REPRODUCTIVE FACTORS, ORAL CONTRACEPTIVE USE AND BREAST CANCER SURVIVAL IN YOUNG WOMEN

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ABSTRACT

KATRINA F. TRIVERS: Reproductive Factors, Oral Contraceptive Use and Breast Cancer Survival In Young Women
(Under the direction of Marilie D. Gammon)

While much is known about the effect of clinical factors such as tumor characteristics and molecular markers on breast cancer survival, little is known about the impact of non-clinical factors on survival. Reproductive factors play an important role in the development of breast cancer, and oral contraceptive use is associated with a modest increase in incidence but their impact on survival is unclear. This study examined whether reproductive factors and oral contraceptives were associated with survival among younger breast cancer cases. A population-based cohort of women diagnosed with a first, primary, invasive breast cancer between 1990-1992, aged 20-54 years (n=1264), were followed until January 1, 2000. Detailed information on a variety of characteristics was collected through structured in-person interviews given shortly after diagnosis. Vital status was ascertained through the National Death Index (n=292 deaths). Cox regression methods were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI). Relative to nulliparity, parity of 4 or more births was positively associated with all-cause mortality, [HR (95%CI) = 1.71 (1.09-2.67)]. Increased mortality was observed for having a recent birth prior to diagnosis (≤5 vs. >5 years) [1.78 (1.28-2.47)], and was more pronounced among women with a pre-diagnostic body mass index of <25 kg/m^2 [2.54 (1.61-4.00)]. Early age at menarche and early age at first birth also modestly increased mortality; history of miscarriage, induced abortion, and ever breastfeeding were not related to survival. Relative to non-recent OC use,

recent use of OCs just prior to diagnosis increased all-cause mortality, both for time since first use [<10 years versus 20+ years = 1.77 (0.98-3.21)] and last use [<1 year versus 1+ year = 1.46 (0.91-2.33)]. In particular, the HR was doubled for use of high dose estrogen pills versus low dose use within 5 years of diagnosis [2.38 (1.22-4.62)], or if the most recent pill included the progestin levonorgestrel (versus all other types) [2.00 (1.03-3.87)]. These results implicate the timing of hormonal characteristics in breast cancer progression and may enable a better understanding of how reproductive characteristics and oral contraceptive use influence breast cancer survival.

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LIST OF ABBREVIATIONS

ADJ	Adjusted
AJCC	American Joint Committee on Cancer
BMI	Body mass index
CBE	Clinical breast exam
CI	Confidence interval
CYP	Cytochrome p450
DMBA	7,12-dimethylbenz[a]anthracene
DNA	Deoxyribonucleic acid
EGF	Epidermal growth factor
ER	Estrogen receptor
f/u	Follow-up
GA	Georgia
hCG	Human chorionic gonadotropin
HR	Hazard Ratio
kg	Kilograms
ln	Natural log
LRT	Likelihood ratio test
m	Meters
µg	Microgram
mg	Milligram
mo	months
NDI	National death index

NJ	New Jersey
OC	Oral contraceptive
OR	Odds ratio
PR	Progesterone receptor
RR	Risk ratio
S	Survival function
SEER	Surveillance Epidemiology and End Results
TGF	Transforming growth factor
WA	Washington
WISH	Women's Interview Study of Health

CHAPTER I: BACKGROUND AND INTRODUCTION

Descriptive Epidemiology of Breast Cancer Incidence and Survival

An estimated 212,920 new cases and 40,970 deaths from invasive breast cancer will occur among American women in 2006, making breast cancer the most commonly diagnosed cancer among women and the second leading cause of cancer death after lung cancer (*1*). Due to relatively high survival rates, the prevalence of invasive female breast cancer was estimated as 2.28 million on January 1, 2002 (*2*). While there is a large pool of survivors, we have limited information on what non-clinical characteristics may influence their risk of death.

The incidence of breast cancer rises rapidly during the reproductive years, until approximately age 50, after which the increase in risk is less steep (*3*). Invasive breast cancer is rare among younger women, with approximately 13% of cases occurring in women younger than 45 and 22% occurring between 45-54 years of age (*2*).

Advances in diagnosis, screening, and treatment have increased survival rates over the past two decades. The 5-year relative survival rate for the period 1995-2001 was 88.2%, statistically significantly better than the survival rate for women diagnosed between 1974-1976 (74.6%) and slightly higher than the rates for women diagnosed between 1989-1991 (84.9%) and 1992-1994 (86.2%) (*2*). Survival is highly dependent upon the stage of disease at diagnosis with 97.9% of localized cases of all ages surviving 5 years, compared to 81.3% and 26.1% of regional and distant cases, respectively, for the period 1995-2001. Age at diagnosis also has prognostic significance with younger women (<45 years) experiencing

worse five-year survival rates (84.8% for the period 1995-2001) than older women (88.4% for those 45-54 years of age, 89.4% for those diagnosed between ages 55-64) (*4*). There are also marked racial disparities in survival. Mortality from breast cancer has been decreasing steadily since the late 1980's, but this decrease is concentrated exclusively among white women. Mortality rates among African-Americans actually rose during the 1980's, stabilized and have only recently begun to decrease. Survival trends over time have improved for both races, but more so for white women. From 1974 to 1976, the 5-year relative survival rates for white and African-American women were 75% and 63% respectively. These rates increased to 90% for white women and 76% for African-American women from 1995 to 2001 (*1*).

Established risk factors for the development of breast cancer include exposures thought to be proxies for endogenous estrogen levels, including a young age at menarche, late age at menopause, nulliparity, late age at first full-term pregnancy, fewer number of full-term pregnancies, and late age at last pregnancy (*5*). Additional factors that increase breast cancer risk and may influence risk through an estrogen-related pathway, include little or no breast-feeding, (*6*), obesity among postmenopausal women (*7*), moderate alcohol consumption (*8*), use of hormone replacement therapy (*9*), and limited physical activity (*10*). Poor diet has been investigated as a potential risk factor, but its role in breast cancer etiology remains controversial (*11*). Risk factors for breast cancer development may differ by a woman's menopausal status at diagnosis. Recent work has concentrated on elucidating factors that may predispose younger women to breast cancer relative to older women and include African-American race, low body mass index (BMI), recent oral contraceptive (OC) use and a recent birth (*12*). Obesity (*12*) and hormone replacement therapy use (*9*) are especially associated with breast cancer among older women. Early age at menarche, late age at first birth, tall

height and alcohol use are equally associated with risk of breast cancer diagnosed at young and old ages (*12*).

Known Clinical and Lifestyle Prognostic Factors for Breast Cancer

Known prognostic factors related to tumor characteristics include estrogen receptor (ER) status, lymph node involvement and other molecular and clinical markers (*13,14*). Typically, estrogen receptor positive (ER+) tumors are associated with better survival, but the role of ER status independent of other prognostic factors is controversial. Many studies find the improved survival associated with ER+ tumors is only present when hormone therapy is given concurrently (*13*). Node positive patients are at higher risk for recurrence and death compared to node negative women (*14*).

Other well-established prognostic factors include the marker of proliferation Ki-67 and over-expression of proto-oncogenes such as HER-2/neu (i.e. tumors that are HER-2/neu positive) (*13*). The estrogen regulated genes pS2 and Cathepsin-D are potentially related to survival. The pS2 protein is associated predominately with ER+ tumors; ER+ tumors that are also pS2+ have particularly good survival. Among women with ER+, progesterone receptor positive (PR+) tumors, the 5-year survival rates were 97% and 54% among pS2+ and pS2- tumors, respectively (*15*). Cathepsin-D is a protease and overexpressed in many breast cancers. Higher levels of Cathepsin-D probably facilitate tumor invasion and metastasis by breaking down basement membranes and extracellular matrices (*13*). Higher levels of Cathepsin-D are associated with a higher risk of recurrence and death (*15*). Among women with node-negative tumors, the strongest independent predictors of survival include grade, tumor size, presence of high levels of Cathepsin-D, measures of cellular proliferation including Ki-67 and S-phase fraction, mitotic index, and amount of vascular invasion (*14*).

Additional well-known clinical factors that are thought to prolong survival through hormonal mechanisms and shed light on the progression of breast cancer include tamoxifen or aromatase inhibitor administration and ovarian ablation. Tamoxifen administration acts as an anti-estrogen in the breast and inhibits tumor growth in ER+ tumors by preventing estrogen from binding to its receptor, thus reducing transcription of estrogen regulated genes, essentially arresting the cell cycle in the G1 phase (*16*). Tamoxifen has been shown to prolong disease-free or overall survival in breast cancer patients as well as decrease incidence rates of contralateral breast cancer and decrease recurrence of breast cancer after lumpectomy and radiation (*17,18*). After 10 years of follow-up, patients with ER+ tumors with no lymph node involvement who received tamoxifen had a relative risk of death of 0.84 (95% CI = 0.71-0.99) relative to those on a placebo (*18*). Similarly, disease-free survival was enhanced in tamoxifen users [HR (95% CI) = 0.66 (0.58 – 0.74)] and the incidence of contralateral tumors was reduced by 37% (*18*). The decreased incidence of contralateral tumors, recurrence rates, and increased survival rates associated with tamoxifen use has resulted in the hypothesis that tamoxifen and other anti-estrogens may be useful as preventive agents in the development of a first, incident breast cancer. Initial results in high-risk women indicate almost a halving of incidence associated with tamoxifen use compared to a placebo (*16*).

In addition to Tamoxifen, adjuvant hormonal therapy with aromatase inhibitors also improve disease-free survival in postmenopausal patients with hormonally responsive (ER or PR+) tumors (*19,20*). Aromatase inhibitors block the peripheral aromatization of androgens to estrogens via the aromatase enzyme (*21*). While aromatase inhibitors are contraindicated as monotherapy in premenopausal patients (*19,22*), there is interest in exploring whether

combining ovarian suppression with an aromatase inhibitor in premenopausal patients would be beneficial (*21*,*22*).

Ovariectomy in experimental animals causes regression of established malignancies (*23*) and, similarly, ovarian ablation in human breast cancer patients younger than 50 years of age results in improved survival (*24*). The mechanism through which this occurs is likely due to the drastic decrease in ovarian hormones after such a procedure (*24*).

While clinical markers are thought to be among the most important characteristics determining survival, lymph node status and tumor grade have been estimated to explain only about 20% of the variation in survival (*25*). Thus, it is clear there are additional factors that may be important to consider, either independent of or in conjunction with known clinical and lifestyle prognostic factors.

Lifestyle and demographic characteristics that are known to influence survival include age, race, and obesity at diagnosis. Women less than 45 years of age at diagnosis and African-American women have worse prognosis than older women or white women (*2*). Body size is known to influence survival among postmenopausal women with overweight and obese women at diagnosis as measured by high body mass index or elevated waist-to-hip ratio experiencing shorter survival relative to leaner women (*26*). This observation is being increasingly noted in younger, premenopausal women as well (*27*) Weight status is hypothesized to affect survival through an estrogen pathway since postmenopausal overweight and obese women produce more estrogen via androstenedione conversion in adipose cells (*28*).

Estrogen and Breast Cancer Incidence and Survival

Estradiol and estrone are the most common estrogens in circulation, of which estradiol is the most biologically active in breast tissue. Among nonpregnant, premenopausal women, most estrogen is produced in the ovaries. Serum estradiol levels are higher in older (28-40 years) premenopausal women then younger (18-23 years) women. Additionally, non-pregnant parous women have lower estradiol levels relative to non-parous women (*29*).

Breast Architecture and Development

The breast is unique in that full development does not occur until after a woman's first full-term pregnancy. Breast lobules can be divided into three types based on age and parity status. Type 1 lobules (the site of origin of ductal carcinomas) are found in younger, nulliparous women, and are characterized by a large percentage of undifferentiated cells with a high proliferative capacity. Type 2 lobules, also found in nulliparous women, are composed of more differentiated cells. Type 3 lobules are the predominant structure in parous, premenopausal women, and are the most differentiated of the three types. After menopause, most lobules regress back to the Type 1 lobule (*30*). After menarche and prior to pregnancy, there are a large number of undifferentiated cells and structures (ducts and alveolar buds) in the breast. During pregnancy, high levels of estrogen and progesterone cause cell proliferation and terminal differentiation. These terminally differentiated cells have longer cell cycles, thus are undergoing less proliferation. These cells spend more time in the G1, or resting, phase thus allowing time for more DNA repair (*31*). While estrogen levels continue to rise throughout pregnancy, estrogen is responsible for the majority of proliferation taking place during the first trimester, whereas progesterone induced differentiation takes place mostly during the second and third trimester (*32*). Estrogen is responsible for duct elongation

and branching and progesterone in conjunction with estrogen is important for lobular gland development and maturation (*33*).

Estrogen and Breast Cancer Incidence

While a hormonal connection to breast cancer has long been known, the specific physiological effects of estrogen and other hormones on normal and cancerous human mammary cells are complex and not fully elucidated. Estrogen could affect breast cancer incidence through a number of pathways. Pregnancy induced differentiation of the mammary gland modifies gland structure and cell kinetics including decreased growth fraction, cell cycle lengthening, decreased ability of carcinogens to bind to DNA, and increased ability of cells to repair carcinogen induced damage (*34*). Estrogen is known to promote human and rodent breast cancer cell growth through mechanisms including direct effects on tumor initiation via induction of DNA synthesis and oncogene activation or indirectly through promotion of prolactin and growth factor secretion (*35*).

In addition to receptor based cell proliferation (which increases the likelihood of error-laden cells replicating), estrogen could act as a genotoxin. For example, estrone and estradiol are metabolized to catechol estrogens that when oxidized, become catechol estrogen quinines allowing formation of DNA adducts and the creation of apurinic sites, subsequent mutations and cancer (*36*). The two generic pathways of action, estrogen induced cell proliferation and indirect or direct genotoxic effects via 4-hydroxy metabolite formation and oxidative DNA damage, likely act complementarily (*37*).

The imbalance of mammary cell proliferation and cell death contributes to tumor formation and metastasis, either of which can be influenced by, or are related to, estrogen levels. Physiologic levels of estrogens and progestins promote the onset and progression of

breast cancer. Imbalanced expression of steroid regulated genes triggers a cascade of events including the regulation of expression of genes that encode growth factors, growth factor-binding proteins and receptors (e.g. the EGF family of ligands and receptors, including TGF-alpha and HER-2/neu). Additionally, sex steroids exert effects on cell cycle and cell survival through regulation of such genes as cyclin D_1, and Bcl-2/Bcl X_c (*38*). In particular, estrogen may promote tumor cell survival by increasing the anti-apoptotic protein Bcl-2 levels, thus decreasing apoptosis (*33*).

Although estrogen is known to stimulate cell proliferation, breast epithelium does not exhibit maximal proliferation during the follicular phase of the menstrual cycle, in which the highest levels of estrogen are noted, but rather during the luteal phase (*30,39-41*). However, ER expression in highest in the follicular phase of the menstrual cycle (*42-44*). These discrepancies remain largely unresolved, but could implicate additional substances or more complicated pathways than are presently understood. For example, there may be additional membrane receptors, not related to the traditionally known estrogen receptor pathway that may stimulate the cell proliferation cascade thereby allowing ER– cells to respond to estrogens. Additionally, estrogen may not need to bond to its nuclear receptors to initiate or promote breast cancer. Estrogen mediated metabolic activation through CYP (p450) complexes could generate reactive intermediates with direct genotoxic effects through increases in mutation rates (*30*). Paradoxically, patients with ER– tumors have worse prognosis than those with ER+ tumors, which is surprising given estrogen's strong influence on cell growth and survival. It is possible that ER– tumors represent a more aggressive and advanced disease due to their ability to evade ER regulated pathways for growth and survival (*33*). Transfecting ER– tumor cells with a protein construct containing estrogen responsive

elements results in cell growth inhibition. Thus, the loss of ER function resulting in ER– tumors may represent a key stage in the progression of certain breast tumors (*33*). Given that approximately 95% of all breast tumors in both premenopausal and postmenopausal women are initially hormone dependent (*45*), there is ample opportunity for hormonally regulated gene expression, even among currently receptor negative tumors.

Estrogen and Breast Cancer Survival

Several different lines of research have provided evidence for the role of estrogen levels on breast cancer survival. First, serum estrogen levels have been inversely correlated with disease free survival (*46*), and women who undergo breast cancer surgery during the follicular (estrogen dominant) phase of the menstrual cycle may have lower survival, possibly due to the release of micrometastases that are promoted by high levels of estrogen (*47*). While the clinical significance of this latter finding is equivocal, the authors of a comprehensive review of the data conclude that survival is likely affected by the timing of surgical resections, as 6 out of 8 high quality studies on the topic indicate a survival advantage for women undergoing procedures during the presumed early luteal phase of their cycle. However, the authors do not make comprehensive clinical recommendations about the optimal time to perform such procedures, due to the limited quality of available data (*48*).

Secondly, several estrogen-regulated genes, including pS2 and Cathepsin-D, potentially influence survival. High expression of estrogen sulfatase (an enzyme which hydrolyzes sulfated steroid hormones into biologically active estrogens) has been associated with increased recurrence rates, but not with overall survival (*49*). Estrogen may also stimulate angiopoietin-2 expression, a protein that promotes angiogenesis and has been associated with decreases in disease-free and overall survival (*50*). Therefore, hormones such as estrogen

may influence survival by acting both directly as a growth promoter and indirectly through known molecular and prognostic factors.

Summary: Estrogen and Breast Cancer

Hormone-related cancers have a unique mechanism of carcinogenesis, in that endogenous and exogenous hormones can drive cell proliferation, increasing cell division and the opportunity for cells to acquire random genetic errors, thus, it is possible no specific initiator would be required for breast cancer development. This is in contrast with other models of cancer development (i.e. chemical carcinogenesis models) in which some initial insult might be required for cancer initiation (*51*). Additional pathways for the role of steroid hormones in breast cancer certainly exist such as cytochrome p450 (CYP) mediated metabolic activation increasing mutation rates. Accumulating biological and clinical evidence indicates estrogens may have wide-ranging effects on tumor promotion and patient survival. Hormonal stimulation of cell proliferation occurs all along the pathway of tumor progression. Thus, it is hypothesized that tumors of women with higher exposures to estrogen may grow more quickly and be more aggressive compared to those with lower levels of estrogen, thus worsening prognosis in such patients. Changes in estrogen-regulated genes have been extensively studied in relation to breast cancer survival, but other factors associated with estrogen levels (e.g. reproductive factors) have not, despite strong biologic plausibility.

Reproductive Factors and Breast Cancer Incidence and Survival

Reproductive Factors and Breast Cancer Incidence

Aspects of women's reproductive lives are known to influence the risk of developing breast cancer. The main reproductive determinants of risk are thought to be proxies for

hormone levels and other physiologic measures (i.e. growth factors), although exact mechanisms of action have not been elucidated.

Menarche and Menopause

Age at menarche is a key component of breast cancer incidence; the younger a girl starts menstruating, particularly below the age of 12, the higher her odds of subsequent breast cancer incidence. Every two-year delay in the onset of menstruation reduces risk by approximately 10% (*5*). The effect of age at menarche is two-fold. First, in a chronological sense, menarche marks the onset of ovarian steroid hormone function, thus the younger a woman is when she experiences menarche, the greater her lifetime exposure to ovarian hormones. Secondly, earlier menarche is associated with earlier onset of regular (i.e. ovulatory) menstrual cycles (*52*), which further adds to hormonal levels. The frequency of ovulatory cycles is related to age at menarche and years since first menstrual period. In a cohort of girls followed from menarche to adulthood, those with early menarche established ovulatory cycles more quickly than those with later age at menarche. Within 2.5 years of menarche, 80% of menstrual cycles were ovulatory for girls with menarche prior to 12 years, whereas only 25% of cycles were ovulatory for the same time period among girls experiencing menarche at 13 years of age or older (*52*). Additionally, women who reach menarche earlier have higher estrogen levels throughout life than women who begin menarche later in life. Age at menarche appears to be related to breast cancer incidence at all ages (*5*). The role of cycle length and regularity of cycles may be related to risk although their influence is debated (*3*,*5*). The menstrual cycle is composed of the follicular phase (when estrogen levels rise prior to ovulation, but progesterone levels are relatively low) and the luteal phase (when both estrogen and progesterone are high) (*53*). The length of the luteal

phase stays relatively constant although the length of the follicular phase can vary dramatically (*54*). Therefore, women with longer cycles would spend a greater percentage of the cycle in the follicular phase and not be exposed to high levels of estrogen and progesterone together, which would be hypothesized to decrease risk of incident breast cancer. Also, shorter cycles could increase risk for breast cancer development since the shorter each menstrual cycle is, the more cycles a woman will experience over her lifetime, thus increasing total lifetime exposure to steroid hormones (*5*). Some evidence indicates that women who developed regular cycles within a year after menarche had twice the risk of developing breast cancer compared to women with 5 or more years between menarche and onset of regular cycles (*52*). Older studies found no evidence for a role of cycle length on risk (e.g. (*55,56*)), although more recent studies (with presumed more accurate cycle length quantification) do indicate that shorter cycles may be associated with an increased incidence of breast cancer. For example, among women less than 40 years of age in the Nurses Health Study, those with long menstrual cycles (>32 days) between the ages of 18 and 22 experienced a decreased incidence of breast cancer relative to those with lengths of 26-31 days [Risk Ratio (95% CI) = 0.71 (0.53 - 0.97)] (*57*).

Women undergoing menopause later in life are at higher risk for developing breast cancer compared to women experiencing menopause at younger ages. For every 5-year increase in age at menopause, breast cancer risk increases by approximately 17%. Again, this may represent a marker for longer exposure to hormones (*5*). Among women older than approximately 40 years of age, the type of menopause, either natural or through bilateral oophorectomy, does not appear to differentially affect risk (*3*).

Childbearing

Childbearing is a key determinant of breast cancer incidence. Pregnancy has a dual effect on breast cancer incidence. Immediately following a full-term pregnancy and for approximately 10 years afterwards, the incidence of breast cancer is temporarily increased (*58,59*). Women who had last given birth within three years had an increased risk of developing breast cancer [OR (95% CI) = 1.21 (1.02 – 1.44)] relative to women who had given birth 10 or more years in the past (*58*), adjusted for parity and age at first birth. This initial, transient increase in risk is likely due to the drastic increase in hormones accompanying a pregnancy. In the first trimester, bioavailable estradiol levels increase rapidly resulting in the equivalent of experiencing several ovulatory menstrual cycles over a short period of time. This dramatic increase in estrogen, while occurring in the first trimester of every pregnancy, is more pronounced during the first pregnancy than in subsequent pregnancies (*52*). This large amount of hormones could then increase the amount of cell division (*60*), and stimulate already initiated cancer cells (*61*). Over time, completed pregnancies decrease risk by causing full differentiation of breast cells (*31*), and permanently changing a woman's hormonal profile. Pregnancy decreases circulating estradiol levels, increases sex hormone binding globulin levels, thus reducing bioavailable estradiol and permanently lowers prolactin levels (*52*). In a recent collaborative meta-analysis of the effects of childbearing and breastfeeding, in the absence of breast feeding, the relative risk of breast cancer is ultimately decreased by 7% (95% CI = 5.0 - 9.0) for each birth a woman experiences after adjustment for age at first birth, study, age, and menopausal status (*6*). In addition to the effect of each birth, breast cancer risk was reduced by an additional 4.3% (95% CI = 2.9 - 5.8) for every 12 months of breastfeeding (*6*).

A key component of the effect of pregnancy on incidence is the age at which a woman gives birth. The younger a women is at her first full-term pregnancy, the lower her incidence as this allows for a shortened time between menarche and age at first birth when the breast would be particularly susceptible to mutations (*52*). In the absence of breastfeeding, the relative risk of breast cancer was reduced by 3% per year for each year earlier at first birth (*6*). The role of a first pregnancy on incidence appears to be limited to pregnancies occurring relatively early in life as women first giving birth at later ages have a higher incidence than nulliparous women (*59*). This discrepancy can be explained by the observation that current exposures to estrogens possibly augmented by progesterone increase breast cancer incidence (*62*). The effect of age at first pregnancy is independent of the total number of pregnancies, but multiparity also appears to further decrease risk beyond the first pregnancy.

Reproductive History and Hormone Levels

For reproductive factors to influence breast cancer incidence and survival through hormonal pathways, hormone levels later in life would have to correlate with past reproductive history. This has long been assumed and empirical evidence supports this assertion. As briefly mentioned previously, childbirth results in life-long changes in the hormonal milieu. Increases in serum estriol (*63*) and decreases in prolactin levels have been observed after pregnancy (*64*). Another investigation found that, when cycle length is taken into account, nulliparous women exhibit higher prolactin and estrogen levels relative to parous women, including free estradiol and urinary levels of estriol (*65*).

Spontaneous and Induced Abortions

Abortions, particularly induced abortions, have been the subject of many epidemiological studies, with most studies finding little evidence for a positive association. Most have been

case-control studies with a few early studies observing small, elevated risks for a history of induced abortions compared to no history. For example, a study by Daling et al. (*66*) observed an OR of 1.50 (95% CI= 1.2-1.9) for breast cancer among women who reported a history of induced abortions compared to gravid women with no history of abortion. Other case-control studies have observed this slight to moderate association with ORs ranging from 1.51 (95% CI=1.24-1.84) (*67*) to 1.9 (95% CI= 1.1-3.2) (*68*). Almost all record linkage and cohort studies are generally null, with ORs hovering around 1 (*69-72*). Most studies find no association between spontaneous abortions and risk (*67,73*) although one record linkage study did yield a positive, yet imprecise estimate (OR = 1.5; 95% CI = 0.7-3.7) (*74*).

The most comprehensive meta-analysis on the topic to date (*75*), combining data from 53 studies and 16 countries, observed the following. There was no association between one or more spontaneous abortions and breast cancer incidence [RR (95% CI) = 0.98 (0.92-1.04)]. The results did not differ by whether the data were obtained from self-report or objective measures or prospective versus retrospective studies. For induced abortions, there was strong evidence of heterogeneity by study design with prospective studies on induced abortions yielding a pooled RR (95% CI) of 0.93 (0.89-0.96) versus 1.11 (1.06, 1.17) for retrospective studies. The authors conclude that this difference in retrospective and prospective data is due to recall bias in retrospective studies with breast cancer cases being more likely to disclose abortions than controls (*75*).

Pregnancy interruptions, especially during the first trimester, could increase breast cancer risk by leaving a large proportion of undifferentiated cells in a state of high proliferative capacity. This rapid rise of undifferentiated cells would not be followed by the differentiation

of the terminal duct-lobular unit that occurs in the second and third trimester. These undifferentiated cells would be potentially more vulnerable to carcinogens (*76*).

Animal models suggest the pregnancy interruption hypothesis is biologically plausible. A study of DMBA induced mammary carcinomas in rats (n=59) found that the rate of mammary cancer was higher in rats undergoing a pregnancy interruption (77%) than rats experiencing a full term pregnancy (0%) or virgin rats (68%). The decreased risk in rats experiencing a full term pregnancy was due to the elimination of the terminal end buds (the undifferentiated structures that differentiate into alveolar buds and lobules) (*31*). This appears to be the only animal data that specifically tests the pregnancy interruption and mammary carcinoma hypothesis.

While no overall association between abortion and breast cancer is supported, it has been suggested that there may be sub-populations of women particularly vulnerable to any possible effects of abortion (*77*). These groups include nulliparous women, those who had an abortion prior to a full term birth, and younger women. Additionally, differences in fetal gestational age have been suggested to influence risk. Nulliparous women never undergo the full differentiation process afforded by a pregnancy, whereas a woman who has an abortion, but then goes on to have a full-term birth (or has an abortion after a full-term birth) would experience some degree of cell differentiation. Younger women, whose breast development is typically more immature than older women, might be hypothesized to be at increased risk. Also, given that hormone levels and cellular differentiation differ over the course of a pregnancy, there could be differing effects based on the gestational age of the fetus.

However, no epidemiologic data support the existence of these vulnerable sub-populations. No differences in incidence appear to exist by the timing of abortion relative to a full-term

birth, or age when the abortion took place (*75*). A handful of studies have found greater effects among nulliparous women and differences by gestational age, with induced abortions at later gestational ages having an increased risk (*66,73*). More recent studies, and most cohort studies (*69,73*), have not found convincing evidence for the existence of these susceptible sub-populations. A meta-analysis (*75*) found no evidence for differences by parity, the timing of the abortion relative to a full-term birth, or age at the abortion. There does not appear to be evidence for a dose-response relationship between the number of abortions and increased risk (*75*)

Approximately 25% of all pregnancies end in induced abortions, representing 1.3 million abortions in 2000 (*78*). There is a very narrow window of gestational ages within which most induced abortions are performed, 88% take place within the first 12 weeks of gestation with 58% taking place at 8 weeks or earlier, and 20% and 10% between 9-10 weeks and 11-12 weeks, respectively (*79*).

The probability of spontaneous pregnancy loss is 8-12% for pregnancies between the gestational ages of 8-28 weeks (*80*) and in 2000, an estimated 1.03 million fetal losses occurred (*81*). This number includes losses at all gestational ages, but the vast majority would likely have been spontaneous abortions rather than stillbirths (*81*). These numbers are clearly an underestimate given how many spontaneous abortions occur before the pregnancy is even recognized. Forty-seven percent of spontaneous abortions occur before 12 weeks of gestation, therefore there is greater variation in gestational ages for spontaneous abortions relative to induced abortions (*77*).

While the etiology of spontaneous abortions is largely unknown, fundamental hormonal and structural (chromosomal) causes that result in non-viable embryos or abnormal

pregnancies have been implicated. Typically, spontaneous abortions are marked by below normal serum hormone levels or levels that do not increase in the predictable fashion. Several studies have found lower levels of serum human chorionic gonadotropin (hCG) in women experiencing miscarriage compared to women who go on to deliver healthy babies (*82-84*). One study observed equivalent hCG activity in women undergoing recurrent loss, but did observe lower estrogen and progesterone levels (*85*). It is difficult to causally connect hormone levels and pregnancy loss since a decrease in hCG levels can be a function of, rather than the cause for, pregnancy loss. However, it does appear that diminishing hCG levels precede fetal death (*85*). Additionally, the etiology of spontaneous abortion is complex and represents a heterogeneous grouping of pregnancy complications. For example, a large proportion of miscarriages are associated with fetal chromosomal abnormalities, 46% in one study (*86*).

Reproductive Factors and Breast Cancer Survival

The limited epidemiologic data available implicates reproductive factors as prognostic factors in a number of populations and settings. Most work has indicated that women who had a full-term birth just prior to being diagnosed with breast cancer experienced shorter survival relative to nulliparous women or those who had children further in the past (*87-96*). In a study of 1,348 breast cancer cases, Reeves et al. (*91*) found those who had given birth within 5 years prior to being diagnosed were 56% more likely to die than women who were nulliparous. Women who had a birth more than 10 years before diagnosis had a 25% decreased risk of death relative to nulliparous women. Having given birth recently in relation to diagnosis was also an independent predictor of survival in another group of young, mostly premenopausal women. Women who had given birth within 2 years of diagnosis were almost

three times more likely to die than nulliparous women (Hazard Ratio (HR) = 2.7, 95% CI = 1.6 - 4.3) (*92*). Another study of 540 women less than 45 years old found that a short time interval between pregnancy and diagnosis is detrimental to survival [HR for having given birth within 2 years of diagnosis (95% CI) = 3.1 (1.8-5.4)] (*90*). Mohle-Boetani et al. (*87*) observed similar estimates. Data from the Cancer and Steroid Hormone Study was also used to analyze reproductive history and mortality after breast cancer diagnosis (*96*). This investigation included 4,299 cases between 20 and 54 years of age and among those <45 years of age and those with a birth within 12 months prior to diagnosis had a 51% increased risk of death [1.51 (1.02-2.23)] (*96*). Recent studies in other countries also confirm the deleterious effects of a recent childbirth. A large, registry-based Swedish study found women who gave birth in the year before diagnosis experienced a 72% (95 % CI = 1.42 - 2.09) increased risk of breast cancer related death compared to those whose last birth was more than 10 years before diagnosis. This survival disadvantage lasted for approximately 10 years after pregnancy and was not modified by age at first birth (*95*). A Danish registry-based study also observed elevated HRs for recent births [HR (95% CI) among parous women only, <2 years versus ≥6 years = 1.58 (1.24-2.02)] (*89*). A Norwegian study of many cancer sites found a slightly stronger effect for timing of childbirth in relation to breast cancer survival relative to other non-reproductive female malignancies, thus reproductive characteristics may be more closely associated with breast cancer survival than other cancers (*93*). An Australian population-based study also found recent births to be associated with worse prognosis (*94*). Only one study found no association between pregnancy timing and breast cancer survival (*97*), however this study suffered from low power. An additional study found no association

between a recent pregnancy and the development of metastases in a study with a median follow-up of 7 years (*98*).

Results for parity have been inconsistent with some studies indicating no effect (*91,93,96,97,99-102*), but others showing decreased survival rates for parous women compared to nulliparous women (*87,90,92,94,103-107*). One detected a 80% increased risk of death for women with 3 or more births relative to nulliparous women, and a 40% increased risk for those with 1 or 2 births (*90*); another observed, among premenopausal Australian women, almost a two-fold increased risk (HR= 1.92; 95% CI= 1.20-3.08) for ever parous women compared to nulliparous women (*94*). Similar results were noted for premenopausal American women (*87*) and Canadian women less than 36 years of age (*103*). Using a series of linked registries in Sweden, Lagerlund et al. (*107*) observed a HR of 1.70 (1.06-2.73) for parous versus nulliparous women. However, most studies did not explore whether these parity associations were confounded by recency of birth. The age distribution of women across studies may explain differences in study results, as analyses indicating an effect of parity are usually undertaken among younger, premenopausal women. Any effect of parity would likely be confined to that group, given the well-established association of recency of pregnancy.

Age at menarche (*87,91,97,101,104,105,108*), and age at first birth (*87,91-93,95-97,100-102,104,108*) have not been consistently associated with survival. A few studies have found inconsistent associations with age at first full-term birth, with one study observing a decreased risk of death in those with a young birth (*92*), two showing increased risks of death in women with younger births (*95,101*) and another observed the best survival in the range of 20-29 years of age (*102*).

Breastfeeding has been studied as a prognostic factor in a few studies (*96,99,104,106,109*). Two found no effect of breastfeeding on breast cancer survival (*96,99*), one found a decreased risk of death among women who had breastfed (*106*), and two found an increased risk of death associated with breastfeeding (*104,109*). One study finding a detrimental effect of breastfeeding on survival considered lactation at diagnosis, and the study did not control for recency of birth, therefore, there is the potential for residual confounding by recency of birth (*109*). The other study did not present any adjusted HRs (*104*). All but one study (*96*) only considered broad categorizations of breastfeeding (e.g. ever-never).

Having had an induced or spontaneous abortion was not associated with survival in 3 studies (*92,105,108*). Daling et al. (*92*) with a total sample size of 1174 and 106 months of median follow-up indicated no overall relationship between either spontaneous or induced abortions. The relative risk of death from breast cancer for women with a history of spontaneous abortion and induced abortion relative to women without a history was 0.9 (95% CI = 0.6-1.2) and 0.9 (95% CI = 0.7-1.1), respectively, adjusted for age and diagnosis year. Survival estimates did not vary by the age at the first induced abortion.

Greenberg et al. (*108*) examined the prognostic significance of a history of miscarriage before a first term birth in a cohort of 582 premenopausal breast cancer cases aged 24 – 50 years. No association (HR= 1.0) was observed.

A third study of 1885 women observed that spontaneous and induced abortions considered together only affected survival in univariate analyses (*105*). Those women whose pregnancies exceeded the number of deliveries had slightly better 10-year overall survival (56%) than those whose pregnancies equaled the number of deliveries (52%). Both survival estimates are lower than the survival in nulligravid women (62%).

Caution in interpreting the results from these 3 studies is warranted. Various survival outcomes were considered including death from breast cancer (breast cancer cases were followed from diagnosis until death from breast cancer) (*92*) and overall survival (breast cancer cases were followed from diagnosis until death from any cause) (*105,108*). Additionally, various definitions of abortions defined by parity, gestational age, age of women at the time of the abortion, or relationship to a full-term birth were not fully explored in any of the three analyses. Thus, the potential of vulnerable sub-groups as hypothesized for risk has not been adequately studied in the survival literature. Other methodological concerns such as recall bias and the use of differing referent groups also have not been consistently evaluated or considered.

Figure 1 in the appendix outlines a conceptual model for how reproductive factors may influence survival. The exact mechanism of action of childbearing and other reproductive factors on prognosis is unknown. It is possible that any associations between recent pregnancies and survival could be due, at least in part, to delays in diagnosis and not reflective of a more aggressive disease. Pregnancy related changes in breast density and architecture make cancer diagnosis difficult, thus, clinicians might ascribe any breast changes to the pregnancy when in fact it could represent subclinical disease (*110*). Certainly, diagnostic delays could be part of the association, but at least one study (*89*) observed lower survival for women with recent births at all tumor stages, providing evidence that even less advanced tumors are affected by a recent pregnancy. Also, since younger women do not routinely undergo mammography, systematic delays in diagnoses for women who recently gave birth versus women without a recent birth are minimized.

Reproductive characteristics such as high parity and recent births may exert their effects on survival through the production of tumors with more aggressive characteristics. Women with high parity or a recent birth are more likely be diagnosed with later stage and node positive disease and with ER-, p53+, high grade, highly mitotic, and high S phase fraction tumors (*88,89,92,103,111*). These studies have concluded that childbearing also appears to exert independent effects, given that estimates were still elevated even after adjustment for tumor size, development and aggressiveness. One study found no evidence that reproductive factors, such as parity, age at menarche, and age at first birth, were associated with tumor growth measured by Ki-67 and mitotic count (*112*). Early spontaneous and induced abortions before a first full-term pregnancy are associated with higher S phase fraction (*113*) and amplification of the INT-2 proto-oncogene (*114*). Amplification of the INT-2 gene has been associated with lower survival, and is more likely to be amplified among younger women. However, this observation was only based on 176 patients and only noted in univariate analyses. In multivariable analysis, HER-2/neu appears to be more important for survival (*115*). HER-2/neu amplification is not associated with a history of abortions (*114*).

In review, previous studies have concluded that there is no overall association between age at menarche or the number of full-term pregnancies on prognosis, although there may be an effect only among younger women. Age at childbirth may be associated with survival. Consistently, the timing of pregnancies relative to the development of breast cancer is an important prognostic factor such that women who give birth relatively close to the time they become diagnosed have lower survival (*116*). Induced or spontaneous abortions do not appear to be associated with survival, but the lack of consistent definitions and limited, comprehensive data available makes definitive conclusions difficult.

Oral Contraceptives (OCs) and Breast Cancer Incidence and Survival

OCs: Background

Women commonly use oral contraceptive pills during their reproductive lives. As measured in the 1995 National Survey of Family Growth, approximately 82% of women aged 15-44 had ever used oral contraceptives (*117*). In the same survey, 10.4 million women were current users of contraceptive pills, representing 17% of all women (*117*) and 27% of contraceptors between 15 and 44 years of age (*118*). The pill was the most common contraceptive used by women less than 30 years of age (*117,118*) and its use increased among older women between 1982 and 1995 (among women aged 30-34, 16% used the pill in 1982 versus 31% in 1995 (*118*).

Oral contraceptives have undergone tremendous changes since their introduction following FDA approval in 1960, unlike almost any other pharmaceutical on the market. Three basic types of OCs have been marketed including sequential OCs, progestin-only pills, and combination OCs. Sequential pills, introduced in 1965 but no longer marketed, included estrogen alone for the first 14-16 days of the cycle then an estrogen/progesterone combination during the last 5 days. Progestin-only pills, available since 1973, contain no estrogen, but a lower dose of progesterone than other pills types and have never been widely used. The best selling type of OC has been the combination pill, which has been available since 1960. Initially, combination pills included a fixed amount of estrogen and progestin taken for 21 days. Phasic combination pills, available since 1983, contain a fixed dose of estrogen with varying progestin levels varying over the cycle. Biphasic OCs increase the progestin dose in the second half of the cycle while triphasics contain three progestin doses over the cycle. Phasics have a total lowered steroid content than other types of pills (*119*).

The content of oral contraceptive pills has also changed drastically. Since 1960, OCs have included two estrogens (ethinyl estradiol and mestranol) and twelve progestins, each varying in dose and potency (*119,120*). The progestins chlormadinone acetate, dimethisterone and medroxyprogesterone acetate are no longer used in OCs; desogestrel, norgestimate, and drospirenone are recently developed progestins (*119,120*). None of the latter three progestins were used by women in this follow-up study. All of the current progestins available are androgen derivatives (particularly of 19-nortestosterone), except for drospirenone, which is derived from the antihypertensive compound spironolactone (*120*). Chlormadinone acetate and medroxyprogesterone acetate (neither of which are currently on the market, but were used by some women in the follow-up study) are 17-alpha-hydroxyprogesterone derivatives (*121*). Table 8 in the appendix lists the pills (by brand name and formulation) that were used by women in this study, and are cross-classified according to their potency. In total, 43 different combination (including sequential) pills were used by women in the follow-up study, including pills with both types of estrogen and eight different progestins.

From 1964 to 1984, there was a dramatic switch from high to lower dose and potency estrogen and progestin formulations. For example, between 1964 and 1970, low dose and potency estrogen pills represented 50% of all dispensed pills, but by 1984 the percentage was 85% (*119*). By the 1990s, OCs contained one-fourth the estrogen and one-tenth the progestin of pills manufactured in the 1960s and early 1970s (*122*). Ethinyl estradiol is 1.7 times more potent then ethinyl estradiol on an equivalent weight basis (*119*); 50 µg of mestranol is equivalent to 35-40 µg of ethinyl estradiol (*120*). Mestranol is metabolized to ethinyl estradiol by the liver (*120*). Of the pills on the market in the mid-1980's, relative progestin potencies were as follows. Norethindrone, norethindrone acetate, ethynodiol diacetate are all

equal, representing those with the lowest potency, norgestrel is 5-10 times as potent as those, and levonorgestrel is 10-20 times as potent (*123*). Progestins also exhibit androgenic activity, since they are derived from 19-nortestosterone. Of pills on the market today, levonorgestrel exhibits the highest level of androgenic activity, followed by norgestrel (*124*). The remaining progestins are devoid of such activity (*125*). Potency is an attempt to define the pharmacological effects of OCs on various target organs (*126*). Estrogen potencies are derived from data on human uterine volume and mouse uterine weight gain (*127-129*). Progestin potencies are determined through data in humans on delay of menses, and the magnitude of glycogen incorporation in human endometrial vacuoles (*130,131*). Total pill potency is a cross-classification of the potencies of the individual steriods, their doses and their interactive effects. Progestins modify the effects of estrogens in ways that are dependent on the type and amount of progestin as well as the ratio of progestin to estrogen. Therefore, the total estrogenic potency of a pill is based on the combined effects of the estrogen and estrogenic/antiestrogenic/androgenic activity of the progestin (*132*).

OCs: Mechanism of Action

The International Agency for Research on Cancer classifies combination OCs as carcinogenic in the human breast, with a group 1 level of evidence, the highest classification scheme possible (*133*). The monograph (*133*) also concludes that there is sufficient evidence in experimental models for carcinogenicity of the following estrogen and progestin combinations; ethinyl estradiol plus ethynodiol diacetate, mestranol plus norethynodrel, and ethinyl estradiol plus levonorgestrel. Sufficient evidence of carcinogenicity was also noted for the estrogens ethinyl estradiol and mestranol and the progestins norethynodrel and

lynestrenol, but there is inadequate evidence for the progestins levonorgestrel, norgestrel and dienogest (*133*).

The exact biological effects of OCs on breast cell proliferation are not well known. OCs inhibit ovulation by blocking surges of gonadotropins, follicular stimulating hormone, and luteinizing hormone (*91*,*120*). Therefore, OCs function by shutting down the body's production of hormones and replacing them with synthetic hormones at a constant rate throughout the menstrual cycle (*3*), making it difficult to directly compare the levels of synthetic hormones in OCs to natural ovarian steroid hormone levels (*62*). However, women on OCs are exposed to progesterone for a longer period of time, 3 weeks, compared to naturally cycling women where progesterone is only present for the second half of the cycle (*62*). Often, OCs are used to regulate menstrual cycle length in those who are anovulatory or have long cycles (*132*), thus estrogen levels may be increased in such women while on OCs. This could be particularly true for young women prior to a full-term birth who are less likely to have regular cycles. It has been suggested that OCs may have a promotional effect rather than an initiating effect since a rapid rise in breast cancer incidence after initiation of use is followed by a sharp decline after discontinuation with little association with duration of use (*134*). While some argue that total breast cell proliferation is likely similar between OC users and non-users compared to women undergoing normal menstrual cycles (*62*), some data do support that cell proliferation is higher among users (*42*,*135-137*). In a study of 216 women with histologically normal breast tissue who underwent surgeries for fibroadenoma or reduction mammoplasty, the relationship between OC use and ER activity was investigated. The mean proportion of proliferating cells was greater in women on OCs and OCs appeared to reduce the number of cells expressing estrogen receptors, but no effect on the progesterone

receptor was observed (*42*). In other words, the authors concluded that, while on OCs, there is a greater suppression of the ER and a longer period of high proliferation during the menstrual cycle (*42*). Similarly, in a study of 58 women undergoing reduction mammoplasties, women who used OC before a first full-term pregnancy had a higher proliferation rate (as measured by the antibody Ki-S5) relative to never users or later users (*113*). Research involving fine needle aspiration biopsies in women with normal breast tissue also confirm this association (*137*). Proliferation (defined as the percentage of Ki-67/MIB-1 positive cells) was increased after 2 months of OC use; mean proliferation was 4.8% versus 2.2% in non users (*137*). Also, in this same study, a positive correlation between cell proliferation and serum progesterone levels in non OC users was observed. Similarly, in OC users, there was a positive association between serum levonorgestrel levels and use of pills containing that synthetic progestin (*137*). Breast cell proliferation, as assessed by 3H-thymidine labeling of normal lobular units from benign biopsis, was positively associated with OC use in another study of 347 women (*135*). Certain progestins may also differentially affect cell proliferation in both malignant and normal breast epithelium and this relationship may be independent of estrogen and growth factor inclusion (*138*), however, the association is complicated. For example, medroxyprogesterone acetate and chlormadinone acetate induced proliferation in normal breast cell lines (MCF10A), whereas levonorgestrel had no effect (*138*). However, in a breast cancer cell line (HCC1500), levonorgestrel enhanced the proliferative effect of growth factors (*138*). Another previous investigation observed that the progestin formulation of the OC did not significantly influence breast cell proliferation differentially; however, women on progestin-only pills exhibited the greatest proliferation (*135*). Increasing estrogen content was associated with increased proliferation (*135*). It

should be noted that investigating possible differences in breast cancer outcomes (or breast epithelial cell proliferation) due to different progestin formulations is difficult since assigning dose and potency is inexact and depends on a number of factors, including the estrogen component of the pill (*119*).

OCs and Breast Cancer Incidence

Oral contraceptive use has long been studied as a potential risk factor for breast cancer development. The most comprehensive meta-analysis to date observed a slight increase in breast cancer incidence for OC use within the past 10 years, but no increase for those who ceased use more than 10 years in the past (*134*). Several unique complexities make studying OC use difficult. For example, OC use is necessarily restricted to relatively young women and tremendous secular changes in pill content and potency have likely led to age-period-cohort effects on incidence that are difficult to disentangle. It has also been hypothesized that incidence may differentially depend upon OC formulation, duration of total use, age at first use, parity, and family history of breast cancer, although no data has borne out these suspicions (*139*).

The most complete data available is a reanalysis of individual data from the majority of epidemiological studies to date (*134,139*); the results of which are as follows. Current users of combination oral contraceptive pills and those who ceased use less than 10 years previously, were at a slightly increased risk of breast cancer [RR (95% CI) in current users = 1.24 (1.15-1.33), 1-4 years after stopping = 1.16 (1.08-1.23), 5-9 years after stopping = 1.07 (1.02-1.13)]. Ten or more years after cessation, the association is null [RR (95% CI) = 1.01 (0.96-1.05)]. The key determinant of risk appears to be recency of use, rather than total duration of use, or age at first use. Due to the low absolute risk of developing breast cancer at

ages younger than 45, the increased number of breast cancer cases due to recent oral contraceptive use would be relatively small overall (*134*). Broadly measured, dose and type of OC did not affect breast cancer incidence differentially. Additionally, breast cancers in OC users were less clinically advanced than in non-users (*134*). This is not likely to be due to surveillance or diagnostic bias since the deficit of advanced disease in OC users is present even among former OC users. In addition, among controls, frequency of mammography was similar among OC users and non-users (*139*).

A relevant issue is whether the OC – breast cancer association varies by age at diagnosis, independent of recency of last use. No data presented in either collaborative report (*134,139*) directly sheds light on this possibility. What is presented is a simultaneous stratification by both age at diagnosis and age at first use simultaneously. It appears that among women diagnosed at younger ages, the association between breast cancer incidence and OC use is larger for those who began using OCs before age 20. Among women diagnosed at less than 30 years of age, the RR was 1.95 for women who began OC use at less than 20 years of age compared to women who were 20 or older at first use (RR=1.14) (*139*).

One limitation of the collaborative report is the small number of women diagnosed at younger ages, for which the magnitude of the association between oral contraceptive use and breast cancer is possibly stronger (*140*). Reports that have concentrated solely on younger women observe that women diagnosed when less than 35 years of age were more likely to be OC users [OR (95% CI) = 1.74 (1.2-3.6)] compared to those diagnosed between 35-39 years of age [OR (95% CI) = 1.36 (1.0-1.8)] or 40-44 years of age [OR (95% CI) = 1.12 (0.9-1.4)] (*141*). The effect of recent OC use was even more pronounced among premenopausal women with ORs (95% CIs) of 2.26 (1.4-3.6) and 1.31 (1.0-1.8) for women less than 35 years of age

and those between 35-44 years of age, respectively (*12*). Most (*142-145*), but not all (*140,146*) studies also support the positive association between oral contraceptives and breast cancer incidence in younger women, particularly for recent or long-duration use. Thus, it appears that OC use may be more risky for women diagnosed at younger ages. This finding does not appear to be explained by the greater likelihood of younger women to be recent users as estimates for younger women are not entirely confined to those women who reported recent use. Rather, associations among women less than 35 years of age are larger than those among 35-44 year olds, and the same pattern of effect by recency of use is noted (i.e. among recent users, associations for OC use were larger for women diagnosed at younger ages) (*12*). Therefore, it is possible that, even after taking recency of use into consideration, there may be a residual effect of age at diagnosis on breast cancer incidence. The small numbers of women in each sub-group hampers disentangling the effects of recency of use and age at diagnosis.

Most epidemiological studies have focused on combination pills, including the largest comprehensive collaborative analysis (*134*), due to the small numbers of women who take other varieties. Examining the potential for differential effects of specific types of OCs (thus implicating certain doses, potencies, or formulations) on breast cancer incidence has yielded contradictory results with some studies finding no effect (*121,134,140,145,147,148*). However, OC content was assessed crudely in these studies and only based on the estrogen dose. OC potency, the actual effect of each drug on physiology, based on clinical and animal studies of the pharmacological effects of each steroid and their interactions (*119*), is rarely considered. A more thorough investigation of possible differences by potency and dose has indicated differences in incidence may be related to such characteristics. In one study, recent

high dose estrogen users (>35 μg ethinyl estradiol or >50 μg mestranol) or users of higher potency pills formulations typically experienced higher ORs (*149*). For example, women taking OC preparations with greater than 35 μg ethinyl estradiol were at approximately two-fold increased odds of breast cancer incidence (95% CI = 1.2-3.2), whereas women on lower dose pills had a lower odds of disease [OR (95% CI) = 1.27 (0.9-1.7)] (*149*). In this same study, progestin type was not consistently related to breast cancer risk, nor did risk appear to increase with increasing androgen activity of pill formulations (*149*). However, there was some suggestion that, among women 35-44 years of age, users of pills containing the progestin levonorgestrel had one of the highest risks of breast cancer [OR (95%CI) = 1.77 (0.8-4.0) (*149*). Another study concluded that increasing cumulative doses of levonorgestrel were associated with increasing risk, but despite a statistically significant p-value for the trend test (p=0.03) the point estimates for low (<0.3) and high levonorgestrel dose (≥0.3) were equivalent [1.31 (1.01-1.68) and 1.28 (0.98-1.66), respectively] (*150*). Two other studies observed that breast cancer risk was associated with particular pill formulations (*151,152*). A case-control study of 747 cases (diagnosed between 1983 and 1990) and 961 controls, all aged 21-45 years and residents of the Seattle metropolitan area was undertaken to examine OC characteristics and breast cancer risk. Use of high-progestin potency pills for at least a year was associated with breast cancer incidence [OR (95% CI) = 1.5 (1.1-2.1)] (*151*). Similarly, Pike et al. (*152*), in a study of 314 cases (diagnosed between 1972 and 1982) and 314 controls younger than 37 years of age, observed that long-term use of high progestin potency pills before the age of 25 was associated with increased risk of breast cancer, but no such increase was noted for pills with a low progestin potency. However, not all studies have observed associations with particular pill formulations (*121,147,148*). In a

study of almost 2100 cases diagnosed between 1980 and 1982 and approximately 2100 controls, use of high progestin potency pills before age 25 was not associated with risk, even for long durations of use (*147*). A hospital based case-control study of 2,754 cases and 18,565 controls concluded that risk of breast cancer did not vary by type of estrogen or progestin compound (*121*). In the Cancer and Steroid Hormone Study (approximately 9400 cases and controls between 20-54 years of age), no association between estrogen or progestin type and breast cancer risk was observed, among women who used only one OC formulation (*148*). Therefore, the role of pill dose, potency and formulation in breast cancer incidence is still unresolved. Discrepancies in study results for pill type could have arisen due to the different populations of women included (different cohorts of women would have been exposed to several types of pills for various lengths of times). In addition, differences in content for pills used in various periods relative to diagnosis (e.g. recent pill use, young pill use, etc.) may not have been adequately explored.

OCs and Breast Cancer Survival

Figure 2 is a conceptual model detailing the potential relationship between OC use and survival. A few studies have considered the prognostic significance of OC use prior to the development of breast cancer (*87,91,97,101,104,108,153-164*). Two studies observed that OC users had decreased mortality relative to non-users (*154,161*). The Schonborn et al. study had a median follow-up of 56 months and observed a HR (95% CI) of 0.56 (0.35-0.89) comparing OC users to non-users (*161*). Contrary to those two studies, several studies have detected a modest trend of increasing risks of death or disease recurrence for OC users compared to non-users (*91,104,158-160,163*). In one study of 1,121 cases, diagnosed between 1971 and 1974 in Alberta, Canada (*104*), oral contraceptive use for more than one

month was associated with greater risks of breast cancer-specific death but only after stage was included in the model. HRs for multivariable models were not presented in the paper, nor were interactions between age at diagnosis or menopausal status and OC use considered. A hospital-based study of 149 patients, diagnosed between 1989 and 1991, aged 26 to 95 years and followed for 5 years (*163*), observed that OC users were at increased risk of local, regional or distant recurrence [HR (95% CI) = 1.28 (1.03-1.60) per 3 years of OC use], but not at increased risk of death from any cause [HR (95% CI) = 1.10 (0.84-1.45)].

Additional studies have found no effect of OC use on survival (*87,97,101,108,153,155-157,162,164*). Sauerbrei et al. (*162*) examined the effect of OCs on survival in 422 node positive, premenopausal breast cancer cases enrolled in a German clinical trial. The exact age ranges of women and exact definitions of OC use were not described. In that study, there was no association between OC use and recurrence-free survival, defined as time from mastectomy to loco-regional recurrence, distant metastases, contralateral tumor, secondary tumor or death [HR (95% CI) = 1.02 (0.71-1.47), or with overall, all-cause death [HR (95% CI) = 1.28 (0.82 - 1.98) (*162*). The Schouten et al. study (*101*) was a large (n=866) clinical investigation of treatment in women less than 71 years of age with Stage I through III disease. OC use was not clearly defined and death from breast cancer was the endpoint of interest. Rosner et al. (*156*) investigated the hypothesis among 347 patients 50 years of age and younger and treated between 1971 and 1981. No statistically significant differences in disease-free interval, metastatic period, or overall survival were observed. Lymph node involvement was the only characteristic investigated as a potential confounder. Adjusted Kaplan-Meier plots and p-values for the differences between the two curves were presented rather than HRs and CIs.

Two studies found that the adverse effect of prediagnostic use of OCs on breast cancer survival was limited to women who began use at younger ages (≤ 20 years) (*158,159*), but this was not confirmed in a larger study (*160*). Survival was not dependent upon latency of OC use (*160*), but may be related to duration (*160*) or recency of use (*91,158*). To date, no one has reported on pill content and survival.

Contradictory results across studies could be due to differences in sample sizes, subject selection and age distributions of the women included or differing formulations of OC preparations over the years. Additionally, inconsistent definitions of survival, such as various definitions of a recurrence or whether death due to breast cancer is the end-point of interest as opposed to all-cause mortality, may contribute to study heterogeneity. Thus, large studies of younger women for whom OC use was more common during their reproductive years are needed to help resolve this issue as well as whether any differences in survival exist by age at onset, recency, or latency of use.

Background: Conclusions

Few comprehensive, large-scale, population-based studies have examined non-clinical and non-molecular predictors of survival in young women with breast cancer. Compared to older or postmenopausal women, younger and premenopausal women have worse prognosis, yet the exact reasons why are unknown. A hormonal component to breast cancer incidence has been long established, and certain clinical observations implicate similar pathways in breast cancer survival. To summarize the literature to date on reproductive and oral contraceptive predictors of survival among younger women, it appears that parity, and having recently given birth may be associated with an increased risk of death. Abortions do not appear to influence survival. Studies examining age at first full-term birth, age at menarche,

breastfeeding and oral contraceptive use have been largely inconsistent. However, there are few studies of survival in younger breast cancer cases and thus there is uncertainty as to their effects.

This dissertation addressed the following research questions in a cohort of breast cancer cases: 1) are characteristics of a woman's reproductive history associated with overall survival, and 2) is a history of OC use associated with overall survival. These aims will add to a growing body of literature on the topic and will aid our understanding of how women's reproductive history and contraceptive methods influence overall survival. Results from studies such as this may shed light on breast cancer progression mechanisms and allow us to understand reasons for differences in mortality in certain sub-populations. This research is important given the tremendous numbers of women who have been exposed to OCs and recent secular changes in childbearing patterns in recent cohorts of women. Previous studies suffered from drawbacks such as a lack of individual data, limited follow-up time, small numbers of study participants, and lack of comprehensive, detailed predictor and covariate data.

CHAPTER II: RESEARCH DESIGN AND METHODS

Dissertation Research Overview

This investigation builds upon a previously conducted population-based case-control study, the Women's Interview Study of Health (WISH) that determined risk factors for breast cancer in women aged 20 through 54 in three centers (Seattle, WA, central New Jersey, and Atlanta, GA). WISH was principally concerned with investigating reproductive factors, OC use, alcohol consumption and adolescent dietary intake as risk factors for breast cancer development among younger women (*141,165,166*). Secondarily, physical activity and weight status across the lifecourse were also of interest (*10,167*). A cohort study was undertaken among the invasive cases from New Jersey and Atlanta, GA (n=1264) to determine predictors of survival among younger breast cancer patients. Specifically, this dissertation investigated whether pre-diagnostic reproductive and contraceptive factors related to the development of breast cancer also affect overall survival after approximately 10 years of follow-up. The majority of exposure and covariate data came from the original case-control interviews, and the outcome data (survival time) was collected through a national death registry and the cancer registries in the two areas. This dissertation was approved the School of Public Health Institutional Review Board at the University of North Carolina at Chapel Hill.

Parent Case-Control Study: WISH

Study Population

The parent case-control study included *in situ* and invasive cancer cases from three population-based cancer registries in the Seattle/Puget sound area, central New Jersey and the metropolitan Atlanta, GA area as well as controls ascertained through random-digit dialing. All primary, incident invasive and *in situ* cases, aged 20-44, residing in one of five counties of central New Jersey (Middlesex, Monmouth, Morris, Somerset, and Union) or the Seattle/Puget Sound area, and diagnosed between May 1, 1990 and December 31, 1992 were eligible for inclusion in the original case-control study. Women diagnosed during the same time period, between the ages of 20-54 years, and residing in three counties of metropolitan Atlanta, GA (Fulton, DeKalb, and Cobb) were also eligible. The extended age range in Atlanta was undertaken to evaluate associations and interactions between age and race (*141*).

Subject Recruitment and Enrollment

Subject recruitment and enrollment in the original case-control study proceeded as follows. All cases were identified through population-based registries using rapid-ascertainment systems, including the population-based New Jersey State Cancer Registry and the Atlanta site of the Surveillance, Epidemiology and End Results (SEER) program. Study personnel visited all hospitals providing care to patients in the study region on a monthly basis and reviewed all pathology reports to identify incident breast cancer patients. Completeness of patient ascertainment was confirmed via period checks with the registries and hospital discharge data (*141*). Study staff contacted each patient's physician to confirm the diagnosis and obtain permission for initial patient contact. After physician confirmation and approval for further contact, trained study personnel contacted eligible patients, explained the study protocol, obtained informed consent, and scheduled an in-home interview. All interviewers

used a standardized protocol and questionnaire across all centers to ensure consistency and quality.

Interviews were completed for 2,203 (86%) of the total case (*in situ* plus invasive) population from all three geographic centers from the original case-control study (*141*). Eighty-four percent of patients were interviewed within 6 months of diagnosis (*167*), and the median time from diagnosis to interview was 4.2 months (*141*). The interview lasted an average of 67 minutes and included detailed questions on many suspected breast cancer etiologic factors, including demographic characteristics, family medical history, personal medical and screening history, menstrual and reproductive history, physical activity, adolescent diet, alcohol consumption, cigarette smoking status, and use of contraceptives and other exogenous hormones. Patients were also asked about any treatment (e.g. chemotherapy, radiation) they received prior to the interview date. Patients were also asked to sign a medical records release form permitting collection and abstraction of additional pertinent medical and clinical characteristics such as tumor stage (SEER summary) (*168*) and grade, and ER/PR status. In Atlanta only (n=831), more detailed staging and treatment information was available through reabstraction of the medical records and through SEER. Specifically, this included American Joint Committee on Cancer (AJCC) stage (I, IIA, IIB, IIIA, IIIB, IV) (*169*) and information on the first course of treatment (breast conserving surgery versus mastectomy, radiation (yes/no), chemotherapy (yes/no) and adjuvant hormonal therapy (yes/no)).

Main Results from Parent Study

The main results from the parent case-control study (including data from all three centers-Seattle, WA, Atlanta, GA and central NJ) were as follows. Increased risks for *in situ* and

invasive breast cancer were observed for nulligravidity, late age at first birth, and early age at menarche (*141*). Women with no previous births had approximately twice the odds of breast cancer compared to women with 4 or more births. The ORs (95% CIs) for late age at first birth (≥ 30 vs. < 20 years of age) and early menarche (< 12 vs. ≥ 14 years of age) were 1.42 (1.1 - 1.9) and 1.17 (0.9 - 1.4), respectively (*141*).

Among participants less than 45 years of age, oral contraceptive use for more than 6 months was associated with an increased incidence of breast cancer [OR (95% CI) = 1.3 (1.1-1.5)] (*141*). There was a suggestion of greater risks for breast cancers arising in women younger than 35 years of age [OR (95% CI) = 1.7 (1.2 - 2.6)] and those who used OCs for 10 or more years [OR (95% CI) = 2.2 (1.2 - 4.1)]. OC use starting before 18 years of age with continued long-term (>10 years) use was associated with a three-fold increase in risk [OR (95% CI) = 3.1 (1.4-6.7) (*141*). When stratifying by stage at diagnosis, analyses from WISH observed stronger OC – breast cancer incidence associations in women diagnosed with local or regional/distant disease relative to women diagnosed with *in situ* tumors. Further investigations (*12,149*) indicated that the effect of OCs were particularly high [OR (95% CI) = 2.26 (1.4-3.6)] among premenopausal women less than 35 years of age. This association was stronger for such women with ER– tumors [OR (95% CI) = 3.56 (1.8-7.1)] compared to women with ER+ tumors [OR (95% CI) = 1.66 (0.9-3.0)] (*12*). Higher breast cancer risks were also observed for women who used high dose estrogen pills (OR = 1.99 vs. 1.27) or high estrogen or high progesterone potency relative to women using lower dose or potency pills. Again, this effect was most pronounced for women diagnosed at less than 35 years of age (*149*).

Among white participants in the WISH study, a history of induced abortion was associated with slightly increased breast cancer incidence [OR (95% CI) = 1.2 (1.0-1.5)] (*170*). This relationship was not modified by the number of abortions or a woman's age at diagnosis, but was observed primarily among nulliparous women who had their abortion prior to 9 weeks of gestation [OR (95% CI) = 2.0 (1.2 - 3.3)]. No association was found in parous women. There was some indication that age at first abortion modified the effect of induced abortion on incidence as larger ORs were observed for women having an induced abortion before the age of 20 [OR (95% CI) = 1.5 (1.0 – 2.3)] or at 30 years of age or older [OR (95% CI) = 1.4 (0.9 – 2.1) (*170*).

Exposure Assessment

All exposure variables (reproductive factors, OC use) and most potential covariates were obtained from the original WISH case-control interview. Clinical characteristics such as tumor stage, grade and hormone receptor status were from medical record abstraction. All exposure variables considered only the exposures prior to the patient's first, primary diagnosis of invasive breast cancer (i.e. all variable were pre-diagnostic in nature). To enhance recall of key exposure of interest during the one-hour interview, several memory aids were used. As the study participant responded to the structured questions, the trained interviewer first recorded the dates of key life events (menarche, marriages, pregnancies, periods of nursing, and last menstrual period) on a reproductive history calendar (a month-by-month, visual reconstruction of the time between menarche and menopause). Subsequently, during the section of the interview involving contraceptive history, all methods and corresponding dates of contraception (as well as periods during which no method was used) were then added to the calendar. Of particular interest to this dissertation

were the periods of OC use. Periods of OC use for "non-contraceptive" reasons (e.g. acne, irregular menstrual periods) were also recorded on the calendar. This calendar enhances recall of OC specifics such as start and stop dates for various periods of use by having women anchor their OC use to other life events that are particularly memorable (*171-173*). For all pills that were ever marketed prior to the study, color photographs of the pills and their packaging and information on their dates of introduction and removal from market, were shown to study participants to enhance brand-specific recall (*171-173*).

Reproductive Factors

Several reproductive factors were considered in this dissertation, all of which were based on women's self-report. Detailed information was collected during the interview on each participant's menstrual, menopause and pregnancy history. The ultimate exposures of interest included age at menarche, gravidity, parity, spontaneous abortions, induced abortions, age at first birth, age at last birth, the timing of births relative to diagnosis (i.e. how soon before diagnosis a woman gave birth), and breastfeeding history. Patients recalled at what age they had their first menstrual period. They were asked how many times they had been pregnant, including all live births, stillbirths, miscarriages, abortions, and tubal/ectopic pregnancies. For each pregnancy, the outcome (live birth, stillbirth, abortion, miscarriage, ectopic/tubal pregnancy, or currently pregnant) was recorded. Subjects were given the definition if they asked, for example, a live birth is a pregnancy lasting at least 6 months that resulted in a child being born alive. Stillbirths were defined as pregnancies lasting at least 5 months in which the fetus was not born alive and were distinguished from fetal losses before 5 months that were defined as miscarriages. Each pregnancy was then asked about in depth concerning how it was confirmed, its duration, the specific date it ended, several pregnancy associated

conditions (frequent nausea, hypertension, diabetes, toxemia and amount of weight gain), and breastfeeding practices. Each reproductive exposure was derived as follows.

Age at menarche

Age at menarche was derived from the question "at what age did you have your first menstrual period?"

Gravidity

Gravidity was defined as ever being pregnant (any pregnancy outcome) prior to diagnosis. Pregnancies at the time of the interview were not included in the calculation.

Parity

Parity was calculated based on the number of still and live births prior to diagnosis. Births after diagnosis were not counted in the parity calculations. Parity was defined in several ways considering parous versus nulliparous, in addition to categorical parity (the number of births).

Abortion (spontaneous and induced)

Spontaneous abortions were considered for those women who respond affirmatively to having had a miscarriage, which if a participant asked, was defined as an incomplete pregnancy lasting less than 5 months that was not medically terminated. Induced abortions were characterized as occurring for those women who answer they had an abortion at any point during the pregnancy. Induced and spontaneous abortions were ultimately analyzed in many ways including among gravid women only, and among nulliparous and parous women only. For induced abortions, several subgroups were analyzed including those based on the gestational length of the corresponding pregnancy (derived from the “how many weeks or months did that pregnancy last” question), which was used to consider differences in risk by

length of gestation. Additional characterizations such as age at first abortion, and timing of abortion in relation to a full-term birth were also considered.

Age at first and last birth

Age at first and last birth was derived from the date and length data corresponding to a woman's first birth and her date of birth.

Time since last birth (recency of birth) relative to diagnosis

This variable was calculated as the date of diagnosis minus the date of the last birth.

Breastfeeding

Ever breastfeeding was defined as having breastfed any child for ≥2 weeks. To examine duration of breastfeeding, lifetime breastfeeding duration until regular supplementation and until complete cessation were calculated by summing all breastfeeding episodes. Supplementation was defined as the point at which the baby regularly began taking any food, formula or milk other than breast milk.

Oral Contraceptive Use

Oral contraceptive use from the time of menarche to the diagnosis date was ascertained during the in-person interview and established by first shading key life events such as marriages and pregnancies on the reproductive calendar (described above). This frame of reference was then used to help women recall months of OC usage as well as changes in use over time. For each type of OC used the brand name, the dates of usage, and the reason for beginning and discontinuing use were recorded. Photographs and a listing of years each type of OC (brand and dosage) was marketed in the U.S. were used to help women recall the specific brand name used (*141*). Various characterizations of pre-diagnostic OC use were considered and included the following:

Ever OC use

Ever use of OCs was primarily defined as any reported use of OC, regardless of duration. Since so many women took OCs, ever use was also secondarily defined as 6 months of use or longer.

Duration of total use

Duration of total use was calculated by adding up all episodes of OC use.

Age at first and last use

These variables were calculated from the date of first and last use of OCs and a woman's date of birth.

Time since first use (recency of first use) and last use (recency of last use)

Recency of first and last use were defined as months between first use of OCs and diagnosis and months since last use of OCs and diagnosis.

Duration of use before age 25 and duration of use before a first birth

Duration of use before age 25 and before a first birth were calculated as total duration of OC use before age 25 and a woman's first birth, respectively.

Pill content

To analyze dose and potency specifics, several pill components were considered. Similar to previous analyses (*149*), participants were excluded from the content analyses if they used OCs for <6 months (n=118, 12% of ever users), could not recall their dates of use or the specific pill types (n=202, 20% of ever users), or exclusively used progestin-only pills (n=6, <1% of ever users), resulting in 689 patients with pill content data. Classification of dose and potency is complicated for women who used multiple pills at different time periods for varying durations, therefore, components of combination OCs used in potentially biologically

relevant time periods were analyzed (*149*). These time periods of prediagnostic use included: 1) the most recently used pill, 2) the pill used for the longest period within 5 years, 3) the pill used for the longest period within 10 years, and 4) the pill used for the longest period ever. For the pill used in the relevant time period, it was classified based on its formulation (estrogen and progestin type), potency (the cross-classification of estrogen and progestin potency) and estrogen dose. Differences in survival by estrogen type (ethinyl estradiol versus mestranol) and grouped progestin types were primarily of interest. Progestins were grouped as follows: norethindrone, ethynodiol diacetate, and norethindrone acetate were considered together, chlormadinone acetate, and medroxyprogesterone acetate were grouped together and norethynodrel, levonorgestreal and norgestrel were considered separately. These groupings were based upon their approximate pharmacological effects (*123*). Limited power precluded analyzing all the progestins separately. Potency (low progestin/low estrogen, low progestin/high estrogen, high progestin/low estrogen, high progestin/high estrogen) was calculated as previously described (*149*), based on the scheme of Piper and Kennedy (*119*). Intermediate progestin potency pills were assigned to the low progestin potency group. Intermediate estrogen potency pills were defined as low potency if they contained ≤35 μg ethinyl estradiol or ≤50 μg mestranol; otherwise they were defined as high potency. Estrogen dose was defined as high or low; since 35 μg ethinyl estradiol is approximately equivalent to 50 μg mestranol (*174*), high dose was defined as pills containing either >35 ethinyl estradiol or >50 mestranol. While progestin dose and potency vary among the pills, progestin doses, in and of themselves, are essentially equivalent (*175*), therefore there are no natural groupings with which to examine progestin dose.

Exposure Data Quality

Due to the self-reported nature of the exposure data, sources of error in reproductive variables could result from poor recall. However, measurement error is known to be minimal for most reproductive factors of interest (*176-179*). Most women are able to accurately recall how many births they have had and when they occurred. Pregnancies were recorded on a calendar during the interview to help women recall other events in their lives, thus women's recall is believed to be high. Evidence suggests that both reliability (*176-178*) and validity (*179*) are high for self-reported reproductive factors. Correlation coefficients comparing recalled versus original reports for number of previous pregnancies ranges from 0.78 (*176*) to 0.9 for previous pregnancies, 1.0 for previous live births and 0.7 for miscarriage (*178*). Olson et al. (*178*) found no evidence of recall being influenced by time since childbirth to interview. Pregnancies and births, although not easily verifiable, were scrutinized using typical statistical programming techniques such as range checks, looking for outliers, and checking for inconsistencies in related variables. Recall of age at menarche is moderately good, with correlation coefficients between 0.7 and 0.8 (*176,177,179*). About 30 to 40 years after adolescence, women participants in prospective studies of adolescent growth were reinterviewed. Approximately 55% could recall their age of menarche within 6 months of the actual date and 80% could recall it within a year (*177,179*). Given that breast cancer incidence differs by as little as a year at menarche, even minor misclassification of this variable in terms of months could influence estimates.

Previous studies have confirmed the validity of self-reported lifetime use of OCs in observational studies, especially when queried using a detailed questionnaire and in conjunction with a reproductive calendar and photographs to aid in the reporting of specific brands (*171-173*). In one study, the correlation coefficient comparing prospective and

retrospective recall of total duration of OC use was 0.95, however, the point at which women started taking OCs was recalled better than stopping points. Recall of specific brands and doses was less accurate, but still acceptable with approximately 48% correctly naming all brands used. Brand recall was influenced by recency of use, with 69% of women able to correctly identify the first OC used compared to 63% of the most recent OC used. Women with more education and from a higher social class were more accurate reporters of their OC histories (*171*). Hunter et al. (*172*) also confirmed the reproducibility of OC data by comparing information obtained from a self-administered questionnaire accompanied by a calendar and book of color photographs of pills in the Nurses Health Study to data subsequently obtained from the same women using a structured telephone interview. Agreement between the two methods was high for both ever use and duration of use (99% and 94%, respectively) (*172*). For a subset of women, physician's records were available to validate brand of pill used. Exact brand name and code were accurately recalled 42% of the time. However, when brands with equivalent pharmacology and dose were collapsed, agreement rose to 75%. Estrogen preparation (ethinyl estradiol or mestranol), estrogen preparation and dose, and estrogen potency agreement was 80, 71, 74%. Progestin potency was in agreement 76% of the time. A small percentage of pills (2.5 - 4%) were misclassified in the extreme alternative potency category (*172*). The use of physician or even pharmacy records as a gold standard in the U.S. is questionable, given the difficulty of obtaining quality data on the relevant OC specifics (duration, timing) for times of interest (recent time periods, time periods in youth). Data from Sweden, which has a more centralized pharmacy record system, compared interview data to pharmacy data confirmed the high agreement for any use, current use, time since first and last use, and duration of use during various times of

interest (*173*). Recall of specific pill types was lower, but still high, with 81% correctly recalling having used a high dose pill, and 92% for low dose pills (*173*).

As expected, there are several methodological issues that hamper the ability to accurately study abortion, including the need to consider induced and spontaneous abortions separately, measurement error, and the use of different referent groups (*77,180*). These issues hinder the study of both risk and survival.

Given the numerous differences between spontaneous and induced abortions in terms of hormone levels and gestational ages, it is imperative induced and spontaneous abortions get analyzed separately. This is now standard practice in the incidence literature, but earlier incidence studies and some survival analyses do not consider the two types individually.

Measurement error is a concern in studies of spontaneous and induced abortions, given the sensitive nature of the topic. Approximately 25% of spontaneous abortions (*181*) and 50% of induced abortions are underreported (*182*). Case-control studies have been concerned with case-control reporting differences leading to recall bias. Survival analyses would not be subject to differential case-control reporting, due to the case-only nature of such analyses. Instead, the difficulties with recalling any event in the distant past would typically result in non-differential measurement error in regards to survival outcomes, usually yielding attenuated effect estimates.

Women's willingness to admit to a history of induced abortion has diminished with time, as evidenced by comparing survey data to the numbers of abortions estimated to have actually occurred. In 1976, about 45% of abortions were reported as compared to only 35% in 1988 (*182*). Women who are older, white, or married are more likely to report having an induced abortion than those who are younger, non-white, or unmarried (*182*). Also, women

who have abortions and identify themselves as Roman Catholic, Mormon or Seventh Day Adventist are less likely to report compared with other religious groups (*183*). Differential reporting among certain sub-groups of cases (*182*) could result in substantial bias in studies of survival, if these sociodemographic characteristics are independently related to survival.

Induced abortions have only been legal nationwide since 1973, thus studies of older women asked women to recall an illegal practice. Recent studies of younger women include a larger percentage of participants for whom part or most of their reproductive history took place after legalization of abortion but in a climate of increasing violence and polarization. The range of birth years for women in this study was from 1935-1970, thus there were some, older women for whom abortions may have been illegal, but for most of the women, abortions would have been legal during most of their reproductive lives.

Several analyses have attempted to determine the degree of recall bias present in case-control studies of abortion. Two reports based on the same set of data have estimated that a spurious increased risk of 16% (*66*) to 50% (*184*) is possible from cases more accurately reporting their history as compared with controls. Additional indirect support for recall bias in case-control studies comes from analyses that consider effect modification by time period of abortion and religion of the area. Newcomb et al. (*185*) observed a higher OR for abortions taking place before 1973 (1.35) compared to those after 1973 (1.12). A Dutch study (*68*) found an OR of 14.6 for induced abortions among women in the southeast and predominately Roman Catholic area of the country versus western regions of the country (OR = 1.3). These are suggestive of recall bias, again that cases would be more likely to report a sensitive activity than controls, but estimates are often incredibly imprecise given the small numbers available.

Another important methodological problem is the use of different referent groups, thus making comparisons across studies difficult. Some studies compare yes versus no termination and adjust for parity, while others compare nulliparous to parous women. It appears the best set of comparisons would be to contrast parous women with a history of abortion or miscarriage to parous women with no incomplete pregnancies. For nulliparous women, one should compare nulliparous women with a history of terminations to nulligravid women (*73*). If one compares nulliparous to parous women, the effects of full-term and interrupted pregnancies are mixed. Therefore, it is key to separate the effects of parity from that of interrupted pregnancies (*73*). Lipworth et al. (*67*) found no association between induced abortions and risk of breast cancer when nulliparous women were compared to nulligravid women or when parous women with a history of abortion were compared to nulligravid women. However, among parous women, an increase in risk was noted (OR= 1.76) when those with a history of abortion were compared to those without.

Cohort (Follow-up) Study Methods

Study Population

The population for the cohort study and this dissertation comprised all women diagnosed with a primary, incident invasive breast cancer who participated in the parent case-control study from the New Jersey (n= 452) and Atlanta (n=831) centers. The cancer registry serving Atlanta did not collect vital status on *in situ* cases, so while they were included in the parent case-control study, they were excluded from the follow-up study (n=224). Cases from the Seattle center were not included in the cohort as site investigators decided to conduct their own cohort study. Cases of bilateral breast cancer were also excluded (n=16 in Atlanta, none were identified in New Jersey). For the follow-up study, patients with missing vital status

data were excluded (n=19, 1.5%), resulting in 1264 patients for analysis. The overall effect on study validity was likely minimal since so few were excluded.

Selected unadjusted demographic and clinical characteristics of the cohort, stratified by study site, are listed in Table 9 of the appendix. Characteristics are further stratified by age at diagnosis since women between the ages of 45-54 were exclusively from the Atlanta center. As expected, there were demographic differences between the two study sites. Compared to patients in New Jersey, patients in Atlanta were more likely to be black and have a lower income. When examining patients younger than 45, the stage distribution was similar across the two sites, but women in Atlanta were more likely to have a higher tumor grade and ER and PR- tumors. Among patients younger than 45, New Jersey residents were more likely to be premenopausal. With respect to the main exposures in this dissertation, younger women from Atlanta were more likely to have an earlier age at menarche, and be nulliparous. New Jersey residents were more likely to have had a recent birth and be non-OC users. Among OC users, women from New Jersey tended to use OCs for a shorter duration of time, and were less likely to be recent last users.

Outcome Assessment

Vital status and dates of death were ascertained through the National Death Index (NDI), a computerized database of national deaths maintained since 1979. State vital records offices submit information about decedents to the National Center of Health Statistics where the NDI is maintained and updated annually approximately a year after the end of each calendar year (*186*). For this study, cancer registries serving the various geographic areas searched for NDI death tape matches using social security numbers and birthdates of study participants. For those not found using those two identifiers, matches were also searched via participant

names. Women found in the NDI were considered to be dead and those not in the NDI were assumed to be alive. The last registry-death tape match was completed in the Fall of 2000 for both study sites and a truncation of January 2000 was used to search for deaths, as this was the latest date thought to be reliable by the registries. By the end of study truncation, 292 patients had died.

Outcome Data Quality

Sources of error in outcome assessment could have arisen from incorrect vital status, dates of diagnosis or dates of death. Determining vital status through the NDI allowed for very complete information as it is a nation-wide service and extremely reliable even for individuals who move away from the area in which the cancer registry serves. Patient consent is not required for NDI searches. The NDI has been estimated to correctly identify 98% of deaths in women with zero false positives (no women known to be alive were found in the NDI) (*187*). Other studies have confirmed the high accuracy of the NDI for determining vital status among both alive and dead participants, particularly when utilizing multiple matching algorithms and Social Security Numbers (*188-192*), as was the protocol in this study. Since the majority of women in this study are young, it is possible some names might have changed and thus by relying on the NDI for vital status, this study might have missed deaths among some women. There was a field in the computer records for maiden name, which was used to search other known names. The accuracy of vital status in this study is also buttressed by the fact that the cancer registry serving one of the geographic areas (Atlanta, GA) was a SEER sponsored registry, thus it was well funded to collect high-quality data. The registry serving the central NJ area was not a SEER sponsored registry at the time of the study, but was re-established as one about a decade after case enrollment

ceased and was required to go back and collect all SEER information on patients diagnosed prior to re-establishment as a SEER site.

All-cause mortality was the primary endpoint of interest in this dissertation rather than breast cancer mortality since the accuracy of cause of death on death certificates has been questioned (*193*). Given that the study population is comprised of younger women, it is believed that the majority of deaths among these breast cancer cases would have been directly attributable to, or influenced by, their breast cancer. Among women 35 to 54 years of age, malignant neoplasms are the leading cause of death, representing 27% of deaths among 35 - 44 year olds and 38% for those 45 - 54 years of age (*194*). In this study, breast cancer was the cause of death for 85% of patients (n=248). The only other substantial cause of death was cardiovascular disease (n=15, 5%). Other causes of death included infections, accidents, other cancers, diabetes, and liver disease. Approximately 5.5% of deceased patients had no listed cause of death.

Study Power

Power estimates were calculated assuming different underlying HRs using the NQuery Advisor (v. 5.0) program, which compares the survival curves in 2 groups with unequal numbers based on the log-rank statistic (*195*). The following assumptions were made in order to calculate power based on a fixed sample size. Sample sizes for the unexposed and exposed groups differed for each exposure of interest and are noted in the footnote of Table 3. For all exposures of interest, the survival rate in the unexposed group was assumed to be 0.80 (the overall survival proportion in the data) and four different relative risks (HRs) were tested (1.3, 1.5, 1.8, 2.0). These values represent plausible estimates based on those cited in the literature. The time-period of the study was assumed to be 10 years, over which the hazard is

assumed to be constant. A two-sided Type I error rate of 0.05 and a conservative loss-to-follow-up rate of 2.5% in each exposure group was used. There was more than sufficient power to examine the relevant reproductive factors in this study population and associations with overall survival. Considering various plausible amounts of loss to follow-up within the cohort, we have 80% power to detect a hazard ratio between 1.5 and 1.8 for parity. Power was additionally excellent (82%) for detecting a relatively modest effect (HR= 1.5) of age at menarche. Power was adequate for determining an effect of timing of births relative to diagnosis (94% for HR=1.8) and ever OC use. Power was more limited for determining timing of OC relative to diagnosis. Details are noted in Table 3 of the appendix.

Data Analysis

Exposure Categorization

After initial exploration of each variable's distribution and its association with survival, most variables were categorized using data-driven cutpoints, based on their relationship with mortality. For the majority of reproductive and oral contraceptive variables, few natural cut-points established from previous work were available; therefore both linear and categorical exposure categorizations were explored. No continuous variables were ultimately fit with linear categorizations as most were not observed to fit this pattern. Even estimates for those variables that were not associated with mortality are presented in this dissertation as categorical in order to show more transparently what the association with mortality was like. All categorical variables were ultimately coded with indicator variables, in order to relax the assumption that the log(hazards) be linear.

Outcome Variable (Time-to-Death) Definition

The main outcome of interest in a survival analysis is time to death. In this dissertation, this variable was defined as the number of months between diagnosis with breast cancer and death from any cause or date of last known follow-up. In survival analysis language, deaths are referred to failures or events and women alive at the end of follow-up or last known follow-up date are censored for the all-cause mortality analyses. In the cause-specific mortality analyses, women who died from causes other than breast cancer were censored. Censoring simply refers to the fact that some women did not have the event of interest prior to the end of follow-up; standard survival analysis techniques readily incorporate most types of censoring (*196*). There is the assumption that the censoring mechanism be noninformative, in other words that the people who are censored at some point are representative of those subjects who survive up to that point in time, conditional on explanatory variables (*196*). In this study, the censoring mechanism was "random" since while there was a single termination point, patients entered the follow-up study randomly based on their date of diagnosis. With random censoring, there is a potential for informative censoring, however, I do not believe that the censoring mechanism was informative in this study. Patients entered based on their date of diagnosis, which took place only over a two-year period, and there is no reason to suspect that time of entry into the study would be predictive of future outcome, conditional on covariates. Therefore, in this dissertation, it is unlikely that this was a large source of bias. Even when informative censoring is present, it is difficult to determine the magnitude or direction of this bias (*196*). This assumption of noninformative censoring extends to cause specific analyses as well. One has to assume that dying of the cause of interest (in this case breast cancer) is independent from dying from other causes, conditional on covariates.

Analyses: Kaplan-Meier

Each variable representing the exposures of interest and covariates were first analyzed with the Kaplan-Meier (product-limit) method (*197*). In the presence of censoring, the Kaplan-Meier estimate of the survival probability is obtained by multiplying a series of conditional survival probability estimates together. Each conditional probability is calculated as the number at risk of dying minus the number of deaths, divided by the number at risk. It is a conditional probability because the probability in any one time period is conditional on surviving until that point in time (*198*). Therefore, in Kaplan-Meier estimates, people contribute to the number at risk and to follow-up time until they die or are censored due to loss-to-follow-up or study end. The Kaplan-Meier method is superior to other methods of estimating survival probabilities (e.g. life-table approaches) for smaller datasets with precisely measured event times (*196*). Survival curves over time were statistically compared via the log-rank test (*199*).

Figures 3-6 are unadjusted plots of the survival function for several variables of interest that appeared to influence survival including parity, recency of birth, and recency of first and last OC use. Nulliparous patients or those with one to three births had increased survival compared to those with four or more births. Nulliparous women had similar survival to those who had given birth more than five years before diagnosis, but patients who had given birth within 5 years before diagnosis had substantially decreased survival. Increasing time since OC initiation was positively associated with survival, and those who were current OC users at diagnosis or had recently ceased use had modestly decreased survival. A median time-to-death was not computed for this population, since there is no point in time at which more than 50% of the women died (77% of women survived until the end of follow-up). Rather, 5 and 8-year survival probabilities for selected reproductive and oral contraceptive variables

are noted in Tables 11-12 of the appendix. Similar conclusions are reached using the 5 and 8-year survival probabilities as the Kaplan-Meier survival curves just discussed. For example, among parous women, after 5 years of follow-up, 75% of women who gave birth within 5 years had survived compared to 84% of those who last gave birth more than 5 years before diagnosis.

Using the reverse Kaplan-Meier estimator (where the outcome of interest is being censored rather than failing) (*200*), the median follow-up time in this population was 102 months (range=3-118 months).

Analyses: Cox Regression Modeling

Multivariable models were ultimately constructed using Cox's proportional hazards regression model (*201*) to determine the prognostic value of various characteristics, adjusted for other variables. Cox regression refers both to the model itself and to the estimation method. The model that he developed estimates the hazard (instantaneous risk of death) for an individual at a particular time as a function of an unspecified baseline hazard and a linear function of a set of covariates. The primary parameter that is estimated from the proportional hazards model is the hazard ratio, which is the ratio of two hazards (instantaneous risk of death) comparing two groups ("exposed" vs. "unexposed"), adjusted for other factors using a maximum partial likelihood method (confounding is discussed in more detail below). When two groups or individuals are being compared, the baseline hazard cancels out of the equation, and thus, the ratio of the hazards is constant over time (i.e., they are proportional). The interpretation of a HR is the relative risk of death comparing those who are exposed to some characteristic to those who are not, over the entire study period. The HR can also be interpreted as a per-unit time rate of death (so, a HR of 2 for gender would mean that, at any

specific time point during the study, the per-unit rate of death for males is twice that of females). In cause specific Cox regression models (i.e. breast cancer-specific mortality analyses), the estimation technique is similar to that described above, but the basic difference is that the model is estimating a separate hazard for each cause of death. Therefore, in this instance, each type of death has its own hazard model influencing the occurrence and timing of it. Whichever type of death occurs first, the individual is then no longer at risk for the other types of deaths (*196*).

Cox regression uses a semi-parametric estimation technique (partial likelihood), which allows for estimation of β coefficients in the model without having to specify the baseline hazard function. Because it is a partial likelihood technique, only the rank orders of the event times are important, not the numerical values (*196*).

There are assumptions to the Cox regression models (*196*). The proportional hazards model does assume proportionality of covariate effects over time (i.e. that the effect of a certain variable does not change with time). This was explored in this dissertation by visual inspections of log(-log(S)) plots and creating interactions with time in the model for potential violators (*196*,*202*). Two variables, income and recency of last OC use, were observed to violate this assumption based on the plots and the statistically significant ($p < 0.05$) time interactions (see figures 7-8 for the corresponding plots). These violations were relaxed by including a continuous time - income interaction term in the model as well as a categorical time (>24 months)-recency of last OC use term. Because of these violations, the model is no longer referred to as a proportional hazards model, but is more accurately described as a Cox regression model. A unique analytical issue in survival analyses is the presence of ties, one or more failures occurring at the same time, which was handled in this dissertation via the Efron

method (*203*) which is more appropriate than the default method, Breslow, for data with a moderate to large number of ties (*196,204,205*).

Confounding and Effect Modification Evaluation

For both study aims, several *a priori* confounders and effect modifiers were examined in this dataset. Given that breast cancer may be etiologically and prognostically different for young versus older women and that different age structures exist in the two centers, separate analyses of all-cause mortality were run pooling both centers for women under age 45 (the upper age limit in NJ) and for those between 45 and 54 in Atlanta only. Because the two centers come from geographically distinct areas of the county, geographic center was also considered as an effect modifier with center specific analyses in the all-cause mortality analyses. In addition to age and site, other effect modifiers that were investigated included menopausal status (women were considered postmenopausal if they had not had a menstrual period within 6 months of the interview and they were not pregnant during that time), ER status, tumor stage (local, regional/distant), family history of breast cancer, method of tumor discovery (routine self exam, accidental by self/partner, routine physical exam, routine mammogram, or other), cigarette smoking status (current, former, or never), and BMI in the year before interview (self-reported non-pregnant weight in kg/measured height at interview in m^2, dichotomized as <25 kg/m^2 and ≥ 25 kg/m^2). Effect modification was initially explored by stratifying on the potential effect modifier and seeing if appreciable differences existed in the stratum specific HRs and whether or not the CIs overlapped. If effect modification appeared to exist based on stratum specific estimates and CIs (i.e. each stratum specific estimate was entirely or almost excluded from the other CI and there was minimal overlap of the CIs), product interaction terms were fit and statistically tested using the likelihood ratio

test (LRT) (*206*). If the p-value for the LRT comparing models with and without the interaction term was less then 0.05 then effect modification was considered statistically significant on the multiplicative scale. A more conservative cut-point of 0.05 was used rather than the commonly used 0.10 (*206*) due to the large number of exposures and effect modifiers that were tested. Significant effect modifiers are noted and presented in Chapters 3-4 of the dissertation.

For both aims the following variables were assessed as potential confounders: age at diagnosis, study site, treatment received prior to interview (radiation, chemotherapy), hormone receptor status (ER, and combined ER/PR status) and prediagnostic, non-clinical factors assessed during the patient interview, such as household income, education, active cigarette smoking (current, former, never), alcohol drinking (never, less than 1 drink per day, one or more drinks per day), BMI at age 20 years and in the year before interview using self-reported weight and measured height, calculated as weight in kilograms divided by height in meters squared (normal/underweight, overweight/obese), race (white, non-white), physical activity (usual weekly physical activity levels measured in metabolic equivalence units at age 20 and in the year before diagnosis, dichotomized at the median level), oral contraceptive use (for the evaluation of the reproductive factors), reproductive history (for the evaluation of oral contraceptive use), age at menarche, the number of Pap smears in the 5 years before diagnosis, the number of clinical breast exams in the 5 years before diagnosis and co-morbidities as reported in the interview (diabetes, thyroid disease, high blood pressure, high cholesterol, other cancers). Per the data-use agreement, race was not examined as a main effect or as an effect modifier, but it was considered as a potential confounder.

Clinical characteristics such as stage and grade may be causal intermediates for some of the exposures of interest, rather than confounders, therefore they were considered carefully. For aim 1 (reproductive factors), stage and grade were ultimately not considered as confounders in the model building process because of the potential for them as biological intermediates. However, stage and grade were considered as confounders for the OC variables since associations between OCs and stage and grade could be due to sociological phenomena (access to health care, etc.). The discussion section of the dissertation outlines this methodological issue more directly.

Confounding, for those variables that were not effect modifiers, and model building proceeded as follows. First, bivariate analyses were conducted between all exposures and survival; and between reproductive exposures and other potential confounders. Full models were fit including all potentially confounding variables that were associated with the specific reproductive or oral contraceptive exposure of interest and that were associated with the outcome in bivariate analyses (*206*). Final models were built using backward elimination and variables were retained and considered as confounders if they produced more than a 10% change in the ln(HR) for the principal exposure variables (*207*,*208*).

Cox Regression Modeling Results: Analyses of Reproductive Factors

Chapter 3 presents highlighted results from the first aim of the dissertation, reproductive factors and breast cancer survival, in manuscript form. Tables 13-14 of the appendix show the results for all reproductive variables that were examined, adjusted for various sets of potential confounders. Estimates were modeled using various referent groups to illustrate how sensitive the results were to the use of different referent groups (e.g. using nulliparous women as the referent versus estimating models in parous women only). Initially, each

reproductive variable (age at menarche, gravidity, parity, spontaneous abortions, induced abortions, age at first birth, age at last birth, recency of last birth, and ever breastfeeding for ≥2 weeks) was modeled separately in order to obtain the most parsimonious estimate for each characteristic. However, across all of these reproductive exposures, consistent confounders were observed for most variables, including age at diagnosis and household income, therefore, all estimates are adjusted for these variables. As noted in Chapter 3, variables are additionally adjusted for confounders specific to that exposure. Results are presented adjusted for the number of Pap smears and clinical breast exams (CBEs) received in the 5 years before diagnosis as a way to attempt to control for access to health care. Particularly since stage was not adjusted for as a confounder, adjustment for Pap smears and CBEs was considered as a way to control for access to health care issues that would have been controlled for via stage, since advanced stage can also be a proxy for limited access to quality health care. For the most part, adjustment for Pap smears and CBEs did not materially alter the estimates. Race was not a confounder of any reproductive factor.

Induced and spontaneous abortions were analyzed in several ways in order to address some of the methodological issues mentioned earlier in Chapter 2. These results are noted in Table 14 of the appendix. In particular, abortion results are shown separately in parous and nulliparous women. Also, results considering the gestational age of the pregnancy when the induced abortion took place and the mother's age at the time of the first abortion are presented (Table 14).

Cox Regression Modeling Results: Analyses of Oral Contraceptives

Chapter 4 highlights results from aim 2 (OCs and breast cancer survival) in manuscript form. In Table 15 of the appendix, more detailed results are presented for considered

variables, adjusted for potential confounders. Again, estimates were modeled among both users only and using never users as the referent group in order to demonstrate the sensitivity of the results to the choice of comparison groups. Each OC characteristic (ever use defined as any use, ever use for ≥6 mo, duration, age at first use, age at last use, duration of use before age 25, duration of use before a first birth, recency of first use, and recency of last use) was initially modeled separately in order to obtain the most unbiased estimate for each characteristic of use. After modeling all characteristics separately, it was clear there were similar, consistent confounders across many of the exposures of interest, therefore, for ease of presentation, all results are adjusted for these variables (age at diagnosis and household income). Each estimate was also adjusted for confounders specific to that association. Adjustment race, stage, grade, and hormonal receptor status did not alter any OC exposure estimates.

As described earlier in Chapter 2 and in Chapter 4, dose and potency data were available on a subset of users (those who used combination OCs for a total duration of ≥6 months and with non-missing pill brand and date data). Content variables of primary interest included the pill used for the longest duration in various time periods (the most recent pill, within 5 years of diagnosis, within 10 years of diagnosis, and the longest pill ever used), as well as the exact duration of the pill used in that time period. Specific derivations of the pill content variables were described in detail earlier in Chapter 2 under the exposure assessment section. Due to the small number of women recently using particular types of pills, limited power was present to examine the effects of duration of use of these specific pill types on survival.

Summary

In this population-based cohort of younger breast cancer patients from the metropolitan Atlanta, GA area and central New Jersey, patients were interviewed shortly after diagnosis on a variety of characteristics. These patients were followed via the NDI for survival end-points from the time of diagnosis (between 1990 and 1992) until death or January 1, 2000. In this dissertation, menstrual, reproductive, and oral contraceptive histories were analyzed for their associations with all-cause and breast cancer-specific mortality.

Increased risks of mortality were observed for a parity of 4 or more births, and having a birth within 5 years prior to diagnosis, especially for leaner women (BMI <25 kg/m^2). Elevated HRs were also observed for young age at menarche (particularly in premenopausal women) and young age at first births, but the effects were modest. Recent use of OCs also tended to modestly increase mortality, for both recent initiators (within 10 years of diagnosis) and for current users at diagnosis (or those who had ceased use within the previous year). Relative to recent use of low-dose estrogen pills, patients recently on high dose estrogen pills and those recently using pills containing the progestin levonorgestrel (versus recent use of pills containing other progestins) were at an increased risk of death.

CHAPTER III: ASSOCIATION BETWEEN REPRODUCTIVE FACTORS AND BREAST CANCER SURVIVAL IN YOUNGER WOMEN

Summary

This analysis investigated whether reproductive factors such as age at menarche, parity, and timing and outcomes of pregnancies were associated with survival among women with breast cancer younger than 55 years. Female residents of Atlanta, Georgia and central New Jersey who were diagnosed with a primary, incident invasive breast cancer between 1990 and 1992 and enrolled in a population-based study (n=1264) were followed for 8-10 years. Detailed exposure and covariate information was collected via in-person interviews administered shortly after diagnosis. Vital status as of January 1, 2000 was ascertained through the National Death Index via the state cancer registries (n=292 deaths). Cox regression methods were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) adjusted for confounders. Parity of 4 or more births, as compared with nulliparity, was positively associated with all-cause mortality, [HR (95%CI) = 1.71 (1.09-2.67)]. Increased mortality was associated with having given birth within 5 years prior to diagnosis (≤5 vs. >5 years) [1.78 (1.28-2.47)], and was more pronounced among women with a pre-diagnostic body mass index of <25 kg/m^2 [2.54 (1.61-4.00)]. Early age at menarche and early age at first birth also modestly increased mortality; history of miscarriage, induced abortion, and ever breastfeeding were not related to survival. These results may help elucidate breast cancer progression mechanisms and enable a better understanding of how reproductive characteristics influence breast cancer survival.

Introduction

An estimated 212,920 new cases of breast cancer and 40,970 deaths from that disease will occur among American women in 2006 (*1*). The prevalence of invasive female breast cancer was estimated to be 2.28 million in 2002 (*2*). Despite the importance of tumor characteristics such as stage and molecular markers in determining survival (*209*), it has been estimated that prognostic classification schemes based on tumor size, grade, and receptor status in node-negative patients explain only a small fraction of the variation (~10%) in survival (*210*). Adding lymph node status may raise this value to 20% (*25*). Thus, other factors warrant investigation. In particular, there are few data on survival in younger women who usually experience higher mortality than older women (*2*).

Reproductive events result in life-long changes in the hormonal milieu. Pregnancy decreases circulating estradiol levels and increases sex hormone binding globulin levels, thus reducing bioavailable estradiol and permanently lowering prolactin levels (*52*). Late age at menarche has also been correlated with lower urinary estrogen metabolite levels (*211*). Reproductive factors such as early menarche, nulliparity, older age at first birth, and fewer births are well-established risk factors for breast cancer incidence (*5*), but their effect on survival is less well understood (*87-108*).

Hormonal influences are implicated in tumor progression since serum estrogen levels have been inversely correlated with disease-free survival (*46*). Estrogen deprivation, through adjuvant systemic therapy or, in younger women, ovarian ablation, is effective in reducing tumor recurrence and death and is recommended for almost all women with estrogen receptor-positive (ER+) tumors (*212*).

Studies investigating the influence of reproductive history on breast cancer mortality may increase our understanding of possible reasons for decreased survival in certain groups of women in the United States. This research is timely given the secular changes in age at menarche and childbearing patterns in recent cohorts of women (*213,214*). For example, any effect of timing of pregnancies on survival after diagnosis may become increasingly relevant as women postpone childbearing into older ages.

This large, population-based study of younger breast cancer patients with carefully constructed reproductive history data was designed, first, to provide additional data on inconsistent and less well-studied reproductive characteristics and survival, including age at menarche, parity, age at first and last birth, pregnancy outcomes, and breastfeeding. Secondly, we sought to confirm the association of poor survival with recency of birth and to more precisely establish the length of time since a woman's last birth that is associated with increased mortality.

Methods

Study Population

This follow-up study included eligible patients previously enrolled in a population-based case-control study of breast cancer (n=1283) (*141*). Those eligible were women, aged 20-54 years, who resided in a 5-county area of central New Jersey (n=452) or in the Atlanta, Georgia, metropolitan area (n=831), and had received a diagnosis of primary, invasive breast cancer between May 1, 1990 and December 31, 1992. Cases were identified through population-based registries using rapid-ascertainment systems. Detailed baseline exposure and covariate information were collected in the original case-control study via structured in-person interviews administered by trained interviewers that lasted an average of 67 minutes.

The interview was completed by 86% of eligible patients with *in situ* and invasive cancer and occurred a median 4.2 months after diagnosis (*141*). Nineteen participants were missing vital status, leaving 1264 subjects for analysis. Institutional Review Boards at collaborating institutions approved this study.

Exposure Assessment

With the exception of clinical data relating to tumor characteristics, the exposure and covariate data used in this investigation came from the case-control interview, which included comprehensive questions on reproductive and menstrual history prior to diagnosis, all of which were captured on a reproductive history calendar. Participants were asked to recall their age at menarche, and number of pregnancies. For each pregnancy, the outcome (live birth, stillbirth, abortion, miscarriage, or ectopic pregnancy), dates and length, and breastfeeding after delivery were queried. Gravidity was defined as ever being pregnant and parity was defined as the number of still and live births prior to diagnosis. Pregnancies at the time of the interview (n=2) or births after diagnosis (n=4) were not counted in the gravidity or parity calculations. Age at each pregnancy, recency of last birth, and gestational length of each pregnancy were derived from the date and length data of the reported pregnancies. Lifetime breastfeeding duration until supplementation and until complete cessation were calculated.

All patients were asked about treatment received prior to interview and medical records were abstracted as part of the case-control study to ascertain clinical data such as Surveillance, Epidemiology, and End Results (SEER) Program summary stage (local, regional, or distant), tumor grade, and hormone receptor status. For the Atlanta participants only (n=831), more detailed data on the first course of treatment (surgery, chemotherapy,

radiation, and hormonal therapy) and American Joint Committee on Cancer (AJCC) stage (I, IIA, etc.) were available through the SEER program and re-abstraction of the medical records.

Outcome Ascertainment

Eligible case participants diagnosed with invasive breast cancer were followed-up for a maximum of 118 months. Vital status and if deceased, date and cause of death were ascertained through the National Death Index, via the cancer registries serving the two geographic locations. By the time of study truncation (January 1, 2000), there had been 292 deaths. Breast cancer was listed on the death certificate as the cause of death for 85% of deceased participants (n=248 deaths).

Statistical Analyses

Prediagnostic reproductive exposures and covariates of interest were initially examined using Kaplan-Meier plots. Follow-up time was calculated from the date of diagnosis to the date of death, last known follow-up or date of study truncation (January 1, 2000). The proportional hazards assumption was assessed by examining log(-log(survival)) plots and including interactions with follow-up time. The interaction term between continuous follow-up time and income was statistically significant; therefore all models include this term. Variables were categorized according to their association with mortality and modeled using indicator variables.

Bivariate analyses were conducted between all exposures and survival; and between reproductive exposures and other potential confounders. Multivariable models were subsequently built using Cox regression methods (*201*), to estimate hazard ratios (HR) and 95% confidence intervals (CI). All-cause mortality was the primary end-point of interest, and

patients alive at the end of the study were censored. In models that considered breast cancer specific-mortality only, participants who died of causes other than breast cancer were censored. Each reproductive characteristic (age at menarche, gravidity, parity, spontaneous abortions, induced abortions, age at first birth, age at last birth, recency of last birth, and ever breastfeeding for ≥ 2 weeks) was modeled separately.

Potential confounders were initially included in multivariable models if they were associated with the specific reproductive characteristic and the outcome in bivariate analyses. Final models were built using backward elimination and variables were retained and considered as confounders if they produced more than a 10% change in the ln(HR) for the reproductive variable. Potential confounders included race, age at diagnosis, education, household income in the year before diagnosis, physical activity at age 20 and in the year before diagnosis, obesity as measured by body mass index (BMI) at age 20 and in the year before diagnosis, chemotherapy, radiation, cigarette smoking status, alcohol consumption, oral contraceptive use, study site, comorbidities (diabetes, thyroid disease, high blood pressure, high cholesterol, other cancers) and the number of Pap smears and clinical breast exams received in the 5 years before diagnosis. The latter 2 variables were considered as proxies for health care access; mammography was not considered as a proxy for health care access given that most women in our study would not have been of the age to be routinely recommended for mammographic screening. All results are adjusted for age (<35, 35-44, or 45-54 years) and income (<$15,000, $15,000-<$25,000, 25,000-<$90,000, or ≥$90,000) as these were consistent confounders of all of the reproductive exposures of interest. Each reproductive exposure-mortality association is also adjusted for additional confounders specific to that association (these are listed in the footnotes to each table). In the Atlanta

subgroup, the additional detailed treatment information did not confound any of the considered exposure-mortality associations. High parity and having a recent birth were positively associated with tumor characteristics such as stage (either summary or AJCC-derived stage) and grade in our data. As such, they may partially act as intermediates in the causal pathway between various reproductive variables and survival. Thus, these tumor characteristics were not considered as confounders or adjusted for in final models.(*215*) Instead, stage-stratified results are presented.

Several potential effect modifiers were evaluated including age (<45, ≥45), menopausal status (women were defined as postmenopausal if they had not menstruated for ≥ 6 months prior to diagnosis), ER status, SEER summary stage, family history, BMI in the year before diagnosis (<25 kg/m^2, ≥25 kg/m^2), and method of cancer detection (accidental, routine self-exam, screening mammogram, etc.). Effect modification was initially assessed by examining stratum-specific estimates, and further analyses explored the inclusion of product interaction terms. If the p-value for the likelihood ratio test comparing models with and without the interaction term(s) was <0.05, then effect modification was considered significant on a multiplicative scale.

Results

At the time of diagnosis with a first primary breast cancer, the majority of patients were between 35 and 44 years of age, and approximately 78% were premenopausal (Table 1). Most were diagnosed with local stage disease and had ER+ tumors. Approximately 60% of women had at least graduated from college, and 19% had a yearly household income of $90,000 or more. About 10% made less than $15,000 per year. Twenty-two percent of women were nulliparous, and among parous women, about 7% first gave birth at <18 years

of age and 18% gave birth within 5 years before diagnosis. Two hundred ninety-two deaths (23.1%) occurred by the end of follow-up.

Because results from Kaplan-Meier curves revealed similar predictors of survival as multivariable models, only the latter are presented (Table 2). Women with an earlier age at menarche (<12 years) tended to have a small increase in mortality relative to women who underwent menarche at 12 or older [HR (95% CI) =1.25 (0.97-1.62)]. Gravidity was not associated with mortality, but parity of ≥4 births remained associated with death [1.71 (1.09-2.67)].

Having ≥1 spontaneous or induced abortions was not associated with survival (Table 2). Results were similar when induced or spontaneous abortions among nulliparous and parous women were examined separately. Risk of death was not influenced by the number of induced abortions, nor did mortality vary among subgroups defined by characteristics of induced abortions, such as age at first abortion (<22 vs. ≥22 years of age), timing of abortion relative to first birth, or the gestational length of the first abortion (>8 vs. ≤8 weeks) (results not shown).

Young age at first birth (<18 years) appeared to modestly increase mortality [1.45 (0.91-2.31)], but mortality was not altered if a first birth was after age 18. After adjustment for recency of birth, age at last birth did not influence survival (results not shown).

Women with a recent birth (≤5 years before diagnosis) had a 78% increased risk of death [1.78 (1.28-2.47)]. Risk of death was similar for those giving birth within 5 years, i.e., when finer categorizations of recency within 5 years were used, little variation in mortality was observed. Survival for those with a birth >5 years before diagnosis was equivalent to survival among nulliparous women (results not shown). Ever breastfeeding was not associated with

survival. Shorter durations of breastfeeding were associated with a decreased risk of death [e.g. HR ≤ 12 months = 0.71 (0.52-0.97)], but longer durations were not (Table 2).

Age at menarche and recency of birth were modified by menopausal status and BMI, respectively. The effect of young age at menarche on overall mortality appears stronger in premenopausal [1.42 (1.08-1.88)] than postmenopausal women [0.69 (0.34-1.38)] (p-value = 0.04). The association between a recent birth and overall mortality was more pronounced in women with a BMI of <25 kg/m^2 [2.54 (1.61-4.00)] versus ≥25 kg/m^2 [1.34 (0.79-2.26)] (p-value=0.05). Parity and recency of birth stratified by summary stage are noted in Table 3. Some modest heterogeneity with stage was observed, but the differences were not statistically significant.

In general, analyses of breast-cancer specific-mortality yielded estimates that were typically stronger, although not considerably so, than those for overall mortality (results not shown). For example, the largest difference for all-cause versus breast cancer-specific mortality was for recency of birth, for which the HR rose from 1.78 to 1.89 (1.32-2.69).

Discussion

In this cohort of younger women with breast cancer, increased mortality was associated with various aspects of prediagnostic reproductive history, particularly high parity and recent births. There was also evidence that the effect of recent births were stronger among women with a BMI <25 kg/m^2. There was some suggestion of increased mortality for early age at menarche and early age at first birth, but the estimates were modest.

Most (*87-96*), but not all (*97,98*), studies have observed that a recent birth (within approximately 1 to 5 years) is associated with an increased risk of death, but the extent to which death is influenced by the exact timing of the birth has remained unresolved. Estimates

within fine categories of recency of birth are often imprecise, making time-specific results difficult to interpret in individual studies. However, many studies report the strongest effects for births within 1 or 2 years, with risk remaining elevated through 4 or 5 years and dropping off substantially in subsequent years (*87,92-94,96*). In contrast, Rosenberg et al. (*95*) reported a slow decrease in risk of death, over a 10-year period, for each year since last giving birth. Our results indicated consistently elevated mortality for women who last gave birth in the 5 years before diagnosis but no association for >5 years since last giving birth. Although this finding corroborates the basic pattern of results from previous studies, it does not necessarily support the notion of a strict linear relationship between time since last birth and mortality.

Similar to our findings, numerous investigators have also found an association with increased mortality for parous versus nulliparous women (*87,90,92,94,103-107*), whereas others have reported null effects for parity (*91,93,96,97,99-102*). Few previous studies have presented parity estimates adjusted for recency of last birth, but our results indicate that the relationship remained even after such adjustment. Whether this effect of high parity is a biological phenomenon or due to residual confounding by other variables (e.g. socioeconomic status) is unclear.

Age at menarche (*87,91,97,101,104,105,108*), age at first birth (*87,91-93,95-97,100-102,104,108*), and breastfeeding (*96,99,104,106*) have previously been inconsistently associated with survival. We found suggestive effects for age at menarche and age at first birth but little effect of ever breastfeeding. Shorter, but not longer, durations of breastfeeding were associated with decreased risk of death. The reasons for this association are unknown, and limited power prevented us from exploring it further.

Similar to our results, other studies have observed that a history of induced or spontaneous abortions did not influence survival (*92,105,108*). Because of the postulated, yet unsubstantiated, link between age at first abortion, abortion timing relative to a first birth, gestational length at the time of the abortion and breast cancer incidence (*77*), we analyzed similar subgroups for differences in survival. None was associated with increased mortality. Likewise, the choice of referent groups (using nulligravid women as the reference group for nulliparous women with a history of an induced abortion and parous women without a history as the comparison group for parous women with a history) yielded no additional information.

The mechanisms of action of childbearing and other reproductive factors on prognosis are unknown. It is possible that associations between recent pregnancies and survival could be due, in part, to delays in diagnosis. Pregnancy-related changes in breast density and architecture make cancer detection and diagnosis more difficult in that breast changes might be ascribed to pregnancy rather than subclinical disease (*110*). However, ours and another study (*89*) did observe lower survival for women with recent births at all tumor stages, providing evidence that even less advanced tumors are affected by a recent pregnancy. Also, since younger women do not routinely undergo mammography, systematic delays in diagnoses for women who recently gave birth versus women without a recent birth are minimized. Also, increases in mortality were observed for recent births across the entire 5-year range before diagnosis; stronger effects were not noted for births closest to diagnosis. This argues against changes in the breast due to pregnancy or breastfeeding delaying the diagnosis of cancer.

Previous studies suggest that high parity and recent births may exert their effects on survival through the production of tumors with more aggressive characteristics. In our data, high parity and having a recent birth were associated with both advanced stage disease and higher grade. Women with high parity or a recent birth are more likely to be diagnosed with later stage and node-positive disease and with ER-, p53+, high grade, highly mitotic, and high S phase fraction tumors (*88,89,92,103*). This is evidence that characteristics such as stage may be on the causal pathway of certain reproductive characteristics and mortality. The practice of adjusting for potential intermediates to test the degree to which an exposure is mediated by another variable has been shown to be invalid except in limited circumstances under stringent assumptions (*216*). In our data, the adverse effects of high parity and recent births were evident at both local and regional/distant stages, and so the effects were not modified by stage. This finding suggests such variables exert effects on survival beyond their associations with advanced stage. Thus, the proposed biological mechanisms may be more complicated than previously considered.

Reproductive factors may also influence survival through hormonally mediated pathways. Estrogen is thought to promote human and rodent breast cancer cell growth (*35*). Increased hormone levels in pregnancy could therefore increase cell division (*60*), and stimulate already initiated cancer cells (*61*). The effect appears to be more than just growth promotion since parity, age at menarche, and age at first birth have not been found to be associated with measures of tumor growth (Ki-67 and mitotic count) in one study (*112*). Our result that recent births exert a stronger effect among leaner women is consistent with an estrogen-mediated pathway.

A limitation of this follow-up study is its reliance on prediagnostic exposure information that was collected shortly after diagnosis and it did not include information on nonclinical factors after diagnosis. This circumstance is likely not an issue for many of the reproductive exposures of interest (e.g., few women get pregnant after a diagnosis of breast cancer). However, potential confounders (e.g., socioeconomic position, employment) may have changed over time, leading to the potential for inadequate control for such factors, with any resultant bias difficult to predict. Other variables such as psychosocial support, stress, and insurance status were not collected as part of the baseline interview.

Although the validity of self-reported reproductive history, including parity and age at menarche, is high (*177*,*179*,*217*), recall of certain exposures such as induced and spontaneous abortions may be lower (*68*,*181*). We conducted a basic sensitivity analysis to explore the potential for recall bias in the association between induced abortion and survival. Two assumptions were made:1) upwards of 50% of all study participants may have underestimated a history of an induced abortion (*182*) and 2) any bias would be non-differential by vital status. Under such conditions, the observed, crude association between induced abortions and vital status (0.92) did not differ from the estimate corrected for underreporting (0.93). In our study the percentage of women who reported having had an induced abortion (22%) is similar to estimates found in surveys that rely on more objective means of gathering abortion data (25%) (*218*). Potential misclassification of outcome is minimal, given that survival was ascertained using the NDI (*187*). However, any bias is likely non-differential since a woman's reproductive history should not be correlated with the likelihood of being correctly classified in the NDI. All-cause mortality was the primary

endpoint of interest since the accuracy of cause of death on death certificates has been questioned (*219*).

Because eligibility for this cohort study of breast cancer patients was contingent on participation in an earlier study, the identified reproductive predictors may not represent prognostic factors in all breast cancer patients. Of eligible patients in the parent case-control study, those who were most ill may not have been interviewed, thus they would not have been included in the subsequent follow-up study. Additionally, exposure status may have differed between patients who were interviewed and were eligible for the case-control study. However, participation was high (86% of breast cancer patients who were eligible were interviewed for the case-control study) and differences in exposure status were small, thus our results are likely generalizable. For example, common reasons why some breast cancer patients were not interviewed in the parent case-control study included refusal (5.4% physician's refusal and 6.4% patient's refusal), death (0.4%), and illness (0.6%). Responders to the case-control interview, as compared with non-responders, had an earlier age at menarche, and were slightly more likely to be parous (*220*).

This study is a comprehensive, population-based study of younger women with long-term follow-up, carefully assessed reproductive data, and detailed individual level data on covariates. In this analysis of a younger cohort, the prognostic factors of interest and the outcome were separated by a comparatively short time, thus preventing the dilution of effects observed in many epidemiological studies. This cohort was also relatively recently diagnosed and therefore more similar to current populations of breast cancer survivors than cohorts established more distantly. The breadth and detail of the reproductive data allowed us to

examine less well-studied reproductive characteristics such as pregnancy outcomes and breastfeeding.

Results from studies such as this one can help elucidate the wide range of factors that influence all-cause mortality and enhance understanding of differences in mortality among subpopulations. In this cohort of younger breast cancer cases we observed an increased risk of death for parity of 4 or more births. We confirmed the association between having had a recent birth and poor survival. In our data, the risk of death remains consistently elevated for births within 5 years before diagnosis, beyond which the risk drops off substantially. Overall survival among younger patients with breast cancer appears to be influenced by some reproductive characteristics, possibly reflecting hormonal influences.

Tables

Table 1: Distribution (n (%)) of baseline characteristics (at or before diagnosis) among breast cancer patients stratified by vital status, central New Jersey and metropolitan Atlanta, Georgia, 1990-1992

Characteristic	Total	Died	Alive
	Total study population		
	n=1264	**n=292**	**n=972**
Age at diagnosis, years			
<35	154 (12.2)	47 (16.1)	107 (11.0)
35-44	705 (55.8)	167 (57.2)	538 (55.4)
45-54	405 (32.0)	78 (26.7)	327 (33.6)
Summary Stage			
Local	721 (57.1)	76 (26.1)	645 (66.4)
Regional	510 (40.4)	188 (64.6)	322 (33.2)
Distant	31 (2.5)	27 (9.3)	4 (0.4)
Menopausal status			
Premenopausal	985 (78.1)	239 (81.9)	746 (77.0)
Postmenopausal	276 (21.9)	53 (18.2)	223 (23.0)
Estrogen receptor status			
Positive	706 (55.9)	143 (49.0)	563 (57.9)
Negative	446 (35.3)	128 (43.8)	318 (32.7)
Unknown/borderline	112 (8.9)	21 (7.2)	91 (9.4)
Education			
<College graduate	508 (40.2)	101 (34.6)	407 (41.9)
≥College graduate	756 (59.8)	191 (65.4)	565 (58.1)
Income, $ per year			
<15,000	126 (10.2)	56 (19.6)	70 (7.4)
15,000-24,999	131 (10.6)	35 (12.2)	96 (10.2)
25,000-89,999	739 (60.0)	155 (54.2)	584 (61.7)
≥90,000	236 (19.2)	40 (14.0)	196 (20.7)
Age at menarche, years			
<12	316 (25.0)	85 (29.2)	231 (23.8)
≥12	946 (75.0)	206 (70.8)	740 (76.2)
Parity			
Nulliparous	275 (21.8)	56 (19.2)	219 (22.5)
1-3	887 (70.2)	199 (68.2)	688 (70.8)
≥4	102 (8.1)	37 (12.7)	65 (6.7)
	Among parous women		
	n=989	**n=236**	**n=753**
Age at first birth, years			
<18	73 (7.4)	28 (11.9)	45 (6.0)
18-21	278 (28.1)	70 (29.7)	208 (27.6)
≥22	638 (64.5)	138 (58.5)	500 (66.4)

Characteristic	Total	Died	Alive
Recency of last birth, years			
≤5	180 (18.2)	65 (27.5)	115 (15.3)
>5	808 (81.7)	171 (72.5)	637 (84.6)

Stratum-specific numbers may not add up to totals because of missing data

Table 2: Adjusted HR (95% CI) for all-cause mortality in relation to prediagnostic reproductive factors among breast cancer patients in central New Jersey and metropolitan Atlanta, Georgia (1990-1992 through 2000)

Characteristic	No. Died	No. Alive	HR[1] (95% CI)
	Total study population		
Age at menarche, years			
≥12	200	723	1.00
<12	85	222	1.25 (0.97-1.62)
Gravidity*			
Never pregnant	39	144	1.00
Ever pregnant	247	801	0.99 (0.70-1.40)
Parity*			
Nulliparous	55	217	1.00
1-3	195	665	1.01 (0.73-1.38)
≥4	36	63	1.71 (1.09-2.67)
	Among gravid women		
Spontaneous abortions			
0	183	612	1.00
≥1	64	190	1.10 (0.83-1.46)
Induced abortions			
0	194	622	1.00
≥1	53	180	0.86 (0.63-1.17)
Number of induced abortions			
0	194	622	1.00
1	37	132	0.80 (0.56-1.15)
≥2	16	48	1.02 (0.61-1.71)
	Among parous women		
Age at first birth, years**			
<18	26	41	1.45 (0.91-2.31)
18-21	69	204	1.00
≥22	134	478	1.05 (0.76-1.44)
Recency of last birth, years			
>5	168	617	1.00
≤5	63	111	1.78 (1.28-2.47)
Breastfeeding			
Never/<2 weeks	125	359	1.00
Ever (≥2 weeks)	106	370	0.90 (0.69-1.18)
Total breastfeeding duration, months until cessation			
Never/<2 weeks	125	359	1.00
≤ 12	61	277	0.71 (0.52-0.97)
>12	41	91	1.36 (0.95-1.95)
Total breastfeeding duration, months until supplementation			
Never/<2 weeks	125	359	1.00
≤3	40	200	0.67 (0.46-0.96)
>3	62	165	1.13 (0.83-1.54)

HR[1]= Adjusted for age at diagnosis (<35, 35-44, 45-54), income (<$15,000, $15,000-$24,999, $25,000-89,999, ≥$90,000) and includes an interaction term between income and continuous time.

*Additionally adjusted for recency of birth (≤5 years vs. >5 years/nulliparous).
**Additionally adjusted for parity (≥4 vs. 1-3) and the number of Pap smears (0-1, 2-4, ≥5) and clinical breast exams (0,1-5,>5) in the past 5 years.

Abbreviations: CI, confidence interval; HR, hazard ratio

Table 3: Adjusted HR (95% CI) for all-cause mortality in relation to parity and recency of birth, stratified by summary stage, among breast cancer patients in central New Jersey and metropolitan Atlanta, Georgia (1990-1992 through 2000)

Characteristic	HR[1] (95% CI) Local stage	HR[1] (95% CI) Regional/distant stage	p-value[2]
Parity			
Nulliparous	1.00	1.00	
1-3	0.71 (0.41-1.25)	1.01 (0.69-1.50)	0.670
≥4	1.42 (0.63-3.21)	1.85 (1.08-3.14)	
Recency of last birth, years (among parous)			
≥5	1.00	1.00	
≤ 5	1.88 (0.93-3.83)	1.38 (0.95-2.01)	0.308

HR[1] = Adjusted for age at diagnosis (<35, 35-44, 45-54), income (<$15,000, $15,000-$24,999, $25,000-89,999, ≥$90,000), and includes an interaction term between income and continuous time. Parity is additionally adjusted for recency of birth (≤5 years vs. ≥5 years/nulliparous).

p-value[2] = p-value of the likelihood ratio test comparing models with and without the interaction term(s) in model

Abbreviations: CI, confidence interval; HR, hazard ratio

CHAPTER IV: ORAL CONTRACEPTIVES AND BREAST CANCER SURVIVAL IN YOUNGER WOMEN

Abstract

Purpose. Recent oral contraceptive (OC) use is associated with a modest increase in breast cancer incidence among younger women, but its impact on survival is unclear. This study examined whether pre-diagnostic OC use was associated with survival among breast cancer patients.

Methods. A population-based sample of women (n=1264) aged 20-54 years diagnosed with a first primary invasive breast cancer between 1990-1992 were followed for 8-10 years. Detailed contraceptive and covariate information was collected through in-person interviews administered shortly after diagnosis. Vital status was ascertained through the National Death Index via the state cancer registries (n=292 deaths). Age- and income-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated via Cox regression methods.

Results. All-cause mortality was not associated with ever use of OCs or duration of total use. However, the HR was increased among recent OC initiators prior to diagnosis [<10 years versus ≥20 years = 1.77 (0.98-3.21)] and among users at diagnosis or those who had ceased use in the year before diagnosis [1.46 (0.91-2.33)]. The HR was doubled for use of high dose estrogen pills within 5 years before diagnosis [versus low dose = 2.38 (1.22-4.62)], or if the most recent pill included the progestin levonorgestrel [versus all other types = 2.00 (1.03-3.87)]. However, the estimates were based on small numbers of exposed individuals thus the data should be interpreted with care.

Conclusion. OC use just prior to diagnosis may negatively impact survival in younger breast cancer patients.

Introduction

Oral contraceptive (OC) pill use is common with 82% of American women between 15 and 44 years of age reporting ever use (*117*). OCs are the most common contraceptive used by women younger than 30 years old (*117*). Worldwide, more than 300 million women have ever used OCs (*221*), thus, understanding the full range of health effects associated with their use is important.

The number of invasive female breast cancer survivors was estimated to be 2.28 million in 2002 (*2*). Obesity at diagnosis has been associated with increased mortality, possibly due to estrogen-mediated mechanisms (*27*). Thus, other hormonally related characteristics (e.g. oral contraceptive use) may influence survival, possibly contributing to the increased mortality in younger versus older women (*2*).

Current or recent OC use is associated with a modest increase in breast cancer incidence among younger women (*134*), but their effect on survival is unclear (*87,91,97,101,104,108,153-164*). Pill content has changed dramatically since 1960 (*119*), and higher dose and potency pills have been associated with breast cancer incidence (*149*). To date, no studies have examined pill characteristics and their effects on survival.

In this large, population-based study of younger breast cancer patients with detailed oral contraceptive data, we investigated the association between survival and pre-diagnostic OC use including ever use, duration, age at first use, age at last use, duration of use before age 25, duration of use before a first birth and recency of first and last use. We also examined whether survival systematically differed according to OC dose, potency, or formulation.

Methods

Study Population

A cohort of invasive breast cancer patients previously enrolled in a population-based case-control study (n=1283) (*141*) was followed to investigate predictors of survival. Participants who were female residents of central New Jersey (n=452) and the Atlanta, GA metropolitan area (n=831), aged 20-54 years, and were diagnosed with a primary, invasive breast cancer between May 1, 1990 and December 31, 1992, were eligible for follow-up. Newly diagnosed breast cancer patients were identified using rapid-ascertainment systems at population-based registries. In the parent case-control study, detailed exposure and covariate information was collected via structured in-person interviews conducted by trained interviewers shortly after diagnosis (median 4.2 months). Interviews lasted an average of 67 minutes and were completed by 86% of eligible *in situ* and invasive cases (*141*). Reasons for patients not being interviewed include refusal (5.4% physician refusal and 6.4% patient refusal), death (0.4%), and illness (0.6%) (*141*). For the follow-up study, participants missing vital status were excluded (n=19), resulting in 1264 subjects for analysis. This study was approved by Institutional Review Boards at collaborating institutions.

Exposure Assessment

All of the pre-diagnostic OC use information and most of the covariate information used in this investigation came from the case-control interview. To aid recall of OC use, a reproductive history calendar was used, thus helping women anchor their OC use to key life events (e.g. menarche, pregnancies). For each episode of OC use since menarche, participants were asked to recall the starting and stopping date and the name of the pill used. Color photographs and listings of all pills ever on the market (including information on dates of introduction and removal from market, color of pill, and pill packaging) were used to help participants identify specific brands.

To analyze the effects of dose and potency, several pill components were considered. Similar to previous analyses (*149*), participants were excluded from the content analyses if they used OCs for <6 months (n=118, 12% of ever users), could not recall their dates of use or the specific pill types (n=202, 20% of ever users), or used progestin-only pills (n=6, <1% of ever users), resulting in 689 participants with pill content data. Classification of dose and potency is complicated for women who used multiple pills at different time periods for varying durations, therefore, components of combination OCs used in potentially biologically relevant time periods were analyzed (*149*). These time periods of pre-diagnostic use included: 1) the most recently used pill, 2) the pill used for the longest period within 5 years of diagnosis, 3) the pill used for the longest period within 10 years of diagnosis, and 4) the pill used for the longest period ever. For each of these periods, the corresponding pill was classified based on its formulation (estrogen and progestin type), potency (the cross-classification of estrogen and progestin potency) and estrogen dose. Potency was calculated as previously described (*149*), based on the scheme of Piper and Kennedy (*119*). Pills defined by Piper and Kennedy as intermediate progestin potency pills were assigned to the low progestin potency group. Intermediate estrogen potency pills were defined as low potency if they contained ≤35 μg ethinyl estradiol or ≤50 μg mestranol; otherwise they were defined as high potency.

Summary stage (local, regional, or distant) as defined by the Surveillance, Epidemiology, and End Results (SEER) program (*168*), tumor grade (low, medium, or high), and estrogen and progesterone receptor status were abstracted from all patient medical records as part of the case-control study. All patients were queried as to treatment received prior to interview. In Atlanta only, detailed information on the first course of treatment (radiation,

chemotherapy, hormonal therapy, and surgery) and American Joint Committee on Cancer (AJCC) stage (I, IIA, IIB, etc.) (*169*) were available from re-abstraction of the medical records and the SEER program.

Outcome Ascertainment

Breast cancer cases were followed-up for a median of 8.5 years (range=3 months-9.8 years). The cancer registries serving hte two geographic locations provided data on vital status, and if deceased, date and cause of death through linkages with the National Death Index (NDI). By the end of follow-up (January 1, 2000), 292 deaths had occurred. Breast cancer was the cause of death for 85% of deceased participants (n=248 deaths).

Statistical Analyses

Follow-up time was calculated from diagnosis to death or study truncation. The proportional hazards assumption was assessed through log(-log(survival)) plots and including interactions with follow-up time. Household income and recency of last use violated this assumption, therefore, an interaction term between continuous follow-up time and income and an interaction term between categorical time (>24 months) and recent last OC use were included in all models. Variables were categorized according to their association with mortality and were modeled using indicator variables.

Pre-diagnostic OC use and covariates were initially analyzed for their relationship with survival via Kaplan-Meier methods. Bivariate analyses were also conducted between OC use variables and covariates. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were then estimated using Cox regression methods (*201*). All-cause mortality was the main end-point and patients alive at study truncation or last known follow-up were censored. Analyses of breast cancer specific-mortality were also conducted and participants who died

of causes other than breast cancer were censored. Each attribute of OC use (ever use defined as any use, ever use for ≥6 mo, duration, age at first use, age at last use, duration of use before age 25, duration of use before a first birth, recency of first use, and recency of last use) was modeled separately. Two sets of estimates are presented. We present effect estimates derived from analyses comparing OC users to non-users. However, we also show estimates based on analyses restricted to ever users only, because the small proportion of women who report never using OCs may be fundamentally different from users and may thererefore not be an appropriate referent group.

Covariates were initially included in multivariable models if they were associated with the particular OC variable and the outcome in bivariate analyses. Model-building proceeded using backward elimination and variables were retained, and defined as confounders, if their inclusion in the model caused more than a 10% change in the ln(HR) for the OC characteristic. For all subjects, potential confounders included age at diagnosis, education, household income, physical activity (at age 20 and in the year before diagnosis), obesity as measured by body mass index (at age 20 and in the year before diagnosis), summary stage, tumor grade, receipt of chemotherapy and radiation prior to interview, race, smoking status, alcohol consumption, parity, age at menarche, recency of birth, study site, and co-morbidities (thyroid disease, diabetes, high cholesterol, high blood pressure, and other cancers). The only consistent confounders of the OC and mortality associations were age and income, thus all results adjusted for age (<35, 35-44, or 45-54 years) and household income (<$15,000, $15,000-<$25,000, 25,000-<$90,000, or ≥$90,000). Each OC use-mortality estimate is also adjusted for additional confounders specific to that association (and are listed in the table footnotes). Summary stage, tumor grade and hormone receptor status did not systematically

confound any of the reported relationships. In the Atlanta subgroup, adjustment for the detailed treatment information or AJCC stage did not alter any of the estimates.

Effect modification by age (<45, ≥45), menopausal status, estrogen receptor (ER) status, summary stage, family history, smoking status at diagnosis, body mass index in the year before diagnosis and method of cancer detection (accidental, routine self-exam, routine mammogram, etc.) was initially evaluated by examining stratum-specific HRs. Additional analyses investigated the inclusion of product interaction terms. Effect modification was considered significant if the p-value for the likelihood ratio test comparing models with and without the interaction term(s) was <0.05.

Results

The majority of women were between 35 and 44 years of age, had local stage disease, and were premenopausal. Twenty percent of participants never used OCs, and among users, 13% started at or before 18 years of age, and 10% were current users at diagnosis or had recently ceased use (Table 4).

Ever OC use defined as any use (Table 5) was not associated with mortality [HR (95% CI) = 0.92 (0.69-1.23)], nor was ever use for ≥6 months (results not shown). Relative to never users, duration of total use (Table 5) was not related to mortality. Among ever users (n=1015), age at first use (Table 5), age at last use, duration of use before age 25, and duration of use before a first birth were not associated with survival (results not shown).

Timing of pre-diagnostic OC use appeared to negatively impact survival (Table 5). Women who began OC use in the 10 years prior to diagnosis had a 77% increased risk of death relative to women who began ≥20 years ago [1.77 (0.98-3.21)]. Current users at diagnosis or those who had ceased use in the year prior also tended to experience increased

mortality [1.46 (0.91-2.33)], but only after 24 months of follow-up (Table 5). Time since first and last use did not confound each other. Most previous literature presents results relative to never users, therefore, for comparison those results are presented in Table 5. For these analyses the effect estimates were slightly attenuated, but the conclusions reached among users only were similar to those reached if never users were used as the referent group.

Table 6 shows HRs associated with pill content. Women who used high dose estrogen pills (>35 μg ethinyl estradiol or >50 μg mestranol) in the 5 years prior to diagnosis were more than twice as likely to die than those on low dose estrogen pills [2.38 (1.22-4.62)]. Pill potency was not associated with mortality after adjustment for use of high estrogen dose pills. Across all examined time periods, use of pills with the progestin levonorgestrel was associated with increased mortality (e.g. levonorgestrel versus all other progestin types in the most recently used pill = 2.00 (1.03-3.87). However, use of levonorgestrel containing pills in multiple time periods was highly correlated, so it is difficult to determine which time period of use is most important. Adjustment for dose and potency did not alter the estimates for recency of first and last use; therefore the detrimental effects of recency and pill content appear to be independent of each other.

No statistically significant effect modification was observed (results not shown). When considering breast cancer-specific mortality only (Table 7), estimates were typically but not substantially, elevated compared to all-cause mortality estimates, and the conclusions are similar.

Discussion

OCs may influence breast cancer survival through hormonal mechanisms, including increased cell proliferation through receptor-mediated mechanisms (*42,135-137*). Previous

studies on OCs and mortality among women with breast cancer have been inconsistent with a few reporting decreased mortality among users (*154,161*), and some reporting increased mortality in users (*91,104,158-160,163*), or no effect (*87,97,101,108,153,155-157,162,164*). Our null results for duration are consistent with most previous work (*97,101,156,160*). Age at first use and use relative to a first birth were not associated with mortality in our study, corroborating one (*160*), but not all (*158,159*) studies. Similar to our study, some previous investigations have observed associations between recent OC use (within 5-10 years prior to diagnosis) and increased mortality (*91,160*), but others have not (*97,101,156,161*). Previous literature has been limited by the use of non-population-based samples of breast cancer patients and broad exposure categorizations. The earliest studies were also limited by the inclusion of few exposed women.

Of interest is our result that time since first and last use was associated with mortality, although duration was not. Despite the modest correlation between time since first and last use and total duration of use, it is possible that duration and timing represent two different aspects of use. Whereas long duration of use can span different time periods relative to a breast cancer diagnosis, it appears that only OC use closer to the time of diagnosis affects subsequent survival. Further the results for time since first and last use do not appear to be explained by unusual characteristics of these patients, either in terms of their OC use patterns, reproductive characteristics or screening practices. Recent OC users were more likely to be younger, be nulliparous or have few children, were more likely to have had a recent birth and to have self-discovered their tumors (rather than through mammography) (data not shown). Most of these associations were likely due to the young age of recent users.

Adjustment for parity or time since last birth did not alter the estimates for time since first and last use.

The dose and potency results are noteworthy; however, because they are based on smaller numbers of exposed individuals, they should be interpreted cautiously. Also, pill types are not prescribed randomly, and we have no data on the underlying reasons women may have been taking certain pill formulations. However, the results mirror those for incidence (*149*) and are consistent with the proposed biological mechanism. The effect of time since first and last use was independent of specific pill characteristics. In other words, mortality was greater among recent pill users, regardless of dose and formulation. Pill content in non-recent time periods was not related to mortality, suggesting that only pills used recently in relation to diagnosis affect mortality. Therefore, time since first and last use and pill content appear to be independent constructs of use. Levonorgestrel, while not typically considered a high potency progestin, is higher in potency relative to other progestins currently on the market (*132*). Also, of the progestins currently dispensed, levonorgestrel exhibits the highest level of androgenic activity (*132*). Few high dose or potency pills are regularly dispensed today and since the time of the study, lower dose OCs have been developed (e.g. estrogen doses have decreased to 20 μg ethinyl estradiol in some pills). However, many of the same pills used by women in the study are still marketed today. Most importantly with regard to the results from this analysis, many currently available pills contain levonorgestrel (*120*). Of the combination OCs available in 2004, 21% contained levonorgestrel (*222*) (in contrast, only 9% of pills used by women in this follow-up study contained levonorgestrel). Therefore, if further studies confirm this association, many currently used pills would be implicated.

Limitations of this study include possibly inadequate control for post-diagnosis changes in certain lifestyle characteristics. Although this investigation did not collect exposure and covariate information after diagnosis, OCs are contraindicated for women with a history of breast cancer (*132*). Thus, our findings reflect the risk of death associated with patterns of use that are common among most women. However, certain factors such as income and obesity may have changed after diagnosis, potentially resulting in residual confounding, with any resulting bias difficult to predict. Although it remains uncertain whether post-diagnosis changes in such factors influence survival (*223*,*224*).

Accurate recall of OC use in observational studies, including specifics such as timing and total duration, may also be of concern. However, previous studies have demonstrated that recall is high when subjects are queried using a detailed questionnaire in conjunction with a reproductive calendar and pill photographs (*171*,*173*). Recall of specific brands is typically less accurate (*171*,*173*), and, in our study, 20% of users could not recall pill brand, leading to missing pill content data. Participants with missing content data, compared to those with complete data, tended to be older (40.8% were ≥ 45 years versus 26.0%) and non-recent OC users (1.5% used <1 year before diagnosis versus 13.5%). However, those missing content data had similar mortality and income levels, therefore bias was likely minimal. Any bias is most likely non-differential however, since the completeness of the NDI is well-validated (*187*) and recall of past OC use is not likely associated with having vital status correctly ascertained by the NDI. All-cause mortality was the primary endpoint of interest since the accuracy of cause of death on death certificates has been questioned by many investigators (*219*), but not others (*225*).

The contraceptive predictors of mortality identified in this study may not be generalizable to all breast cancer patients. Non-participation in the parent case-control study was often due to refusal or patient illness (*141*), thus it is likely that subsequent mortality was higher among non-responders than among responders. Participation in the initial case-control study was satisfactory (86%), although there were differences in OC use between responders and non-responders (83% of responders and 76% of non-responders were ever OC users) (*220*). Therefore, had we been able to include all women, the influence on the observed effect estimates is unknown.

Study benefits include use of data from a population-based study of younger breast cancer patients with long-term follow-up and a comprehensive assessment of OC use. The focus on younger women, many of whom were of reproductive age, is important since this population would have had ample opportunity for exposure. This population was diagnosed comparatively recently and is therefore more similar to current breast cancer survivors in terms of exposure status than cohorts established further in the past. To our knowledge, no one has published on pill attributes such as dose and potency and breast cancer survival. The detailed nature of the oral contraceptive data allowed us to examine this possibility.

Many women take OCs, often for years; therefore a greater understanding of their specific health effects is important. Mortality among OC users is less than mortality associated with childbirth until age 40 for non-smokers and age 35 for smokers (*132*). Comprehensive clinical recommendations about OC use at various ages would therefore depend upon a complex risk/benefit ratio that is outside the realm of this investigation. Hopefully, results from studies such as ours will eventually allow clinicians to appropriately target contraceptive methods based on the potential for the largest benefit and the least harm.

To conclude, in this population-based study of younger breast cancer patients, recent OC use was associated with modest increased risks of all-cause and breast cancer-specific mortality. The two-fold increase in mortality associated with recent use of high-dose pills or the progestin levonorgestrel is of concern, and deserves further investigation.

Tables

Table 4: Distribution (n (%)) of baseline characteristics (at or pre-diagnosis) among breast cancer patients stratified by vital status, New Jersey and Atlanta, Georgia, 1990-1992

Characteristic Total study population	Total n=1264	Died n=292	Alive n=972
Age at diagnosis, years			
<35	154 (12.2)	47 (16.1)	107 (11.0)
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15,000-24,999	131 (10.6)	35 (12.2)	96 (10.2)
25,000-89,999	739 (60.0)	155 (54.2)	584 (61.7)
≥90,000	236 (19.2)	40 (14.0)	196 (20.7)
Duration of oral contraceptive use, months			
Never-users	249 (19.7)	63 (21.6)	186 (19.1)
≤12	236 (18.7)	55 (18.8)	181 (18.6)
13-36	189 (15.0)	40 (13.7)	149 (15.3)
37-72	226 (17.9)	51 (17.5)	175 (18.0)
≥73	364 (28.8)	83 (28.4)	281 (28.9)
Among ever oral contraceptive users	**n=1015**	**n=229**	**n=786**
Age at first use, years			
≤18	136 (13.4)	35 (15.3)	101 (12.9)
18.1-25.9	748 (73.7)	162 (70.7)	586 (74.6)
≥26	131 (12.9)	32 (14.0)	99 (12.6)

Time since first use, years before diagnosis			
<10	58 (5.7)	20 (8.7)	38 (4.8)
10-19.9	379 (37.3)	97 (42.4)	282 (35.9)
≥20	578 (57.0)	112 (48.9)	466 (59.3)
Time since last use, years before diagnosis			
Current use/<1	97 (9.6)	28 (12.2)	69 (8.8)
≥1	918 (90.4)	201 (87.8)	717 (91.2)

Stratum specific numbers may not add up to totals due to missing data

Table 5: Adjusted HR (95% CI) for all-cause mortality in relation to pre-diagnostic oral contraceptive use among 1,264 breast cancer patients in New Jersey and Atlanta, Georgia (1990-1992 through 2000)

OC characteristic	Number Died	Number Alive	HR[1] (95% CI)	HR[2] (95% CI)
Ever-never				
Never	60	182	1.00	1.00
Ever	226	764	0.92 (0.69-1.23)	
Duration, months				
≤12	54	179	1.00	0.91 (0.63-1.31)
13-36	40	144	0.96 (0.63-1.44)	0.87 (0.58-1.30)
37-72	50	170	1.01 (0.69-1.49)	0.93 (0.64-1.36)
≥73	82	271	1.04 (0.73-1.46)	0.95 (0.68-1.33)
Age at first use, years[3]				
≤18	33	97	1.03 (0.69-1.54)	0.82 (0.52-1.29)
18.1-25.9	162	572	1.00	0.81 (0.58-1.12)
≥26	31	95	1.17 (0.76-1.80)	0.95 (0.57-1.57)
Time since first use, years				
≥20	111	452	1.00	0.82 (0.60-1.12)
10-<19.9	95	274	1.28 (0.92-1.77)	1.04 (0.74-1.47)
<10	20	38	1.77 (0.98-3.21)	1.42 (0.80-2.51)
Time since last use, years: >24 months follow-up				
≥1	148	696	1.00	0.98 (0.69-1.40)
Current use/<1 year	25	68	1.46 (0.91-2.33)	1.46 (0.86-2.49)

HR[1]= Adjusted for age at diagnosis (<35, 35-44, 45-54), income (<$15,000, $15,000-$24,999, $25,000-89,999, ≥$90,000) and includes an interaction term between income and continuous time.

HR[2]= Adjusted for same variables as HR[1], but referent group is never OC users.

[3]Additionally adjusted for recency of first OC use (<10 years, 10-20 years, ≥20 years in ever-users, <10 years, 10-20 years, ≥20 years/never users in all women)

Abbreviations: CI, confidence interval; HR, hazard ratio

Table 6: Adjusted HR (95% CI) for all-cause mortality in relation to pre-diagnostic combination oral contraceptive use, examining dose and potency characteristics, among breast cancer patients in New Jersey and Atlanta, Georgia (1990-1992 through 2000)

OC characteristic	Number (%) Died	Number (%) Alive	HR[1](95% CI)
Estrogen dose of pill used for longest period within 5 years of diagnosis (n=149)[2]			
Low dose[3]	29 (67.4)	89 (84.0)	1.00
High dose[3]	14 (32.6)	17 (16.0)	2.38 (1.22-4.62)
Type of progestin in most recently used pill (n=673)			
All other types	148 (93.1)	502 (97.7)	1.00
Levonorgestrel	11 (6.9)	12 (2.3)	2.00 (1.03-3.87)
Type of progestin in pill used for longest period within 5 years of diagnosis (n=151)[2]			
All other types	36 (83.7)	99 (91.7)	1.00
Levonorgestrel	7 (16.3)	9 (8.3)	1.94 (0.85-4.44)
Type of progestin in pill used for longest period within 10 years of diagnosis (n=246)[2]			
All other types	61 (91.0)	170 (95.0)	1.00
Levonorgestrel	6 (9.0)	9 (5.0)	1.43 (0.60-3.39)
Type of progestin in pill used for longest period (n=673)			
All other types	153 (96.2)	507 (98.6)	1.00
Levonorgestrel	6 (3.8)	7 (1.4)	2.00 (0.84-4.73)

HR[1]= Adjusted for age at diagnosis (<35, 35-44, 45-54), income (<$15,000, $15,000-$24,999, $25,000-89,999, ≥$90,000) and includes an interaction term between income and continuous time.

All models include only combination OC users for a total of ≥ 6 months with non-missing data on dose and date specifics

[2]= Models include only OC users who used in that particular time period

[3]Low estrogen dose = ≤ 35 µg of ethinyl estradiol or ≤ 50 µg mestranol; high dose = >35 µg of ethinyl estradiol or > 50 µg mestranol

Abbreviations: CI, confidence interval; HR, hazard ratio

Table 7: Adjusted HR (95% CI) for breast cancer specific-mortality in relation to age at first use, recency of use and pill content (in users) among breast cancer patients in New Jersey and Atlanta, Georgia (1990-1992 through 2000)

OC characteristic	Number Died	Number Censored	HR[1] (95% CI)
Age at first use, years[2]			
≤18	24	106	0.85 (0.53-1.35)
18.1-25.9	136	598	1.00
≥26	29	97	1.36 (0.86-2.14)
Time since first use, years			
≥20	92	471	1.00
10-<19.9	77	292	1.22 (0.85-1.75)
<10	20	38	2.01 (1.08-3.73)
Time since last use, years: >24 months follow-up			
≥1	124	720	1.00
Current use/<1 year	24	69	1.63 (1.00-2.66)
Estrogen dose of pill used for longest period within 5 years of diagnosis (n=149)[3]			
Low dose[4]	27	91	1.00
High dose[4]	14	17	2.47 (1.26-4.83)
Type of progestin in most recently used pill (n=673)			
All other types	127	523	1.00
Levonorgestrel	10	13	2.08 (1.04-4.17)
Type of progestin in pill used for longest period within 5 years of diagnosis (n=151)[3]			
All other types	34	101	1.00
Levonorgestrel	7	9	2.00 (0.87-4.60)
Type of progestin in pill used for longest period within 10 years of diagnosis (n=246)[3]			
All other types	56	175	1.00
Levonorgestrel	6	9	1.51 (0.63-3.59)
Type of progestin in pill used for longest period (n=673)			
All other types	132	528	1.00
Levonorgestrel	5	8	1.82 (0.71-4.66)

HR[1] = Adjusted for age at diagnosis (<35, 35-44, 45-54), income (<$15,000, $15,000-$24,999, $25,000-89,999, ≥$90,000) and includes an interaction term between income and continuous time.

[2]Additionally adjusted for recency of first OC use (<10 years, 10-20 years, ≥20 years)
Pill content models include only combination OC users for a total of ≥ 6 months with non-missing data on dose and date specifics
[3]= Models include only OC users who used in that particular time period
[4]Low estrogen dose = ≤ 35 μg of ethinyl estradiol or ≤ 50 μg mestranol; high dose = >35 μg of ethinyl estradiol or > 50 μg mestranol

Abbreviations: CI, confidence interval; HR, hazard ratio

CHAPTER V: DISCUSSION

Summary of Key Dissertation Results

To review, in this cohort study of younger breast cancer patients, increased mortality was associated with key reproductive events, including high parity (≥4 births, HR = 1.71), and having given birth recently (within 5 years prior to diagnosis, HR = 1.78). The effect of recent births was stronger in women with a prediagnostic BMI of <25 kg/m^2 (2.54). Early age at menarche (<12) and early age at first birth (<18) were associated with modest increases in mortality (1.25, 1.45, respectively). The effect of young age at menarche appeared to be confined to premenopausal women (1.42). Other reproductive characteristics were not associated with survival, including induced or spontaneous abortions, age at last birth, and ever breastfeeding. Shorter, but not longer durations of breastfeeding were associated with decreased risks of death; this was true for both total duration until supplementation and total duration until cessation.

Prediagnostic OC use, in particular time since first and last use, also appeared to influence survival after breast cancer in this population. Women with breast cancer who had either recently started taking OCs (within 10 years before diagnosis) or were current users at diagnosis or ceased use within a year were more likely to die than those who had started or ended use more distantly (1.77, 1.46, respectively). With regard to pill content, those who used high dose estrogen pills in the 5 years before diagnosis had increased risks of death relative to low dose users during the same period. In addition, use of pills containing the progestin levonorgestrel tended to double the risk of death. The effect of recency appears to

be independent of pill content because adjustment of the recency associations by dose, potency, and formulation did not result in altered estimates of effect. Thus, it appears it is still risky to have recently used OCs, regardless of pill content. No statistically significant effect modification of the OC estimates was observed. In general, for both reproductive and OC exposures, results for breast cancer-specific mortality were slightly elevated relative to all-cause mortality estimates.

Biologic Plausibility of Results

These results implicate the timing of hormonal exposures as central to breast cancer progression. As discussed in detail in Chapter 1, reproductive history influences the hormonal milieu. These hormonal changes could influence survival through growth promotion, production of tumors with more aggressive characteristics, and/or through associations with hormone regulated genes (estrogen-regulated genes that are associated with survival). These results indicate that a woman's reproductive history influences not only her likelihood of developing breast cancer initially, but also of its progression once clinically evident. After childbirth, women have a modest, transient increase in breast cancer incidence for up to approximately 10 years (*58*). This may occur due to the dramatic increases in pregnancy-associated hormones. Increasing evidence, including results from this dissertation, indicate that these high levels of hormones may influence survival as well.

OCs could influence survival through their role in cell proliferation, or may influence survival indirectly via hormone levels. Synthetic, exogenous hormones may act differently than endogenous hormones. For example, women on combination OCs are exposed to progesterone for 50% longer than naturally cycling women not taking OCs. Additionally, due

to differences in pill content over time (*119,123,132,226*), it is plausible differences in survival may be associated with different pill formulations.

These data suggest that hormonally associated factors appear to affect breast cancer incidence and survival in similar ways, allowing for an integrated mechanism for breast cancer initiation, promotion and progression. However, interesting and important differences are apparent between incidence and survival. It is possible, but speculative, that hormones may have a larger effect on breast cancer survival than incidence. For example, obesity increases breast cancer incidence in postmenopausal women (*227,228*), but not in premenopausal women (*228,229*). The rationale for a lack of an effect in overweight or obese premenopausal women has been that the increase in hormones from aromatization of androstenedione in fat cells (*227*) would not be enough to swamp the already high levels of ovarian-produced hormones present. Amenorrhea and anovulation (*57,230*) have also been proposed as mechanisms for the decreased or null associations between obesity and premenopausal breast cancer incidence. However, it appears that obesity is negatively associated with survival in premenopausal women (*27*), so what explains this difference? Are survival outcomes more estrogen dependent (or sensitive) than incidence? This would explain the above observation. Perhaps estrogen acts more quickly on already established tumors, thus allowing for enhanced growth. Alternatively, it could be due to the rapid onset of menopause in women undergoing chemotherapy or radiation. However, I did observe that the effect of recency of birth was stronger in leaner women, thus suggesting women who were overweight or obese were not as affected by the additional hormonal load due to a pregnancy. It is also interesting to note that the effect estimates are larger for survival outcomes than incidence. For example, reproductive factors and oral contraceptives both

appear to cause modest increases in breast cancer incidence, with risk ratios between 1.2 and 1.5. Typically, most studies of survival have observed HRs in the range of 1.5-2.0. Whether or not this is a true difference, or simply because the discipline of cancer survival is still young and therefore, we are observing elevated estimates due to publication bias, is currently unknown.

Adjustment for Tumor Characteristics

Whether or not to adjust for tumor characteristics such as stage and grade in analyses of cancer survival is controversial. The issue is complex and not easily resolved in a straightforward manner. A discussion of this methodological issue follows.

Tumor stage and grade are often used clinical markers for determining prognosis and a tumor's natural history, in a sense. Stage is a composite measure of a tumor's size, extent of invasion into surrounding tissue, lymph node status and metastatic potential (*231*). Grade is a measure of tumor aggressiveness and is an indication of how a tumor, on a cellular level, is organized and whether it more closely resembles the "normal", non-cancerous tissue of origin or cancerous tissue, in that the usual cellular processes organizing growth, development and organization have been overcome (*231*). Thus, both are proxies of tumor severity as well as an indication of a tumor's natural history. Granted, the pathobiology of tumors is complex and simply because a tumor has a more advanced stage or higher grade, this does not guarantee knowledge of its previous activity or future behavior. To be clear, having a more advanced tumor does not mean that it has been around longer than a less advanced tumor. While not well completely understood, some cancers will progress rapidly and behave in a particularly aggressive manner. However, there is a general belief that stage and grade are indicators of tumor severity and patient's prognosis.

In epidemiologic parlance, tumor stage and grade may represent intermediates on the causal pathway between certain exposures and survival. To recapitulate the biology of how these exposures may work, using the example of recency of birth; women with a recent birth may have higher exposures to pregnancy-related hormones then either nulliparous women or those with a non-recent birth. These hormones, could in turn, increase cell proliferation and speed tumor growth, result in tumors with more aggressive characteristics as well as influence estrogen regulated genes thought to influence prognosis (see Figure 1 for a schematic). Therefore, in one sense, reproductive exposures clearly represent biologic intermediates.

Even ignoring the issue of causal intermediates, treating these as confounders does not make epidemiologic sense, because it is difficult to argue that stage and grade affect exposure (one of the basic criteria for confounding to be present), rather, as just described they are likely affected by exposure.

The basic criticism for adjusting for causal intermediates is as follows: adjusting for explanatory characteristics will not provide an unbiased estimate of the direct effect of the potential exposure on the outcome in all circumstances, particularly when there is unmeasured confounding between the explanatory factor and the outcome (*232*,*233*). Until recently, many have argued that the data supporting these potential pitfalls are based on hypothetical data with extreme distributions of covariates, thus little was known about the potential for bias in more typical epidemiological data (*234*). Given the uncertainty in the prevalence of this bias, it was originally suggested (*234*) that the practice of adjusting for potential explanatory characteristics not be abandoned but that data on potential confounders of the explanatory factor — outcome relationship be collected and adjusted for in the

analyses. Recent work has further criticized this technique of adjusting for intermediates to test the degree to which something mediates a variable. The conditions under which this would be a valid approach are rarely observed and the assumptions needed are strict (*216*). In addition to the assumption that there be no residual confounding between the intermediate variable and outcome, there can be no effect modification by the intermediate variable and even if the two previous assumptions are met, decomposition is only valid on the risk difference scale, since ratio measures of effect are not easily interpretable in a decomposition scheme (*216*).

Despite these statistical, epidemiologic, and theoretical concerns, others believe that stage is such a strong determinant of survival that not to adjust for it may result in bias, since one would be ignoring differences that may have arisen outside of biological mediation. For example, any association between a reproductive exposure and stage that did not arise through biology (e.g. women with high parity could be more likely to be poor which could be associated with advanced stage) would not be adequately addressed. In other words, it is likely that, for most variables, stage represents both a confounding and intermediate variable. Ignoring stage in statistical models is problematic. It assumes that the effect on survival is 0, and we know this is not true and there are, currently, no satisfying ways to test the magnitude of indirect versus direct effects, leaving limited ways to address this in a methodologically rigorous fashion.

In this dissertation, I choose not to consider stage and grade as confounders for the reproductive factor analyses; however, I did consider them for the OC analyses. This is because the biological relationship between OC and stage is less well understood and any such relationship, if it existed, could be due to sociological, rather than biological, factors.

For example, OC users, by definition, have to be consistently interfacing with the health care system. Thus, OC users could be more likely to have tumors diagnosed at less advanced stages, simply by virtue of having health care access. For the reproductive factors, I ran and presented results stratified by stage. While this may not be ideal, or directly answer the question of interest (how much of the association between these variables and survival can be explained by tumor characteristics), I come to the same conclusion as other studies on this topic. Since I observe elevated HRs for parity and recency of birth at all stages, to me, this indicates that the associations are not completely "due to" more advanced stage.

Comparison of Dissertation Study Results to Other Studies

The previous literature on reproductive characteristics and survival is scant and what is available is inconsistent. Our results are similar to many others on these topics, however. As in our study, most literature has found recent births to be associated with decreased survival (*87-96*). Pinpointing the exact time since last birth that is associated with increased mortality has been more difficult, and has remained unresolved. Some have concluded or implied that there is a linear relationship between time since last birth and risk of death (i.e. for every few years since a last birth before diagnosis, the risk of death drops correspondingly (*87,92-96*). Consistent with the findings reported here, others have reported results that are more compatible with a threshold effect (risk remains consistently elevated for a certain period then drops precipitously) (*88-91*). However, many of these studies did not comment further on the type or specifics of the relationship observed. Similar to the results of this dissertation, a handful of studies have found parous women to have lower survival relative to nulliparous women (*87,90,92,94,103-107*). Since many previous studies did not present results adjusted

for recency of birth, it has been unclear whether recency of birth confounded the parity effect. Our results indicate that there is an independent effect of high parity.

The previous literature on OCs and breast cancer survival is even more inconsistent. Two studies found recent use to increase risk of death (*91,160*), which is consistent with our results; however, unlike our results, two additional studies found young age at first use to be associated with increased mortality (*158,159*). At least in the New Jersey/Atlanta population, recency of OC use appears to be the more important determinant of mortality, rather than duration or age at first use. Previous work has been limited by crude exposure categorization, limited follow-up and lack of inclusion of women who would have had ample opportunity for exposure. No one has previously considered characteristics of pill content as determinants of survival.

Study Limitations

Lack of post-diagnostic lifestyle data

Limitations to this data include the lack of information on changes in covariate information after diagnosis, thus leading to the potential for residual confounding by these variables. This lack of post-diagnostic data was likely not an issue for many of the reproductive exposures of interest (e.g. few women get pregnant after a diagnosis of breast cancer) and OC use is contraindicated for women with a known or suspected history of breast cancer (*132*), and this has been true since the late 1960's (*235,236*). However, factors such as physical activity, obesity and income may have changed after diagnosis, therefore if these are important confounders of certain exposures of interest, we may not have adequately controlled for their effect. Previous research suggests that breast cancer survivors often gain weight after diagnosis, typically as a side-effect of chemotherapy administration (*237-239*),

but that physical activity patterns may be similar to women without cancer (*239-241*). However, only a few studies (e.g. *223,242,243*) have addressed whether post-diagnosis levels of physical activity or obesity affect mortality, thus the impact of omitting these variables from the present analysis cannot be easily quantified. Even less work has established whether income or socioeconomic changes after diagnosis affect mortality. Breast cancer treatment often requires extended work absences (*244*), which could cause decreases in individual and household market earnings (*224*). Since it is unknown whether a) these post-diagnostic changes are associated with survival independent of pre-diagnostic levels, and b) whether they are associated with the exposures of interest, the ultimate affect on the results reported here are unknown. Since pre-diagnostic physical activity and BMI levels did not confound the reproductive and contraceptive associations with mortality and that pre- and post-diagnostic levels of these covariates have been shown to be correlated, it is possible that having data on post-diagnostic changes would not have altered the results substantially.

Additional covariates that were not measured in the original case-control study, and thus could not be considered, included psychosocial support, psychological coping strategies, and insurance status (*245-247*).

An additional limitation in this data is the detailed treatment information was available only from the Atlanta center only. All women in the follow-up study were queried about whether radiation and chemotherapy had been initiated prior to the case-control study interview, which occurred a median of 4.2 months after diagnosis. For the Atlanta participants only, additional resources were available to reabstract the medical records and link with SEER databases to obtain more detailed information on the first course of treatment, including chemotherapy, radiation, surgery (breast conserving versus

mastectomy), and adjuvant hormonal therapy. Thus, in subgroup analyses, this more detailed data from Atlanta was used to adjust for potential confounding by treatment. However, for treatment to confound the effect of various reproductive factors or OCs on survival, it would have to be strongly associated with reproductive factors (or OCs) and an independent predictor of survival. While the survival advantage associated with various treatment regimens is well established, currently no evidence exists to suggest that clinicians systematically base treatment decisions on prior reproductive histories or past use of oral contraceptives, thus it is unlikely treatment would be a strong confounder. As expected, when the additional treatment data was considered in the Atlanta sub-group only, no confounding was observed. Therefore, it seems unlikely that the addition of the data for the New Jersey group would have greatly altered the results or conclusions for the entire cohort.

Misclassification of Exposures, Confounders and Outcome

Self-reported contraceptive and reproductive histories, including specifics such as age at menarche, parity, and timing of births have been shown to have high validity. Thus, it is unlikely that there is substantial misclassification of these exposures. Additionally, given that survival was ascertained using the NDI, any bias is likely to be non-differential since a woman's reproductive history should not be influenced by her likelihood of being correctly classified in the NDI. Recall of certain exposures such as induced and spontaneous abortions will likely be low, but sensitivity analyses were undertaken to explore the degree to which recall bias may be influencing these results. For example, as discussed in Chapter 3, even if one assumed that 50% of patients underreported a history of induced abortion, if this underreporting was non-differential by vital status, no differences between the observed and corrected estimates were observed.

Most characteristics of lifetime OC use have also been shown to be recalled fairly accurately in in-person interviews, including for such determinants as duration and timing, especially when interviews are paired with reproductive calendars and color photographs to enhance recall. However, accurate recall of specific pills brands is typically lower. In this population, pill brand data was missing data for approximately 20% of women, thus they could not be classified according to dose and potency. Participants with missing content data, compared to those with complete data were, respectively, older (40.8% were ≥ 45 years at diagnosis versus 26.0%) and less likely to be recent OC users (1.5% used <1 year before diagnosis versus 13.5%). Otherwise, they were similar on vital status, and income, therefore bias was likely minimal.

Misclassification of potential confounders may have occurred, especially for those that were assessed broadly such as obesity and household income. To minimize the potential for bias, variables were ultimately categorized based on the most specific designation possible while balancing the need for groups to have enough numbers to result in reasonably stable estimates. It also seems unlikely that misclassification of key confounders was differentially related to the outcome or key exposure variables.

Misclassification of outcome was likely minimal as the NDI is a large nation-wide registry of deaths with documented completeness and accuracy. The state cancer registries used patient's names, birthdates and social security numbers to make matches with the NDI, thereby enhancing accuracy. Breast cancer-specific mortality was not the primary outcome of interest for this dissertation given that the accuracy of cause of death on death certificates is thought to be less optimal (*193,219,248,249*). A recent study observed that the sensitivity of the death certificate was 0.65 for all malignant causes of death, using necropsy as the gold

standard (*219*). From a public health perspective, a primary objective is prevention of mortality from any cause, regardless of the underlying reason. For example, pregnancy and oral contraceptive use have been associated with increased mortality from non-cancer causes, including cardiovascular diseases, primarily in women >35 years of age and those with risk factors for cardiovascular diseases (*250,251*). However, from the biological standpoint of understanding specific mechanisms of breast cancer progression, it would be important to consider differences by causes. Especially for the exposures focused on in this dissertation, it is logical to assume that they would affect likelihood of dying from breast cancer more than mortality from other causes. Most patients in this study were young; therefore, outside of the few numbers of deaths that occurred due to accidents, it seems unlikely that their cancer did not influence their mortality in some way.

Generalizability

Because eligibility for this follow-up study was conditional on participation in an earlier study, there is always the concern that those who participated in the case-control study, and thus were eligible for the follow-up study, could be different than those who did not participate, in terms of both exposure and outcome status. However, our results are likely generalizable to most breast cancer patients since a high proportion (86%) of patients eligible for the parent study participated in the original case-control study. Differences in exposure status between responders and non-responders were also small. Among patients in the parent study, respondents were similar to non-respondents on age at diagnosis, number of births, and age at first birth. Relative to non-respondents, respondents had an earlier age at menarche, were slightly more likely to be parous and use oral contraceptives, and were more highly educated (*220*). Cases who did not participate in the original case-control study may

have been sicker and thus, more likely to die. For example, 5.4% of physicians refused contact with the patient, 0.4% of cases died before interview and 0.6% were too ill to be interviewed (*141*). Thus, the survival experience among participating case women may be slightly better than those who did not and interpretations of our results should consider the possibility that women in this cohort could represent a relatively healthier cohort of breast cancer survivors (i.e. a health survivor effect, akin to the healthy worker effect). Therefore, it is possible that the magnitude of the effects observed in this dissertation may not be the same in all breast cancer patients. Without having more data on the cross-classification of response probabilities for exposure and outcome status, the direction and magnitude of our results cannot be easily predicted. For example, because responders were more likely to be OC users, we may have enriched our resulting sample for a risky exposure (assuming they were recent users), thus overestimating the effect of recent OC use. However, we may have not interviewed the patients who were sickest and thus most likely to die, thus we may have enrolled a sample of women with particularly high survival rates, thus underestimating certain effects. However, to determine more accurately whether our results are generalizable, we would have to know the joint probability of response rates by OC use and vital status; however this information is not available.

Power

A final caveat is that this study was underpowered to consider some exposures of interest, especially some of the OC specifics and had even less power to evaluate effect modification by such variables. For example, there were only 58 patients who were recent first users of OCs (<10 years), 20 of whom died by the end of follow-up. However, for most exposure-outcome associations of interest in this study, power was adequate.

Study Strengths

Large, population-based sample of younger patients

There are a number of strengths present in this study. This was a large population-based, study of younger breast cancer patients, with almost 1300 breast cancer patients from a well-characterized study base. This study focused on younger women, which is a strength of the study since the prognostic factors of interest and the outcome were separated by a comparatively short period of time, thus preventing the dilution of effects observed in many epidemiological studies. This possibly resulted in the observation of stronger exposure effects. Especially for OCs, the inclusion of a large number of younger women who were diagnosed relatively recently is important since this population would have had ample opportunity for exposure, including long-term and recent exposure to pills still marketed today.

Long follow-up

The 10-year follow-up in this cohort is longer than other cohorts that often discontinue follow-up after 3 or 5 years, limiting the power to examine effects on survival time. Outcome ascertainment was complete and thought to be valid for the vast majority of participants. The use of the NDI allowed us to search nationwide for deaths and resulted in minimal lost-to-follow-up. Therefore, we were not reliant on women remaining in the same geographic area that they were diagnosed in to get accurate outcome data.

Data breadth, depth, and quality

The original case-control study was specifically designed to examine reproductive history and OC specifics in relation to incidence, therefore, the variables of interest in this study were carefully measured and are thought to have high validity and reliability. The

comprehensive nature of the original case-control study interview allowed a consideration of a number of unique variables in a breadth and depth that few other studies have had the ability to do. In particular, the reproductive history calendar and color photographs of all OCs allowed for a detailed reconstruction of patient's reproductive and contraceptive histories. This enabled a thorough investigation of their relationship to survival. The results of this dissertation will add to the literature on predictors of survival in younger breast cancer patients. In particular, previously understudied characteristics such as breastfeeding and pregnancy outcomes were carefully considered and analyzed. With regard to recency of birth, we were able to confirm the previous association with mortality, and we observed an important interaction with body mass index. One remaining question is what the exact relationship is between timing of birth and mortality. In other words, is the relationship strongest in the first two (or one or five) years, and then falls off slowly, or is there a threshold effect? In my analysis, I carefully considered both these possibilities and these results will add to the existing data on this association. In addition, we had information about OC pill brands used across time, thus we were able to report on these associations, which, to date have not been reported on. Also, individual level data on a number of potential confounders were collected, including physical activity and weight status, both of which were key constructs of interest in the original case-control study.

Perhaps the biggest strength of the study is that these results have implications for elucidation of the etiology of breast cancer progression (at a population, rather than cellular, level) as well as public health implications, as discussed below.

Public Health Implications

These dissertation results have various public health implications. In general, there are very few studies of predictors of breast cancer survival in younger patients. Thus, these studies will add to our knowledge about what might influence survival in these populations. Younger women experience lower survival after diagnosis then older women, but the exact reasons are unknown and these results shed light on certain possibilities. Secondly, these results help elucidate possible reasons for differences in mortality across populations.

The public health implications of the specific exposures of interest are also important to consider. Concerning reproductive factors, clinicians who see younger breast cancer patients should be aware that those with a recent birth might be at an increased risk of death. This may become increasingly salient given the secular changes towards earlier menarche (*214*) and as more women postpone childbearing until older ages (*213*).

In terms of OCs, it is important to understand the specific health effects of an exposure, like OCs that many women are exposed to, often for years. Clinical recommendations for its use depend on a complex risk/benefit analysis across a wide range of health outcomes that is outside this realm of this dissertation. Obviously, for most young women, pregnancy prevention is a more important health consideration than any breast cancer outcomes. For example, mortality among OC users is less than that associated with childbirth until age 35 for smokers and 40 for non-smokers (*132*). OCs are contraindicated for those with a known or suspected history of breast cancer (*132*), so clinical recommendations for its use based on the potential for future breast cancer outcomes would, at this point, be difficult. Eventually, clinicians may be better able to target contraceptive methods based on more information about the specific health risks and benefits, thus allowing for more accurate risk assessment for an individual. It is also possible that better recommendations for age caps for OC use

could be implemented. Currently, no such guidelines are present (*132*); it is up to individual clinicians to make such decisions. When additional risk/benefit analyses are done and we have a better understanding about the profiles of women who might be harmed by their use, we could recommend ceasing use at certain ages when mortality from increasingly common diseases exceeds that from childbirth for the majority of women. It is also important to note that the absolute risk of getting and dying from breast cancer associated with OCs is low, particularly for women <45 years, given the low prevalence of the disease and its high survivability. The dose and potency results are noteworthy, but since they are based on small numbers, caution in interpretation is warranted. However, they do fit the proposed biological mechanism and the results are similar to those for incidence in the same population (*149*). Most high dose or potency pills are not readily available or dispensed today (*120*). However, out of the approximately 56 combination OC pills that were available in 2004, 12 (21%) contained levonorgestrel (*196*) (in contrast, only 9% of pills used by women in this follow-up study contained levonorgestrel). So, if future results confirm that levonorgestrel is particularly risky, a number of pills would be implicated.

Dissertation Conclusions

Despite the relatively high survival rates associated with breast cancer, much of the variation in survival rates remains unexplained. Tremendous advances in the clinical and molecular aspects of breast cancer have lead to a greater understanding of disease incidence and progression. Other characteristics such as reproductive factors and oral contraceptive use have not been fully examined in relation to survival after diagnosis. Reproductive factors and OCs are associated with small to moderate increases in risk of incident breast cancer and appear to influence breast cancer survival in ways that are consistent with our understanding

of the biological mechanisms influencing progression. In particular, the timing of hormonal exposures appears to be involved in the progression of breast cancer. This work also has public health implications in terms of better elucidation of how non-clinical characteristics influence survival.

APPENDICES

Table 8: Combination OC use among participants in the NJ/Atlanta follow-up study by brand name and cross-classified by pill content and potency (n=43 pills, formulations include 2 estrogens and 8 progestins)

	Low Progestin (mg)/ Low Estrogen (µg) Potency		**Low Progestin (mg)/ High Estrogen (µg) Potency**		**High Progestin (mg)/ Low Estrogen (µg) Potency**	**High Progestin(mg)/ High Estrogen (µg) Potency**	
Estrogen	Mestranol	Ethinyl Estradiol	Mestranol	Ethinyl Estradiol	Ethinyl Estradiol	Mestranol	Ethinyl Estradiol
Progestin							
Chlormadinone Acetate			*C-Quens* 1.5/100*				
			C-Quens* 2/80				
Ethynodiol diacetate					Demulen 1/35	Ovulen* 1/100	Demulen 1/50
Medroxyprogesterone acetate							Provest* (10/50)
Norethynodrel			Enovid E* (2.5/100)			Enovid 10 mg* (9.85/150)	
			Enovid 5* (5/75)				
Norethindrone		Ovcon 35 (0.4/35)		Ovcon 50 (1/50)			
	Ortho-Novum 1/50	Ortho-Novum 1/35	Ortho-Novum* 1/80			Ortho-Novum 10mg* 10/60	
		Ortho-Novum 10/11 (0.5,1/35)	Ortho-Novum 2mg* 2/100				
		Ortho-Novum 7/7/7 (0.5,0.75,1/35)	Ortho-Novum SQ* (2/80)				
	Norinyl 1/50	Norinyl 1/35	Norinyl* 1/80				
			Norinyl 2 mg* 2/100				
		Modicon 0.5/35					
		Tri-Norinyl (0.05,1.0,0.5/35)					

	Low Progestin (mg)/ Low Estrogen (µg) Potency		**Low Progestin (mg)/ High Estrogen (µg) Potency**		**High Progestin (mg)/ Low Estrogen (µg) Potency**	**High Progestin(mg)/ High Estrogen (µg) Potency**	
Estrogen	Mestranol	Ethinyl Estradiol	Mestranol	Ethinyl Estradiol	Ethinyl Estradiol	Mestranol	Ethinyl Estradiol
Progestin							
Norethindrone (cont'd)		Brevicon (0.5/35)					
	Noriday* (1/50)						
		ORF 1557-BE (0.5/35)*		*ORF 1557-BA* (0.5/50)*			
		ORF 1557-BF (1/35)*					
Norethindrone acetate		Loestrin 1/20		*Norlestrin low* 0.5/50*			
		Loestrin 1.5/30		*Norlestrin* 1/50*			
				Norlestrin 2.5/50*			
Norgestrel		Lo/Ovral (0.3/30)					
		Ovral Blue (0.15/30)*					Ovral (0.5/50)
		Ovral Brown (0.15/15)*					
Levonorgestrel		Triphasil (0.05,0.075,0.125/ 30,40,30)					
		Trilevlen (0.05,0.075,0.125/30,40,30)					
		Nordette (0.15/30)					
		Levlen (0.15/30)					

*Pill not longer marketed or discontinued in the United States (as of 2006)- based on FDA Electronic Orange Book Search 2/06 (*252*) and Mosby's Drug Consult 2005 (*253*)
Pills in italics were assigned by Althuis et al. 2003 (*149*)
Potencies calculated based on description in Althuis et al. 2003 (*149*) (N.B. there are mistakes in that paper). Potencies were assigned based on Piper and Kennedy (*119*) scheme. Intermediate progestin potency pills were assigned to 'low' progestin potency group and intermediate estrogen potencies assigned to low potency group if ≤ 35 μg ethinyl estradiol or ≤ 50 μg mestranol, otherwise they were coded as high.

Table 9: Distribution [n (%)] of key baseline characteristics (at or pre-diagnosis) among 1264 breast cancer patients, stratified by study site and age at diagnosis, central New Jersey and the metropolitan Atlanta, Georgia area, 1990-1992

Characteristic	New Jersey, 20-44 years (n=440)	Atlanta, GA, 20-44 years (n=419)	Atlanta, GA, 45-54 years (n=405)
Race			
White	376 (85.5)	260 (62.1)	314 (77.5)
Black	41 (9.3)	159 (38.0)	91 (22.5)
Other	23 (5.2)	0	0
Summary stage			
Local	245 (55.7)	229 (54.7)	247 (61.0)
Regional	185 (42.1)	177 (42.2)	148 (36.5)
Distant	10 (2.3)	11 (2.6)	10 (2.5)
Missing	0	2 (0.5)	0
Tumor grade			
Low	13 (3.0)	26 (6.2)	45 (11.1)
Medium	100 (22.7)	139 (33.2)	132 (32.6)
High	177 (40.2)	214 (51.1)	172 (42.5)
Unknown	150 (34.1)	40 (9.6)	56 (13.8)
Estrogen receptor status			
Positive	252 (57.3)	201 (48.0)	253 (62.5)
Negative	146 (33.2)	180 (43.0)	120 (29.6)
No test	42 (9.6)	38 (9.1)	32 (7.9)
Progesterone receptor status			
Positive	248 (56.4)	198 (47.3)	224 (55.3)
Negative	140 (31.8)	184 (43.9)	146 (36.1)
No test	52 (11.8)	37 (8.8)	35 (8.6)
Age at diagnosis, years			
<35	75 (17.1)	79 (18.9)	
35-39	134 (30.5)	124 (29.6)	N/A
40-44	231 (52.5)	216 (51.6)	
45-50	N/A	N/A	259 (64.0)
51-54			146 (36.1)
Menopausal status			
Premenopausal	420 (95.5)	361 (86.2)	204 (50.4)
Postmenopausal	19 (4.3)	57 (13.6)	200 (49.4)
Missing	1 (0.2)	1 (0.2)	1 (0.3)
Education			
≤ High school	119 (27.1)	109 (26.0)	123 (30.4)
Some college	133 (30.2)	137 (32.7)	135 (33.3)
College grad	108 (24.6)	106 (25.3)	71 (17.5)
Post college	80 (18.2)	67 (16.0)	76 (18.8)

Characteristic	New Jersey, 20-44 years (n=440)	Atlanta, GA, 20-44 years (n=419)	Atlanta, GA, 45-54 years (n=405)
Household income, $/year			
< 15,000	27 (6.1)	51 (12.2)	48 (11.9)
15,000-24,999	28 (6.4)	59 (14.1)	44 (10.9)
25,000-34,999	39 (8.9)	59 (14.1)	42 (10.4)
35,000-49,999	67 (15.2)	55 (13.1)	61 (15.1)
50,000-69,999	99 (22.5)	69 (16.5)	68 (16.8)
70,000-89,999	79 (18.0)	48 (11.5)	53 (13.1)
≥ 90,000	91 (20.7)	69 (16.5)	76 (18.8)
Missing	10 (2.3)	9 (2.2)	13 (3.2)
Age at menarche: <12 years			
	104 (23.6)	126 (30.1)	86 (21.2)
Nulliparous			
	87 (19.8)	115 (27.5)	73 (18.0)
Age at first birth >32 years (among parous)			
	45 (12.8)	45 (14.8)	28 (8.4)
Recency of last birth, years before diagnosis (among parous)			
<5	102 (28.9)	76 (25.0)	2 (0.60)
5-20	230 (65.2)	193 (63.5)	126 (38.0)
20+	21 (6.0)	34 (11.2)	204 (61.5)
Missing	0	1 (<1)	0
Ever OC use			
	336 (76.4)	378 (90.2)	301 (74.3)
Duration OC use >72 months (among users)			
	90 (26.8)	165 (43.7)	109 (36.2)
Recency of first OC use, years before diagnosis (among users)			
<10	30 (8.9)	28 (7.4)	0
10-20	175 (52.1)	189 (50.0)	15 (5.0)
20+	131 (39.0)	161 (42.6)	286 (95.0)
Recency of last OC use, years before diagnosis (among users)			
<1	40 (11.9)	57 (15.1)	0
1+	296 (88.1)	321 (84.9)	301 (100)

Table 10: Study Power Estimates* (expressed as a percent) assuming different true hazard ratios, with 2.5% loss to follow-up in each exposure group for all cause survival after 10 years for various variables of interest

Characteristic	Hazard Ratios			
	1.3	**1.5**	**1.8**	**2.0**
Parity[1]	37	77	98	99
Age at menarche[2]	40	82	99	99
Timing of birth[3]	26	67	94	98
Ever Oral Contraceptive use[4]	36	74	97	99
Recency of first OC use[5]	17	33	59	73
Recency of last OC use[6]	22	47	77	90

*All calculations are based on the log-rank statistic and assume the survival rate in the unexposed group is 0.80, and Type I error rate of 5%

[1]Parous (≥ 1 birth (n=989) vs. nulliparous (n=275))
[2] <12 years (n= 316) vs. ≥12 yrs. (n=948)
[3]Having a birth within 5 years prior to diagnosis (n=180) vs. ≥5 years/nulliparous (n=1084)
[4]Ever (n=1015) vs. never (n=249)
[5]= <10 years (n=58) vs 20+ (578) (among users)
[6]=Current/<1 yr (n=97) vs 1+ plus (n=918) (among users)

Table 11: Unadjusted 5 and 8-year survival probabilities for selected reproductive characteristics in breast cancer patients, n=1264, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

Characteristic	Survival probability at year 5	Survival probability at year 8	Log-rank test p-value
Age at menarche, years			
12+	0.84	0.78	0.05
<12	0.80	0.74	
Gravidity			
Never pregnant	0.85	0.78	0.56
Ever pregnant	0.83	0.77	
Parity			
Nulliparous	0.86	0.79	<0.01
1-3	0.83	0.78	
4+	0.75	0.66	
Among gravid women (n=1078)			
Spontaneous abortions			
0	0.83	0.77	0.54
1+	0.81	0.76	
Induced abortions			
0	0.82	0.77	0.61
1+	0.84	0.78	
Among parous women (n=989)			
Age at first birth, years			
<18	0.66	0.62	<0.01
18-21	0.81	0.76	
22+	0.85	0.79	
Recency of last birth, years			
>5	0.84	0.79	<0.01
≤5	0.75	0.66	
Breastfeeding			
Never/<2 weeks	0.80	0.75	0.16
Ever (2+ weeks)	0.85	0.78	

Table 12: Unadjusted 5 and 8-year survival probabilities for selected oral contraceptive characteristics in breast cancer patients, n=1264, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

Characteristic	Survival probability at year 5	Survival probability at year 8	Log-rank test p-value
Ever-never OC			
Never	0.82	0.75	0.32
Ever	0.83	0.78	
Ever-never OC			
Never/<6 months	0.81	0.76	0.44
6 months+	0.84	0.78	
Duration, months			
≤12	0.81	0.78	0.93
13-36	0.88	0.79	
37-72	0.85	0.77	
73+	0.86	0.78	
Age at first use, years			
≤18	0.85	0.76	0.66
18.1-25.9	0.84	0.79	
26+	0.81	0.76	
Time since first use, years before diagnosis			
20+	0.85	0.81	<0.01
10-19.9	0.82	0.75	
<10	0.74	0.65	
Time since last use, years before diagnosis			
1+	0.84	0.78	0.12
Current use/<1 year	0.79	0.73	

Table 13: Associations between age at menarche, gravidity, parity, age at first and last birth, recency of birth, and breastfeeding history and all-cause mortality in breast cancer patients, n=1264, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

Variable	Crude	Age adj	Age, income adj	Fully adj[1]	Fully adj[2]	Fully adj[3]
Age at menarche (< 12 vs. 12+)	1.28 (1.00-1.65)	1.25 (0.97-1.61)	1.25 (0.97-1.62)	1.24 (0.96-1.61)		
Gravid (Ever vs. never pregnant)	1.10 (0.79-1.54)	1.15 (0.82-1.60)	1.14 (0.81-1.60)	1.18 (0.83-1.66)	1.02 (0.72-1.45)	0.99 (0.70-1.40)
Parity						
Nulliparous	1.00	1.00	1.00	1.00	1.00	1.00
1-3	1.12 (0.83-1.50)	1.20 (0.89-1.62)	1.18 (0.87-1.60)	1.22 (0.90-1.66)	1.04 (0.75-1.43)	1.01 (0.73-1.38)
4+	1.95 (1.29-2.96)	2.34 (1.52-3.59)	2.06 (1.34-3.19)	2.05 (1.32-3.20)	1.70 (1.08-2.67)	1.71 (1.09-2.67)
Age at first birth, years						
<18	2.29 (1.46-3.61)	2.53 (1.60-4.00)	1.67 (1.02-2.73)	1.94 (1.18-3.18)	1.67 (1.00-2.79)	1.41 (0.85-2.36)
18-21	1.28 (0.90-1.82)	1.43 (1.00-2.04)	1.23 (0.86-1.77)	1.23 (0.85-1.78)	1.15 (0.79-1.67)	1.13 (0.78-1.64)
22+	1.06 (0.78-1.45)	1.12 (0.82-1.54)	1.22 (0.89-1.67)	1.25 (0.91-1.73)	1.22 (0.88-1.69)	1.18 (0.86-1.63)
Nulliparous	1.00	1.00	1.00	1.00	1.00	1.00
Age at first birth (among parous), years						
<18	1.79 (1.15-2.77)	1.76 (1.13-2.73)	1.34 (0.85-2.13)	1.58 (1.00-2.51)	1.45 (0.91-2.31)	1.23 (0.78-1.96)
18-21	1.00	1.00	1.00	1.00	1.00	1.00
22+	0.83 (0.62-1.11)	0.77 (0.58-1.03)	0.97 (0.71-1.33)	1.00 (0.73-1.37)	1.05 (0.76-1.44)	1.03 (0.75-1.41)

Variable	Crude	Age adj	Age, income adj	Fully adj[1]	Fully adj[2]	Fully adj[3]
Age at last birth, years						
<24	1.39 (0.94-2.06)	1.50 (1.01-2.23)	1.18 (0.79-1.77)	1.20 (0.80-1.81)	1.15 (0.76-1.73)	1.14 (0.76-1.71)
24-29	1.01 (0.71-1.44)	1.09 (0.77-1.55)	1.06 (0.74-1.52)	1.08 (0.75-1.54)	1.00 (0.69-1.43)	0.98 (0.69-1.41)
30+	1.27 (0.93-1.75)	1.36 (0.99-1.89)	1.46 (1.05-2.02)	1.54 (1.10-2.14)	1.19 (0.81-1.73)	1.12 (0.77-1.62)
Nulliparous	1.00	1.00	1.00	1.00	1.00	1.00
Age at last birth (among parous), years						
<24	1.09 (0.78-1.54)	1.11 (0.79-1.56)	0.80 (0.56-1.16)	0.78 (0.54-1.13)	0.95 (0.64-1.43)	0.99 (0.66-1.48)
24-29	0.79 (0.59-1.07)	0.80 (0.60-1.08)	0.73 (0.54-0.99)	0.70 (0.52-0.96)	0.84 (0.60-1.17)	0.87 (0.62-1.22)
30+	1.00	1.00	1.00	1.00	1.00	1.00
Recency of last birth, years before diagnosis						
≤5	1.93 (1.35-2.76)	1.84 (1.28-2.65)	1.97 (1.36-2.84)	2.05 (1.41-2.98)		
>5	1.05 (0.78-1.42)	1.11 (0.81-1.52)	1.06 (0.78-1.45)	1.09 (0.80-1.50)		
Nulliparous	1.00	1.00	1.00	1.00		
Recency of last birth (among parous), years before diagnosis						
≤5	1.91 (1.33-2.75)	1.36 (0.84-2.20)	1.78 (1.28-2.47)	1.80 (1.29-2.51)		
>5	1.00	1.00	1.00	1.00		

Variable	Crude	Age adj	Age, income adj	Fully adj[1]	Fully adj[2]	Fully adj[3]
Breastfeeding (among parous)						
Ever (2 weeks+) vs. Never	0.83 (0.65-1.08)	0.79 (0.61-1.03)	0.90 (0.69-1.18)	0.89 (0.68-1.16)		
Breastfeeding duration, months until complete stop (among parous)						
No	1.00	1.00	1.00	1.00		
≤12	0.67 (0.49-0.90)	0.63 (0.47-0.86)	0.71 (0.52-0.97)	0.70 (0.51-0.95)		
>12	1.19 (0.84-1.69)	1.17 (0.82-1.66)	1.36 (0.95-1.95)	1.37 (0.95-1.96)		
Breastfeeding duration, months until partial stop (among parous)						
	1.00	1.00	1.00	1.00		
≤ 3	0.61 (0.43-0.87)	0.59 (0.41-0.83)	0.67 (0.46-0.96)	0.66 (0.46-0.95)		
> 3	1.05 (0.77-1.41)	1.00 (0.74-1.35)	1.13 (0.83-1.54)	1.12 (0.82-1.52)		

Fully adjusted[1] = Adjusted for age, income, the number of Pap smears in past 5 years, and the number of clinical breast exams in the past 5 years, and includes an interaction term between income and continuous time

Fully adjusted[2] = Adjusted for everything in model 1 plus the following for each variable in parentheses:

Recency of birth (≤5 vs. 5+/nulliparous in all women, ≤5 vs. 5+ in parous women) (gravidity, parity, age at last birth)

Parity (4+ vs. 1-3/nulliparous in all women, 4+ vs. 1-3 in parous women) (age at first birth)

Fully adjusted[3] = Adjusted for age, income (+continuous time*income interaction term) plus the following for each variable in parentheses:

Recency of birth (≤5 vs. 5+/nulliparous in all women, ≤5 vs. 5+ in parous women) (gravidity, parity)

Parity (4+ vs. 1-3/nulliparous in all women, 4+ vs. 1-3 in parous women) (age at first birth)

Number of Pap smears, number of CBEs (age at first birth)

Numbers in subgroups: parous (n=989)

Table 14: Associations between spontaneous and induced abortions and all-cause mortality in breast cancer patients, n=1264, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

Variable	Crude	Age adj	Age and income adj	Fully adj[1]	Fully adj[2]	Fully adj[3]
Spontaneous abortion (among nulliparous)						
1+ vs. 0	1.04 (0.42-2.61)	1.03 (0.41-2.57)	0.96 (0.38-2.44)	0.94 (0.37-2.41)	0.96 (0.36-2.55)	0.95 (0.36-2.52)
Spontaneous abortion (among parous)						
1+ vs. 0	1.09 (0.81-1.46)	1.12 (0.83-1.50)	1.12 (0.83-1.50)	1.13 (0.84-1.53)		
Spontaneous abortion (among gravid)						
1+ vs. 0	1.09 (0.82-1.45)	1.12 (0.85-1.49)	1.10 (0.83-1.46)	1.10 (0.83-1.47)		
Induced abortion (among nulliparous)						
1+ vs. 0	0.78 (0.41-1.48)	0.80 (0.42-1.53)	0.88 (0.46-1.71)	0.92 (0.47-1.81)	1.04 (0.52-2.06)	0.97 (0.50-1.90)
Induced abortion (among parous)						
1+ vs. 0	1.01 (0.72-1.42)	0.93 (0.66-1.31)	0.91 (0.65-1.28)	0.92 (0.65-1.29)		
Induced abortion (among gravid)						
1+ vs. 0	0.92 (0.68-1.25)	0.84 (0.62-1.14)	0.86 (0.63-1.17)	0.86 (0.63-1.17)		

Fully adjusted[1] = Adjusted for age, income, the number of Pap smears in past 5 years, and the number of clinical breast exams in the past 5 years, and includes an interaction term between income and continuous time

Fully adjusted[2] = Adjusted for everything in model 1 plus the following for each variable in parentheses:

BMI at age 20, BMI in the year before diagnosis, age at menarche (spontaneous abortions among nulliparous)

Smoking (induced abortion among nulliparous)

Fully Adjusted[3] = Adjusted for age, income (+continuous time*income interaction term) plus the following for each variable in parentheses:

BMI at age 20, BMI in the year before diagnosis, age at menarche (spontaneous abortions among nulliparous)
Smoking (induced abortion among nulliparous)

Numbers in subgroups: nulliparous (n=275), parous (n=989), gravid (n=1078)

Table 15: Associations between oral contraceptives and all-cause mortality in breast cancer patients, n=1264, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

Variable	Crude	Age adj	Age and stage adj	Age, income adj	Fully adj[1]	Fully adj[2]
Ever vs. never	0.87	0.84	0.79	0.92	0.94	
	(0.66-1.15)	(0.63-1.11)	(0.59-1.04)	(0.69-1.23)	(0.70-1.26)	
Ever (≥6 mo)	0.91	0.87	0.86	1.00	1.02	
vs. <6 mo/never	(0.71-1.16)	(0.68-1.12)	(0.67-1.10)	(0.77-1.29)	(0.79-1.32)	
Duration of use, months						
Never users	1.00	1.00	1.00	1.00	1.00	
≤12	0.91	0.90	0.80	0.91	0.91	
	(0.63-1.31)	(0.62-1.29)	(0.56-1.15)	(0.63-1.31)	(0.63-1.32)	
13-36	0.80	0.77	0.75	0.87	0.88	
	(0.54-1.18)	(0.52-1.15)	(0.50-1.12)	(0.58-1.30)	(0.59-1.32)	
37-72	0.87	0.83	0.84	0.93	0.95	
	(0.60-1.25)	(0.57-1.21)	(0.58-1.22)	(0.64-1.36)	(0.65-1.40)	
≥73	0.88	0.84	0.77	0.95	0.99	
	(0.63-1.22)	(0.60-1.16)	(0.55-1.07)	(0.68-1.33)	(0.70-1.40)	
Duration of use (among ever users), months						
≤12	1.00	1.00	1.00	1.00	1.00	
13-36	0.88	0.87	0.94	0.96	0.97	
	(0.58-1.31)	(0.58-1.30)	(0.62-1.41)	(0.63-1.44)	(0.64-1.46)	
37-72	0.95	0.92	1.04	1.01	1.03	
	(0.65-1.39)	(0.63-1.35)	(0.71-1.54)	(0.69-1.49)	(0.70-1.52)	
≥73	0.96	0.93	0.96	1.04	1.06	
	(0.69-1.36)	(0.66-1.31)	(0.68-1.35)	(0.73-1.46)	(0.75-1.51)	

Variable	Crude	Age adj	Age and stage adj	Age, income adj	Fully adj[1]	Fully adj[2]
Age at first use, years						
Never users	1.00	1.00	1.00	1.00	1.00	1.00
≤18	1.01 (0.67-1.53)	0.87 (0.57-1.33)	0.75 (0.49-1.15)	0.86 (0.55-1.32)	0.88 (0.56-1.37)	0.82 (0.52-1.29)
18.1-25.9	0.83 (0.62-1.11)	0.80 (0.60-1.07)	0.77 (0.57-1.03)	0.89 (0.66-1.20)	0.91 (0.67-1.24)	0.81 (0.58-1.12)
≥26	0.96 (0.62-1.46)	1.02 (0.67-1.57)	0.91 (0.60-1.40)	1.17 (0.76-1.82)	1.18 (0.75-1.84)	0.95 (0.57-1.57)
Age at first use (among ever users), years						
≤18	1.23 (0.85-1.77)	1.08 (0.74-1.57)	0.97 (0.66-1.43)	0.95 (0.65-1.41)	0.95 (0.64-1.41)	1.03 (0.69-1.54)
18.1-25.9	1.00	1.00	1.00	1.00	1.00	1.00
≥26	1.16 (0.79-1.69)	1.31 (0.89-1.94)	1.21 (0.82-1.78)	1.33 (0.90-1.98)	1.31 (0.87-1.95)	1.17 (0.76-1.80)
Duration of use before age 25, months						
Never users	1.00	1.00	1.00	1.00	1.00	
No use before 25	0.99 (0.67-1.45)	1.05 (0.71-1.54)	0.99 (0.67-1.46)	1.21 (0.82-1.80)	1.21 (0.81-1.81)	
≤12	0.85 (0.59-1.22)	0.82 (0.57-1.19)	0.76 (0.52-1.09)	0.85 (0.59-1.24)	0.89 (0.61-1.29)	
13-47	0.69 (0.49-0.97)	0.67 (0.47-0.94)	0.66 (0.46-0.93)	0.76 (0.53-1.08)	0.76 (0.53-1.09)	
48+	1.07 (0.75-1.51)	0.96 (0.67-1.36)	0.85 (0.59-1.21)	1.02 (0.71-1.46)	1.06 (0.73-1.53)	

Variable	Crude	Age adj	Age and stage adj	Age, income adj	Fully adj[1]	Fully adj[2]
Duration of use before age 25 (among users), months						
No use before 25	1.00	1.00	1.00	1.00	1.00	
≤12	0.86 (0.58-1.28)	0.78 (0.52-1.16)	0.76 (0.50-1.14)	0.70 (0.46-1.06)	0.73 (0.48-1.12)	
13-47	0.70 (0.48-1.02)	0.62 (0.42-0.92)	0.65 (0.44-0.97)	0.62 (0.42-0.91)	0.62 (0.42-0.93)	
48+	1.08 (0.74-1.58)	0.89 (0.59-1.33)	0.84 (0.56-1.27)	0.83 (0.55-1.25)	0.86 (0.57-1.30)	
Time since first OC use, years before diagnosis						
Never users	1.00	1.00	1.00	1.00	1.00	
<10	1.46 (0.88-2.41)	1.26 (0.72-2.21)	1.29 (0.75-2.23)	1.42 (0.80-2.51)	1.39 (0.78-2.50)	
10-19.9	1.00 (0.73-1.37)	0.93 (0.66-1.29)	0.85 (0.60-1.19)	1.04 (0.74-1.47)	1.09 (0.77-1.54)	
20+	0.73 (0.54-1.00)	0.75 (0.55-1.03)	0.72 (0.52-0.98)	0.82 (0.60-1.12)	0.83 (0.60-1.14)	
Time since first OC use (among users), years before diagnosis						
<10	2.00 (1.24-3.21)	1.72 (0.96-3.10)	1.87 (1.07-3.27)	1.77 (0.98-3.21)	1.67 (0.97-3.06)	
10-19.9	1.36 (1.04-1.79)	1.24 (0.90-1.71)	1.21 (0.87-1.67)	1.28 (0.92-1.77)	1.31 (0.94-1.83)	
20+	1.00	1.00	1.00	1.00	1.00	

Variable	Crude	Age adj	Age and stage adj	Age, income adj	Fully adj[1]	Fully adj[2]
Time since last OC use, years before diagnosis*						
≤24 mo of f/u						
Never users	1.00	1.00	1.00	1.00	1.00	
Current	0.36	0.29	0.27	0.38	0.41	
use/<1 year	(0.11-1.20)	(0.09-0.98)	(0.08-0.91)	(0.11-1.29)	(0.12-1.41)	
1+ year	0.65	0.64	0.62	0.74	0.77	
	(0.39-1.08)	(0.39-1.07)	(0.37-1.04)	(0.44-1.25)	(0.45-1.31)	
>24 mo of f/u						
Never users	1.00	1.00	1.00	1.00	1.00	
Current	1.55	1.26	1.12	0.46	1.54	
use/<1 year	(0.94-2.54)	(0.74-2.12)	(0.66-1.89)	(0.86-2.49)	(0.89-2.65)	
1+ year	0.93	0.92	0.86	0.98	0.99	
	(0.66-1.31)	(0.65-1.30)	(0.61-1.21)	(0.69-1.40)	(0.69-1.41)	
Time since last OC use (among users), years before diagnosis*						
≤24 mo of f/u						
Current	0.55	0.45	0.43	0.50	0.51	
use/<1 year	(0.17-1.76)	(0.14-1.45)	(0.13-1.41)	(0.15-1.63)	(0.16-1.68)	
1+ year	1.00	1.00	1.00	1.00	1.00	
>24 mo of f/u						
Current	1.66	1.36	1.30	1.46	1.49	
use/<1 year	(1.09-2.54)	(0.85-2.16)	(0.82-2.07)	(0.91-2.33)	(0.92-2.41)	
1+ year	1.00	1.00	1.00	1.00	1.00	

Variable	Crude	Age adj	Age and stage adj	Age, income adj	Fully adj[1]	Fully adj[2]
Duration of use before first birth (among parous), months						
Never users	1.00	1.00	1.00	1.00	1.00	
No use before first birth	1.00 (0.70-1.43)	1.04 (0.73-1.48)	0.99 (0.69-1.41)	0.95 (0.66-1.37)	0.98 (0.68-1.43)	
<12	0.88 (0.56-1.37)	0.83 (0.53-1.29)	0.83 (0.53-1.30)	0.90 (0.58-1.42)	0.94 (0.59-1.48)	
12-71	0.63 (0.43-0.94)	0.58 (0.39-0.86)	0.61 (0.41-0.90)	0.67 (0.45-1.02)	0.69 (0.46-1.05)	
72+	0.93 (0.56-1.55)	0.81 (0.48-1.36)	0.64 (0.38-1.08)	1.02 (0.60-1.73)	1.09 (0.64-1.86)	
Duration of use before first birth (among parous users), months						
No use before first birth	1.00	1.00	1.00	1.00	1.00	
<12	0.88 (0.59-1.31)	0.79 (0.53-1.19)	0.84 (0.56-1.27)	0.92 (0.60-1.40)	0.92 (0.61-1.40)	
12-71	0.63 (0.45-0.90)	0.55 (0.38-0.78)	0.61 (0.42-0.87)	0.68 (0.46-0.99)	0.68 (0.46-0.99)	
72+	0.93 (0.57-1.49)	0.76 (0.47-1.24)	0.64 (0.39-1.05)	1.00 (0.60-1.67)	1.04 (0.62-1.73)	

Fully Adjusted[1] = Adjusted for age, income, number of Pap smears in the past 5 years, and the number of clinical breast exams in the past 5 years, and includes an interaction term between income and continuous time

Fully adjusted[2] = Adjusted for age and income, and includes an interaction term between income and continuous time and additionally adjusted for following characteristics:
Recency of first use (<10 years, 10-19.9 years, 20+ years in ever-users, <10 years, 10-19.9 years, 20+ years/never users in all women)

*Time since last OC use violated proportional hazards assumption

Numbers in subgroups: ever users (n=1015), parous users (n=810)

Figure 1: Biological Schematic of Reproductive Characteristics (Study Aim 1) and Overall Survival after Breast Cancer Diagnosis (using recency of birth as an example)

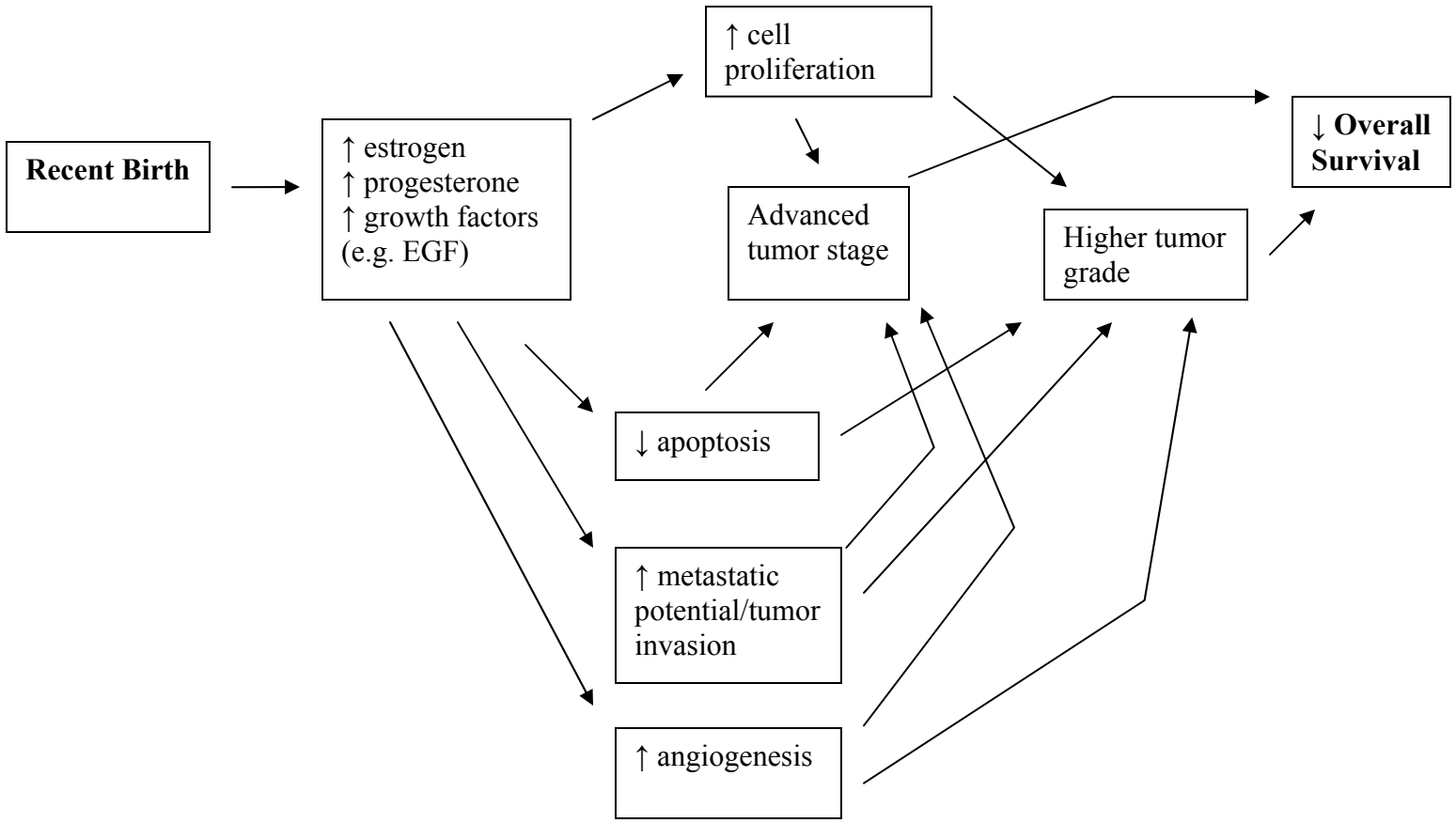


Figure 2: Biological Schematic of Oral Contraceptives (Study Aim 2) and Overall Survival after Breast Cancer Diagnosis

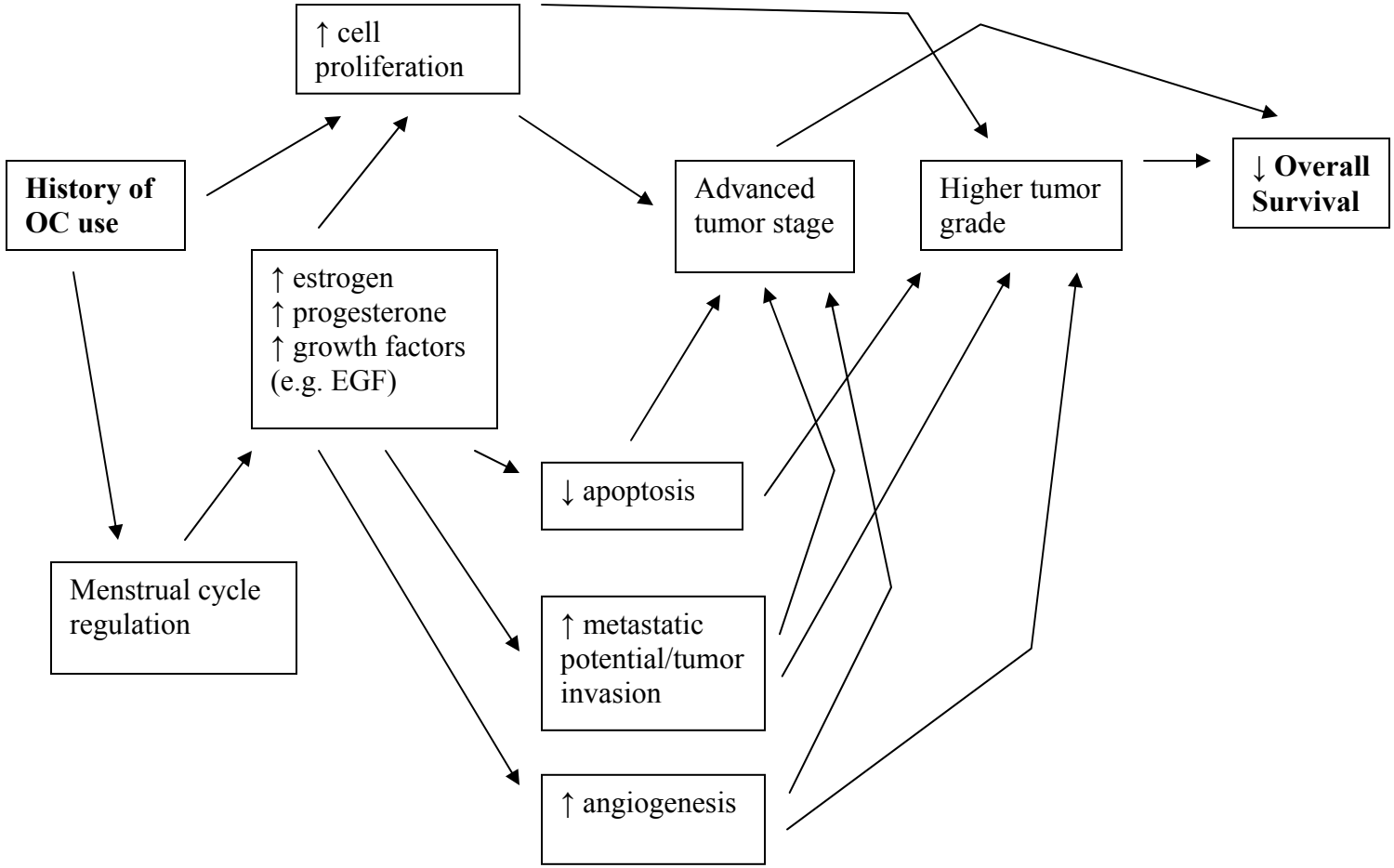


Figure 3: Kaplan-Meier survival curves [proportion surviving across time (months)] stratified by number of births in a cohort of invasive breast cancer cases, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

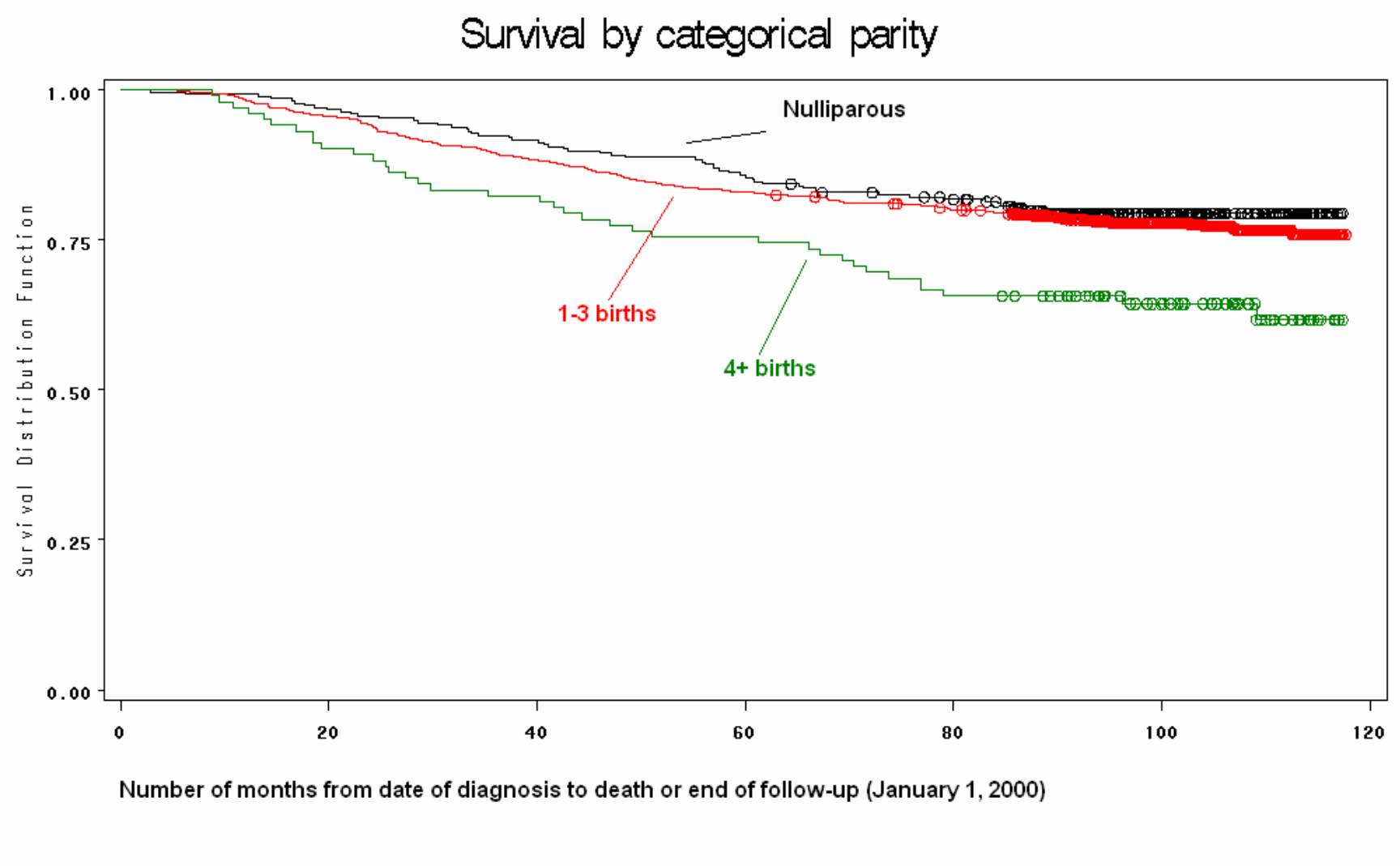


Figure 4: Kaplan-Meier survival curves [proportion surviving across time (months)] stratified by recency of last birth in a cohort of invasive breast cancer cases, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

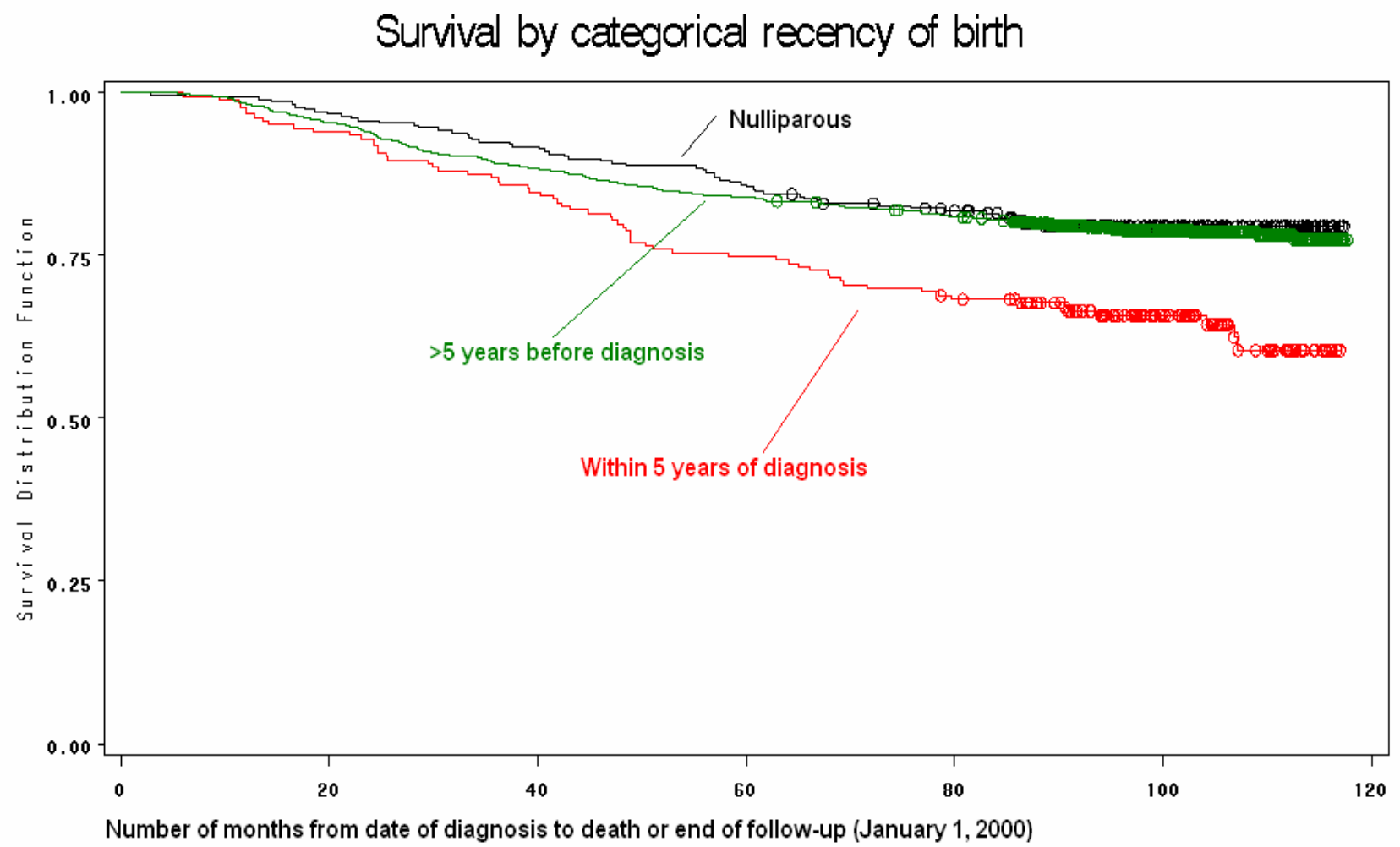


Figure 5: Kaplan-Meier survival curves [proportion surviving across time (months)] stratified by time since first OC use in a cohort of invasive breast cancer cases, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

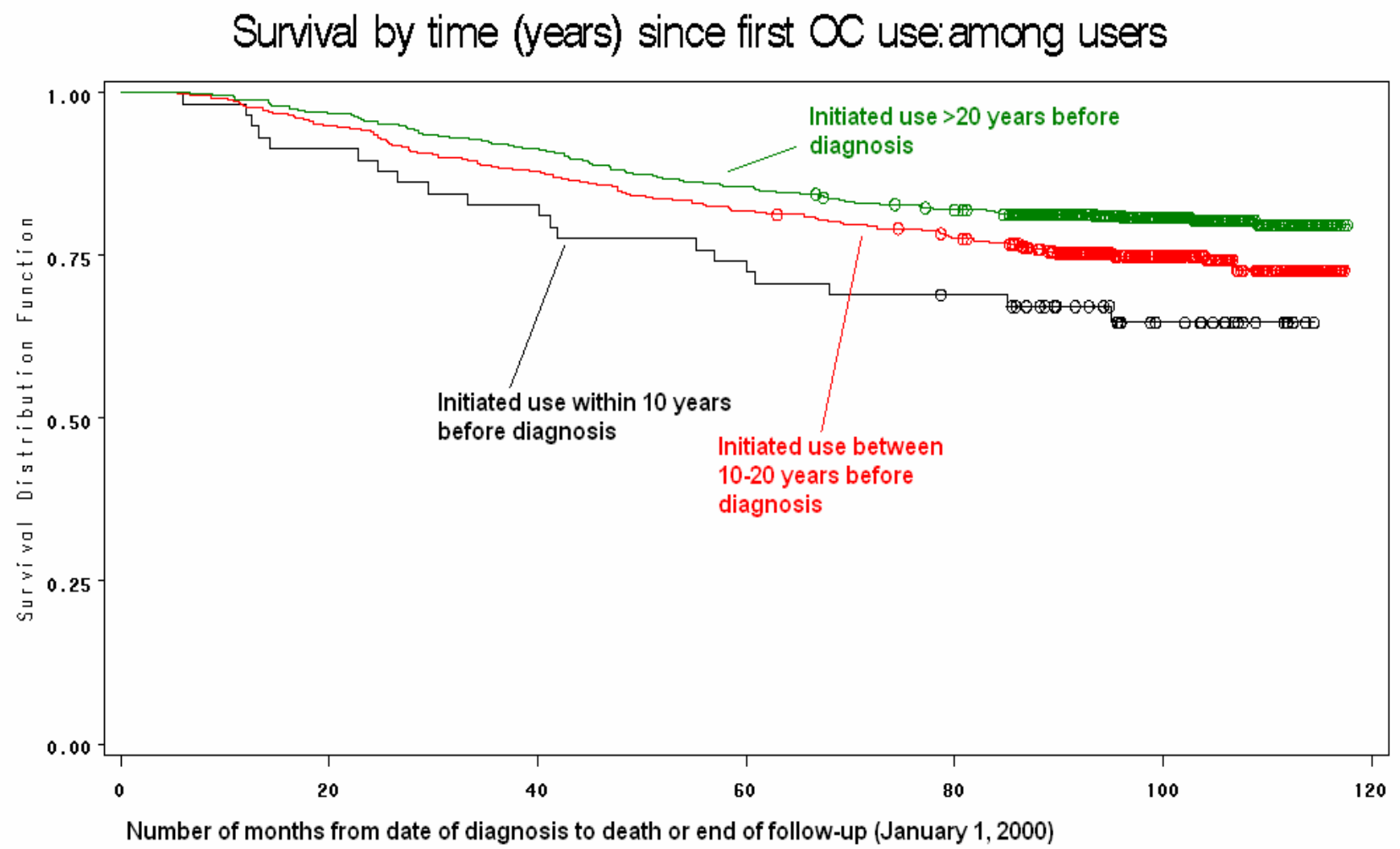


Figure 6: Kaplan-Meier survival curves [proportion surviving across time (months)] stratified by time since last OC use in a cohort of invasive breast cancer cases, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

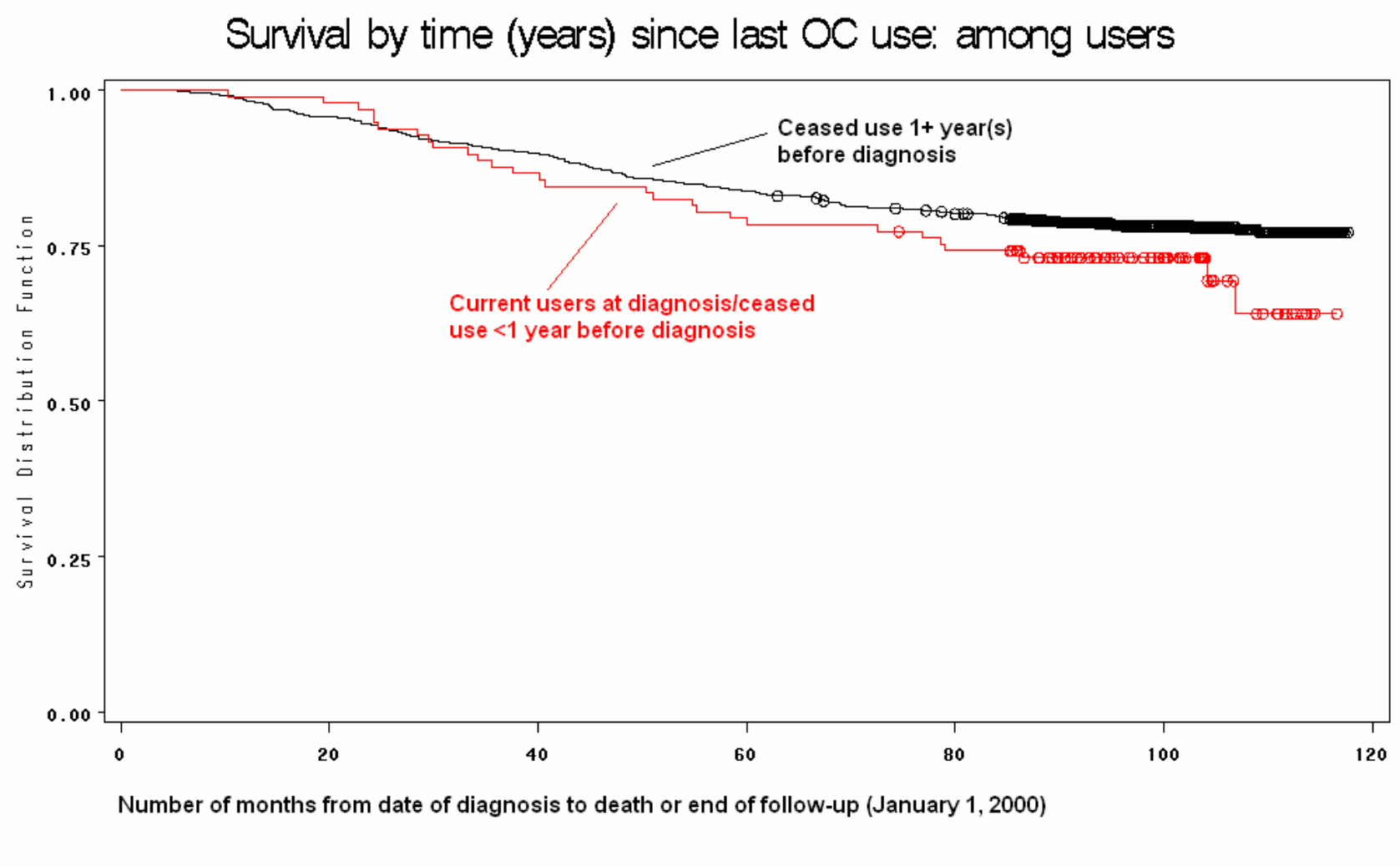


Figure 7: Log(-log(survival)) curves of household income in a cohort of invasive breast cancer cases, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000

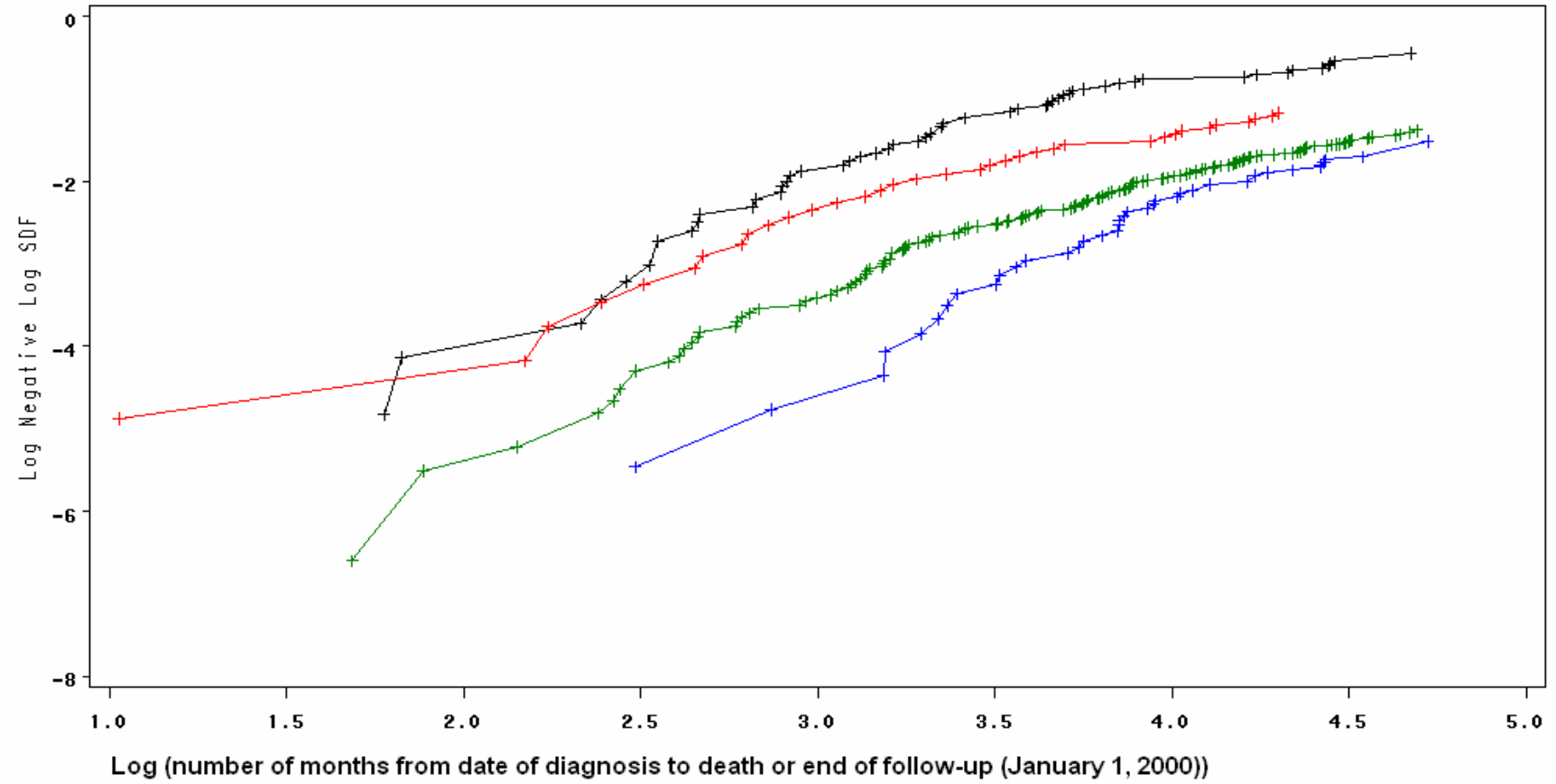
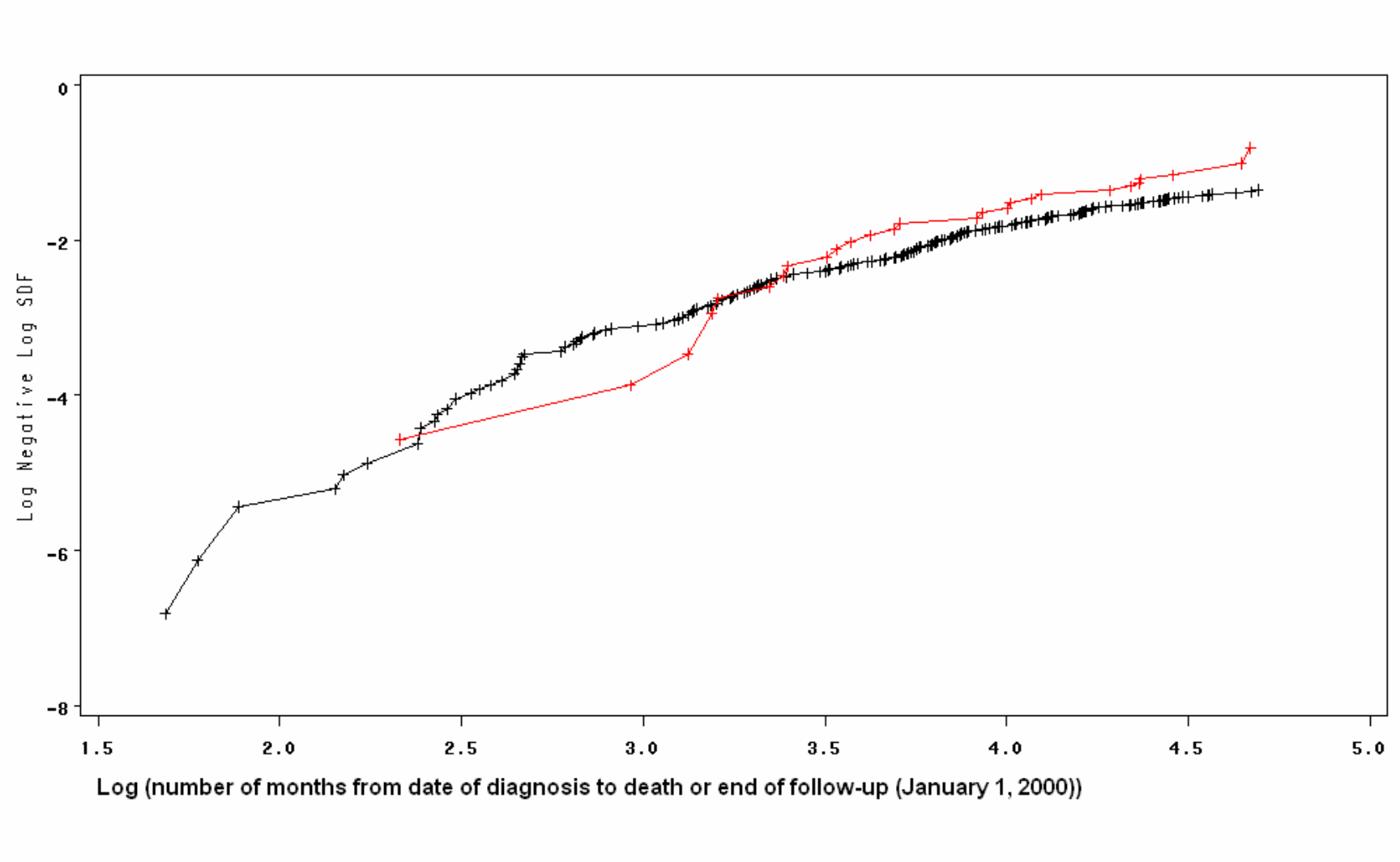


Figure 8: Log(-log(survival)) curves of time since last OC use in a cohort of invasive breast cancer cases, metropolitan Atlanta, GA and central NJ, 1990-1992 through 2000



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