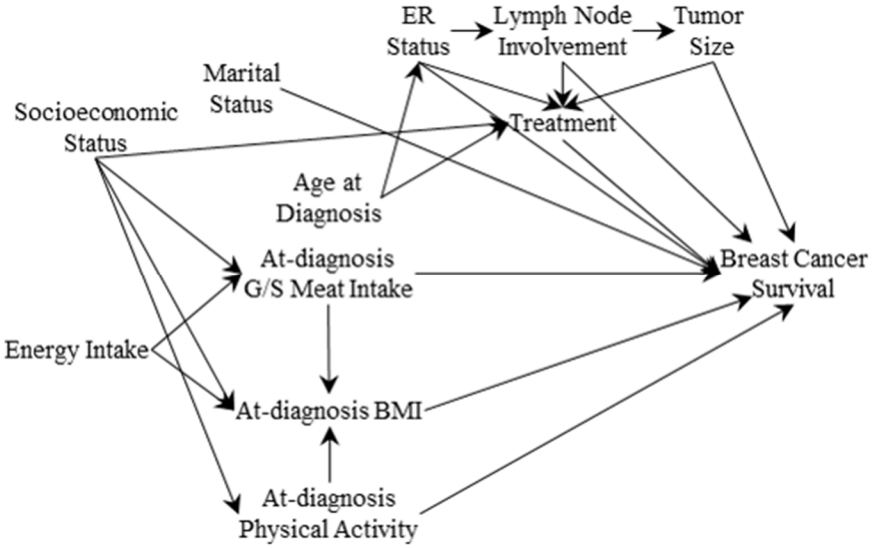


Figure II-3. Directed Acyclic Graphs of the association between breast cancer survival and at-diagnosis ETS exposure (A) and post-diagnosis changes ETS exposure (B).

A)



B)

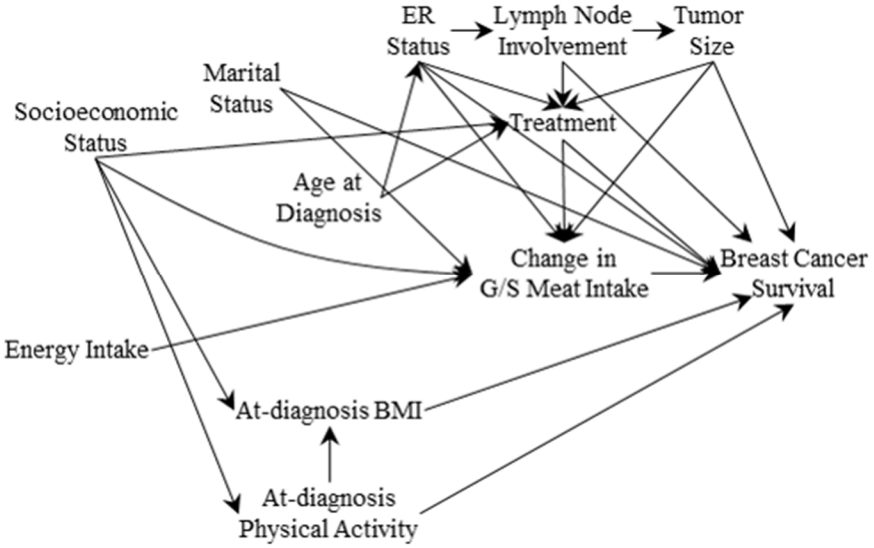


Figure II-4. Directed Acyclic Graphs of the association between breast cancer survival and at-diagnosis grilled/barbecued and smoked meat intake (A) and post-diagnosis changes in intake (B).

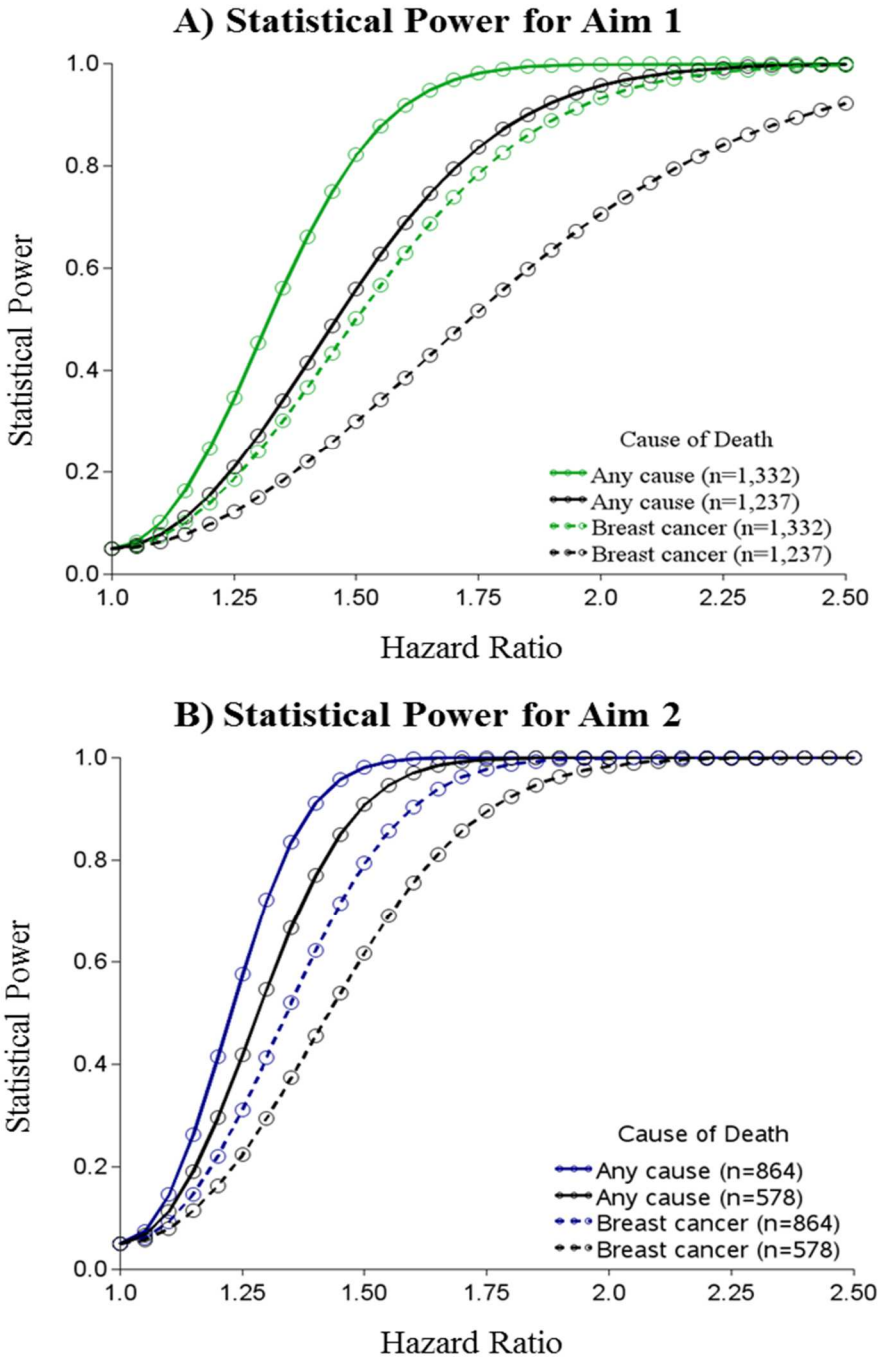


Figure II-5. Study Statistical Power for Aims 1 (Panel A) and 2 (Panel B).

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CHAPTER III: POST-DIAGNOSIS CHANGES IN SMOKING AND SURVIVAL FOLLOWING BREAST CANCER

Overview

Cigarette smoking at the time of breast cancer diagnosis is associated with increased mortality, but whether changes in smoking behavior after diagnosis impact mortality is understudied. We examined whether at-diagnosis smoking and post-diagnosis changes in smoking within 5 years after breast cancer were associated with long-term all-cause and breast cancer mortality. The population-based cohort study was conducted in Nassau and Suffolk Counties on Long Island, NY beginning in 1996. Participants were 1,508 English-speaking women over the age of 20 who were residents of Long Island, NY and who were diagnosed with first primary invasive or *in situ* breast cancer during August 1, 1996 through July 31, 1997. History of smoking status, intensity, and duration was assessed by self-report using interviewer-administered questionnaires at baseline shortly after diagnosis and again approximately 5 years post-diagnosis. Participants were followed for vital status through December 31, 2014 using the National Death Index. After 18^{+} years of follow-up, 597 deaths were identified, of which 237 were breast cancer-related. Multivariable Cox regression was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality as related to at-diagnosis and at-/post-diagnosis changes in smoking. Compared to never smokers, risk of all-cause mortality among women with breast cancer was elevated among the 19% of women who were smokers at-diagnosis (HR=1.69, 95% CI=1.36-2.11), those who smoked ≥20 cigarettes/day (HR=1.85, 95% CI=1.42-2.40), women who had smoked for ≥30 years (HR=1.62, 95% CI=1.28-2.05), and

women who had smoked ≥30 pack-years (HR=1.82, 95% CI=1.39-2.37). At-diagnosis smoking was not associated with breast cancer-specific mortality. Risk of all-cause mortality was further increased among the 8% of women who were at- and post-diagnosis smokers (HR=2.30, 95% CI=1.56-3.39), but was attenuated among the 11% of women who quit smoking after diagnosis (HR=1.83, 95% CI=1.32-2.52). Risk of breast cancer-specific mortality was elevated in association with post-diagnosis pack-years (HR=2.75, 95% CI=1.26-5.99). Smoking negatively impacts long-term survival after breast cancer. Smokers who quit smoking after breast cancer diagnosis may have an attenuated, but still elevated risk of all-cause mortality.

Introduction

Breast cancer is a significant public health problem in the United States with more than 246,000 new breast cancer cases expected in 2016 (Siegel et al. 2016). Although there have been vast improvements in breast cancer treatment over the last few decades (Sledge et al. 2014) and breast cancer survival rates are high, estimated at 90% at 5-years after diagnosis, approximately 40,000 women will die from breast cancer in 2016.(Siegel et al. 2016) This makes breast cancer the second leading cause of cancer-related death among women.(Siegel et al. 2016) The high incidence of breast cancer together with the high rate of survival contribute to an estimated 3.1 million breast cancer survivors as of January 1, 2014 (American Cancer Society 2014).

After breast cancer diagnosis, survivors may be motivated to make behavioral and lifestyle changes if they believe it will help improve prognosis, quality of life, and survival (McBride and Ostroff 2003). For the approximately 10-20% of women who are smokers at the time of breast cancer diagnosis (Bérubé et al. 2014; Westmaas et al. 2015), smoking cessation is one important behavioral change that may improve survival after breast cancer. Cigarettes are

known to contain more than 7,000 chemicals, including 69 known carcinogens such as benzene, arsenic and heavy metals, formaldehyde, vinyl chloride, N-nitrosamines, and polycyclic aromatic hydrocarbons (PAHs) (IARC 2004), which have the potential to increase the risk of treatment complications (Zhan et al. 2007), recurrence (Bishop et al. 2014), and second primary cancers (Neugut et al. 1994). Unlike studies of smoking and breast cancer incidence, which have yielded mixed results (Gaudet et al. 2013), most studies of smoking at the time of diagnosis and survival after breast cancer conducted to date report a positive association between smoking and breast cancer-specific mortality (Bérubé et al. 2014; Braithwaite et al. 2012; Calle et al. 1994; Dal Maso et al. 2008; Hellmann et al. 2010; Holmes et al. 1999, 2007; Manjer 2000; Pierce et al. 2014; Tominaga et al. 1998; Warren et al. 2012; Yu et al. 1997). However, to date only one study (Passarelli et al. 2016) has prospectively considered the impact of post-diagnosis changes in smoking on survival.

This current study aimed to examine whether smoking at the time of diagnosis and changes in smoking within five years after diagnosis were associated with long-term all-cause and breast cancer mortality among a population-based sample of women diagnosed with first primary breast cancer.

Methods

The present study used resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study of newly diagnosed breast cancer cases who were residents of Nassau and Suffolk counties on Long Island, NY at the time of diagnosis. Details of the LIBCSP design have been published previously (Gammon et al. 2002c, 2002a). Institutional Review Board approval was obtained from all participating institutions and in accordance with

an assurance filed with and approved by the US Department of Health and Human Services.

Study Population

English-speaking women with a first primary diagnosis of *in situ* or invasive breast cancer were identified for inclusion using rapid-case ascertainment via active daily or weekly contact with local hospitals and confirmed by a physician and medical records. Additional eligibility criteria included being over the age of 20 and a resident of Nassau or Suffolk county on Long Island, NY, at the time of diagnosis between August 1, 1996, through July 31, 1997. The study reported here includes the 1,508 case women who were interviewed at baseline, on average within three months of diagnosis (mean=3.19 months). These women were primarily white (94%), with a mean age of 59 years (range: 25-98 years), and postmenopausal (68%) at diagnosis (**Table III-1**).

Of the 1,508 women who provided signed informed consent and completed the 100-minute, in-home, interviewer-administered, structured baseline questionnaire, 1,414 agreed to continued contact. Approximately 5 years after the initial diagnosis of breast cancer, these 1,414 women were re-contacted for the follow-up interview. Informed consent was obtained by telephone from 1,120 of the 1,414 women (i.e., 60 refused by mail, 83 refused by telephone, no proxy was identified for 96 women who were not alive at follow-up, and 55 could not be located). A 45-minute interviewer-administered, structured questionnaire that assessed information similar to that obtained at the time of diagnosis, but regarding the time period since the initial diagnosis of breast cancer, was completed by telephone with 1,033 (68.5%) women (Bradshaw et al. 2012).

Smoking Assessment

Smoking history, including smoking status, intensity and duration, was determined via interviewer-administered questionnaires at baseline and at the 5-year follow-up (Gammon et al. 2004). Smoking status at baseline was defined as never, former, and current smoking in the year before diagnosis, and smoking status at the follow-up was similarly defined but in the year before the follow-up interview; approximately 19% of women reported being current smokers in the year before diagnosis and 8% reported being current smokers at the follow-up questionnaire. Intensity of smoking, or the number of cigarettes smoked/day, was categorized as <20 cigarettes/day, and ≥20 cigarettes/day. Duration of smoking, or the total number of years of smoking excluding any time periods the women reported having not smoked, was categorized as <15 years, ≥15–<30 years, and ≥30 years of smoking. Cigarette pack-years was calculated by multiplying the average number of cigarette packs smoked per day and the total number of years of smoking and was categorized as >15 pack-years, >15–<30 pack-years, and ≥30 pack years. At baseline, smoking cessation (recency) among former smokers was categorized as <5 years, ≥5–<10 years, and ≥10 years. In the analyses of post-diagnosis changes in smoking, each combination of pre-diagnosis/post-diagnosis smoking was examined (i.e., never/never smokers, former/former smokers, current/former smokers, and current/current smokers).

Covariate assessment

Covariates were assessed by interviewer-administered questionnaire. Potential confounders were selected using directed acyclic graphs (Greenland et al. 1999) and putative relationships based on previous studies of smoking and breast cancer survival. These covariates included age at diagnosis (years), at-diagnosis menopausal status (pre-menopausal versus post-

menopausal), total annual household income (<$15,000–$24,999, $25,000–$49,999, and ≥$50,000), education (<high school or high school graduate, some college or college graduate, and post-college), marital status (married or living as married versus not married, divorced, or widowed), body mass index (continuous, kg/m^2), at-diagnosis recreational physical activity (never, former, and current physical activity of least 1 hour per week for 3 months or more), and at-diagnosis intake of alcoholic beverages such as beer, wine, or liquor (never, former, and current intake at least once a month for 6 months or more).

Estrogen receptor status and nodal involvement were determined by medical record review and tumor size was obtained from the New York State Cancer Registry. At baseline, women were interviewed after surgery, but before initiation of most other components of the first course of treatment for the first primary breast cancer. Therefore, treatment received (radiation therapy, chemotherapy, or hormone therapy) was assessed by self-report at the follow-up questionnaire, which showed high agreement with medical record data (radiation therapy κ=0.97, chemotherapy κ=0.96, hormone therapy κ=0.92) (Cleveland et al. 2007), but were more complete.

Outcome Assessment

We used the National Death Index (NDI) (Centers for Disease Control and Prevention 2014c) to ascertain date of death and cause of death among the 1,508 women diagnosed with breast cancer in 1996/1997. Breast cancer-related deaths were identified using International Statistical Classification of Diseases codes 174.9 and C-50.9 listed on the death certificate. Follow-up for mortality occurred from the date of diagnosis in 1996-1997 until December 31, 2014. The median duration of follow-up was 17.61 years (range: 0.23-18.41 years). Among the

1,508 women, 597 deaths occurred by the end of follow-up at 18^{+} years of which 237 included breast cancer as a cause of death on the death certificate.

Statistical Analysis

We used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for the associations between at-diagnosis as well as at-/post-diagnosis cigarette smoking and all-cause and breast cancer mortality. The proportional hazards assumption was assessed using exposure by time interactions and no violations of the proportional hazards assumptions were observed. All analyses were done using the Cox Regression function in IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY) and used never smokers as the referent group. In the analyses of at-diagnosis smoking, survival time began at the date of breast cancer diagnosis and continued until the earlier of date of death or December 31, 2014. Age-adjusted and multivariable-adjusted models were fit for each of the exposures (smoking status, intensity, duration, pack-years, and recency) and for all-cause as well as breast cancer-specific mortality. The analyses of at-diagnosis smoking were not adjusted for disease and treatment characteristics, which occur and are ascertained after diagnosis and therefore do not meet the temporal condition necessary to be confounders. Furthermore, disease and treatment characteristics could be mediators if, for example, smoking influences the likelihood of estrogen receptor positive breast cancer, which influences treatment and subsequent prognosis (Gaudet et al. 2013).

The analyses of post-diagnosis change in smoking were restricted to women who survived at least 5 years after diagnosis (n=1,339). Accordingly, survival time began at the date of completion of the follow-up questionnaire to the date of death or December 31, 2014, if alive.

After excluding an additional 7 women who reported being former smokers before diagnosis and current smokers at the follow-up questionnaire, the analytic sample consisted of 1,332 women. Of these, 377 (28%) were lost to follow-up and were, therefore, missing post-diagnosis smoking data. Because a complete-case analysis when data are not missing completely at random is inefficient and can potentially lead to biased results (Ibrahim et al. 2012), we employed multiple imputation to account for the missing data. Missing values were imputed using SPSS, which employs a fully conditional specification (FCS) algorithm (van Buuren 2007). The FCS method is an iterative Markov Chain Monte Carlo procedure that sequentially imputes missing values starting from the first variable with missing values by specifying a linear regression or logistic regression model for each continuous or categorical variable, respectively. We used 25 imputations with 1,000 iterations and included demographics (age at diagnosis, menopausal status, income, education, marital status, BMI, physical activity, and alcohol intake), post-diagnosis smoking exposures (smoking status, number of cigarettes smoked per day at follow-up [minimum=0], cumulative years of smoking [minimum=0], and cumulative pack-years of smoking [minimum=0]), disease characteristics (stage, tumor size, nodal status, estrogen receptor status), treatment (radiation therapy, chemotherapy, and hormone therapy), and the outcome (the event indicator and the Nelson-Aalen estimator of the cumulative hazard (White and Royston 2009)).

Results

Prevalence of smoking among women with breast cancer

Among the LIBCSP population-based sample of women diagnosed with first primary breast cancer in 1996-1997, 19% reported smoking within a year of their diagnosis (i.e., were

current smokers). About five years after diagnosis, 8% of women reported continued smoking and 11% reported that they had quit smoking since diagnosis.

At-diagnosis smoking and survival after breast cancer

As shown in **Table III-2**, compared to never smokers, current smoking at the time of breast cancer diagnosis was associated with a 69% increased hazard of all-cause mortality (HR=1.69, 95% CI=1.36-2.11), after adjustment for age at diagnosis, body mass index, marital status, income, alcohol intake, and physical activity. Risk of all-cause mortality was increased 50% (HR=1.50, 95% CI=1.10-2.03) for current smokers who smoked <20 cigarettes/day and 85% (HR=1.85, 95% CI=1.42-2.40) for current smokers who smoked ≥20 cigarettes/day. Current smokers who had smoked for ≥15-<30 years had a 107% increased hazard (HR=2.07, 95% CI=1.28-3.35) and women who smoked ≥30 years had a 62% increased hazard (HR=1.62, 95% CI=1.28-2.05) of all-cause mortality. All-cause mortality was also increased among former smokers (HR=1.36, 95% CI=1.05-1.76) and current smokers (HR=1.82, 95% CI=1.39-2.37) who had smoked ≥30 pack-years. Additionally, risk of all-cause mortality was elevated among former smokers who had quit smoking within 5 years of diagnosis (HR=1.97, 95% CI=1.33-2.93), but not among women who had quit smoking ≥5 years before diagnosis (HR=0.94, 95% CI=0.64-1.37). These findings were similar, but attenuated when we considered women with estrogen receptor positive tumors only. At-diagnosis smoking was not associated with breast cancer-specific mortality. Results did not substantially differ when the analyses was restricted to women with invasive cancer only (**Table III-3**) or women with estrogen receptor-positive breast cancer (**Table III-4**).

At-/post-diagnosis smoking and survival after breast cancer

Table III-5 shows the results of the full-case analyses utilizing the imputed data and **Table III-6** shows the results of the complete-case analysis for the age-adjusted estimates. Overall, the results of both analyses are consistent. As shown in **Table III-5**, risk of all-cause mortality was elevated among women who continued smoking after diagnosis (HR=2.30, 95% CI=1.56-3.39) as compared to never smokers, after confounder adjustment. However, risk of all-cause mortality was attenuated among women who quit smoking after diagnosis (HR=1.83, 95% CI=1.33-2.52). This pattern of association for women who quit smoking after diagnosis and women who continued smoking was consistent across high smoking intensity (HR =1.86, 95% CI=0.92-3.88 versus HR =2.95, 95% CI=1.77-4.93, respectively) and high cumulative duration of smoking (HR =1.87, 95% CI=1.24-2.83 versus HR =2.23, 95% CI=1.49-3.33, respectively). However, women with ≥30 cumulative pack-years of smoking who quit after diagnosis had a slightly greater risk of mortality (HR =2.36, 95% CI=1.43-3.89) as compared to women who did not quit after diagnosis (HR =2.12, 95% CI=1.32-3.43). Results did not substantially differ when the analyses was restricted to women with invasive cancer only (**Table III-7**), but appeared to be stronger among women with estrogen receptor positive tumors (**Table III-8**) and those with a BMI ≥25 kg/m^2 (**Table III-9**), though data were sparse.

Pre-/post-diagnosis smoking status, intensity, and duration were not significantly associated with breast cancer-specific mortality. However, we noted elevations in the breast cancer-specific mortality rate among women who continued smoking after diagnosis (HR=1.60, 95% CI=0.79-3.23) and among women who continued smoking <20 cigarettes/day (HR=1.98, 95% CI=0.94-4.17). Additionally, risk of breast cancer-specific mortality was elevated among women who continued smoking and who had smoked <30 cumulative pack-years (HR=2.75,

95% CI=1.26-5.99). Due to small numbers, we were unable to estimate the risk of mortality among women who continued smoking and who had smoked ≥30 cumulative pack-years.

Discussion

In this population-based study of women with newly diagnosed first primary breast cancer, smoking in the year before diagnosis was associated with a 69% increase in the risk of long-term all-cause mortality, but not breast cancer-specific mortality. Among women who continued smoking after breast cancer, risk of all-cause mortality was elevated by 130%, but was attenuated by approximately 20% among women who quit smoking after diagnosis. Additionally, among women who continued smoking, <30 cumulative pack-years of smoking was associated with more than a two-fold increase in the risk of breast cancer-specific mortality.

While the carcinogenic constituents in tobacco smoke have been hypothesized to increase risk of incident breast cancer (Gaudet et al. 2013), very little is known about how these chemicals may act to increase risk of recurrence and subsequent mortality. PAHs which are present in tobacco smoke, for example, can exert estrogenic as well as anti-estrogenic effects (Santodonato 1997). Exposure to PAHs and the many other chemicals found in tobacco smoke may be important in hormonally sensitive breast tumors and could potentially influence survival. In the study reported here, at-diagnosis smoking was associated with all-cause mortality, but not breast cancer-specific mortality. This is inconsistent with most studies conducted to date which report approximately a 30% increased risk of breast cancer-specific mortality in association with at-diagnosis cigarette smoking (Bérubé et al. 2014). Reasons for this discrepancy are not clear.

Studies examining smoking and mortality after breast cancer have primarily examined at-diagnosis smoking only, and have reported positive findings (Bérubé et al. 2014). One recently

published study (Passarelli et al. 2016) prospectively evaluated changes in smoking status approximately 6 years after breast cancer diagnosis, which is an approach similar to that used in the study reported here. In their study, Passarelli and colleagues reported similar hazard ratios that were slightly larger in magnitude than those reported here for women who continued smoking after breast cancer for all-cause (HR=2.57, 95% CI=2.06-3.21, versus 2.30, 95% CI=1.56-3.39, respectively) and breast cancer-specific (HR=1.73, 95% CI=1.13-2.60, versus HR=1.60, 95% CI=0.79-3.23, respectively) mortality. These differences may arise from different approaches in addressing missing data. The response rate for the completion of our follow-up assessment was approximately 70%, which is higher than the 40% in the study by Passarelli et al., and we addressed the missing data due to potential biases that may arise from relying on a complete-case analysis only (Ibrahim et al. 2012).

Similar to prior studies of smoking and mortality among breast cancer survivors, our study has several limitations. Our assessments of smoking relied on self-report; however, smoking history has been shown to be reliably recalled and self-reported (Krall et al. 1989). Nevertheless, it is also possible that women, particularly those that have been diagnosed with cancer, may misreport smoking status at- and post-diagnosis; however, our prevalence estimates for at-diagnosis (19%) (Bérubé et al. 2014) and post-diagnosis smoking (8%) are consistent with prior studies (Mayer and Carlson 2011; Westmaas et al. 2015). Third, although our study shows that smoking may adversely impact survival, we can only hypothesize about the biological mechanisms driving these associations given the complex nature of tobacco smoke. It is possible that our findings are confounded by changes in other behaviors such as alcohol intake after diagnosis, which we were unable to consider in the same models due to insufficient power; however, most studies of alcohol intake and breast cancer mortality have been negative (Gou et

al. 2013). Last, while the prospective design of our study allowed us to assess changes in smoking status several years after breast cancer diagnosis, a proportion of women were lost to follow-up and thus did not complete the follow-up assessment; however, we addressed the missing data using multiple imputation, which results in valid statistical inferences that properly reflect the uncertainty due to missing values (Sterne et al. 2009).

Conclusions

The results of our study show that smoking negatively impacts long-term survival after breast cancer. Post-diagnosis cessation of smoking may be important in reducing, in part, the elevated risk of all-cause as well as breast cancer mortality due to smoking. Breast cancer survivors may be motivated to quit smoking and may therefore benefit from aggressive smoking cessation programs starting as early as the time of diagnosis, but continued throughout the survivorship continuum. Emphasis should also be placed on systematically assessing the impact of smoking history, smoking status, and post-diagnosis changes in smoking on outcomes in clinical trials, which often fail to account for this important exposure (Land et al. 2016).

Table III-1. Distribution of selected at-diagnosis participant and disease characteristics of the LIBCSP women diagnosed with breast cancer in 1996-1997 (N=1,508), overall and by pre- and at-diagnosis smoking status.

		At-diagnosis Smoking Status[c]		
	Total (N=1,508)	Never Smokers (n=674)	Former smokers (n=544)	Current Smokers (n=290)
At-diagnosis characteristic	n (%)	n (%)	n (%)	n (%)
Age at diagnosis (years)				
<50	407 (27.0%)	192 (28.5%)	122 (22.4%)	93 (32.1%)
50–64	582 (38.6%)	230 (34.1%)	219 (40.3%)	133 (45.9%)
≥65	519 (34.4%)	252 (37.4%)	203 (37.3%)	64 (22.1%)
Mean (SD)	58.8 (12.7)	59.4 (13.6)	59.9 (11.9)	55.5 (11.3)
Menopausal status				
Premenopausal	472 (31.9%)	216 (32.6%)	146 (27.3%)	110 (39.0%)
Postmenopausal	1,006 (68.1%)	446 (67.4%)	388 (72.7%)	172 (61.0%)
Income				
<$15,000–$24,999	286 (19.0%)	154 (22.9%)	78 (14.4%)	54 (18.7%)
$25,000–$49,999	488 (32.4%)	205 (30.5%)	189 (34.9%)	94 (32.5%)
≥$50,000	730 (48.5%)	314 (46.7%)	275 (50.7%)	141 (48.8%)
Education				
<HS/HS graduate	721 (48.0%)	334 (49.7%)	240 (44.3%)	147 (51.0%)
Some college/college graduate	551 (36.7%)	223 (33.2%)	214 (39.5%)	114 (39.6%)
Post-college	230 (15.3%)	115 (17.1%)	88 (16.2%)	27 (9.4%)
Marital Status				
Married or living as married	1,029 (68.3%)	459 (68.1%)	388 (71.3%)	182 (63.0%)
Not married	478 (31.7%)	215 (31.9%)	156 (28.7%)	107 (37.0%)
BMI at diagnosis (kg/m^2)				
<25.0	683 (45.8%)	284 (42.6%)	237 (44.1%)	162 (56.3%)
25.0–29.9	476 (31.9%)	227 (34.1%)	174 (32.4%)	75 (26.0%)
≥30.0	332 (22.3%)	155 (23.3%)	126 (23.5%)	51 (17.7%)
Mean (SD)	26.6 (5.7)	26.9 (5.8)	26.9 (5.6)	25.5 (5.5)
Physical activity[a]				
Never	334 (22.5%)	157 (23.6%)	109 (20.3%)	68 (23.9%)
Former	253 (17.0%)	102 (15.4%)	97 (18.0%)	54 (18.9%)
Current	900 (60.5%)	405 (61.0%)	332 (61.7%)	163 (57.2%)
Alcohol intake[b]				
Never	588 (39.0%)	329 (48.8%)	163 (30.0%)	96 (33.1%)
Former	212 (14.1%)	76 (11.3%)	90 (16.6%)	46 (15.9%)
Current	707 (46.9%)	269 (39.9%)	290 (53.4%)	148 (51.0%)
Stage				
Invasive	1,273 (84.4%)	567 (84.1%)	454 (83.5%)	252 (86.9%)
In situ	235 (15.6%)	107 (15.9%)	90 (16.5%)	38 (13.1%)
Nodal involvement				
No	213 (25.5%)	89 (24.7%)	86 (27.4%)	38 (23.6%)
Yes	622 (74.5%)	271 (75.3%)	228 (72.6%)	123 (76.4%)
Tumor size (cm)				
≤2.0	622 (75.5%)	258 (72.1%)	247 (79.2%)	117 (76.0%)
>2.0	202 (24.5%)	100 (27.9%)	65 (20.8%)	37 (24.0%)
Mean (SD)	1.7 (1.6)	1.8 (1.6)	1.6 (1.5)	1.8 (1.8)
Estrogen receptor status				
Negative	264 (26.7%)	123 (28.0%)	88 (25.1%)	53 (26.6%)

At-diagnosis characteristic	Total (N=1,508) n (%)	At-diagnosis Smoking Status[c] Never Smokers (n=674) n (%)	Former smokers (n=544) n (%)	Current Smokers (n=290) n (%)
Positive	726 (73.3%)	317 (72.1%)	263 (74.9%)	146 (73.4%)
Treatment received				
Radiation	625 (60.9%)	261 (57.1%)	235 (63.5%)	129 (64.8%)
Chemotherapy	423 (41.4%)	197 (43.4%)	146 (39.6%)	80 (40.2%)
Hormone therapy	616 (61.1%)	280 (62.5%)	228 (63.0%)	108 (54.3%)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.

[a]At-diagnosis recreational physical activity was defined as never, former, and current physical activity of least 1 hour per week for 3 months or more.

[b]At-diagnosis intake of alcoholic beverages was defined as never, former, and current intake of alcoholic beverages such as beer, wine, or liquor at least once a month for 6 months or more.

[c]At-diagnosis smoking status was defined as never, former, and current cigarette smoking in the year prior to breast cancer diagnosis.

Table III-2. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre- and at-diagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with breast cancer in 1996-1997 (N=1,508).

	All-Cause Mortality (n deaths=597)				Breast Cancer-Specific Mortality (n deaths=237)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Never smokers[a]	258	416	1 (Ref)	1 (Ref)	112	562	1 (Ref)	1 (Ref)
Cigarette smoking status								
Former smokers	206	338	0.98 (0.82-1.18)	1.01 (0.84-1.22)	74	470	0.81 (0.60-1.09)	0.82 (0.61-1.11)
Current smokers	133	157	1.69 (1.37-2.10)	1.69 (1.36-2.11)	51	239	1.14 (0.81-1.59)	1.08 (0.77-1.51)
Intensity of smoking								
Former smokers								
<20 cigarettes/day	93	416	0.80 (0.63-1.01)	0.86 (0.67-1.09)	35	255	0.70 (0.48-1.03)	0.72 (0.49-1.06)
≥20 cigarettes/day	109	138	1.21 (0.96-1.51)	1.18 (0.93-1.48)	39	208	0.96 (0.67-1.39)	0.97 (0.67-1.41)
Current smokers								
<20 cigarettes/day	53	73	1.47 (1.09-1.98)	1.50 (1.10-2.03)	23	103	1.15 (0.73-1.80)	1.10 (0.70-1.73)
≥20 cigarettes/day	80	83	1.90 (1.48-2.46)	1.85 (1.42-2.40)	28	135	1.13 (0.75-1.72)	1.06 (0.70-1.61)
Duration of smoking								
Former smokers								
<15 years	45	131	0.79 (0.58-1.09)	0.84 (0.61-1.17)	23	153	0.75 (0.48-1.18)	0.78 (0.49-1.24)
≥15–<30 years	61	123	0.90 (0.68-1.19)	0.94 (0.70-1.25)	20	164	0.65 (0.40-1.04)	0.65 (0.40-1.06)
≥30 years	100	84	1.17 (0.93-1.48)	1.17 (0.92-1.49)	31	153	1.04 (0.69-1.56)	1.04 (0.69-1.57)
Current smokers								
<15 years	5	6	1.72 (0.71-4.17)	1.57 (0.57-4.28)	<5	9	–	–
≥15–<30 years	21	48	2.09 (1.30-3.37)	2.07 (1.28-3.35)	15	54	1.39 (0.79-2.46)	1.32 (0.74-2.36)
≥30 years	106	103	1.62 (1.29-2.03)	1.62 (1.28-2.05)	34	175	1.05 (0.72-1.54)	0.99 (0.67-1.46)
Pack-years of smoking								
Former smokers								
<15 pack-years	87	196	0.84 (0.66-1.07)	0.90 (0.70-1.15)	37	246	0.77 (0.53-1.11)	0.80 (0.55-1.17)
≥15–<30 pack-years	30	70	0.74 (0.51-1.09)	0.73 (0.49-1.08)	11	89	0.61 (0.33-1.14)	0.61 (0.33-1.14)
≥30 pack-years	83	63	1.39 (1.08-1.78)	1.36 (1.05-1.76)	26	120	1.14 (0.74-1.76)	1.16 (0.75-1.79)
Current smokers								
<15 pack-years	27	47	1.50 (1.00-2.25)	1.58 (1.05-2.39)	13	61	1.10 (0.62-1.97)	1.18 (0.66-2.11)
≥15–<30 pack-years	29	43	1.58 (1.07-2.34)	1.39 (0.94-2.06)	16	56	1.37 (0.81-2.33)	1.10 (0.65-1.89)
≥30 pack-years	76	65	1.78 (1.38-2.30)	1.82 (1.39-2.37)	22	119	1.04 (0.66-1.64)	1.01 (0.63-1.60)
Smoking cessation recency								
Former smokers								
<5 years	29	31	1.92 (1.30-2.82)	1.97 (1.33-2.93)	12	48	1.43 (0.79-2.60)	1.46 (0.80-2.67)
≥5–<10 years	30	62	0.94 (0.64-1.37)	0.94 (0.64-1.37)	11	81	0.68 (0.37-1.27)	0.66 (0.35-1.22)

	All-Cause Mortality (n deaths=597)				Breast Cancer-Specific Mortality (n deaths=237)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
≥10 years	147	245	0.90 (0.74-1.11)	0.94 (0.76-1.16)	51	341	0.76 (0.55-1.06)	0.79 (0.56-1.10)
Current smokers	133	157	1.70 (1.38-2.11)	1.70 (1.36-2.12)	51	239	1.14 (0.82-1.59)	1.08 (0.77-1.52)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
[a]Never smokers were the referent group in all analyses.
[b]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, and physical activity.

Table III-3. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre- and at-diagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with *invasive* breast cancer in 1996-1997 (n=1,273).

	All-Cause Mortality (n deaths=548)				Breast Cancer-Specific Mortality (n deaths=229)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Never smokers[a]	240	327	1 (Ref)	1 (Ref)	107	460	1 (Ref)	1 (Ref)
Cigarette smoking status								
Former smokers	187	267	0.97 (0.80-1.17)	1.00 (0.82-1.22)	74	380	0.86 (0.64-1.15)	0.88 (0.65-1.19)
Current smokers	121	131	1.59 (1.27-1.99)	1.57 (1.25-1.98)	48	204	1.07 (0.76-1.51)	1.01 (0.71-1.43)
Intensity of smoking								
Former smokers								
<20 cigarettes/day	85	157	0.80 (0.61-1.00)	0.84 (0.65-1.09)	35	207	0.74 (0.51-1.08)	0.76 (0.51-1.13)
≥20 cigarettes/day	98	107	1.20 (0.95-1.52)	1.17 (0.92-1.50)	39	166	1.03 (0.72-1.49)	1.05 (0.72-1.53)
Current smokers								
<20 cigarettes/day	51	57	1.47 (1.09-2.00)	1.51 (1.10-2.05)	23	85	1.18 (0.75-1.86)	1.11 (0.70-1.76)
≥20 cigarettes/day	70	74	1.69 (1.29-2.22)	1.62 (1.22-2.14)	25	119	0.98 (0.63-1.53)	0.93 (0.60-1.44)
Duration of smoking								
Former smokers								
<15 years	43	107	0.78 (0.56-1.08)	0.82 (0.58-1.15)	23	127	0.76 (0.48-1.19)	0.77 (0.48-1.23)
≥15–<30 years	56	92	0.93 (0.69-1.24)	0.98 (0.73-1.33)	20	128	0.72 (0.44-1.15)	0.73 (0.45-1.19)
≥30 years	88	68	1.13 (0.88-1.44)	1.14 (0.88-1.47)	31	125	1.12 (0.74-1.68)	1.15 (0.76-1.74)
Current smokers								
<15 years	5	6	1.51 (0.62-3.67)	1.30 (0.47-3.55)	<5	9	–	–
≥15–<30 years	19	39	1.82 (1.11-2.99)	1.76 (1.06-2.91)	14	44	1.28 (0.71-2.30)	1.21 (0.67-2.18)
≥30 years	96	86	1.53 (1.21-1.95)	1.53 (1.20-1.96)	32	150	1.00 (0.67-1.48)	0.94 (0.63-1.40)
Pack-years of smoking								
Former smokers								
<15 pack-years	80	160	0.81 (0.63-1.05)	0.87 (0.67-1.13)	37	203	0.79 (0.54-1.15)	0.81 (0.55-1.20)
≥15–<30 pack-years	27	51	0.75 (0.50-1.11)	0.76 (0.50-1.15)	11	67	0.69 (0.37-1.29)	0.72 (0.38-1.34)
≥30 pack-years	74	48	1.40 (1.08-1.82)	1.37 (1.05-1.80)	26	96	1.25 (0.81-1.93)	1.27 (0.82-1.98)
Current smokers								
<15 pack-years	26	38	1.45 (0.96-2.19)	1.49 (0.97-2.27)	13	51	1.11 (0.62-1.98)	1.14 (0.64-2.05)
≥15–<30 pack-years	27	34	1.55 (1.03-2.31)	1.36 (0.91-2.05)	15	46	1.32 (0.76-2.27)	1.06 (0.61-1.85)
≥30 pack-years	67	59	1.61 (1.23-2.12)	1.63 (1.23-2.15)	20	106	0.92 (0.57-1.48)	0.89 (0.55-1.45)
Smoking cessation recency								
Former smokers								
<5 years	29	21	2.04 (1.38-2.99)	2.10 (1.41-3.13)	12	38	1.59 (0.87-2.88)	1.64 (0.90-2.99)

	All-Cause Mortality (n deaths=548)				Breast Cancer-Specific Mortality (n deaths=229)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
≥5–<10 years	24	50	0.84 (0.55-1.28)	0.85 (0.56-1.30)	11	63	0.73 (0.39-1.36)	0.72 (0.39-1.35)
≥10 years	134	196	0.89 (0.72-1.10)	0.93 (0.74-1.16)	51	279	0.80 (0.57-1.12)	0.83 (0.59-1.17)
Current smokers	121	131	1.59 (1.27-2.00)	1.57 (1.25-1.98)	48	204	1.07 (0.76-1.51)	1.01 (0.71-1.43)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
[a]Never smokers were the referent group in all analyses.
[b]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, and physical activity.

Table III-4. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre- and at-diagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with *estrogen receptor-positive* breast cancer in 1996-1997 (n=726).

Among women with estrogen receptor-positive breast cancer	All-Cause Mortality (n deaths=317)				Breast Cancer-Specific Mortality (n deaths=237)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Never smokers[a]	138	179	1 (Ref)	1 (Ref)	60	257	1 (Ref)	1 (Ref)
Cigarette smoking status								
Former smokers	124	149	1.01 (0.79-1.29)	1.02 (0.78-1.32)	41	222	0.83 (0.56-1.23)	0.86 (0.57-1.30)
Current smokers	65	81	1.41 (1.04-1.91)	1.36 (0.99-1.86)	23	123	0.81 (0.50-1.32)	0.75 (0.46-1.24)
Intensity of smoking								
Former smokers								
<20 cigarettes/day	51	80	0.83 (0.60-1.15)	0.88 (0.63-1.23)	19	112	0.75 (0.45-1.26)	0.80 (0.47-1.36)
≥20 cigarettes/day	62	68	1.22 (0.91-1.65)	1.18 (0.86-1.62)	22	108	0.92 (0.57-1.50)	0.93 (0.57-1.55)
Current smokers								
<20 cigarettes/day	24	37	1.14 (0.74-1.77)	1.16 (0.75-1.82)	11	50	0.89 (0.47-1.70)	0.86 (0.45-1.65)
≥20 cigarettes/day	41	44	1.66 (1.16-2.37)	1.54 (1.06-2.23)	12	73	0.75 (0.40-1.40)	0.68 (0.36-1.28)
Duration of smoking								
Former smokers								
<15 years	26	53	0.83 (0.54-1.26)	0.85 (0.55-1.30)	15	64	0.91 (0.52-1.61)	0.94 (0.53-1.68)
≥15–<30 years	32	52	0.97 (0.66-1.43)	1.06 (0.71-1.58)	12	72	0.76 (0.41-1.42)	0.79 (0.42-1.50)
≥30 years	56	44	1.15 (0.84-1.57)	1.11 (0.80-1.54)	14	86	0.81 (0.45-1.46)	0.83 (0.45-1.51)
Current smokers								
<15 years	<5	<5	–	–	<5	6	–	–
≥15–<30 years	11	21	2.05 (1.06-3.95)	1.90 (0.97-3.73)	9	23	1.37 (0.65-2.89)	1.19 (0.55-2.57)
≥30 years	50	56	1.32 (0.95-1.83)	1.29 (0.92-1.81)	13	93	0.65 (0.36-1.19)	0.62 (0.34-1.14)
Pack-years of smoking								
Former smokers								
<15 pack-years	51	82	0.90 (0.66-1.25)	0.95 (0.69-1.32)	22	111	0.85 (0.52-1.39)	0.89 (0.54-1.47)
≥15–<30 pack-years	14	35	0.62 (0.36-1.07)	0.60 (0.33-1.09)	6	43	0.57 (0.25-1.32)	0.58 (0.25-1.36)
≥30 pack-years	48	30	1.46 (1.05-2.03)	1.38 (0.98-1.96)	13	65	1.04 (0.57-1.90)	1.06 (0.57-1.98)
Current smokers								
<15 pack-years	13	22	1.27 (0.71-2.27)	1.29 (0.70-2.36)	8	27	1.11 (0.53-2.35)	1.19 (0.56-2.52)
≥15–<30 pack-years	16	23	1.39 (0.82-2.35)	1.19 (0.70-2.36)	8	31	1.00 (0.47-2.11)	0.76 (0.35-1.64)
≥30 pack-years	35	36	1.42 (0.98-2.06)	1.40 (0.95-2.06)	7	64	0.54 (0.25-1.17)	0.52 (0.24-1.24)
Smoking cessation recency								
Former smokers								

Among women with estrogen receptor-positive breast cancer	All-Cause Mortality (n deaths=317)				Breast Cancer-Specific Mortality (n deaths=237)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-diagnosis Smoking	Deaths	Censored	HR (95% CI)	HR (95% CI)	Deaths	Censored	HR (95% CI)	HR (95% CI)
<5 years	18	13	1.93 (1.18-3.15)	2.07 (1.23-3.48)	6	25	1.24 (0.54-2.88)	1.36 (0.58-3.22)
≥5–<10 years	10	25	0.75 (0.39-1.42)	0.73 (0.38-1.41)	<5	32	0.40 (0.12-1.26)	0.39 (0.12-1.23)
≥10 years	86	111	0.95 (0.73-1.25)	0.96 (0.73-1.28)	32	165	0.86 (0.56-1.33)	0.91 (0.58-1.42)
Current smokers	65	81	1.41 (1.04-1.91)	1.36 (0.99-1.86)	23	123	0.81 (0.50-1.31)	0.75 (0.46-1.23)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
[a]Never smokers were the referent group in all analyses.
[b]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, and physical activity.

Table III-5. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between at-/post-diagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with breast cancer in 1996-1997 (n=1,332).

	All-Cause Mortality (n deaths=426)				Breast Cancer-Specific Mortality (n deaths=125)			
			Age-Adjusted	Multivariable-Adjusted[c]			Age-Adjusted	Multivariable-Adjusted[c]
At-/Post-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Never/Never smokers[a]	185	416	1 (Ref)	1 (Ref)	59	542	1 (Ref)	1 (Ref)
Cigarette smoking status								
Former/Former smokers	144	333	0.96 (0.86-1.07)	1.00 (0.80-1.25)	40	437	0.84 (0.68-1.03)	0.86 (0.57-1.30)
Current/Former smokers	55	90	1.73 (1.27-2.36)	1.83 (1.32-2.52)	12	133	0.92 (0.47-1.80)	1.01 (0.51-1.98)
Current/Current smokers	42	67	2.25 (1.54-3.28)	2.30 (1.56-3.39)	14	95	1.48 (0.75-2.90)	1.60 (0.79-3.23)
Intensity of smoking[b]								
Former/Former smokers								
<20 cigarettes/day	79	198	0.89 (0.67-1.18)	0.91 (0.69-1.22)	19	258	0.73 (0.43-1.24)	0.73 (0.43-1.26)
≥20 cigarettes/day	65	135	1.05 (0.78-1.42)	1.11 (0.82-1.51)	21	179	0.97 (0.57-1.66)	1.03 (0.60-1.78)
Current/Former smokers								
<20 cigarettes/day	35	70	1.70 (1.17-2.49)	1.79 (1.21-2.66)	10	95	0.94 (0.41-2.13)	1.00 (0.44-2.29)
≥20 cigarettes/day	20	20	1.79 (0.89-3.60)	1.86 (0.92-3.88)	<5	38	–	–
Current/Current smokers								
<20 cigarettes/day	22	39	1.80 (1.06-3.05)	1.85 (1.09-3.16)	11	50	1.93 (0.93-4.00)	1.98 (0.94-4.17)
≥20 cigarettes/day	20	28	2.93 (1.77-4.85)	2.95 (1.77-4.93)	<5	45	–	–
Duration of smoking								
Former/Former smokers								
<30 years	82	241	0.91 (0.70-1.19)	0.94 (0.71-1.23)	23	300	0.75 (0.46-1.24)	0.74 (0.45-1.23)
≥30 years	62	92	1.03 (0.76-1.39)	1.10 (0.80-1.50)	17	137	1.00 (0.54-1.86)	1.15 (0.61-2.16)
Current/Former smokers								
<30 years	31	47	1.76 (1.12-2.77)	1.77 (1.11-2.82)	5	73	0.72 (0.20-2.55)	0.79 (0.22-2.83)
≥30 years	24	43	1.71 (1.15-2.55)	1.87 (1.24-2.83)	7	60	1.07 (0.48-2.41)	1.17 (0.51-2.67)
Current/Current smokers								
<30 years	<5	12	–	–	<5	12	–	–
≥30 years	38	55	2.17 (1.47-3.20)	2.23 (1.49-3.33)	10	83	1.27 (0.58-2.75)	1.36 (0.61-3.03)
Pack-years of smoking								
Former/Former smokers								
<30 pack-years	90	260	0.87 (0.67-1.13)	0.90 (0.69-1.18)	24	326	0.71 (0.44-1.15)	0.71 (0.44-1.17)
≥30 pack-years	54	73	1.15 (0.83-1.59)	1.23 (0.88-1.72)	16	111	1.17 (0.64-2.16)	1.28 (0.69-2.38)

	All-Cause Mortality (n deaths=426)				Breast Cancer-Specific Mortality (n deaths=125)			
			Age-Adjusted	Multivariable-Adjusted[c]			Age-Adjusted	Multivariable-Adjusted[c]
At-/Post-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Current/Former smokers								
<30 pack-years	33	66	1.51 (1.01-2.27)	1.56 (1.03-2.39)	7	91	0.78 (0.33-1.86)	0.83 (0.35-2.01)
≥30 pack-years	22	24	2.15 (1.32-3.50)	2.36 (1.43-3.89)	5	42	1.18 (0.41-3.42)	1.35 (0.46-3.99)
Current/Current smokers								
<30 pack-years	14	27	2.43 (1.32-4.46)	2.65 (1.45-4.84)	9	32	2.44 (1.14-5.21)	2.75 (1.26-5.99)
≥30 pack-years	28	40	2.14 (1.35-3.40)	2.12 (1.32-3.43)	<5	63	-	-

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
Missing data analyses exclude women who died within 5 years of breast cancer diagnosis (n=169) and women who reported post-, but not pre-, diagnosis smoking (n=7).

[a]Never/Never smokers were the referent group in all analyses.

[b]Intensity of smoking was based on most recent smoking status

[c]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, physical activity, stage, tumor size, nodal status, estrogen receptor status, and chemotherapy treatment.

Table III-6. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between at-/post-diagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with breast cancer in 1996-1997, using a complete-case analysis (n=955).

COMPLETE-CASE ANALYSIS	All-Cause Mortality (n deaths=426)			Breast Cancer Mortality (n deaths=125)		
			Age-Adjusted			Age-Adjusted
At-/Post-diagnosis Smoking	Deaths	Censored	HR (95% CI)	Deaths	Censored	HR (95% CI)
Never/Never smokers[a]	107	305	1 (Ref)	37	375	1 (Ref)
Cigarette smoking status						
Former/Former smokers	90	248	0.98 (0.74-1.29)	26	312	0.85 (0.51-1.40)
Current/Former smokers	20	53	1.50 (0.93-2.44)	7	66	1.10 (0.49-2.48)
Current/Current smokers	29	54	2.25 (1.48-3.43)	10	73	1.50 (0.74-3.04)
Intensity of smoking[b]						
Former/Former smokers						
<20 cigarettes/day	44	142	0.86 (0.61-1.22)	12	174	0.70 (0.37-1.35)
≥20 cigarettes/day	45	104	1.12 (0.79-1.59)	14	35	1.05 (0.57-1.95)
Current/Former smokers						
<20 cigarettes/day	18	46	1.59 (0.96-2.65)	6	58	1.09 (0.46-2.59)
≥20 cigarettes/day	<5	7	–	<5	8	–
Current/Current smokers						
<20 cigarettes/day	14	30	1.82 (1.04-3.20)	8	36	2.13 (0.99-4.61)
≥20 cigarettes/day	15	23	3.07 (1.76-5.34)	<5	36	–
Duration of smoking						
Former/Former smokers						
<30 years	47	181	0.88 (0.63-1.25)	15	213	0.72 (0.40-1.32)
≥30 years	43	67	1.10 (0.77-1.58)	11	99	1.11 (0.56-2.22)
Current/Former smokers						
<30 years	<5	18	–	<5	20	–
≥30 years	17	35	1.54 (0.92-2.58)	6	46	1.32 (0.56-3.12)
Current/Current smokers						
<30 years	3	10	–	<5	10	–
≥30 years	26	44	2.15 (1.39-3.33)	7	63	1.23 (0.55-2.77)
Pack-years of smoking						
Former/Former smokers						
<30 pack-years	54	191	0.86 (0.62-1.20)	16	229	0.71 (0.40-1.28)
≥30 pack-years	34	50	1.26 (0.86-1.86)	10	74	1.36 (0.67-2.77)
Current/Former smokers						
<30 pack-years	12	37	1.36 (0.74-2.49)	<5	45	–
≥30 pack-years	8	15	1.73 (0.84-3.55)	<5	20	–

COMPLETE-CASE ANALYSIS	All-Cause Mortality (n deaths=426)			Breast Cancer Mortality (n deaths=125)		
			Age-Adjusted			Age-Adjusted
At-/Post-diagnosis Smoking	Deaths	Censored	HR (95% CI)	Deaths	Censored	HR (95% CI)
Current/Current smokers						
<30 pack-years	12	21	2.90 (1.57-5.36)	8	25	3.02 (1.38-6.64)
≥30 pack-years	16	31	1.89 (1.11-3.21)	<5	45	–

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014. Complete-case analyses exclude women who died within 5 years of breast cancer diagnosis (n=169), women who reported post-, but not pre-, diagnosis smoking (n=7), and women who were lost to follow-up (n=377.)

[a]Never/Never smokers were the referent group in all analyses.

[b]Intensity of smoking was based on most recent smoking status

Table III-7. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between at-/post-diagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with *invasive* breast cancer in 1996-1997 (n=1,106).

	All-Cause Mortality (n deaths=385)				Breast Cancer-Specific Mortality (n deaths=120)			
			Age-Adjusted	Multivariable-Adjusted[c]			Age-Adjusted	Multivariable-Adjusted[c]
At-/Post-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Never/Never smokers[a]	172	327	1 (Ref)	1 (Ref)	57	442	1 (Ref)	1 (Ref)
Cigarette smoking status								
Former/Former smokers	127	263	0.92 (0.82-1.03)	0.95 (0.75-1.21)	40	350	0.88 (0.71-1.08)	0.89 (0.58-1.35)
Current/Former smokers	47	78	1.62 (1.17-2.26)	1.72 (1.22-2.41)	13	115	0.82 (0.41-1.65)	0.92 (0.45-1.86)
Current/Current smokers	39	53	1.96 (1.30-2.93)	2.06 (1.36-3.13)	10	79	1.24 (0.61-2.51)	1.44 (0.69-3.00)
Intensity of smoking[b]								
Former/Former smokers								
<20 cigarettes/day	66	154	0.83 (0.62-1.12)	0.86 (0.63-1.17)	19	201	0.76 (0.44-1.29)	0.75 (0.44-1.30)
≥20 cigarettes/day	61	109	1.03 (0.75-1.42)	1.08 (0.78-1.50)	21	149	1.03 (0.60-1.77)	1.07 (0.61-1.85)
Current/Former smokers								
<20 cigarettes/day	30	59	1.56 (1.05-2.33)	1.65 (1.10-2.49)	8	81	0.85 (0.37-1.95)	0.93 (0.41-2.15)
≥20 cigarettes/day	17	19	1.80 (0.88-3.72)	1.91 (0.89-4.07)	<5	34	–	–
Current/Current smokers								
<20 cigarettes/day	21	29	1.69 (0.98-2.92)	1.78 (1.02-3.11)	10	40	1.65 (0.77-3.57)	1.80 (0.82-3.96)
≥20 cigarettes/day	18	24	2.34 (1.36-4.03)	2.46 (1.40-4.34)	<5	39	–	–
Duration of smoking								
Former/Former smokers								
<30 years	79	193	0.88 (0.67-1.17)	0.90 (0.67-1.21)	24	248	0.79 (0.48-1.29)	0.76 (0.46-1.26)
≥30 years	48	70	0.96 (0.70-1.32)	1.03 (0.74-1.44)	16	102	1.06 (0.57-1.98)	1.20 (0.64-2.27)
Current/Former smokers								
<30 years	24	41	1.55 (0.95-2.54)	1.57 (0.95-2.59)	<5	61	–	–
≥30 years	23	37	1.69 (1.11-2.55)	1.85 (1.21-2.83)	6	54	1.03 (0.46-2.31)	1.13 (0.49-2.61)
Current/Current smokers								
<30 years	<5	10	–	–	<5	11	–	–
≥30 years	34	43	1.92 (1.27-2.90)	2.04 (1.33-3.12)	9	68	1.12 (0.51-2.46)	2.19 (0.52-9.13)
Pack-years of smoking								
Former/Former smokers								
<30 pack-years	79	201	0.82 (0.62-1.08)	0.85 (0.64-1.13)	24	256	0.74 (0.45-1.20)	0.73 (0.45-1.20)

At-/Post-diagnosis Smoking	All-Cause Mortality (n deaths=385)				Breast Cancer-Specific Mortality (n deaths=120)			
			Age-Adjusted	Multivariable-Adjusted[c]			Age-Adjusted	Multivariable-Adjusted[c]
	Deaths	Censored	HR (95% CI)	HR (95% CI)	Deaths	Censored	HR (95% CI)	HR (95% CI)
≥30 pack-years Current/Former smokers	48	62	1.13 (0.80-1.61)	1.19 (0.84-1.70)	16	94	1.27 (0.69-2.35)	1.34 (0.72-2.52)
<30 pack-years	24	52	1.37 (0.89-2.12)	1.43 (0.91-2.24)	6	70	0.71 (0.29-1.78)	0.78 (0.31-1.95)
≥30 pack-years Current/Current smokers	23	26	2.12 (1.29-3.49)	2.33 (1.39-3.91)	<5	45	–	–
<30 pack-years	15	20	2.43 (1.29-4.58)	2.61 (1.39-4.90)	9	26	2.16 (0.97-4.81)	2.58 (1.13-5.88)
≥30 pack-years	24	33	1.74 (1.04-2.89)	1.82 (1.08-3.08)	<5	53	–	–

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
Missing data analyses exclude women who died within 5 years of breast cancer diagnosis (n=169) and women who reported post-, but not pre-, diagnosis smoking (n=5).
[a]Never/Never smokers were the referent group in all analyses.
[b]Intensity of smoking was based on most recent smoking status
[c]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, physical activity, tumor size, nodal status, estrogen receptor status, and chemotherapy treatment.

Table III-8. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between at- and post-diagnosis cigarette smoking and mortality in the LIBCSP women diagnosed with *estrogen receptor positive* breast cancer in 1996-1997 (n=992).

Among women with estrogen receptor-positive breast cancer	All-Cause Mortality (n deaths=337)				Breast Cancer-Specific Mortality (n deaths=100)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-/Post-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Never smokers[a]	148	296	1 (Ref)	1 (Ref)	49	395	1 (Ref)	1 (Ref)
Cigarette smoking status								
Former/Former smokers	111	245	0.95 (0.73-1.22)	0.99 (0.75-1.29)	31	325	0.78 (0.49-1.24)	0.79 (0.48-1.28)
Current/Former smokers	49	76	1.70 (1.20-2.40)	1.80 (1.26-2.59)	10	114	0.82 (0.39-1.69)	0.93 (0.44-1.97)
Current/Current smokers	29	38	2.40 (1.55-3.72)	2.48 (1.55-3.95)	10	57	1.57 (0.76-3.26)	1.82 (0.85-3.91)
Pack-years of smoking								
Former/Former smokers								
<30 pack-years	70	183	0.89 (0.66-1.20)	0.92 (0.67-1.26)	20	234	0.68 (0.39-1.17)	0.67 (0.38-1.18)
≥30 pack-years	41	62	1.06 (0.72-1.57)	1.13 (0.75-1.68)	12	91	1.03 (0.51-2.08)	1.09 (0.53-2.24)
Current/Former smokers								
<30 pack-years	29	53	1.51 (0.97-2.34)	1.56 (0.98-2.49)	6	75	0.72 (0.28-1.86)	0.79 (0.30-2.09)
≥30 pack-years	20	23	2.04 (1.16-3.60)	2.31 (1.28-4.15)	<5	39	-	-
Current/Current smokers								
<30 pack-years	10	14	2.98 (1.43-6.23)	3.54 (1.71-7.33)	7	17	3.15 (1.34-7.39)	4.17 (1.72-10.13)
≥30 pack-years	19	25	2.16 (1.27-3.68)	2.12 (1.20-3.77)	<5	41	-	-

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.

Missing data analyses exclude women who died within 5 years of breast cancer diagnosis (n=169) and women who reported post-, but not pre-, diagnosis smoking (n=7).

[a]Never/Never smokers were the referent group in all analyses.

[b]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, physical activity, stage, tumor size, nodal status, and chemotherapy treatment.

Table III-9. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between at- and post-diagnosis cigarette smoking and mortality among LIBCSP *overweight and obese (BMI ≥25 kg/m^2)* women diagnosed with breast cancer in 1996-1997 (n=711).

Among overweight and obese women	All-Cause Mortality (n deaths=255)				Breast Cancer-Specific Mortality (n deaths=71)			
			Age-Adjusted	Multivariable-Adjusted[a]			Age-Adjusted	Multivariable-Adjusted[a]
At-/Post-diagnosis Smoking	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Never/Never smokers	120	220	1 (Ref)	1 (Ref)	34	306	1 (Ref)	1 (Ref)
Cigarette smoking status								
Former/Former smokers	93	168	0.97 (0.74-1.27)	1.04 (0.78-1.38)	26	235	0.98 (0.59-1.63)	0.96 (0.56-1.64)
Current/Former smokers	28	44	1.56 (1.02-2.38)	1.62 (1.04-2.51)	7	65	1.09 (0.46-2.59)	1.22 (0.50-2.97)
Current/Current smokers	14	24	2.36 (1.24-4.49)	2.29 (1.20-4.36)	<5	34	-	-
Pack-years of smoking								
Former/Former smokers								
<30 pack-years	60	126	0.91 (0.66-1.25)	0.97 (0.69-1.36)	16	171	0.81 (0.43-1.52)	0.75 (0.39-1.43)
≥30 pack-years	33	42	1.11 (0.73-1.68)	1.18 (0.77-1.79)	10	65	1.40 (0.65-2.99)	1.47 (0.68-3.16)
Current/Former smokers								
<30 pack-years	17	31	1.44 (0.82-2.54)	1.47 (0.81-2.66)	<5	44	-	-
≥30 pack-years	11	13	1.77 (0.84-3.77)	1.93 (0.88-4.25)	<5	21	-	-
Current/Current smokers								
<30 pack-years	7	10	3.08 (1.34-7.11)	3.35 (1.44-7.80)	<5	14	-	-
≥30 pack-years	7	13	1.93 (0.80-4.65)	1.75 (0.73-4.18)	<5	20	-	-

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
Missing data analyses exclude women who died within 5 years of breast cancer diagnosis (n=169) and women who reported post-, but not pre-, diagnosis smoking (n=7).
[a]Adjusted for age at diagnosis, marital status, income, alcohol intake, physical activity, stage, tumor size, nodal status, estrogen receptor status, and chemotherapy treatment.

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CHAPTER IV: POST-DIAGNOSIS CHANGES IN ENVIRONMENTAL TOBACCO SMOKE EXPOSURE AND SURVIVAL FOLLOWING BREAST CANCER

Overview

Environmental tobacco smoke (ETS) exposure is hypothesized to influence survival after breast cancer, but few studies have examined this association. A population-based cohort of women (N=1,508) diagnosed with first primary invasive or *in situ* breast cancer in 1996-1997 was interviewed shortly after diagnosis and again approximately 5 years later to assess ETS exposure, and women were followed for over 18 years using the National Death Index; 597 deaths (237 associated with breast cancer) were identified. Multivariable Cox regression was used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for mortality among women with breast cancer as related to at-diagnosis and at-/post-diagnosis changes in ETS exposure. There was little or no association between at-diagnosis ETS exposure and all-cause (HR=1.04, 95% CI=0.78-1.40) or breast cancer-specific (HR=0.98, 95% CI=0.63-1.52) mortality. Mortality was elevated among women who reported cessation in post-diagnosis ETS exposure up to one year before the follow-up assessment, for all-cause (HR=1.81, 95% CI=0.87-3.74) and breast cancer mortality (HR=1.89, 95% CI=0.68-5.24); however, estimates were imprecise. We found little evidence of an association between at-diagnosis ETS exposure and mortality after breast cancer. Post-diagnosis cessation of ETS exposure was positively associated with mortality, although we could not rule out chance and reverse causation as possible explanations. Exposure to ETS does not appear to influence mortality after breast cancer.

Introduction

Few studies (Boone et al. 2015; Kakugawa et al. 2015; Sagiv et al. 2007; Wartenberg et al. 2000) have examined whether exposure to environmental tobacco smoke (ETS) increases the risk of mortality among women with breast cancer and no studies to date have prospectively examined whether post-diagnosis changes in ETS exposure impact mortality. This study examined whether ETS exposure was associated with long-term all-cause and breast cancer-specific mortality among a population-based sample of women.

Methods

Participants of the Long Island Breast Cancer Study Project (LIBCSP), a population-based cohort of women newly diagnosed with breast cancer, were interviewed shortly after diagnosis and again about 5 years later, and now continue to be followed for vital status. Details of the LIBCSP have been published previously (Bradshaw et al. 2012; Sagiv et al. 2007). Institutional Review Board approval was obtained from of all participating institutions.

Environmental Tobacco Smoke Exposure Assessment

ETS exposure was determined via structured interviews (Sagiv et al. 2007). Women were asked to report whether any members of the household smoked in their presence, the relationship of the smoker, the participant's ages at first and last exposure, and any time periods the household member did not smoke. Duration of exposure (years) was categorized as <15 years, ≥15–<30 years, and ≥30 years of exposure. Recency of exposure (years) was categorized as <5 years, ≥5-<10 years, and ≥10 years.

Covariate assessment

Covariates assessed via questionnaire included: at-diagnosis age, menopausal status, total annual household income, education, marital status, body mass index, physical activity, and intake of alcoholic beverages, and cigarette smoking, and treatment. Estrogen receptor status and nodal involvement were determined by medical record review and tumor size was obtained from the New York State Cancer Registry.

Outcome Assessment

Vital status of the 1,508 women diagnosed with breast cancer was determined using the National Death Index. Follow-up for mortality occurred from the date of diagnosis in 1996-1997 until December 31, 2014 (median=17.61 years). We identified 597 deaths; 234 were associated with breast cancer.

Statistical Analysis

We used multivariable Cox models to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for the associations between at-diagnosis as well as at-/post-diagnosis changes in ETS exposure and mortality. All analyses were conducted using the Cox Regression function in IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY).

In the analyses of at-diagnosis ETS exposure, survival time began at the date of breast cancer diagnosis and ended on the date of death or, if alive, December 31, 2014. In the analyses examining post-diagnosis ETS exposure, survival time began at the date of completion of the follow-up questionnaire and ended on the date of death or, if alive, December 31, 2014. Missing covariates were imputed using SPSS. We used 25 imputations with 1,000 iterations and the

imputation models included age at diagnosis, menopausal status, income, education, marital status, BMI, physical activity, and alcohol intake, smoking status), post-diagnosis ETS exposure [minimum=0], disease characteristics (stage, tumor size, nodal involvement estrogen receptor status), treatment (radiation therapy, chemotherapy, and hormone therapy), and the outcome (the event indicator and the Nelson-Aalen estimator of the cumulative hazard).

Results

Approximately 15% of women reported ETS exposure in the year before diagnosis and 14% reported current exposure at the follow-up questionnaire.

At-Diagnosis Environmental Tobacco Smoke Exposure

There was little or no association between current ETS exposure and all-cause (HR=1.04, 95% CI=0.78-1.40) or breast cancer-specific (HR=0.98, 95% CI=0.63-1.52) mortality after adjustment for covariates (**Table IV-1**). Results did not substantially differ when the analyses was restricted to women with invasive cancer only (**Table IV-2**). Risk of mortality was slightly elevated for all-cause (HR=1.17, 95% CI=0.74-1.86) and breast cancer-specific mortality (HR=1.13, 95% CI=0.57-2.27) when we restricted the analyses to never smokers, though data were sparse and the corresponding estimates imprecise.

At-/Post-Diagnosis Environmental Tobacco Smoke Exposure

Though no associations were observed among women with ongoing ETS exposure, HRs were elevated 81% (HR=1.81, 95% CI=0.87-3.74) for all-cause mortality and 89% (HR=1.89, 95% CI=0.68-5.24) for breast cancer-specific mortality among women who reported cessation in

post-diagnosis ETS exposure up to the year before the follow-up assessment (**Table IV-3**). Results did not substantially differ when the analyses was restricted to women with invasive cancer only (**Table IV-4**).

Discussion

Exposure to the constituents of tobacco smoke, either through active smoking or exposure to ETS, is hypothesized to influence breast cancer progression through several mechanisms, including directly by influencing cell proliferation, tumor growth, and metastasis (Dasgupta et al. 2009), and indirectly by disrupting the endocrine system (Bekki et al. 2013). Additionally, because up to 70% of tar in ETS is in the vapor phase, whereas all of the tar in direct smoking is in the particulate phase, ETS may be an important source of exposure to carcinogens since particulate smoke is cleared into the mouth and swallowed, but vapor phase constituents are inhaled and absorbed into the bloodstream and into the lymph system (Wells 1991). Despite these hypothesized mechanisms, the few studies conducted to date (Boone et al. 2015; Kakugawa et al. 2015; Sagiv et al. 2007; Wartenberg et al. 2000), including the sufficiently powered study reported here, provide limited or no evidence of an association between ETS exposure and survival after breast cancer. While we observed an elevated risk of mortality among women with post-diagnosis cessation of ETS exposure, we could not rule out chance and reverse causation as possible explanations.

Table IV-1. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre-diagnosis and at-diagnosis environmental tobacco smoke (ETS) exposure and mortality in the LIBCSP women diagnosed with breast cancer in 1996-1997 (N=1,508).

ETS Exposure	All-Cause Mortality (n deaths=597)				Breast Cancer-Specific Mortality (n deaths=237)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-diagnosis	Deaths	Censored	HR (95% CI)	HR (95% CI)	Deaths	Censored	HR (95% CI)	HR (95% CI)
ETS exposure status[a]								
Never	119	176	1 (Ref)	1 (Ref)	49	246	1 (Ref)	1 (Ref)
Former	376	585	1.00 (0.81-1.23)	0.98 (0.80-1.22)	141	820	0.87 (0.63-1.21)	0.89 (0.64-1.24)
Current	84	138	1.25 (0.94-1.66)	1.04 (0.78-1.40)	38	184	1.04 (0.68-1.59)	0.98 (0.63-1.52)
Duration of ETS exposure								
Never	119	176	1 (Ref)	1 (Ref)	49	246	1 (Ref)	1 (Ref)
Former								
<15 years	50	91	1.05 (0.75-1.46)	1.13 (0.80-1.59)	24	117	1.02 (0.62-1.66)	1.10 (0.67-1.81)
≥15–<30 years	131	289	0.89 (0.69-1.14)	0.90 (0.69-1.16)	60	360	0.84 (0.57-1.23)	0.84 (0.57-1.24)
≥30 years	175	187	1.06 (0.84-1.34)	1.00 (0.79-1.28)	54	308	0.90 (0.61-1.33)	0.89 (0.60-1.33)
Current								
<15 years	7	7	1.74 (0.81-3.73)	1.52 (0.70-3.27)	<5	12	–	–
≥15–<30 years	13	22	1.59 (0.89-2.84)	1.32 (0.74-2.36)	6	29	1.08 (0.46-2.55)	0.97 (0.41-2.29)
≥30 years	62	106	1.14 (0.83-1.55)	0.93 (0.67-1.29)	30	138	1.07 (0.68-1.69)	1.01 (0.63-1.61)
ETS exposure recency								
Never	119	176	1 (Ref)	1 (Ref)	49	246	1 (Ref)	1 (Ref)
Former								
<5 years	26	41	1.05 (0.69-1.60)	0.95 (0.62-1.47)	12	55	1.07 (0.57-2.01)	0.99 (0.52-1.87)
≥5–<10 years	47	69	1.07 (0.77-1.51)	1.00 (0.71-1.41)	16	100	0.82 (0.47-1.45)	0.76 (0.43-1.35)
≥10 years	303	475	0.99 (0.80-1.22)	0.99 (0.79-123)	113	665	0.86 (0.62-1.21)	0.90 (0.64-1.27)
Current	84	138	1.25 (0.94-1.66)	1.04 (0.78-1.40)	38	184	1.04 (0.68-1.59)	0.98 (0.63-1.53)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
[a]ETS exposure status was defined as never, former, and current exposure to tobacco smoke from any household members.
[b]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, physical activity, and active cigarette smoking status.

Table IV-2. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre-diagnosis and at-diagnosis environmental tobacco smoke (ETS) exposure and mortality in the LIBCSP women diagnosed with *invasive* breast cancer in 1996-1997 (n=1,273).

ETS Exposure	All-Cause Mortality (n deaths=548)				Breast Cancer-Specific Mortality (n deaths=229)			
			Age-Adjusted	Multivariable-Adjusted[b]			Age-Adjusted	Multivariable-Adjusted[b]
At-diagnosis	Deaths	Censored	HR (95% CI)	HR (95% CI)	Deaths	Censored	HR (95% CI)	HR (95% CI)
ETS exposure status[a]								
Never	113	131	1 (Ref)	1 (Ref)	48	196	1 (Ref)	1 (Ref)
Former	342	473	0.94 (0.76-1.16)	0.94 (0.75-1.17)	134	681	0.82 (0.59-1.14)	0.85 (0.60-1.19)
Current	76	112	1.18 (0.88-1.59)	1.01 (0.74-1.37)	38	150	1.01 (0.65-1.55)	1.00 (0.64-1.55)
Duration of ETS exposure								
Never	113	131	1 (Ref)	1 (Ref)	48	196	1 (Ref)	1 (Ref)
Former								
<15 years	47	67	1.03 (0.73-1.45)	1.12 (0.79-1.60)	22	92	0.97 (0.58-1.60)	1.04 (0.62-1.73)
≥15–<30 years	122	236	0.83 (0.64-1.08)	0.86 (0.66-1.12)	58	300	0.78 (0.53-1.15)	0.81 (0.54-1.19)
≥30 years	156	153	0.99 (0.78-1.26)	0.96 (0.75-1.24)	52	257	0.86 (0.58-1.27)	0.88 (0.59-1.32)
Current								
<15 years	7	6	1.75 (0.82-2.62)	1.46 (0.67-3.15)	<5	11	–	–
≥15–<30 years	13	19	1.46 (0.82-2.62)	1.36 (0.76-2.44)	6	26	0.95 (0.40-2.25)	0.95 (0.40-2.24)
≥30 years	56	86	1.08 (0.78-1.49)	0.91 (0.65-1.27)	30	112	1.04 (0.66-1.65)	1.03 (0.64-1.66)
ETS exposure recency								
Never	113	131	1 (Ref)	1 (Ref)	48	196	1 (Ref)	1 (Ref)
Former								
<5 years	25	34	1.05 (0.68-1.62)	0.99 (0.64-1.54)	11	48	0.93 (0.48-1.78)	0.90 (0.46-1.74)
≥5–<10 years	43	48	1.15 (0.81-1.63)	1.12 (0.78-1.60)	15	76	0.84 (0.47-1.50)	0.82 (0.46-1.48)
≥10 years	274	391	0.90 (0.73-1.13)	0.91 (0.73-1.14)	108	557	0.80 (0.57-1.13)	0.85 (0.60-1.20)
Current	76	112	1.18 (0.88-1.59)	1.01 (0.74-1.37)	38	150	1.01 (0.65-1.55)	1.00 (0.64-1.55)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
[a]ETS exposure status was defined as never, former, and current exposure to tobacco smoke from any household members.
[b]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, physical activity, and active cigarette smoking status.

Table IV-3. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between at-/post-diagnosis environmental tobacco smoke exposure (ETS) and mortality in the LIBCSP women diagnosed with breast cancer in 1996-1997 (n=1,339).

ETS Exposure	All-Cause Mortality (n deaths=428)				Breast Cancer-Specific Mortality (n deaths=126)			
			Age-Adjusted	Multivariable-Adjusted[a]			Age-Adjusted	Multivariable-Adjusted[a]
At-diagnosis/Post-diagnosis	Deaths	Censored	HR (95% CI)	HR (95% CI)	Deaths	Censored	HR (95% CI)	HR (95% CI)
ETS exposure status								
Never/Never	79	163	1 (Ref)	1 (Ref)	23	219	1 (Ref)	1 (Ref)
Never/Former	10	18	1.14 (0.44-2.94)	0.94 (0.35-2.58)	<5	24	–	–
Former/Never	251	529	1.03 (0.79-1.35)	1.03 (0.78-1.36)	69	711	0.93 (0.56-1.54)	0.92 (0.55-1.54)
Former/Former	5	14	0.96 (0.21-4.54)	0.72 (0.14-3.58)	<5	18	–	–
Former/Current	21	48	1.32 (0.72-2.43)	1.05 (0.56-1.99)	8	61	1.16 (0.43-3.18)	0.87 (0.31-2.46)
Current/Never	22	43	1.29 (0.76-2.20)	1.19 (0.67-2.09)	6	58	1.00 (0.38-2.63)	0.88 (0.32-2.42)
Current/Former	14	18	1.99 (0.97-4.09)	1.81 (0.87-3.74)	6	26	2.20 (0.81-5.97)	1.89 (0.68-5.24)
Current/Current	26	78	1.18 (0.70-1.99)	1.02 (0.59-1.77)	8	96	0.82 (0.33-2.06)	0.66 (0.24-1.81)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014. Complete-case analyses exclude women who died within 5 years of breast cancer diagnosis (n=169)

[a]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, physical activity, stage, tumor size, nodal involvement, estrogen receptor status, chemotherapy treatment, and post-diagnosis active cigarette smoking status.

Table IV-4. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between at-/post-diagnosis environmental tobacco smoke exposure (ETS) and mortality in the LIBCSP women diagnosed with *invasive* breast cancer in 1996-1997 (n=1,111).

ETS Exposure	All-Cause Mortality (n deaths=386)				Breast Cancer-Specific Mortality (n deaths=121)			
			Age-Adjusted	Multivariable-Adjusted[a]			Age-Adjusted	Multivariable-Adjusted[a]
At-diagnosis/Post-diagnosis	Deaths	Censored	HR (95% CI)	HR (95% CI)	Deaths	Censored	HR (95% CI)	HR (95% CI)
ETS exposure status								
Never/Never	74	123	1 (Ref)	1 (Ref)	23	174	1 (Ref)	1 (Ref)
Never/Former	9	12	1.26 (0.51-3.11)	1.01 (0.37-2.78)	<5	17	–	–
Former/Never	225	425	0.98 (0.74-1.29)	0.99 (0.74-1.32)	66	585	0.86 (0.52-1.42)	0.86 (0.52-1.45)
Former/Former	5	13	0.83 (0.17-4.13)	0.64 (0.12-3.32)	<5	16	–	–
Former/Current	18	39	1.12 (0.58-2.17)	0.93 (0.47-1.84)	6	50	0.90 (0.31-2.58)	0.71 (0.24-2.15)
Current/Never	18	35	1.17 (0.66-2.08)	1.07 (0.58-1.96)	6	48	0.94 (0.36-2.47)	0.85 (0.31-2.37)
Current/Former	13	14	1.98 (0.94-2.08)	1.80 (0.86-3.74)	6	21	2.13 (0.78-5.83)	1.90 (0.69-5.27)
Current/Current	24	64	1.17 (0.68-2.03)	1.03 (0.58-1.83)	8	80	0.77 (0.31-1.94)	0.67 (0.25-1.82)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014. Complete-case analyses exclude women who died within 5 years of breast cancer diagnosis (n=169)

[a]Adjusted for age at diagnosis, body mass index, marital status, income, alcohol intake, physical activity, stage, tumor size, nodal involvement, estrogen receptor status, chemotherapy treatment, and post-diagnosis active cigarette smoking status.

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CHAPTER V: POST-DIAGNOSIS CHANGES IN GRILLED, BARBECUED, AND SMOKED MEAT INTAKE AND SURVIVAL FOLLOWING BREAST CANCER

Overview

Grilled, barbecued and smoked meat intake, a prevalent dietary source of polycyclic aromatic hydrocarbon (PAH) carcinogens, may increase the risk of incident breast cancer. However, no studies have examined whether intake of this PAH source influences survival after breast cancer. We interviewed a population-based cohort of 1,508 women diagnosed with first primary invasive or *in situ* breast cancer in 1996-1997 at baseline and again approximately 5 years later to assess grilled/barbecued and smoked meat intake. After 18^{+} years of follow-up, 597 deaths, of which 237 were breast cancer-related, were identified. Multivariable Cox regression was used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for mortality as related to pre-diagnosis intake, comparing high (above the median) to low intake, as well as post-diagnosis changes in intake, comparing every combination of pre-/post-diagnosis intake to low pre-/post-diagnosis intake. High pre-diagnosis grilled/barbecued and smoked meat intake was associated with a 23% increased risk of all-cause mortality (HR=1.23, 95% CI=1.03-1.46). High pre-diagnosis smoked beef/lamb/pork intake was positively associated with all-cause (HR=1.17, 95% CI=0.99-1.38) and breast cancer-specific (HR=1.23, 95% CI=0.95-1.60) mortality. Among women with continued high grilled/barbecued and smoked meat intake after diagnosis, all-cause mortality risk was elevated 31% (HR=1.31, 95% CI=0.96-1.78). Breast cancer-specific mortality was decreased (HR=0.55, 95% CI=0.31-0.97) among women with any

pre- and post-diagnosis intake of smoked poultry/fish. High pre- and post-diagnosis intake of grilled/barbecued and smoked meat may increase mortality after breast cancer.

Introduction

In the United States (US), there are over 3.1 million women who are survivors of breast cancer; these women represent approximately 40% of female cancer survivors (American Cancer Society 2014). After a diagnosis of breast cancer, survivors are faced with making behavioral and dietary choices as they attempt to improve their long-term prognoses. Dietary changes after breast cancer diagnosis and treatment are one area in which breast cancer survivors may choose to make more healthful changes. To aid in this decision making, recommendations and guidelines are available for cancer survivors in general (Rock et al. 2012) and, more recently, for breast cancer survivors specifically (Runowicz et al. 2016). For example, the American Cancer Society, together with the American Society of Clinical Oncology, recently released their breast cancer survivorship care guidelines which recommend that survivors be counseled to "achieve a dietary pattern that is high in vegetables, fruits, whole grains, and legumes, and limit alcohol intake to no more than one drink per day (Runowicz et al. 2016)." These recommendations are based on limited, but suggestive, evidence of improved survival among women with such diets (Chlebowski et al. 2006; Pierce et al. 2007a). No recommendations exist for breast cancer survivors that specifically address intake of high-temperature cooked meat, including intake of grilled, barbecued, and smoked meat, though, in relation to primary prevention of breast cancer incidence, it is recommended (World Cancer Research Fund / American Institute for Cancer Research 2009) that women limit intake of processed meats and high temperature cooked meat due to the formation of polycyclic aromatic hydrocarbons (PAHs) and other carcinogenic

chemicals during the cooking process (Moorthy et al. 2015).

Grilled/barbecued and smoked meat intake is a highly prevalent source of PAHs among US women (Steck et al. 2007) and has been associated with breast cancer incidence (White et al. 2016), but whether intake is related to survival after breast cancer is unknown. This study examined whether intake of grilled/barbecued and smoked meat prior to breast cancer diagnosis and post-diagnosis changes in intake were associated with long-term all-cause and breast cancer-specific mortality among a population-based sample of women diagnosed with first primary breast cancer.

Methods

Study Population

Adult female residents of Nassau and Suffolk counties on Long Island, NY with a first diagnosis of *in situ* or invasive breast cancer during August 1, 1996 and July 31, 1997 were identified for inclusion in the Long Island Breast Cancer Study Project (LIBCSP) (Gammon et al. 2002a). Identification of patients was done via active daily or weekly contact with local hospitals and by confirmation by a physician and medical records. After obtaining informed consent, the cohort of 1,508 women with breast cancer were interviewed in person by trained interviewers via structured questionnaire at baseline, on average within three months of breast cancer diagnosis.

Approximately five years after the initial diagnosis of breast cancer, the 1,414 women who at baseline consented to continued contact were re-contacted for the follow-up interview. Of these, 143 refused, no proxy was identified for 96 women who were not alive at follow-up, and

55 could not be located, resulting in 1,120 women providing consent and 1,033 women completing the follow-up questionnaire (Bradshaw et al. 2012). The follow-up interview was conducted over the telephone by trained interviewers using a structured questionnaire that assessed information similar to that obtained at the time of diagnosis, but regarding the time period since the initial diagnosis of breast cancer.

Grilled, Barbecued, and Smoked Meat Intake Assessment

As part of the main baseline questionnaire, participants were asked about their intake (number of times per week, month, or year) of four types of grilled/barbecued and smoked meats: (1) grilled/barbecued beef, lamb, and pork, (2) smoked beef, lamb, and pork, such as bacon or ham, (3) grilled/barbecued poultry and fish, and (4) smoked poultry and fish, such as smoked turkey or lox. The women were asked about their intake in each decade of life (<20 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, ≥60 years) and were asked to specify the seasons in which the foods were most frequently consumed (Gammon et al. 2002b; Steck et al. 2007). At baseline, intake during the decade prior to breast cancer diagnosis was used to represent the average intake before diagnosis; we also examined whether lifetime intake of grilled/barbecued meat was associated with mortality. At the 5-year follow-up, participants responded to the same questions which asked about the time-period since the baseline questionnaire.

Responses given as per week or per month were first multiplied by 52 or by 12, respectively, and then multiplied by the proportion of the year that the foods were consumed (i.e., 25% if they were consumed during one season, 50% if they were consumed during two seasons, etc.) to obtain measures of intake in number of times/year. The continuous measures

were dichotomized at the median for each of the four meat types: grilled/barbecued beef/lamb/pork (Low=0-10 vs. High=11+ times/year pre-diagnosis; Low=0-8 vs. High=9+ times/year post-diagnosis), grilled/barbecued poultry/fish (Low=0-9 vs. High=10+ times/year pre-diagnosis; Low=0-6 vs. High=7+ times/year post-diagnosis), smoked barbecued beef/lamb/pork (Low=0-4 vs. High=5+ times/year pre-diagnosis and post-diagnosis), and smoked poultry/fish (None=0 vs. Any intake=1+ times/year pre-diagnosis and post-diagnosis), separately. Intake of the four meat types were also summed to create an overall measure of intake of grilled/barbecued and smoked meat (times/year), which was dichotomized at the median (Low=0-43 vs. High=44+ times/year pre-diagnosis; Low=0-35 vs. High=36+ times/year post-diagnosis). Lifetime intake of each of the four types of meat was dichotomized at the median as Low=0-4,724 vs. High=4,725+ times throughout the lifetime. In the analysis of post-diagnosis intake of grilled/barbecued and smoked meat, every combination of pre-diagnosis/post-diagnosis annual intake was examined (i.e., low/low intake, low/high intake, etc.).

Covariate assessment

Most covariates were assessed by interviewer-administered questionnaire. Potential confounders included age at diagnosis (years), menopausal status (pre-menopausal versus post-menopausal), annual household income (<$15,000–$24,999, $25,000–$49,999, and ≥$50,000), education (<high school/high school graduate, some college/college graduate, and post-college), marital status (married or living as married versus not married, divorced, or widowed), body mass index (continuous, kg/m^2), at-diagnosis physical activity (never, former, and current physical activity of least 1 hour per week for 3 months or more), at-diagnosis intake of alcoholic beverages such as beer, wine, or liquor (never, former, and current intake at least once a month

for 6 months or more), at-diagnosis consumption of energy (kcal/day), at-diagnosis fruit and vegetable intake (servings/day), and at-diagnosis multivitamin supplement use (ever/never).

Other covariates, including estrogen receptor status and nodal involvement were determined by medical record review, and tumor size was obtained from the New York State Cancer Registry. At baseline, women were interviewed after surgery, but before initiation of most other components of the first course of treatment for the first primary breast cancer. Therefore, treatment received (radiation therapy, chemotherapy, or hormone therapy) was assessed by self-report at the follow-up questionnaire, which showed high agreement with medical record data (kappas ranged from 0.92 to 0.97) (Cleveland et al. 2007), but were more complete.

Outcome Assessment

Vital status, date of death and cause of death, was determined using the National Death Index (Centers for Disease Control and Prevention 2014c) among the 1,508 women diagnosed with breast cancer in 1996/1997. Indicators for death from any cause, and those associated with breast cancer were created with breast cancer deaths identified using International Statistical Classification of Diseases codes 174.9 and C-50.9 listed on the death certificate. Follow-up for mortality occurred from the date of diagnosis in 1996-1997 until December 31, 2014. The median duration of follow-up was 17.6 years (range=0.2-18.4 years). Among the 1,508 case women, 597 deaths were identified, 237 (40%) of which were related to breast cancer.

Statistical Analysis

Age-adjusted and multivariable-adjusted Cox proportional hazards models were fit for

each of the four types of grilled and smoked meat intake, separately, and for the total measure of annual intake and for all-cause and breast cancer-specific mortality. For analyses using breast cancer-specific mortality as the outcome, non-breast cancer deaths were censored at time of death. We estimated hazard ratios (HR) and 95% confidence intervals (CIs) for the associations between pre-diagnosis, lifetime and average annual intake, as well as post-diagnosis changes in grilled, barbecued, and/or smoked meat intake and all-cause and breast cancer-specific mortality. Tests for trend used continuous measures of grilled/barbecued and smoked intake in the proportional hazards models. Survival time began at the date of breast cancer diagnosis in the analyses of pre-diagnosis grilled/barbecued and smoked meat intake, and at the date of the follow-up interview for the corresponding analyses on post-diagnosis intake. Survival times for all analyses ended at the date of death or, if alive, date of censoring. All analyses were done using the Cox Regression function in IBM SPSS Statistics Version 22.0 (IBM Corp., Armonk, NY).

In the analyses of post-diagnosis changes in grilled/barbecued and smoked meat intake and survival, we employed multiple imputation to account for the missing exposure data after excluding 169 women who died within 5 years of diagnosis; 377 (28%) participants were lost to follow-up and thus were missing data on intake of grilled/barbecued and smoked meat. Missing values were imputed using SPSS, which employs a fully conditional specification algorithm, an iterative Markov Chain Monte Carlo procedure that sequentially imputes missing values starting from the first variable with missing values (van Buuren 2007). SPSS applies linear regression to continuous scale variables and logistic or multinomial logistic regression to categorical variables. We used 25 imputations with 1,000 iterations and included demographics (age at diagnosis, menopausal status, income, education, marital status, BMI, physical activity, and alcohol intake,

smoking status), pre-diagnosis and post-diagnosis categorized grilled and smoked meat intake, disease characteristics (stage, tumor size, nodal involvement estrogen receptor status), treatment (radiation therapy, chemotherapy, and hormone therapy), and the outcome (the event indicator and the Nelson-Aalen estimator of the cumulative hazard (White and Royston 2009)). As a sensitivity analysis, we also conducted a complete-case analysis, where the missing exposure data are ignored. This alternative approach is commonly employed in follow-up studies with multiple exposure assessments over time. However, the imputation approach is designed to reduce the bias associated with the complete case analysis (Sterne et al. 2009). In analyses that used follow-up data, survival time began at the date of completion of the follow-up questionnaire to the date of death or December 31, 2014, if alive.

Results

Participant demographic characteristics as well as disease, tumor, and treatment characteristics are presented in **Table V-1**. Women with high intake of total grilled/barbecued and smoked meat were younger at diagnosis (56.7 years versus 60.9 years) and a higher proportion had an annual income ≥$50,000 (54.2% versus 40.4%) compared to women with low intake. Women with high intake were also more likely to be married (73.2% versus 60.4%). A higher proportion of women with high intake reported being physically active at diagnosis (64.5% versus 58.7%) and were current alcohol drinkers (48.9% versus 43.2%). Disease and treatment characteristics were similar across total intake of grilled/barbecued and smoke meat.

Pre-diagnosis intake of grilled/barbecued and smoked meat

Table V-2 shows the associations between pre-diagnosis annual intake of

grilled/barbecued and smoked meat and mortality. Compared to low intake, high intake of grilled/barbecued and smoked meat prior to diagnosis was associated with a 23% increased hazard (HR=1.23, 95% CI=1.03-1.46; P_{Trend}=0.02) of all-cause mortality. High intake of smoked beef, lamb, and pork intake was associated with a 17% increased hazard (HR=1.17, 95% CI=0.99-1.38; P_{Trend}=0.10) of all-cause and a 23% increased hazard (HR=1.23, 95% CI=0.95-1.60; P_{Trend}=0.09) of breast cancer-specific mortality, but the confidence intervals include the null value. In contrast, any intake of, relative to no intake, was associated with a 20% decreased hazard of breast cancer-specific mortality (HR=0.80, 95% CI=0.59-1.07; P_{Trend}=0.63), but again the confidence intervals included the null. Lifetime grilled/barbecued and smoked meat intake and pre-diagnosis annual intake of grilled/barbecued beef/lamb/pork and poultry/fish were not associated with mortality (**Table V-2**). Results did not substantially differ when the analyses was restricted to women with invasive cancer only (**Table V-3**).

Post-diagnosis changes in intake grilled, barbecued, and smoked meat

Table V-4 shows the associations between post-diagnosis changes in annual intake of grilled/barbecued and smoked meat and mortality after imputation of missing covariates. Compared to women with low pre-diagnosis and low post-diagnosis intake of grilled/barbecued and smoked meat, continued high intake was associated with a 31% increased hazard (HR=1.31, 95% CI=0.96-1.78) of all-cause mortality. The increase in risk of death from any cause was similar in magnitude (HR=1.28, 95% CI=0.97-1.68) among women who reported high pre-diagnosis and low post-diagnosis intake of grilled/barbecued and smoked meat. Smoked beef/lamb/pork intake was positively associated with all-cause (HR=1.36, 95% CI=1.01-1.82) and breast cancer-specific mortality (HR=1.71, 95% CI=1.00-2.92) among women who had high

intake at pre-diagnosis and low post-diagnosis intake, relative to low pre- and low post-diagnosis intake, but not among women with continued high post-diagnosis intake. Additionally, women who reported any post-diagnosis intake of smoked poultry and fish had a reduced risk of breast cancer mortality for both those who reported no intake at baseline (HR=0.56, 95% CI=0.23-1.34) and high intake at baseline (HR=0.55, 95% CI=0.31-0.97) compared to no intake at pre- and post-diagnosis. Post-diagnosis changes in intake of grilled/barbecued poultry/fish were not associated with all-cause and breast cancer-specific mortality. Results did not substantially differ when the analyses was restricted to women with invasive cancer only (**Table V-5**). Age-adjusted results from the complete-case analyses are presented in **Table V-6**, which are mostly similar to the imputation-based results, except for total grilled/barbecued and smoked meat intake, which are null in the complete case-analysis.

Discussion

In this population-based prospective study of grilled/barbecued and smoked meat intake and mortality among a cohort of women diagnosed with first primary breast cancer, high pre-diagnosis annual intake of total grilled/barbecued and smoked meat was associated with an elevated risk of all-cause mortality. When each of the four types of grilled/barbecued and smoked meat were examined individually, pre-diagnosis annual intake of smoked beef/lamb/pork was positively associated with all-cause and breast cancer-specific mortality, whereas intake of smoked poultry/fish was inversely associated with mortality. Additionally, when considering post-diagnosis changes in intake, we observed that women who continued to consume a high amount of grilled/barbecued and smoked meat after diagnosis had a 31% increased risk of all-cause mortality. Post-diagnosis smoked beef/lamb/pork intake was also

positively associated with all-cause and breast cancer mortality, with risk of mortality highest among women who reported high pre-diagnosis and low post-diagnosis intake. Consistent with the associations observed for pre-diagnosis intake, risk of breast cancer-specific mortality was inversely associated with high post-diagnosis intake of smoked poultry/fish.

Grilled and smoked meat intake is a source of polycyclic aromatic hydrocarbons, including benzo[a]pyrene, chrysene, and fluoranthene, and is the primary route of PAH exposure among non-smokers (Phillips 1999). PAHs, a group of over 100 different chemicals, are formed during the incomplete combustion or pyrolysis of organic substances (Agency for Toxic Substances and Disease Registry (ATSDR) 1995b). Specifically, during grilling and barbecuing, PAHs are formed when fat and juices from meat grilled directly over an open fire drip onto the fire, creating flames and smoke. The PAHs adhere to the surface of the meat upon contact (Larsson 1986). Wood smoke, which is used to cook and preserve foods, contains a large number of PAHs, which also contaminate the foods upon contact (Stumpe-Vīksna et al. 2008).

Dietary PAH exposures from intake of grilled/barbecued and smoked meat have been associated with increased risk of breast cancer incidence; effect estimates range from 1.5 to 2.2 when comparing the highest to the lowest quantiles of intake of well-done meat (Dai et al. 2002; De Stefani et al. 1997; Knekt et al. 1994; Steck et al. 2007; Zheng et al. 1998). Dietary PAH exposures are hypothesized to be etiologically related to breast carcinogenesis as PAHs are known to form DNA adducts which can cause mutations during DNA replication and may alter promoter methylation or promoter binding, leading to inheritable abnormal gene expression, early steps in carcinogenesis (Moorthy et al. 2015). While a second primary cancer due to PAH exposure is one possible mechanism by which intake of grilled and smoked foods may influence survival after the initial primary breast cancer diagnosis, PAHs may be more likely to influence

prognosis by other mechanisms, including endocrine disruption; several PAHs or derivatives including chrysene and fluoranthene show estrogenic activity *in vitro,* while others, such as benzo[k]fluoranthene, benzo[a]pyrene, and benz[a]anthracene, can be anti-estrogenic (Arcaro 1999; Chaloupka et al. 1992; Fertuck et al. 2001).

Our findings of a positive association with death and intake for smoked beef/lamb/pork may possibly be explained by the higher saturated fat content of these meats compared to poultry and fish. Though results are inconsistent, higher risk of mortality has been observed among women with high intake of total fat, saturated fat, and monounsaturated fat (Makarem et al. 2013; Rock 2002; Zhang et al. 1995). Furthermore, the higher fat content may also result in the formation of more PAHs (Phillips 1999). However, we did not observe the same elevated risk of mortality among women with continued post-diagnosis high intake when we examined at-diagnosis intake of these meats cooked by grilling/barbecuing. The lack of association between mortality and intake of grilled/barbecued beef/lamb/pork may be due to the method of preparation; marinating meat before grilling, as is often done, may inhibit the formation of PAHs (Viegas et al. 2014). Our finding of an inverse association between smoked poultry/fish intake and mortality could also be related to the different fat composition of these meats. Moreover, it has been hypothesized that the amino acid content of white meat supports proper immune system function (Delfino et al. 2000), while intake of fish, a source of omega-3 polyunsaturated fatty acids, could improve survival (Khankari et al. 2015; Makarem et al. 2013) by reducing pro-inflammatory derivatives (Fabian et al. 2015). Nonetheless, we did not observe reductions in mortality risk associated with the intake of grilled/barbecued poultry/fish intake.

Ours is the first study to examine the associations between grilled/barbecued and smoked meat intake and mortality after breast cancer. Strengths of our study include the population-based

cohort design, which utilized data collected shortly after diagnosis and again 5-year post-diagnosis. Women were followed for over 18 years using the National Death Index, which has accurate ascertainment of vital status (Cowper et al. 2002). However, this study also has several limitations. Women were asked to self-report their intake of grilled/barbecued and smoked meats. This could have resulted in non-differential misclassification of the exposure; which would bias estimates towards the null (Wacholder et al. 1995). Given the prospective design, approximately 28% of women did not complete the follow-up assessment. Analyses using a complete-case approach could result in biased estimates (Ibrahim et al. 2012); therefore, we used multiple imputation, a methodologically sound approach, to address the missing data. Lastly, given the complexity of diet, it is possible that our results are confounded by other correlated dietary factors; however, few dietary exposures have been consistently linked to breast cancer survival (Rock 2002).

Results of our study indicate that grilled/barbecued and, particularly, smoked meat consumed prior to and after breast cancer diagnosis may influence survival. Our findings, which imply that women should avoid intake of smoked red meat and perhaps increase intake of smoked white meat and fish, coupled with confirmation from future studies, may help inform the limited dietary intake guidelines currently available (Runowicz et al. 2016) for the more than 3 million women who are survivors of breast cancer (American Cancer Society 2014).

Table V-1. Distribution of participant characteristics at diagnosis among the LIBCSP women diagnosed with first primary breast cancer in 1996-1997, overall and by grilled/barbecued and smoked meat intake (N=1,508).

		Pre-diagnosis grilled/barbecued, and smoked meat intake[c]	
	Total (N=1,508)	Low (n=732)	High (n=726)
At-diagnosis Characteristic	n (%)	n (%)	n (%)
Age at diagnosis (years)			
<50	407 (27.0%)	160 (21.9%)	128 (26.7%)
50–64	582 (38.6%)	271(37.0%)	201 (42.0%)
≥65	519 (34.4%)	301 (41.1%)	150 (31.3%)
Mean (SD)	58.8 (12.7)	60.9 (12.7)	56.7 (12.3)
Menopausal status			
Premenopausal	472 (31.9%)	180 (25.1%)	155 (33.2%)
Postmenopausal	1,006 (68.1%)	538 (74.9%)	312 (66.8%)
Income			
<$15,000–$24,999	286 (19.0%)	165 (22.7%)	85 (17.8%)
$25,000–$49,999	488 (32.4%)	269 (36.9%)	134 (28.0%)
≥$50,000	730 (48.5%)	294 (40.4%)	259 (54.2%)
Education			
<HS/HS graduate	721 (48.0%)	355 (48.8%)	223 (46.6%)
Some college/college graduate	551 (36.7%)	271 (37.3%)	171 (35.8%)
Post-college	230 (15.3%)	101 (13.9%)	84 (17.6%)
Marital Status			
Married or living as married	1,029 (68.3%)	442 (60.4%)	350 (73.2%)
Not married	478 (31.7%)	290 (39.6%)	128 (26.8%)
BMI at diagnosis (kg/m^2)			
<25.0	683 (45.8%)	343 (47.4%)	224 (47.0%)
25-29.9	476 (31.9%)	237 (32.8%)	152 (31.9%)
≥30.0	332 (22.3%)	143 (19.8%)	101 (21.2%)
Mean (SD)	26.6 (5.7)	26.3 (5.5)	26.8 (5.8)
Physical activity[a]			
Never	334 (22.5%)	176 (24.4%)	88 (18.7%)
Former	253 (17.0%)	122 (16.9%)	79 (16.8%)
Current	900 (60.5%)	424 (58.7%)	304 (64.5%)
Alcohol intake[b]			
Never	588 (39.0%)	297 (40.6%)	179 (37.5%)
Former	212 (14.1%)	119 (16.3%)	65 (13.6%)
Current	707 (46.9%)	316 (43.2%)	234 (48.9%)
Stage			
Invasive	1,273 (84.4%)	608 (83.1%)	402 (83.9%)
In situ	235 (15.6%)	124 (16.9%)	77 (16.1%)
Nodal involvement	622 (74.5%)	286 (73.0%)	192 (73.6%)
Tumor size (cm)			
≤2.0	622 (75.5%)	299 (76.9%)	200 (78.1%)
>2.0	202 (24.5%)	90 (23.1%)	56 (21.9%)
Mean (SD)	1.7 (1.6)	1.7 (1.7)	1.7 (1.5)
Estrogen receptor status			
Negative	264 (26.7%)	129 (27.3%)	87 (28.1%)
Positive	726 (73.3%)	343 (72.7%)	223 (71.9%)
Treatment received			
Radiation	625 (60.9%)	295 (59.5%)	192 (59.3%)
Chemotherapy	423 (41.4%)	181 (36.7%)	121 (37.5%)
Hormone therapy	616 (61.1%)	292 (59.8%)	193 (60.1%)

		Pre-diagnosis grilled/barbecued, and smoked meat intake[c]	
	Total (N=1,508)	Low (n=732)	High (n=726)
At-diagnosis Characteristic	**n (%)**	**n (%)**	**n (%)**

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.

[a]At-diagnosis recreational physical activity was defined as never, former, and current physical activity of least 1 hour per week for 3 months or more.

[b]At-diagnosis intake of alcoholic beverages was defined as never, former, and current intake of alcoholic beverages such as beer, wine, or liquor at least once a month for 6 months or more.

[c]Low intake=0-43 vs High intake=44+ times/year in the most recent decade prior to diagnosis.

Table V-2. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre-diagnosis **lifetime and annual intake of grilled/barbecued and smoked meat and mortality in the LIBCSP women diagnosed with breast cancer in 1996-1997 and followed for 18+ years (N=1,508).**

	All-Cause Mortality (n=597 deaths)				Breast Cancer Specific-Mortality (n=237 deaths)			
Type of Meat Intake			**Age-Adjusted**	**Multivariable-Adjusted[g]**			**Age-Adjusted**	**Multivariable-Adjusted[g]**
Pre-diagnosis	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**
Lifetime grilled, barbecued, and smoked meat intake[a]								
Low	280	441	1 (Ref)	1 (Ref)	117	604	1 (Ref)	1 (Ref)
High	285	4365	0.99 (0.84-1.17)	1.02 (0.86-1.21)	105	616	0.88 (0.68-1.15)	0.89 (0.68-1.17)
P_{Trend}			0.34	0.16			0.47	0.59
Annual grilled, barbecued, and smoked meat intake[b]								
Low	297	435	1 (Ref)	1 (Ref)	112	620	1 (Ref)	1 (Ref)
High	279	447	1.14 (0.96-1.34)	1.23 (1.03-1.46)	114	612	1.03 (0.79-1.34)	1.11 (0.85-1.46)
P_{Trend}			0.06	0.02			0.17	0.07
Annual grilled, barbecued beef, lamb, and pork intake[c]								
Low	323	422	1 (Ref)	1 (Ref)	118	627	1 (Ref)	1 (Ref)
High	262	478	1.02 (0.86-1.21)	1.09 (0.91-1.30)	113	627	0.94 (0.72-1.22)	1.04 (0.79-1.37)
P_{Trend}			0.21	0.10			0.50	0.40
Annual smoked beef, lamb, and pork intake[d]								
Low	288	453	1 (Ref)	1 (Ref)	106	635	1 (Ref)	1 (Ref)
High	302	441	1.13 (0.96-1.33)	1.17 (0.99-1.38)	127	616	1.20 (0.93-1.55)	1.23 (0.95-1.60)
P_{Trend}			0.06	0.10			0.10	0.09
Annual grilled, barbecued poultry and fish intake[e]								
Low	330	403	1 (Ref)	1 (Ref)	115	618	1 (Ref)	1 (Ref)
High	254	492	0.95 (0.80-1.12)	1.06 (0.89-1.26)	114	632	0.94 (0.72-1.23)	1.07 (0.81-1.41)
P_{Trend}			0.95	0.38			0.59	0.31
Annual smoked poultry and fish intake[f]								
None	428	556	1 (Ref)	1 (Ref)	169	815	1 (Ref)	1 (Ref)
Any	161	341	0.80 (0.67-0.97)	0.89 (0.74-1.08)	66	436	0.72 (0.54-0.96)	0.80 (0.59-1.07)
P_{Trend}			0.43	0.09			0.99	0.63

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.

[a]Low intake =0-4,724 vs High intake=4,725+ times throughout the lifetime.

[b]Low intake=0-43 vs High intake=44+ times/year in the most recent decade prior to diagnosis.

[c]Low intake=0-10 vs High intake=11+ times/year in the most recent decade prior to diagnosis.

[d]Low intake=0-4 vs High intake=5+ times/year in the most recent decade prior to diagnosis.

[e]Low intake=0-9 vs High intake=10+ times/year in the most recent decade prior to diagnosis.

[f]None=0 vs Any intake= 1+ times/year in the most recent decade prior to diagnosis.

[g]Adjusted for age at diagnosis, marital status, income, alcohol intake, body mass index, and physical activity.

Table V-3. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre-diagnosis **lifetime and annual intake of grilled/barbecued and smoked meat and mortality in the LIBCSP women diagnosed with *invasive* breast cancer in 1996-1997 and followed for 18^{+} years (N=1,273).**

	All-Cause Mortality (n=548 deaths)				Breast Cancer Specific-Mortality (n=229 deaths)			
Type of Meat Intake Pre-diagnosis	**Deaths**	**Censored**	**Age-Adjusted HR (95% CI)**	**Multivariable-Adjusted[g] HR (95% CI)**	**Deaths**	**Censored**	**Age-Adjusted HR (95% CI)**	**Multivariable-Adjusted[g] HR (95% CI)**
Lifetime grilled, barbecued, and smoked meat intake[a]								
Low	254	349	1 (Ref)	1 (Ref)	113	490	1 (Ref)	1 (Ref)
High	264	353	0.98 (0.83-1.17)	1.01 (0.85-1.21)	101	516	0.86 (0.66-1.12)	0.86 (0.66-1.14)
P_{Trend}			0.62	0.47			0.36	0.39
Annual grilled, barbecued, and smoked meat intake[b]								
Low	268	340	1 (Ref)	1 (Ref)	106	502	1 (Ref)	1 (Ref)
High	259	363	1.09 (0.92-1.30)	1.16 (0.97-1.39)	112	510	1.02 (0.78-1.33)	1.08 (0.82-1.43)
P_{Trend}			0.07	0.04			0.13	0.08
Annual grilled, barbecued beef, lamb, and pork intake[c]								
Low	295	332	1 (Ref)	1 (Ref)	115	512	1 (Ref)	1 (Ref)
High	241	383	1.01 (0.84-1.20)	1.07 (0.89-1.28)	108	516	0.89 (0.68-.17)	0.98 (0.74-1.30)
P_{Trend}			0.20	0.13			0.47	0.44
Annual smoked beef, lamb, and pork intake[d]								
Low	264	356	1 (Ref)	1 (Ref)	102	518	1 (Ref)	1 (Ref)
High	277	356	1.09 (0.92-1.30)	1.12 (0.94-1.33)	123	510	1.18 (0.91-1.54)	1.21 (0.92-1.58)
P_{Trend}			0.09	0.20			0.09	0.09
Annual grilled, barbecued poultry and fish intake[e]								
Low	302	327	1 (Ref)	1 (Ref)	110	519	1 (Ref)	1 (Ref)
High	233	387	0.96 (0.80-1.14)	1.06 (0.88-1.27)	111	509	0.97 (0.74-1.28)	1.09 (0.82-1.45)
P_{Trend}			0.80	0.33			0.48	0.27
Annual smoked poultry and fish intake[f]								
None	394	452	1 (Ref)	1 (Ref)	165	681	1 (Ref)	1 (Ref)
Any	146	263	0.80 (0.66-0.96)	0.89 (0.73-1.09)	62	347	0.72 (0.54-0.97)	0.80 (0.59-1.08)
P_{Trend}			0.43	0.12			0.84	0.59

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
[a]Low intake =0-4,724 vs High intake=4,725+ times throughout the lifetime.
[b]Low intake=0-43 vs High intake=44+ times/year in the most recent decade prior to diagnosis.
[c]Low intake=0-10 vs High intake=11+ times/year in the most recent decade prior to diagnosis.
[d]Low intake=0-4 vs High intake=5+ times/year in the most recent decade prior to diagnosis.
[e]Low intake=0-9 vs High intake=10+ times/year in the most recent decade prior to diagnosis.
[f]None=0 vs Any intake= 1+ times/year in the most recent decade prior to diagnosis.
[g]Adjusted for age at diagnosis, marital status, income, alcohol intake, body mass index, and physical activity.

Table V-4. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre-diagnosis/post-diagnosis **annual intake of grilled/barbecued and smoked meat and mortality in the LIBCSP women diagnosed with breast cancer in 1996-1997 and followed for 18+ years (n=1,339).**

Type of Meat Intake Pre-diagnosis/ Post-diagnosis	All-Cause Mortality (n=428 deaths)				Breast Cancer Specific-Mortality (n=126 deaths)			
			Age-Adjusted	Multivariable-Adjusted[f]			Age-Adjusted	Multivariable-Adjusted[f]
	Deaths	Censored	HR (95% CI)	HR (95% CI)	Deaths	Censored	HR (95% CI)	HR (95% CI)
Total grilled, barbecued, and smoked meat intake[a]								
Low/Low	160	295	1 (Ref)	1 (Ref)	42	413	1 (Ref)	1 (Ref)
Low/High	60	156	1.05 (0.73-1.50)	1.10 (0.75-1.62)	16	201	0.78 (0.38-1.63)	0.77 (0.36-1.64)
High/Low	101	158	1.24 (0.96-1.62)	1.28 (0.97-1.68)	28	231	1.18 (0.71-1.98)	1.14 (0.67-1.93)
High/High	108	302	1.18 (0.88-1.58)	1.31 (0.96-1.78)	41	169	1.09 (0.66-1.80)	1.08 (0.63-1.83)
Grilled, barbecued beef, lamb, and pork intake[b]								
Low/Low	183	291	1 (Ref)	1 (Ref)	43	430	1 (Ref)	1 (Ref)
Low/High	52	137	0.98 (0.68-1.40)	1.00 (0.69-1.45)	16	174	0.93 (0.48-1.81)	0.88 (0.45-1.75)
High/Low	81	156	1.06 (0.80-1.40)	1.10 (0.83-1.46)	19	219	0.86 (0.48-1.56)	0.88 (0.48-1.61)
High/High	112	327	1.10 (0.84-1.43)	1.14 (0.87-1.51)	48	390	1.25 (0.78-1.98)	1.24 (0.76-2.03)
Smoked beef, lamb, and pork intake[c]								
Low/Low	142	326	1 (Ref)	1 (Ref)	36	432	1 (Ref)	1 (Ref)
Low/High	66	138	1.25 (0.87-1.80)	1.18 (0.81-1.71)	20	185	1.29 (0.65-2.58)	1.22 (0.60-2.50)
High/Low	93	148	1.34 (1.01-1.77)	1.36 (1.01-1.82)	31	210	1.75 (1.04-2.94)	1.71 (1.00-2.92)
High/High	126	299	1.20 (0.92-1.56)	1.20 (0.91-1.59)	40	386	1.25 (0.76-2.04)	1.19 (0.71-1.99)
Grilled, barbecued poultry and fish intake[d]								
Low/Low	201	302	1 (Ref)	1 (Ref)	45	459	1 (Ref)	1 (Ref)
Low/High	41	110	1.01 (0.64-1.59)	1.04 (0.65-1.65)	13	138	0.97 (0.43-2.19)	0.95 (0.41-2.19)
High/Low	93	180	1.01 (0.78-1.31)	1.03 (0.78-1.34)	29	244	1.21 (0.73-2.02)	1.22 (0.72-2.05)
High/High	93	318	0.98 (0.73-1.30)	1.06 (0.79-1.43)	39	373	1.06 (0.64-1.76)	1.11 (0.66-1.88)
Smoked poultry and fish intake[e]								
None/None	275	489	1 (Ref)	1 (Ref)	83	682	1 (Ref)	1 (Ref)
None/Any	32	76	0.82 (0.52-1.30)	0.84 (0.51-1.37)	8	100	0.62 (0.27-1.45)	0.56 (0.23-1.34)
Any/None	51	122	0.89 (0.64-1.24)	0.97 (0.69-1.35)	19	154	0.96 (0.56-1.63)	0.97 (0.57-1.67)
Any/Any	70	224	0.79 (0.59-1.06)	0.88 (0.64-1.20)	18	277	0.52 (0.30-0.92)	0.55 (0.31-0.97)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
Missing data analyses exclude women who died within 5 years of breast cancer diagnosis (n=169).

[a]Low intake=0-43 vs High intake=44+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-35 vs High intake=36+ times/year post-diagnosis

[b]Low intake=0-10 vs High intake=11+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-8 vs High intake=9+ times/year post-diagnosis

[c]Low intake=0-4 vs High intake=5+ times/year pre-diagnosis in the most recent decade prior to diagnosis and post-diagnosis

[d]Low intake=0-9 vs High intake=10+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-6 vs High intake=7+ times/year post-diagnosis

[e]None=0 vs Any intake= 1+ times/year in the most recent decade prior to diagnosis and post-diagnosis

[f]Adjusted for age at diagnosis, marital status, income, alcohol intake, body mass index, physical activity, tumor size, lymph node involvement, and estrogen receptor status.

Table V-5. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre-diagnosis/post-diagnosis **annual intake of grilled/barbecued and smoked meat and mortality in the LIBCSP women diagnosed with *invasive* breast cancer in 1996-1997 and followed for 18^{+} years (n=1,111).**

Type of Meat Intake Pre-diagnosis/ Post-diagnosis	All-Cause Mortality (n=386 deaths)				Breast Cancer Specific-Mortality (n=121 deaths)			
			Age-Adjusted	Multivariable-Adjusted[f]			Age-Adjusted	Multivariable-Adjusted[f]
	Deaths	Censored	HR (95% CI)	HR (95% CI)	Deaths	Censored	HR (95% CI)	HR (95% CI)
Total grilled, barbecued, and smoked meat intake[a]								
Low/Low	133	237	1 (Ref)	1 (Ref)	41	329	1 (Ref)	1 (Ref)
Low/High	62	115	1.00 (0.68-1.48)	1.07 (0.72-1.61)	14	163	0.68 (0.31-1.48)	0.68 (0.30-1.50)
High/Low	91	135	1.14 (0.87-1.50)	1.16 (0.87-1.54)	27	201	1.01 (0.60-1.72)	0.99 (0.58-1.70)
High/High	100	236	1.18 (0.87-1.59)	1.28 (0.93-1.75)	39	297	1.08 (0.65-1.78)	1.06 (0.63-1.81)
Grilled, barbecued beef, lamb, and pork intake[b]								
Low/Low	160	239	1 (Ref)	1 (Ref)	43	356	1 (Ref)	1 (Ref)
Low/High	50	99	0.98 (0.66-1.43)	1.01 (0.68-1.52)	14	135	1.02 (0.52-2.01)	0.94 (0.46-1.91)
High/Low	68	123	1.06 (0.79-1.41)	1.08 (0.80-1.45)	16	175	0.84 (0.46-1.46)	0.83 (0.44-1.54)
High/High	108	264	1.12 (0.84-1.48)	1.15 (0.86-1.53)	48	324	1.23 (0.77-1.99)	1.18 (0.71-1.95)
Smoked beef, lamb, and pork intake[c]								
Low/Low	121	255	1 (Ref)	1 (Ref)	32	344	1 (Ref)	1 (Ref)
Low/High	68	108	1.30 (0.89-1.90)	1.20 (0.81-1.78)	21	155	1.33 (0.66-2.68)	1.26 (0.62-2.58)
High/Low	83	113	1.27 (0.94-1.72)	1.29 (0.95-1.76)	31	165	1.69 (0.99-2.89)	1.75 (1.00-3.05)
High/High	114	249	1.20 (0.91-1.59)	1.19 (0.88-1.59)	37	326	1.23 (0.74-2.04)	1.23 (0.72-2.10)
Grilled, barbecued poultry and fish intake[d]								
Low/Low	171	256	1 (Ref)	1 (Ref)	41	386	1 (Ref)	1 (Ref)
Low/High	48	78	1.05 (0.65-1.70)	1.10 (0.67-1.81)	15	111	1.04 (0.47-2.31)	0.96 (0.41-2.23)
High/Low	82	152	1.01 (0.77-1.33)	1.01 (0.76-1.35)	28	206	1.21 (0.73-2.02)	1.18 (0.70-2.00)
High/High	85	239	1.00 (0.74-1.36)	1.07 (0.78-1.47)	37	287	1.10 (0.66-1.84)	1.08 (0.63-1.85)
Smoked poultry and fish intake[e]								
None/None	244	393	1 (Ref)	1 (Ref)	80	557	1 (Ref)	1 (Ref)
None/Any	33	64	0.80 (0.50-1.29)	0.80 (0.48-1.31)	7	90	0.64 (0.28-1.47)	0.51 (0.21-1.23)
Any/None	40	105	0.80 (0.56-1.15)	0.88 (0.61-1.27)	17	128	0.89 (0.51-1.57)	0.92 (0.52-1.64)
Any/Any	69	163	0.82 (0.60-1.11)	0.90 (0.65-1.24)	17	215	0.57 (0.33-0.99)	0.55 (0.31-0.97)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014.
Missing data analyses exclude women who died within 5 years of breast cancer diagnosis (n=169).

[a]Low intake=0-43 vs High intake=44+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-35 vs High intake=36+ times/year post-diagnosis

[b]Low intake=0-10 vs High intake=11+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-8 vs High intake=9+ times/year post-diagnosis

[c]Low intake=0-4 vs High intake=5+ times/year pre-diagnosis in the most recent decade prior to diagnosis and post-diagnosis

[d]Low intake=0-9 vs High intake=10+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-6 vs High intake=7+ times/year post-diagnosis

[e]None=0 vs Any intake= 1+ times/year in the most recent decade prior to diagnosis and post-diagnosis

[f]Adjusted for age at diagnosis, marital status, income, alcohol intake, body mass index, physical activity, tumor size, lymph node involvement, and estrogen receptor status.

Table V-6. Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between pre-diagnosis/post-diagnosis annual intake of grilled/barbecued and smoked meat and mortality in the LIBCSP women diagnosed with breast cancer in 1996-1997 and followed for 18+ years, using a complete-case analysis (n=962).

COMPLETE-CASE ANALYSIS	All-Cause Mortality (n=276 deaths)			Breast Cancer Specific-Mortality (n=92 deaths)		
Type of Meat Intake			Age-Adjusted			Age-Adjusted
Pre-diagnosis/ Post-diagnosis	Deaths	Censored	HR (95% CI)	Deaths	Censored	HR (95% CI)
Total grilled, barbecued, and smoked meat intake[a]						
Low/Low	89	192	1 (Ref)	26	255	1 (Ref)
Low/High	39	107	1.12 (0.76-1.64)	10	136	0.74 (0.36-1.55)
High/Low	53	114	1.10 (0.79-1.55)	16	151	1.05 (0.56-1.95)
High/High	63	234	1.00 (0.72-1.40)	29	268	1.05 (0.60-1.81)
Grilled, barbecued beef, lamb, and pork intake[b]						
Low/Low	106	206	1 (Ref)	28	284	1 (Ref)
Low/High	33	104	0.96 (0.65-1.42)	11	126	0.93 (0.46-1.88)
High/Low	44	110	1.04 (0.73-1.48)	12	142	0.90 (0.45-1.77)
High/High	73	247	1.08 (0.79-1.47)	34	286	1.23 (0.72-2.09)
Smoked beef, lamb, and pork intake[c]						
Low/Low	82	229	1 (Ref)	21	290	1 (Ref)
Low/High	44	95	1.44 (1.00-2.08)	13	126	1.45 (0.72-2.89)
High/Low	56	111	1.29 (0.92-1.81)	22	145	1.99 (1.09-3.61)
High/High	73	231	1.08 (0.79-1.49)	28	276	1.36 (0.77-2.41)
Grilled, barbecued poultry and fish intake[d]						
Low/Low	112	211	1 (Ref)	25	298	1 (Ref)
Low/High	24	83	0.97 (0.62-1.52)	8	99	0.97 (0.43-2.19)
High/Low	56	128	1.06 (0.77-1.47)	21	163	1.50 (0.84-2.69)
High/High	62	245	0.95 (0.69-133)	28	279	1.17 (0.66-2.08)
Smoked poultry and fish intake[e]						
None/Any	162	353	1 (Ref)	54	461	1 (Ref)
Any/None	19	56	0.76 (0.47-1.22)	6	69	0.74 (0.32-1.71)
Any/Any	31	89	0.84 (0.57-1.23)	13	107	1.00 (0.54-1.83)
None/Any	46	173	0.77 (0.55-1.07)	12	207	0.50 (0.27-0.94)

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997, followed-up for vital status through December 31, 2014. Missing data analyses exclude women who died within 5 years of breast cancer diagnosis (n=169).

[a]Low intake=0-43 vs High intake=44+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-35 vs High intake=36+ times/year post-diagnosis

[b]Low intake=0-10 vs High intake=11+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-8 vs High intake=9+ times/year post-diagnosis

[c]Low intake=0-4 vs High intake=5+ times/year pre-diagnosis in the most recent decade prior to diagnosis and post-diagnosis

[d]Low intake=0-9 vs High intake=10+ times/year pre-diagnosis in the most recent decade prior to diagnosis and Low intake=0-6 vs High intake=7+ times/year post-diagnosis

[e]None=0 vs Any intake= 1+ times/year pre-diagnosis in the most recent decade prior to diagnosis and post-diagnosis

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CHAPTER VI: DISCUSSION

Summary

The purpose of this dissertation was to examine whether the primary PAH sources of exposure (active cigarette smoking [Aim 1A], environmental tobacco smoke [Aim 1B], and intake of grilled and smoked meat [Aim 2]) pre- or at diagnosis, as well as changes in exposure after diagnosis, were associated with all-cause and breast cancer-specific mortality among a cohort of women diagnosed with first primary breast cancer in 1996/1997. Results of Aim 1A, examining tobacco smoke exposure from active smoking, showed that smoking in the year before diagnosis was associated with a 69% increase in the risk of long-term all-cause mortality, but not breast cancer-specific mortality. Among women who continued smoking after breast cancer, risk of all-cause mortality was elevated by 130%, but this was attenuated by approximately 20% among women who quit smoking after diagnosis. Additionally, <30 cumulative pack-years of smoking was associated with more than a two-fold increase in the risk of breast cancer-specific mortality. My Aim 1A effect estimates for at-diagnosis smoking were consistent with most studies conducted to date for all-cause mortality, but inconsistent with the approximate 30% increase in risk of breast cancer-specific mortality reported by others (Bérubé et al. 2014). However, for changes in smoking after diagnosis, my Aim 1 findings were consistent with the one other study conducted to date (Passarelli et al. 2016), which reports an attenuated, but still elevated risk in all-cause and breast cancer-specific mortality among women who have post-diagnosis cessation in active smoking.

Results of Aim 1B on environmental tobacco smoke exposure were largely null despite hypothesized mechanisms linking the constituents of tobacco smoke with breast cancer progression, including directly by influencing cell proliferation, tumor growth, and metastasis (Dasgupta et al. 2009) and indirectly by disrupting the endocrine system (Bekki et al. 2013). The results of the Aim 1B regarding at-diagnosis ETS exposure were in agreement with the few studies conducted to date (Kakugawa et al. 2015; Sagiv et al. 2007; Wartenberg et al. 2000), but not all (Boone et al. 2015), which provide little evidence of an association with survival after breast cancer. No previous studies have examined changes in post-diagnosis ETS exposure, and my null results for both all-cause and breast cancer-specific mortality await confirmation by others.

In Aim 2, examining intake of grilled/barbecued and smoked meat intake, at-diagnosis high intake of total grilled, barbecued, and smoked meat was associated with a 23% increased risk of all-cause mortality. When each of the four categories of grilled/smoked meat were examined individually, at-diagnosis intake of smoked beef/lamb/pork was positively associated with all-cause and breast cancer mortality while intake of smoked poultry and fish was inversely associated with mortality. Additionally, women who continued to consume high intake of grilled/barbecued and smoked meat after diagnosis had a further elevated risk of all-cause mortality; risk increased slightly from 23% to 31%. Post-diagnosis smoked beef/lamb/pork intake was also positively associated with all-cause and breast cancer mortality with risk of mortality highest among women who reported high at-diagnosis and low post-diagnosis intake. Consistent with the associations I observed for at-diagnosis intake, risk of breast cancer-specific mortality was inversely associated with high post-diagnosis intake of smoked poultry/fish. Mine is the first study to examine whether dietary PAH exposures from intake of grilled/barbecued and

smoked meat are associated with mortality after breast cancer.

Biologic Plausibility

This dissertation examined the primary sources of PAH exposure, tobacco smoke and intake of grilled/barbecued and smoked meat. PAHs are generally lipophilic, a property which increases with increasing complexity of the compounds (Boström et al. 2002), and known to be stored in adipose tissues, including the breast (Li et al. 1999; Perera et al. 1995). PAHs are hypothesized to be etiologically related to breast carcinogenesis (Gammon and Santella 2008) because they are able to form DNA adducts which can cause mismatch in DNA replication and may alter promoter methylation or promoter binding, leading to somatic DNA mutations or abnormal gene expression, early steps in carcinogenesis (Moorthy et al. 2015). While a second primary cancer due to PAH exposure is one possible mechanism by which PAHs may influence survival after the initial primary breast cancer diagnosis, PAHs may be more likely to influence prognosis by other mechanisms including endocrine disruption. Several PAHs or derivatives including chrysene and fluoranthene show estrogenic activity *in vitro* while others such as benzo[k]fluoranthene, benzo[a]pyrene, and benz[a]anthracene can be anti-estrogenic (Arcaro 1999; Chaloupka et al. 1992; Fertuck et al. 2001), which may be especially important for hormonally sensitive tumors, such as breast cancer.

Study Advantages and Limitations

Results of my dissertation are based on the LIBCSP population-based cohort of 1,508 women with a first primary breast cancer, all diagnosed within a single year. The LIBCSP was initiated as a case-control study to examine risk factors for breast cancer incidence, and

continued as a follow-up study to examine factors related to survival. Thus, the LIBCSP follow-up approach, allowed for assessment of exposures in early life that were self-reported at the time of diagnosis (participants were interviewed on average within three months of breast cancer diagnosis), in addition to exposures that occurred close to the time of breast cancer diagnosis. The follow-up assessment five years after diagnosis further allowed for examination of changes in these risk and prognostic factors. For my dissertation, specifically, I was able to evaluate exposure to tobacco smoke and intake of grilled/barbecued meat and changes in exposure in relation to survival after establishing temporality of exposures (PAH sources) and outcome (mortality). In addition to being a necessary condition for causation, establishing temporality also allowed me to consider various windows of exposure (pre-diagnosis, at-diagnosis, 5-years post-diagnosis) as related to survival. This is in contrast to alternative but other commonly used strategies, including either recruitment of a convenience sample of survivors anywhere from two to ten years after diagnosis (Pierce et al. 2007a; Zhang et al. 1995) or prospective cohort studies initiated to examine etiologic associations but extended to also consider prognostic associations (Allemani et al. 2011; Blair et al. 2007; Kroenke et al. 2005). Both of these alternative strategies, can obscure important exposure-outcome associations by masking key windows of exposure (although with care, the extended cohort design could potentially avoid this pitfall). Because of the LIBSCP approach, my dissertation should yield results that are more easily interpretable and generalizable. Nonetheless, despite several methodologic advantages, there are corresponding limitations to my dissertation approach, which are discussed below.

First, the LIBCSP follow-up included comprehensive questionnaires administered by trained interviewers shortly after diagnosis and again approximately five years later to assess potential prognostic factors for breast cancer including PAH sources. While a limitation of my

dissertation is that I only had data regarding one post-diagnosis change in exposure, most studies rely on one measurement of exposure – generally pre- or at-diagnosis assessments only. The LIBCSP approach of using repeated structured interviews with trained interviewers at specific time intervals is likely to provide more valid responses, compared to either single or multiple self-completed questionnaires, for example, where the timing of the exposure relative to the diagnosis is ambiguous or perhaps not reflective of the appropriate window of susceptibility. For example, for other exogenous hormone exposures, including pregnancies and oral contraceptive use, risk of mortality after breast cancer is only elevated for exposures that occur within five years of diagnosis (Trivers et al. 2007a, 2007b), which underscores the need to adequately assess endocrine-related exposures during the most likely appropriate window of exposure relative to the disease diagnosis and the outcome.

A concern with the interview approach, however, is the reliance on self-reported measures of active smoking, environmental tobacco smoke exposure, and intake of grilled/barbecued and smoked meat which were therefore subject to errors in participant recall. The assessments of smoking and ETS exposure were not confirmed by biomarker. The measure of ETS exposure, in particular, could have benefitted from an objective measure of exposure as I did not have data on intensity of exposure; however, biochemical confirmation of tobacco smoke exposure is costly and repeated measurements may not be feasible in a large epidemiologic study. Additionally, self-reported smoking history has been shown to be reliably recalled and reported (Krall et al. 1989) and the prevalence estimates for at-diagnosis (19%) (Bérubé et al. 2014) and post-diagnosis smoking (8%) are consistent with estimates from prior studies (Mayer and Carlson 2011; Westmaas et al. 2015). In the LIBCSP, approximately 15% of women reported at-diagnosis residential ETS exposure, which is lower than previous studies in which

current ETS exposure was estimated at 25% (Wartenberg et al. 2000) to 30% (Boone et al. 2015). Women were asked to report their intake of grilled/barbecued, and smoked meats. To limit the potential bias that may result from exposure misclassification, my study focused on intake shortly prior to diagnosis and in the five years after diagnosis, though long-term intake was also examined. Any misclassification that may have occurred would likely have been non-differential with respect to mortality, which would bias estimates towards the null (Wacholder et al. 1995).

Second, despite the long follow-up of over 18 years currently available in the LIBCSP, an additional limitation of my dissertation is that we only observed 597 deaths from any cause and 237 due to breast cancer. In survival analyses, power is directly related to the number of events rather than to the number of participants (Bradburn et al. 2003); larger studies are needed to confirm the findings presented here and obtain more precise estimates of association. The modest number of deaths also precluded me from examining effect measure modification of the hazard ratio for potentially important covariates including estrogen receptor status and body mass index. However, I was able to conduct restricted analyses among women with ER^+ disease and those considered overweight or obese based on body mass index (i.e., BMI $\geq$25 kg/m^2).

A third limitation is that given the prospective design, approximately 28% of women did not complete the follow-up assessment and only one follow-up questionnaire was conducted. Due to the missingness in the 5-year post-diagnosis variables, I chose to address this issue rather than ignore it as is often done in prospective epidemiologic studies, including those focused on breast cancer prognosis (Passarelli et al. 2016). This is an important consideration as analyses using a complete-case approach could potentially bias estimates (Ibrahim et al. 2012). I used

multiple imputation to address missing data and patterns of association were similar when I imputed data using a fully Bayesian approach (data not shown).

Lastly, the LIBCSP cohort of women with breast cancer is comprised primarily of white women, which reflects the underlying source population residing in Long Island NY, but may limit its generalizability to the nation as a whole. However, white postmenopausal women are at highest risk of developing breast cancer in the US (Ban and Godellas 2014), and white women comprise the largest proportion of breast cancer survivors in the US (DeSantis et al. 2014). Therefore, my dissertation results are applicable to the largest group of women in the US currently living with breast cancer. Importantly, the majority of women in the LIBCSP cohort were diagnosed with hormone responsive tumors, and ER^+ breast cancer is the most commonly diagnosed tumor among all women in the US, regardless of race or ethnicity (DeSantis et al. 2014). Further, the biologic behavior of a tumor within a specific subtype is not believed to vary substantially by race (O'Brien et al. 2010). Thus, my results for ER^+ are generalizable to the most common tumor diagnosed in the US, regardless of race or ethnicity – and therefore are informative to the majority of American women living with breast cancer.

Future Directions

The results of my dissertation should be replicated and confirmed. Emphasis should be placed on addressing the limitations identified in the previous section (**Chapter VI. Study Advantages and Limitations**) and on exploring these associations in other race and ethnicity groups where there are differences in the prevalence of exposures such as smoking (Centers for Disease Control and Prevention 2014b) and survival (National Cancer Institute 2016). Future studies should rely on resources from population-based studies, rather than convenience sample

recruitment and all attempts should be made to recruit, enroll, and interview participants as close to diagnosis as possible. This will limit the potential biases introduced through selection of participants and recall of exposures before breast cancer diagnosis and will allow for examination of relevant exposure windows for survival.

If associations observed in my dissertation are confirmed by others, as prior researchers have noted (Land et al. 2016), efforts should be made to develop effective smoking cessation interventions among breast cancer patients and to understand the optimal strategies for and timing of tobacco dependence treatment. Future research should continue to address the gaps in our understanding of the biological mechanisms underlying these associations.

In my dissertation results focused on active smoking status and survival, at-diagnosis and post-diagnosis changes in smoking were associated with all-cause mortality, but not breast cancer-specific mortality. These results may highlight an association between smoking and mortality from cardiovascular disease or other outcomes, rather than to breast cancer recurrence. It has been well documented that long-term breast cancer survivors are at increased risk for cardiovascular-related mortality compared to women in the general population (Bradshaw et al. 2016) most likely due to the cardiotoxic effects of breast cancer treatments (Carver et al. 2007). It is also known that the constituents of cigarette smoke, including nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons (PAHs) can cause cardiovascular disease (Centers for Disease Control and Prevention 2010); however how cigarette smoke constituents influence tumor proliferation, angiogenesis, metastasis, and the tumor microenvironment is poorly understood.(Land et al. 2016). Together, the chemicals in cigarette smoke and breast cancer treatment(s) may act synergistically to increase risk of long-term mortality from cardiovascular disease, but the LIBCSP was underpowered to examine disease-specific causes of death other

than breast cancer as related to post-diagnosis changes in smoking and ETS exposure for which the baseline prevalences were 19% and 15%, respectively. The results of Aim 1A, however, do not appear to provide strong evidence that PAHs influence survival after breast cancer through an estrogen pathway; at-diagnosis cigarette smoking was not strongly associated with breast cancer-specific mortality. This hypothesis, however, is difficult to rule out as PAHs can be both estrogenic and anti-estrogenic, as mentioned in the previous section (Chapter VI. Biologic Plausibility). Although estimates were imprecise, I did observe elevated risks in breast cancer-specific mortality when I considered post-diagnosis changes in active smoking, which highlights the need to identify and examine the appropriate timing of exposure as it relates to prognosis. Given the consistent associations observed between tobacco smoke exposure through active smoking and all-cause and breast cancer-specific mortality in my dissertation and the findings from others (Bérubé et al. 2014), potential prognostic associations with other tobacco products including cigars, pipe tobacco, snuff, and chewing tobacco should be also examined.

In regards to the findings of my second aim, a better understanding of the biological mechanisms linking dietary PAH exposure and mortality after breast cancer also require elucidation. How the PAHs found in grilled/barbecued and smoked meats impact tumor growth, angiogenesis, and metastasis may help us understand how other similar chemicals work to impact mortality after breast cancer. Furthermore, understanding how diet and breast cancer treatment interact to impact mortality would be an interesting question to address, given that patients may be especially receptive to dietary counseling during cancer treatment, and surgery, radiation, and chemotherapy can significantly affect nutritional needs (Rock et al. 2012). In addition, future studies, with increased power to adequately explore effect modification, should also consider interactions between intake grilled/barbecued and smoked meat and other dietary

exposures such intake of fruits and vegetables, use of multivitamin supplements, and even specific macro and micronutrients.

It may also be important to consider assessing multiple post-diagnosis changes in exposures. An innovation of my dissertation was that I considered how post-diagnosis changes impacted survival; however, I was limited by only having data related to exposures pre-/at-diagnosis and five years post-diagnosis. My dissertation assumes that exposures at 5-years post-diagnosis persist throughout the 18 years of follow-up, which may not be a realistic assumption. If feasible, multiple questionnaires should be used to assess how exposures change at all the points of the breast cancer continuum including pre-diagnosis, at-diagnosis and post-diagnosis before initiation of treatment, during breast cancer treatment, and long-term post-treatment. Importantly, careful attention should be given in regard to the study design. Studies initiated as prospective cohort studies, in which all participants are free of the outcome at baseline and cases develop over time, may have serial measurements of exposure; however, selecting the exposure or exposures that best represent important windows of exposure may require careful attention. Often, multiple measurements are made *before* the disease develops, in which case selecting the exposure measured at the time point closest to diagnosis would be important. Similarly, measurements made after diagnosis should be consistent across participants so that the exposures are examined in consideration to the participants' time of diagnosis and treatment. Understanding how epidemiologic exposures influence survivals at all points of the breast cancer continuum will help us to identify the optimal point(s) of intervention.

Public Health Impact

The more than 3.1 million women who are survivors of breast cancer - the largest group

of cancer survivors in the US (American Cancer Society 2014) - are faced with making behavioral and dietary choices to help improve long-term prognosis. How epidemiologic factors impact breast cancer survival is understudied. This is an important area of research as it is projected that by 2030 the number of breast cancer survivors will increase by as much as 50% (AACR 2015). A better understanding of the contribution of environmental exposures, especially exogenous compounds which are modifiable and with the potential to influence estrogen, estrogen receptors, or biologically relevant pathways involved in breast cancer progression, on survival can help us to substantially reduce the burden of breast cancer.

Conclusions

The biologically plausible results of this dissertation showed that the primary sources of PAH exposure, active smoking and intake of grilled/barbecued and smoked meat, were associated with mortality after breast cancer. Importantly, results of the first aim indicate that post-diagnosis cessation of active smoking may be important to reduce mortality. Results of the second aim indicate that women should avoid intake of smoked meat, in particular smoked red meat. The results of this dissertation strengthen the scientific evidence supporting smoking cessation efforts and inform the limited dietary intake guidelines currently available (Runowicz et al. 2016) for the more than 3 million women who are survivors of breast cancer (American Cancer Society 2014).

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APPENDIX: EXCERPTS FROM THE LIBSCP BASELINE QUESTIONNAIRE

SECTION I: SMOKING

Now I have some questions about smoking.

I1. Before (REFERENCE DATE), did you ever smoke at least 1 cigarette a day for 6 months or longer?

YES……...……1
NO…….2 (I8)

I2. How old were you when you first started smoking cigarettes on a regular basis?

AGE STARTED |__|__|

I3. Were you smoking cigarettes on (REFERENCE DATE), that is when you were (AGE)?

YES...……1 (I5)
NO…….2

I4. At what age did you stop smoking cigarettes?

AGE STOPPED |__|__|

I5. Thinking about the years between (AGE FROM I2) and (AGE FROM I4/AGE FROM I3), was there ever a period of 1 year or more in which you did not smoke cigarettes?

YES...……1
NO…….2 (I7)

I6. For how many years between (AGE FROM I2) and (AGE FROM I4/AGE FROM I3), did you not smoke cigarettes?

YEARS |__|__|

I7. (During periods when you smoked), how many cigarettes (do/did) you usually smoke per day or per week? One package contains 20 cigarettes.

NUMBER |__|__|__| Per: (circle one)

DAY……..…1
WEEK……...2
MONTH……3

I8. At any time in your life, did any member of your household, including caregivers, smoke in your presence?

YES...……1
NO…….2 (SECTION J)

	I9. What was the relationship to you of the (first/next) person who smoked?	I10. How old were you when you were first exposed to your (HOUSEHOLD MEMBER)'s smoke?	I11. How old were you when you were last exposed to your (HOUSEHOLD MEMBER)'s smoke?	I12. For how many years since (REFERENCE DATE) were you exposed to their smoke?
a.	____	____ AGE	____ AGE STILL SMOKING…00	____ YEARS
b.	____	____ AGE	____ Age STILL SMOKING…00	____ YEARS
c.	____	____ AGE	____ Age STILL SMOKING…00	____ YEARS
d.	____	____ AGE	____ Age STILL SMOKING…00	____ YEARS
e.	____	____ AGE	____ Age STILL SMOKING…00	____ YEARS
f.	____	____ AGE	____ Age STILL SMOKING…00	____ YEARS

Now I have a few questions about grilled, barbecued, or smoked foods.

C52. Have you ever eaten grilled, barbecued, or smoked foods?

YES……1
NO……..….2 (C61)

C53. Have you ever eaten (FOOD)?	C54. Before the age of 20, how often did you usually eat (FOOD)?	C55. Between the ages of 20 and 20, how often did you usually eat (FOOD)?	C56. Between the ages of 30 and 39, (how often did you usually eat (FOOD))?
a. Grilled or barbecued beef, lamb or pork Yes……1 No…….2 (C53b)	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000
b. Grilled or barbecued poultry or fish Yes……1 No…….2 (C53c)	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000
c. Smoked beef, lamb or pork such as bacon or ham Yes……1 No…….2 (C53d)	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000
d. Smoked poultry or fish such as smoked turkey or lox Yes……1 No…….2 (C61)	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000	|__|__| Times Week……..1 Per Month……2 Year……...3 Never……...000

C57. Between the ages of 40 and 40, (how often did you usually eat FOOD))?	C58. Between the ages of 50 and 59, (how often did you usually eat FOOD))?	C59. Since the age of 60, (how often did you usually eat (FOOD))?	C60. Which seasons of the year did you usually eat (FOOD)? (CIRCLE ALL THAT APPLY)
|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	WINTER……………..1 SPRING……………...2 SUMMER…………....3 FALL………………....4 ALL YEAR…………..5
|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	WINTER……………..1 SPRING……………...2 SUMMER…………....3 FALL………………....4 ALL YEAR…………..5
|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	WINTER……………..1 SPRING……………...2 SUMMER…………....3 FALL………………....4 ALL YEAR…………..5
|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	|__|__| Times Week………..1 Per Month………2 Year………...3 Never……………...000	WINTER……………..1 SPRING……………...2 SUMMER…………....3 FALL………………....4 ALL YEAR…………..5