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Kylee Madison Borger Date

Association of Breast Cancer Treatment Type and Death due to Cardiovascular Disease Comparing Black Women to White Women

By

Kylee Madison Borger
Master of Public Health

Global Epidemiology

_____

Lauren E. McCullough, PhD, MSPH
Committee Chair

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By

Kylee Madison Borger

B.A.
New York University Shanghai
2017

Thesis Committee Chair: Lauren E. McCullough, PhD, MSPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology
2019

Abstract

Association of Breast Cancer Treatment Type and Death due to Cardiovascular Disease Comparing Black Women to White Women

By Kylee Madison Borger

In 2017, an estimated 316,120 women were newly diagnosed with breast cancer [1]. Over the past decades, improvements in treatment and earlier detection of breast cancer have greatly improved survival rates of women [2] corresponding to relative 5-, 10-, and 15-year survival rates of 89%, 83%, and 78%, respectively in 2016 [1]. Increased survival rate has led to new concerns about the long-term effects of breast cancer treatment, particularly cardiometabolic disease—which is the number one cause of mortality among U.S. women [3]. However, overall- and breast cancer-specific mortality rates are more pronounced among black women compared to white women, the former having a 40% increased risk of death. We utilized population-based registry data from the Georgia Comprehensive Cancer Registry (GCR) on newly diagnosed breast cancer cases from the greater Atlanta region within the state of Georgia for non-Hispanic white (NHW) and non-Hispanic black (NHB) women who had breast cancer diagnoses between from January 1, 2010 and December 31, 2014 (n=8,523). Women were followed until December 31, 2016 to investigate racial disparities in death due to cardiovascular disease (CVD) and modified by breast cancer treatment using Cox Proportional Hazard Models. Endocrine therapy was associated with a higher hazard of death by CVD for NHB women compared to NHW women with a hazard ratio (HR) of 2.1 (95% confidence interval (CI): 1.3, 3.5) for those who received the therapy compared to a null hazard ratio (95% CI of 0.5, 1.9) for NHB who did not receive the therapy. NHB women who received radiation and chemotherapy had HRs of 1.4 (CI: 0.7, 2.8) and 0.7 (CI: 0.3, 2.0), respectively compared to NHW women. We observed no difference in CVD-related outcomes by race. Further research with larger samples and longer follow-up are necessary to investigate potential CVD mortality disparities among NHW and NHB women.

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I would first like to thank my thesis advisor Dr. Lauren McCullough of the Rollins School of Public Health at Emory University. Professor McCullough was always available and willing to help whenever I had a question about my research or writing. She consistently allowed this paper to be my own work, but steered me in the right the direction whenever she thought I needed it. Thank you for sharing your passion with me for researching racial disparities and breast cancer.

I would also like to thank Dr. McCullough's doctoral students—Lindsay Collin and Alyssa Troeschel. Thank you for your willingness to talk through coding conundrums and DAG decisions. Without your continuous support and SAS coding genius, analysis of this study could not have been successfully conducted.

Finally, I must express my very profound gratitude to my parents and siblings for providing me with unfailing support and encouragement throughout my years of study away from home from China to New York to D.C. to Atlanta. Thank you for keeping me motivated and focused through the process of researching and writing this thesis.

This accomplishment would not have been possible without them. Thank you.

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Background

In 2016, breast cancer was by far the most prevalent cancer type among women with an estimated 3,560,570 women living with breast cancer, 316,120 women were newly diagnosed in 2017 [1,4]. Though many women continue to be diagnosed with breast cancer, improvements in treatment and earlier detection of breast cancer have greatly improved survival rates of women [2] corresponding to relative 5-, 10-, and 15-year survival rates of 89%, 83%, and 78%, respectively in 2016 [1].

Though breast cancer survival has improved overall, improvements are not equitable across racial groups of women. Overall- and breast cancer-specific mortality rates are more pronounced among black women compared to white women, the former having a 40% increased risk of death [5] This may, in part, be driven by stage at diagnosis [6,7]. Black women are less likely to be diagnosed with local stage breast cancer (53% vs. 62% among white counterparts) which has a 5-year relative survival rate of 99% [4]. Yet, even within strata of stage, black women have lower survival[1]. These disparities have been attributed to some combination of factors, including: genetics, comorbidities (which are more prevalent among black women than white women); differences in tumor characteristics; and disparities in healthcare access [8,9]. Though not equitable across racial groups, increased survival of breast cancer has led to new concerns about the long-term effects of breast cancer treatment, particularly cardiometabolic disease—which is the number one cause of mortality among U.S. women [3].

Cardiovascular disease and breast cancer have overlapping risk factors, including: age, genetics, diet, alcohol consumption, physical inactivity, obesity, tobacco use, and receipt of postmenopausal hormone replacement therapy [3]. Seventy-five percent of breast

cancer survivors (more than 2.6 million women) are aged 60 years or older [1], and already at a higher risk of cardiovascular disease [3] with comorbidities such as hypertension, diabetes and obesity more prevalent among black women compared to white women [10-12].

Jones, et. al. postulate a "multi-hit" hypothesis that suggests those with more cardiovascular risk factors are more vulnerable to the cardiac toxicity of breast cancer treatment [13]. This hypothesis implies that black women, due to higher rates of cardiovascular risk factors overall would, therefore, be subject to greater cardiotoxicity due to their breast cancer treatments. Previous research has investigated the cardiotoxic effect of anthracyclines, alkylating agents, taxanes, antimetabolites, endocrine therapy, HER-2 directed therapies, Cyclin-dependent kinase 4/6 inhibitors, and radiation therapy [3,11-17]. As certain cardiotoxic therapies [18], are more common among African-American women, in a background of heightened cardio metabolic co-morbid conditions could explain the black-white disparity in overall mortality.

Previous observational epidemiologic studies have reported on associations of various breast cancer treatments on cardiovascular outcomes, however many did not report racial composition of their study population or did not investigate outcomes by race. We, therefore, have limited understanding of the association between specific treatment regimens and CVD mortality following a diagnosis of breast cancer, particularly by race. The latter may be important for identifying causal drivers of elevated overall mortality among black women diagnosed with breast cancer who often have higher risk of cardiovascular disease at baseline and more aggressive treatment. We seek to fill this gap by reporting the results of a retrospective cohort study of the effect of breast cancer treatment and race on cardiovascular disease mortality, which is, to the best

of our knowledge, the first to investigate the role of breast cancer-specific treatment regimens on cardiovascular disease mortality, stratified by race.

Methods

Study Population

The data for this retrospective cohort study came from the Georgia Comprehensive Cancer Registry (GCR), which is a population-based registry that seeks to collect information on all newly diagnosed cancer cases within the state of Georgia. The GCR has collected information on newly diagnosed cancer cases among Georgia residents since January 1, 1995 and contains information regarding patient, tumor, and treatment characteristics. The GCR links cancer diagnoses to the Georgia vital statistics registry and the US National Death Index on an annual basis to identify deaths and causes of death. This study has deaths recorded up until December 31, 2016. Underlying causes of death are determined from the death certificate with valid ICD-9 and ICD-10 codes. CVD deaths are defined according to the International Classification of Diseases (ICD), tenth revision codes I00–I99 (ICD9 codes 390–459), and BC deaths classified using ICD10 code C50 (ICD9 codes 174–175).

Our study population included non-Hispanic white and non-Hispanic black women who had breast cancer diagnoses that occurred between January 1, 2010 and December 31, 2014 with stage I-IV first primary breast cancer diagnosis (ICD10=C50). Race was determined for GCR through self-reported racial categories as defined by the US Census Bureau. Hispanic ethnicity was determined by the North American Association of Central Cancer Registries Hispanic Identification Algorithm by using a combination of standard variables to classify cases as Hispanic or non-Hispanic for analytic purposes. Women were included if they resided in the greater Atlanta region at the time of diagnosis, which includes residents of Clayton, Cobb, Dekalb, Fulton, or

Gwinnet, counties. Exclusion criteria included having a diagnosis before age 18, being a member of other racial or ethnic groups, a breast cancer diagnosis identified via autopsy, missing stage information, stage 0 breast carcinomas, any secondary tumor diagnoses, and unknown cause of death.

Exposure, Outcome, and Covariate Assessment

The primary exposure for this analysis was race, as reported in the GCR. A secondary exposure examined was type and amount of treatment received, also reported in the GCR. The outcome of interest was cardiovascular mortality. Covariates considered included age at diagnosis (<40, 40–49, 50–65, >65 years of age), various tumor characteristics, surgery (yes, no), chemotherapy (yes, no/unknown), radiation (yes, no/unknown), insurance type (uninsured, private, Medicaid, and Medicare), marital status (married, single, divorced/widowed/separated), and socio-economic (SES) index (0%– <5%, 5%– <10%, 10%– <20%, 20%–100%).

Tumor characteristics, abstracted from the registry, included cancer stage at diagnosis, tumor grade, expression of the estrogen receptor (ER), and molecular subtype. Cancer stage at diagnosis was based on the AJCC 7th edition staging manual, with stages I–IV included in this analysis. Tumor grade was categorized as 1, 2 or 3+. ER expression was classified as positive or negative. Molecular subtype was based on the expression of ER and HER2 — Luminal A (ER+/HER2−), Luminal B (ER+/HER2+), HER2 overexpressing (ER−/HER2+) and Triple Negative (TNBC) was a lack of expression of either tumor biomarker. HR status was determined by a combination of the estrogen receptor (ER) and progesterone receptor (PR) variables. Participants with either a positive

ER or PR were coded as HR+, while negativity in both receptors were necessary for a woman to be classified as HR−. Women with at least one borderline score were coded as HR+.

We considered different treatments as possible contributors to the observed disparities. This included primary surgery (no surgery, breast conserving surgery and mastectomy/radical), neoadjuvant, and adjuvant therapy. The adjuvant therapies included chemotherapy (yes/no or unknown), receipt of radiation therapy (yes/no or unknown), receipt of endocrine therapy (yes/no) and receipt of Herceptin (yes/no). Receipt of endocrine therapy and Herceptin were identified from text fields accompanying patient diagnoses. Therefore, patients with a note regarding receipt of such therapy were considered to have received the therapy and those without a corresponding physician note were considered to not have received it. As chemotherapy and radiation therapy were categorized as "yes-treatment received" or "no/unknown", the latter classification includes a mixture of women who may or may not have received the specific treatment modality. Person-years of follow-up were calculated from the date of diagnosis until the first of death or December 31, 2016.

Statistical Analyses

Participant characteristics were described according to race/ethnicity using frequencies and percentages. Estimates for the cumulative incidence of mortality due to CVD and BC were obtained using Cox proportional hazard models and reported within strata of race/ethnicity and treatment received. Proportional hazard assumptions were assessed graphically for race/ethnicity by each outcome and model covariate for each sub

distribution via log-log survival curves and goodness-of-fit testing. All outcomes and utilized covariates met the proportional hazard assumption. Covariates to be included in the model for each treatment group were determined based on previous literature and directed acyclic graphs (DAG)[19] based on known association between the exposure, outcome and covariates of interest (Figures 1-5). All final models were adjusted for race, age, and insurance. The final model for chemotherapy also adjusted for stage at diagnosis and ER status; the radiation final model for chemotherapy and molecular subtype; the endocrine final model for chemotherapy, radiation therapy, and receipt of Herceptin; and the receipt of Herceptin final model for molecular subtype and radiation therapy.

Based on previous evidence suggesting racial disparities may vary by age, interactions with age were considered on the multiplicative scale using likelihood ratio tests (LRT). Non-Hispanic white women were the reference group for analysis. All analyses were conducted using SAS® version 9.4[20].

Results

NHB women had the same rate of death due to CVD as NHW women in this cohort (1.3%), but had more than double the rate of deaths due to breast cancer (13.6%) than NHW women (6.5%). Baseline tumor characteristics were differential by race; NHB women had a higher stage at diagnosis (9.4% stage IV compared to 4.8% stage IV NHW women; 55.2% NHW women stage I versus 39.0% NHB women) and a greater proportion were ER negative (25.5%) than NHW women (13.0%). Consequently, treatment was differential across racial groups. A much greater proportion of NHB women had chemotherapy compared to NHW women (56.8% vs. 39.7%) and more NHW women had endocrine therapy compared to NHB women (65.8% vs. 55.8%). (**Table 1**)

With regards to treatment, endocrine therapy (Hazard Ratio (HR) = 1.0, 95% CI: 0.6, 1.5) and receipt of Herceptin (HR = 0.7, 95% CI: 0.2, 2.3) were not associated with a higher hazard of death by CVD in main effect models. Conversely, chemotherapy and radiation therapy were inversely associated with death due to CVD—HRs were 0.4 (95% CI: 0.2, 0.8) and 0.5 (95% CI: 0.3, 0.8), respectively (**Table 2**).

For the age-adjusted racial main effects model, NHB women had a HR of 1.3 in comparison to the NHW referent group, however the 95% confidence interval included the null (0.9, 1.9). Although NHB women who received radiation and chemotherapy had HRs of 1.4 (CI: 0.7, 2.8) and 0.7 (CI: 0.3, 2.0) compared to NHW women, confidence intervals were wide and included the null. NHB women who did not receive chemotherapy had a HR of 0.7 compared to NHW women who also did not receive chemotherapy with a 95% confidence interval of 0.3 to 2.0. Receipt of endocrine therapy was associated with a higher hazard of death by CVD for NHB women compared to

NHW women (HR of 2.1, CI: 1.3, 3.5) in contrast, we observed no difference by race among women who did not receive endocrine therapy (HR of 1.0, CI: 0.5, 1.9). We were unable to report racially-stratified estimates for Herceptin due to fewer than five events per strata. (**Table 3**)

Discussion

In this analysis, receipt of endocrine therapy was statistically significantly associated with a higher hazard of death by cardiovascular disease for NHB women compared to NHW women. Overall, with wide confidence intervals overlapping the null for chemotherapy and radiation therapy, there appears to be no racial disparity for these treatments in death by CVD in this cohort. However, chemotherapy and radiation analyzed in absence of racial interaction were protective against cardiovascular disease mortality.

The long-term cardiovascular disease burden of endocrine therapy is unclear. Gallicchio, et. al. investigated racial differences in the cardiovascular health effects of a specific endocrine therapy—aromatase inhibitors and found no acute large adverse CVD health effects during the first year of therapy, but did not investigate long-term consequences [12]. Several studies found the endocrine therapy tamoxifen was not associated with increased CVD mortality. The Early Breast Cancer Trialists' Collaborative Group [21], Fisher, et. al. [22] and Goss, et. al. [23]conducted a randomized control trial that determined aromatase inhibitors after 5 years of tamoxifen did not demonstrate any difference in cardiovascular disease end points in early-stage breast cancer compared to a placebo group while Saphner, Tormey, & Gray 1991 determined tamoxifen increases risk of venous thrombosis and thromboembolism which in turn is associated with mortality and significant morbidity related to deep venous thrombosis and pulmonary embolism [24,25]. Our results investigating the effect of treatment without racial interaction were similar to [21] the results of The Early Breast Cancer Trialists' Collaborative Group, Fisher, et. al. and Goss, et. al., showing no increased risk of

cardiovascular disease mortality. These previous studies, however, did not investigate any racial differences that may exist among those receiving specific endocrine therapies.

Prior research regarding the long-term cardiovascular effects of radiation therapy are mixed. For example, Darby, et. al. found radiation therapy for breast cancer increases patient's subsequent rate of ischemic heart disease and persists for at least 20 years [16], while Harris, et. al found no association between irradiation and higher risk of cardiac death, but did note increased rate of diagnoses of coronary artery disease and myocardial infarction [17].

Previous research demonstrating the cardiotoxicity of chemotherapy is much clearer [3]. For example, Bowles, et. al. found recipients of anthracycline and trastuzumab chemotherapy were at increased risk of cardiomyopathy and heart failure compared to no chemotherapy [15]. Doyle et. al., likewise found breast cancer patients who receive chemotherapy are at a much higher risk long-term for congestive heart failure, heart disease, and cardiomyopathy [26].

Our results suggesting chemotherapy and radiation are actually protective against death by cardiovascular disease is contrary to prior research noted above. The body of evidence regarding the long-term cardiotoxicity is mixed for recipients of radiation as a breast cancer treatment but no prior studies have suggested a protective effect. These counterintuitive results could indicate that this cohort is not a good population for investigating cardiovascular disease mortality as women who received chemotherapy and radiation were still more likely to die of breast cancer than of any other cause and thus our results may be due to survivor bias.

Additionally, Jones, et. al. noted lifestyle modification after breast cancer treatment and diagnosis can mitigate cardiovascular adverse outcomes [13]; as we do not have longitudinal data on cardiovascular disease risk factors women who received radiation and chemotherapy treatments in this cohort could have made lifestyle changes after breast cancer treatment leading to lower cardiovascular disease mortality.

The results of this analysis consistently had wide confidence intervals due to low event rates overall and specifically within each strata. This limitation may have resulted in an inability to detect differences that actually exist between racial groups those who received chemotherapy or radiation therapy due to lack of power.

In conclusion, our findings suggest racial disparities do exist for women who receive endocrine therapy, but there might not unexplained racial disparities in cardiovascular disease mortality for women who receive radiation or chemotherapy. Further research with more participants and longer follow-up is necessary to investigate these preliminary finding with sufficient power to detect differences in CVD mortality between NHW and NHB women.

Tables

Table 1: Demographic characteristics of study population by race, according to selected characteristics*****

	Overall Study Population (n=8,523)	Non-Hispanic White (n=4,943)	Non-Hispanic Black (n=3,580)
Deaths:			
Due to CVD	110 (1.3)	62 (1.3)	48 (1.3)
Due to BC	807 (9.5)	319 (6.5)	488 (13.6)
Due to other causes	335 (3.9)	189 (3.8)	146 (4.1)
Age at diagnosis:			
<55	3439 (40.4)	1807 (36.6)	1632 (45.6)
≥55	5084 (59.7)	3136 (63.4)	1948 (54.4)
Treatment:			
Surgery			
None	872 (10.2)	344 (7.0)	528 (14.8)
BCS	4092 (48.0)	2492 (50.4)	1600 (44.7)
Mastectomy/Radical	3555 (41.7)	2105 (42.6)	1450 (17.0)
Neoadjuvant Therapy			
No	7469 (87.6)	4452 (90.1)	3017 (84.3)
Yes	1054 (12.4)	491 (9.9)	563 (15.7)
Adjuvant Therapy			
Chemotherapy			
No	3935 (46.2)	2668 (54.0)	1267 (35.4)
Yes	3997 (46.9)	1962 (39.7)	2035 (56.8)
Discordant	388 (4.6)	198 (4.0)	190 (5.3)
Missing	203 (2.4)	115 (2.3)	88 (2.5)
Radiation therapy			
No	3213 (37.7)	1895 (38.3)	1318 (36.8)
Yes	4807 (56.4)	2805 (56.8)	2002 (55.9)
Discordant	129 (1.5)	79 (1.6)	50 (1.4)
Missing	374 (4.4)	164 (3.3)	210 (5.9)
Endocrine Therapy			
No	3270 (38.4)	1689 (34.2)	1581 (44.2)
Yes	5253 (61.6)	3254 (65.8)	1999 (55.8)
Receipt of Herceptin			
No	7461 (87.5)	4395 (88.9)	3066 (85.6)
Yes	1062 (12.5)	548 (11.1)	514 (14.4)
Stage at diagnosis:			
I	4124 (48.4)	2727 (55.2)	1397 (39.0)
II	2878 (33.8)	1537 (31.1)	1341 (37.5)
III	949 (11.1)	444 (9.0)	505 (14.1)
IV	572 (6.7)	235 (4.8)	337 (9.4)
ER status:			
Negative	1552 (18.2)	640 (13.0)	912 (25.5)
Positive/Borderline	6866 (80.6)	4250 (86.0)	2616 (73.1)
Missing	105 (1.2)	53 (1.1)	52 (1.5)
Tumor subtypes:			
Luminal A	5585 (65.5)	3511 (71.0)	2074 (57.9)

Luminal B	957 (11.2)	525 (10.8)	432 (12.1)
HER2	357 (4.2)	172 (3.5)	185 (5.2)
TNBC	1047 (12.3)	401 (8.1)	646 (18.0)
Unknown	577 (6.8)	334 (6.8)	243 (6.8)
Insurance type:			
Uninsured	201 (2.4)	57 (1.2)	144 (4.0)
Private	5054 (59.3)	3101 (62.7)	1953 (54.6)
Medicaid	655 (7.7)	139 (2.8)	516 (14.4)
Medicare	2389 (28.0)	1545 (31.3)	844 (23.6)
Military	96(1.1)	39 (0.8)	57 (1.6)
Other/Unknown	128 (1.5)	62 (1.3)	66 (1.8)
Marital status:			
Single	1724 (20.2)	615 (12.4)	1109 (31.0)
Married	4270 (50.1)	3017 (61.0)	1253 (35.0)
Other	2216 (26.0)	1168 (23.6)	1048 (29.3)
Missing	313 (3.7)	143 (2.9)	170 (4.8)
SES Index[†]:			
0-<5%	1740 (20.4)	1529 (30.9)	211 (5.9)
5-10%	1924 (22.6)	1469 (29.7)	455 (12.7)
10-20%	2617 (30.7)	1320 (26.7)	1297 (36.2)
20-100%	2242 (26.3)	625 (12.6)	1617 (45.2)

BC=Breast Cancer; CVD=Cardiovascular disease

*Characteristics are reported as number of observations (percentage of subpopulation)

[†]Percentage of census tract at or below the federal poverty line

Table 2: Multivariable Cox Proportional Hazard Model of the association between breast cancer treatment and cardiovascular mortality.

	Cardiovascular disease mortality		
	Events	Hazard Ratio	95% CI
Chemotherapy*			
No/ Discordant	84	1.0	Ref
Yes‡	18	0.4	0.2, 0.8
Radiation therapy**			
No/ Discordant	70	1.0	Ref
Yes	35	0.5	0.3, 0.8
Endocrine Therapy^			
No	47	1.0	Ref
Yes	63	1.0	0.6, 1.5
Receipt of Herceptin^^			
No	105	1.0	Ref
Yes	5	0.7	0.2, 2.3

CI=confidence intervals

‡Adjuvant and neoadjuvant chemotherapy

*Model adjusts for chemotherapy (exposure), race, age, insurance, stage at diagnosis, and ER status

**Model adjusts for radiation (exposure), race, age, chemotherapy, insurance, and molecular subtype

^Model adjusts for endocrine therapy (exposure), race, age, chemotherapy, radiation therapy, insurance, and receipt of Herceptin

^^Model adjusts for receipt of Herceptin (exposure), race, age, molecular subtype, insurance, and radiation therapy

Table 3: Multivariable Cox Proportional Hazard Model of the association between race and cardiovascular mortality.

	Cardiovascular disease mortality		
	Events	Hazard Ratio	95% CI
Main effect[†]			
Non-Hispanic White	62	1.0	Ref
Non-Hispanic Black	48	1.3	0.9, 1.9
Race*Treatment			
Chemotherapy*			
No/ Discordant, NHW	49	1.0	Ref
NHB	35	1.6	1.0, 2.6
Yes[‡], NHW	9	1.0	Ref
NHB	9	0.7	0.3, 2.0
Radiation therapy**			
No/ Discordant, NHW	40	1.0	Ref
NHB	30	1.4	0.8, 2.6
Yes, NHW	21	1.0	Ref
NHB	14	1.4	0.7, 2.8
Endocrine Therapy^			
No, NHW	29	1.0	Ref
NHB	18	1.0	0.5, 1.9
Yes, NHW	33	1.0	Ref
NHB	30	2.1	1.3, 3.5

CI=confidence intervals; NHW=Non-Hispanic White; NHB=Non-Hispanic Black

[†]Adjusted for age at diagnosis

[‡]Adjuvant and neoadjuvant chemotherapy

*Model adjusts for chemotherapy (exposure), race, age, insurance, stage at diagnosis, and ER status

**Model adjusts for radiation (exposure), race, age, chemotherapy, insurance, and molecular subtype

^Model adjusts for endocrine therapy (exposure), race, age, chemotherapy, radiation therapy, insurance, and receipt of Herceptin

^^ Model adjusts for receipt of Herceptin (exposure), race, age, molecular subtype, insurance, and radiation therapy

Figures and Figure Legends

Figure 1: Directed Acyclic Graph Demonstrating the Effect of Race on Death by Cardiovascular Disease.

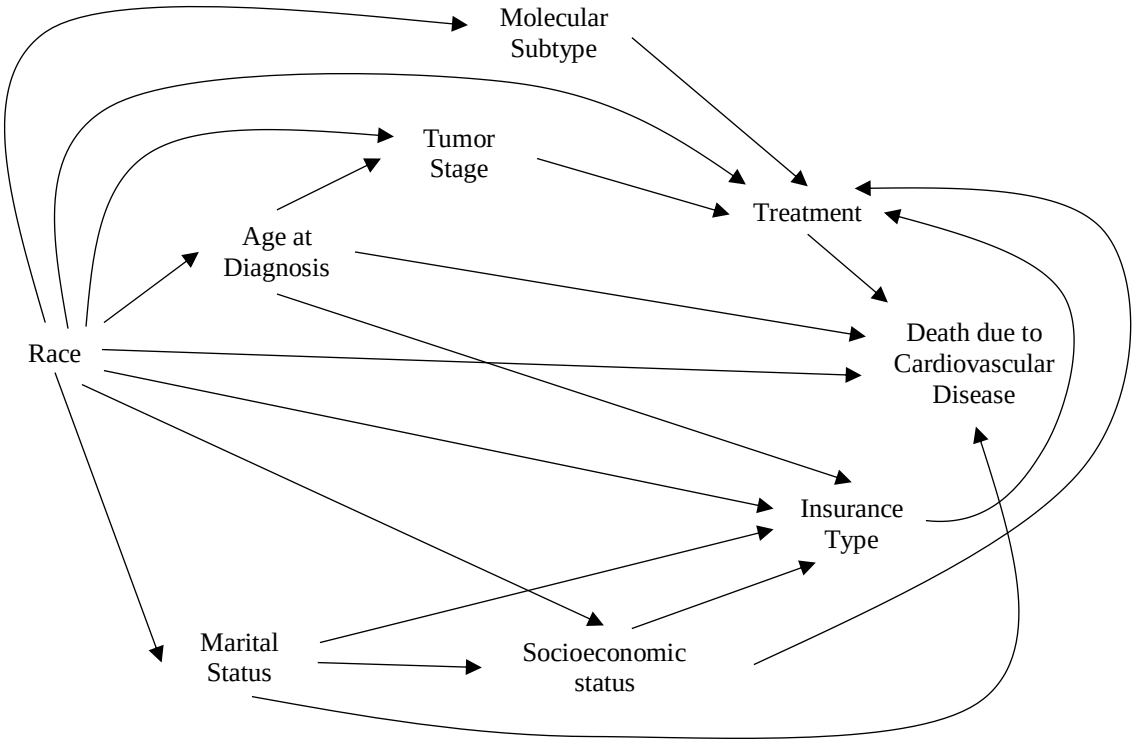


Figure 2: Directed Acyclic Graph Demonstrating the Effect of Chemotherapy on Death by Cardiovascular Disease.

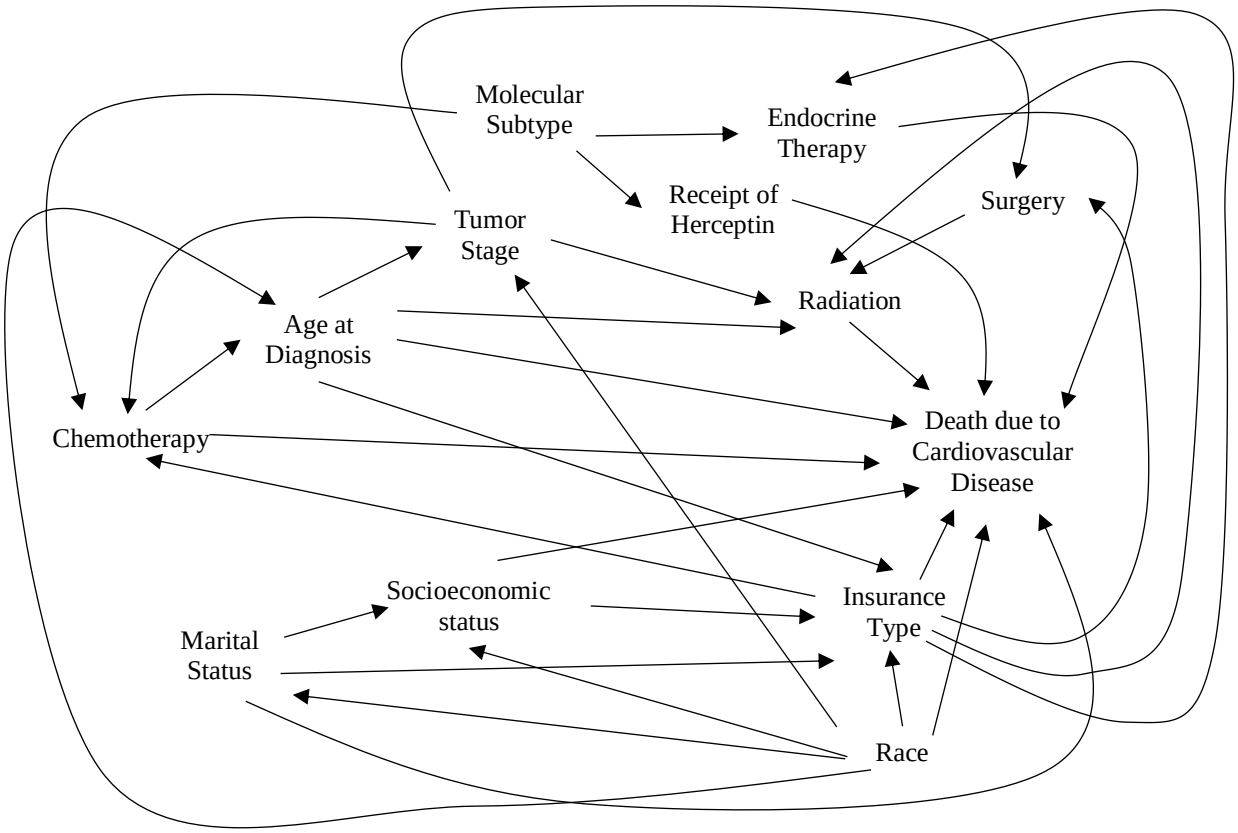


Figure 3: Directed Acyclic Graph Demonstrating the Effect of Radiation on Death by Cardiovascular Disease.

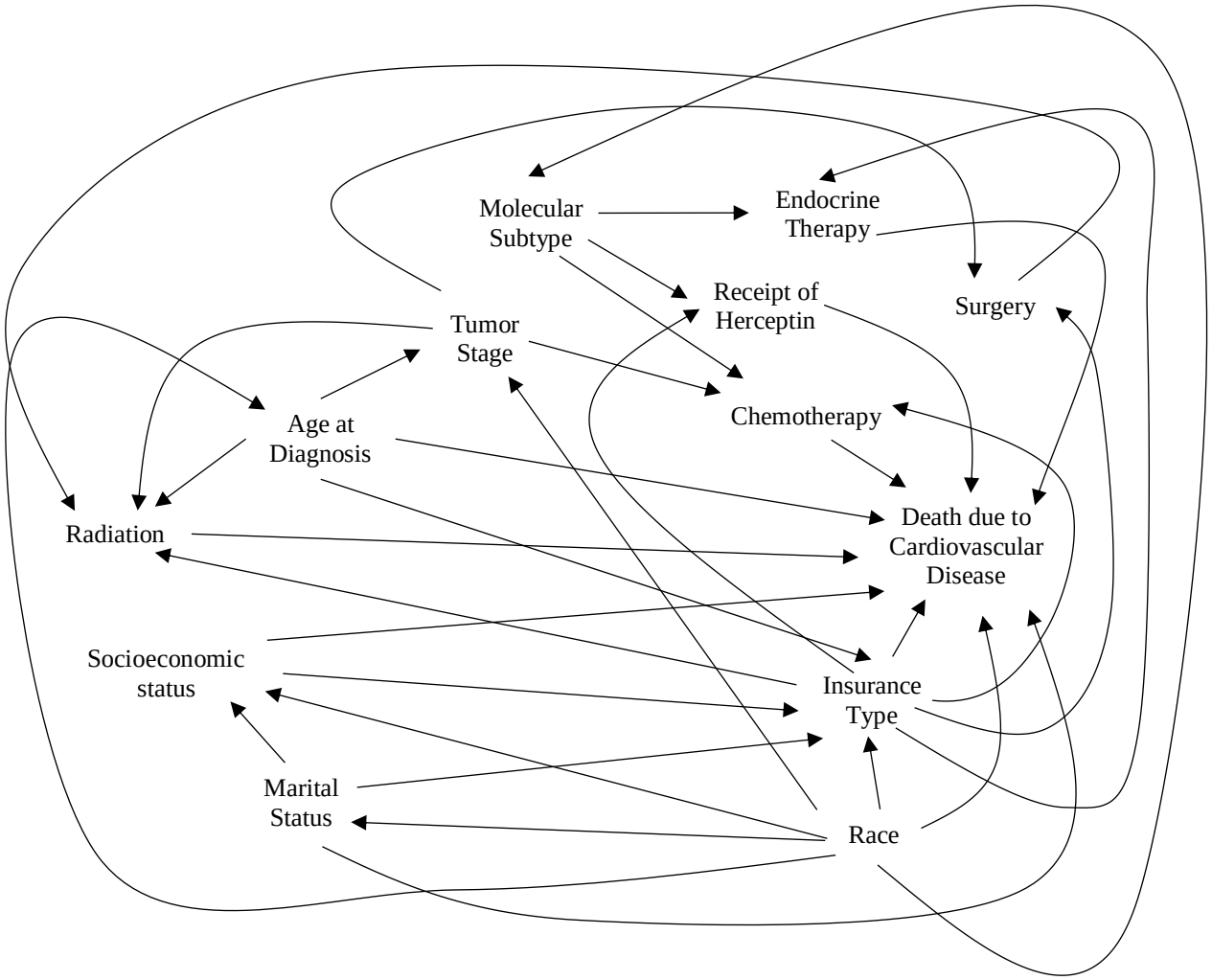


Figure 4: Directed Acyclic Graph Demonstrating the Effect of Endocrine Therapy on Death by Cardiovascular Disease.

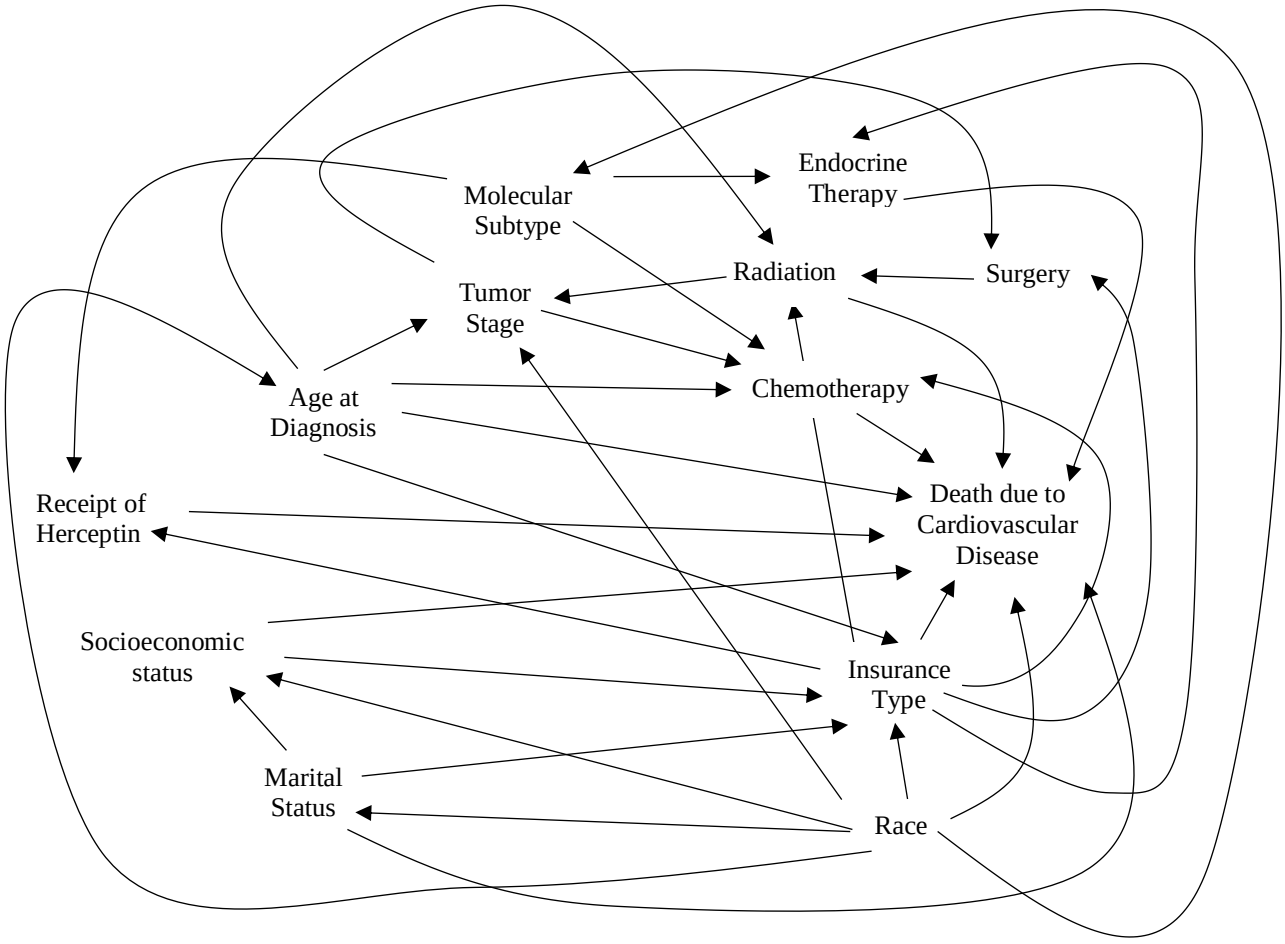
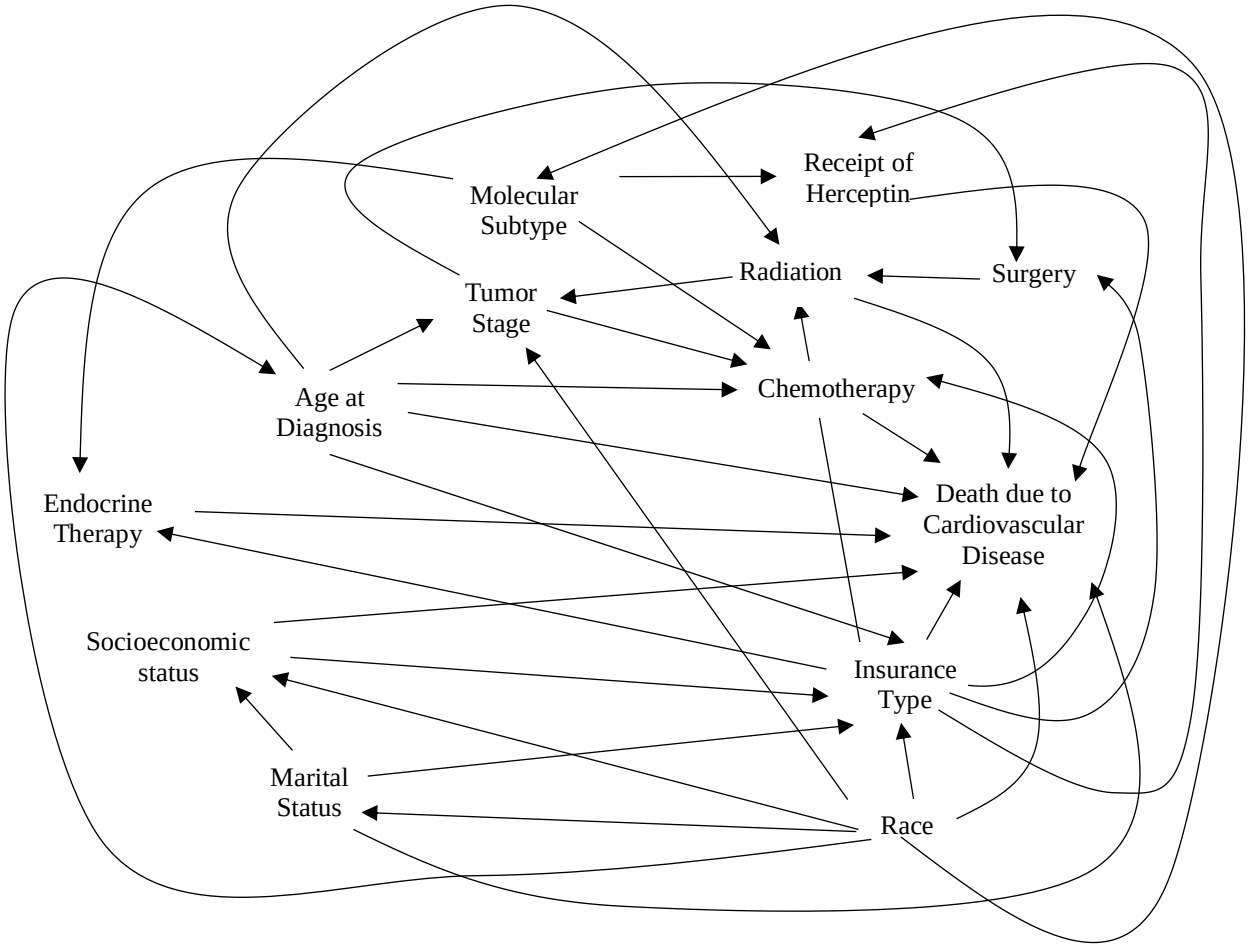


Figure 5: Directed Acyclic Graph Demonstrating the Effect of Receipt of Herceptin on Death by Cardiovascular Disease.



Appendices

Appendix A: Institutional Review Board Exemption

EMORY UNIVERSITY | Institutional Review Board

Date: October 24, 2017

Lauren McCullough, PhD, MSPH
Principal Investigator
*SPH: Epidemiology

RE: **Exemption of Human Subjects Research**
IRB00099875
Black-White breast cancer mortality disparities in Atlanta: examining effects of tumor, treatment and individual characteristics (01/01/2010-12/31/2014)

Dear Principal Investigator:

Thank you for submitting an application to the Emory IRB for the above-referenced project. Based on the information you have provided, we have determined on **10/24/2017** that although it is human subjects research, it is exempt from further IRB review and approval.

This determination is good indefinitely unless substantive revisions to the study design (e.g., population or type of data to be obtained) occur which alter our analysis. Please consult the Emory IRB for clarification in case of such a change. Exempt projects do not require continuing renewal applications.

This project meets the criteria for exemption under 45 CFR 46.101(b)(4). Specifically, you will conduct a secondary analysis of publicly available data of GCR - SEER Databases containing Breast cancer information of both black and white women. Zip codes are attached, but it would be difficult to directly identify individuals. As part of the review process, the following documents were approved:

- GCR protocol (V.1)_10-12-17.pdf

Please note that the Belmont Report principles apply to this research: respect for persons, beneficence, and justice. You should use the informed consent materials reviewed by the IRB unless a waiver of consent was granted. Similarly, if HIPAA applies to this project, you should use the HIPAA patient authorization and revocation materials reviewed by the IRB unless a waiver was granted. CITI certification is required of all personnel conducting this research.

Unanticipated problems involving risk to subjects or others or violations of the HIPAA

Privacy Rule must be reported promptly to the Emory IRB and the sponsoring agency (if any).

In future correspondence about this matter, please refer to the study ID shown above. Thank you.

Sincerely,

Will Smith, MPH
Research Protocol Analyst
This letter has been digitally signed

CC:

Ward Kevin *SPH: Epidemiology

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
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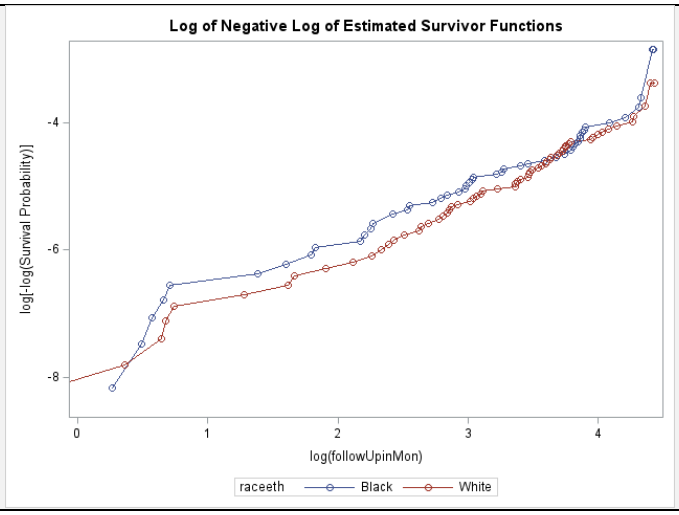
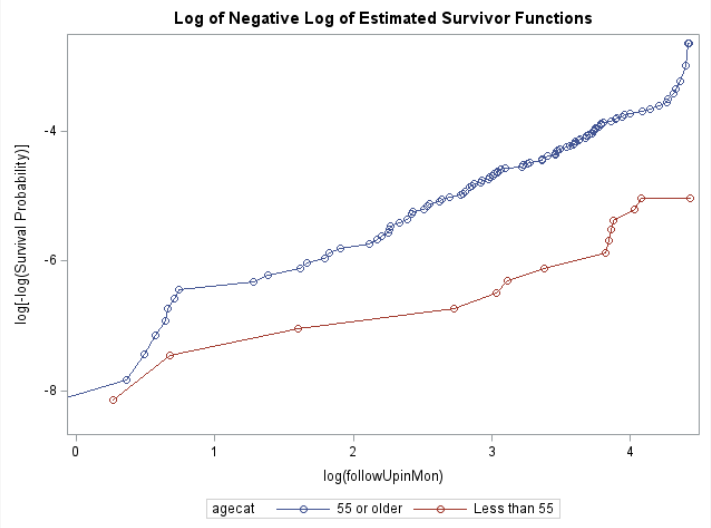
An equal opportunity, affirmative action university

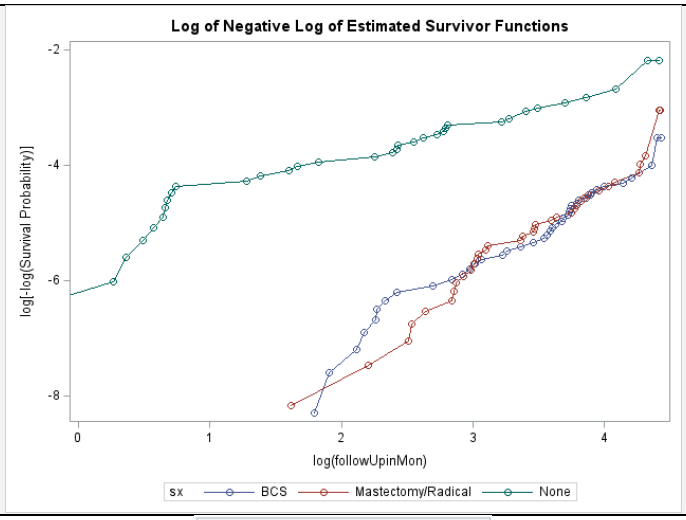
Appendix B: Results From Evaluating the Proportional Hazards Assumptions for Predictors

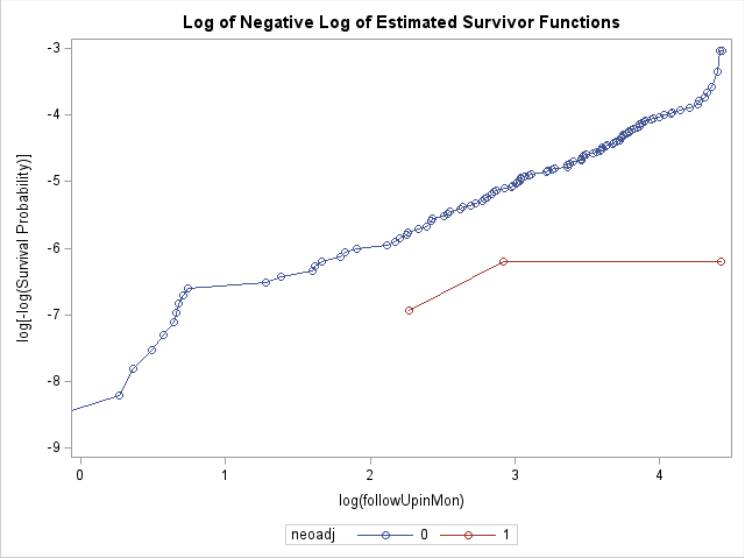
Evaluating the Proportional Hazards Assumption for Race

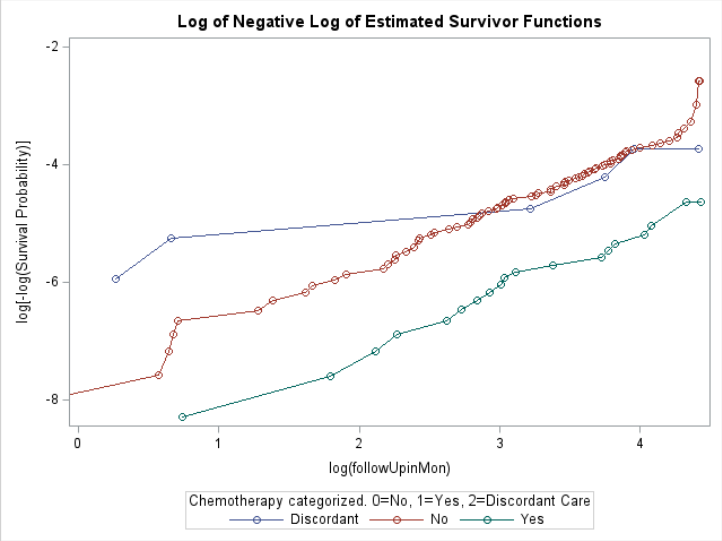
METHOD	RESULTS	NOTES
Graphical		The PH assumption does not appear to be violated as lines appear to be roughly parallel.
Goodness-of-fit	Pearson Correlation Coefficients, N = 110 Prob > |r| under H0: Rho=0 sh_rc timerank: -0.03101 Rank for Variable followUpinMon: 0.7477	With a p-value > 0.05 at 0.75, we fail to reject the null hypothesis and conclude the goodness-of-fit test for race suggests that the PH assumption is met
Time-dependent covariates	Analysis of Maximum Likelihood Estimates Parameter | DF | Parameter Estimate | Standard Error | Chi-Square | Pr > ChiSq | Hazard Ratio raceeth | 1 | 0.16030 | 0.32629 | 0.2414 | 0.6232 | 1.174 rc_t | 1 | -0.00137 | 0.00935 | 0.0216 | 0.8831 | 0.999 For g(t) = t, p-value = 0.999 Analysis of Maximum Likelihood Estimates Parameter | DF | Parameter Estimate | Standard Error | Chi-Square | Pr > ChiSq | Hazard Ratio raceeth | 1 | 0.32772 | 0.55797 | 0.3450 | 0.5570 | 1.388 rc_lnt | 1 | -0.07025 | 0.17864 | 0.1547 | 0.6941 | 0.932 For g(t) = ln(t), p-value = 0.932	With p-values > 0.05, we fail to reject the null hypothesis. This suggests the PH assumption is met for race when using both g(t) = t and g(t)=ln(t)
DECISION	With nearly parallel log-log survival curves, non-statistically significant interactions with time (g(t)=t and g(t)=ln(t)), and a GOF test with an associated p-value of 0.75, it is reasonable to conclude that the PH assumption is met for race.	

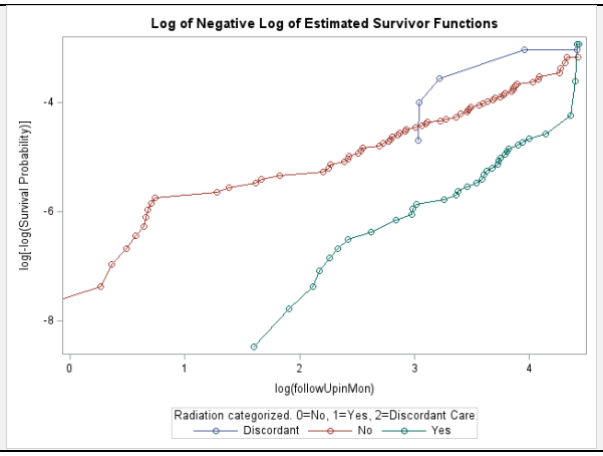
<table>
<tr><th colspan="3">Evaluating the Proportional Hazards Assumption for Age at Diagnosis</th></tr>
<tr><th>METHOD</th><th>RESULTS</th><th>NOTES</th></tr>
<tr><td>Graphical</td><td> 
</td><td>As the lines do not cross, the PH assumption does not appear to be violated</td></tr>
<tr><td>Goodness-of-fit</td><td>
<table>
<tr><th colspan="2">Pearson Correlation Coefficients, N = 110
Prob > |r| under H0: Rho=0</th></tr>
<tr><th></th><th>sh_age</th></tr>
<tr><td>timerank
Rank for Variable followUpinMon</td><td>-0.06139
0.5240</td></tr>
</table>
p-value = 0.52</td><td>With a p-value > 0.05 at 0.52, we fail to reject the null hypothesis and conclude the goodness-of-fit test for age at diagnosis suggests that the PH assumption is met</td></tr>
<tr><td>Time-dependent covariates</td><td>
<table>
<tr><th colspan="7">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th></tr>
<tr><td>ageDxNum</td><td>1</td><td>0.11255</td><td>0.01360</td><td>68.4545</td><td><.0001</td><td>1.119</td></tr>
<tr><td>age_t</td><td>1</td><td>-0.0003273</td><td>0.0003907</td><td>0.7019</td><td>0.4022</td><td>1.000</td></tr>
</table>
For g(t) = t, p-value = 0.40

<table>
<tr><th colspan="7">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th></tr>
<tr><td>ageDxNum</td><td>1</td><td>0.11014</td><td>0.02304</td><td>22.8606</td><td><.0001</td><td>1.116</td></tr>
<tr><td>age_lnt</td><td>1</td><td>-0.00228</td><td>0.00745</td><td>0.0940</td><td>0.7591</td><td>0.998</td></tr>
</table>
For g(t) = ln(t), p-value = 0.76</td><td>With p-values > 0.05, we fail to reject the null hypothesis. This suggests the PH assumption is met for age at diagnosis when using both g(t) = t and g(t)=ln(t)</td></tr>
<tr><td>DECISION</td><td colspan="2">With non-overlapping log-log survival curves, non-statistically significant interactions with time (g(t)=t and g(t)=ln(t)), and a GOF test with an associated p-value of 0.52, it is reasonable to conclude that the PH assumption is met for age at diagnosis.</td></tr>
</table>

<table>
<tr><th colspan="3">Evaluating the Proportional Hazards Assumption for Surgery</th></tr>
<tr><th>METHOD</th><th>RESULTS</th><th>NOTES</th></tr>
<tr><td>Graphical</td><td> 
</td><td>As the lines Mastectomy/Radical and BCS cross multiple times, the PH assumption appears to be violated</td></tr>
<tr><td>Goodness-of-fit</td><td>Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations
<table><tr><th></th><th>sh_sx</th></tr><tr><td>timerank
Rank for Variable followUpinMon</td><td>0.36271
0.0001
109</td></tr></table>
p-value = 0.001</td><td>With a p-value < 0.05 at 0.001, we reject the null hypothesis and conclude the goodness-of-fit test for surgery suggests that the PH assumption is not met</td></tr>
<tr><td>Time-dependent covariates</td><td>Analysis of Maximum Likelihood Estimates
<table><tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th></tr><tr><td>sx</td><td>1</td><td>-1.79454</td><td>0.26558</td><td>45.6589</td><td><.0001</td><td>0.166</td></tr><tr><td>sx_t</td><td>1</td><td>0.03331</td><td>0.00806</td><td>17.0615</td><td><.0001</td><td>1.034</td></tr></table>
For g(t) = t, p-value < 0.001
Analysis of Maximum Likelihood Estimates
<table><tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th></tr><tr><td>sx</td><td>1</td><td>-3.61844</td><td>0.58025</td><td>38.8878</td><td><.0001</td><td>0.027</td></tr><tr><td>sx_lnt</td><td>1</td><td>0.92533</td><td>0.18323</td><td>25.5030</td><td><.0001</td><td>2.523</td></tr></table>
For g(t) = ln(t), p-value < 0.001</td><td>With p-values < 0.001, we reject the null hypothesis. This suggests the PH assumption is not met for surgery when using both g(t) = t and g(t)=ln(t)</td></tr>
<tr><td>DECISION</td><td colspan="2">With overlapping log-log survival curves, statistically significant interactions with time (g(t)=t and g(t)=ln(t)), and a GOF test with an associated p-value of 0.001, it is reasonable to conclude that the PH assumption is not met for surgery</td></tr>
</table>

<table>
<tr><th colspan="3">Evaluating the Proportional Hazards Assumption for Neoadjuvant Therapy</th></tr>
<tr><th>METHOD</th><th>RESULTS</th><th>NOTES</th></tr>
<tr><td>Graphical</td><td> 
</td><td>As the lines do not cross, the PH assumption does not appear to be violated.</td></tr>
<tr><td>Goodness-of-fit</td><td><table>
<tr><th colspan="2">Pearson Correlation Coefficients, N = 110
Prob > |r| under H0: Rho=0</th></tr>
<tr><th></th><th>sh_na</th></tr>
<tr><td>timerank
Rank for Variable followUpinMon</td><td>-0.08136
0.3981</td></tr>
</table>
p-value = 0.398</td><td>With a p-value > 0.05 at 0.40, we fail to reject the null hypothesis and conclude the goodness-of-fit test for neoadjuvant therapy suggests that the PH assumption is met</td></tr>
<tr><td>Time-dependent covariates</td><td><table>
<tr><th colspan="7">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th></tr>
<tr><td>neoadj</td><td>1</td><td>-1.03633</td><td>1.06880</td><td>0.9402</td><td>0.3322</td><td>0.355</td></tr>
<tr><td>na_t</td><td>1</td><td>-0.04823</td><td>0.05562</td><td>0.7520</td><td>0.3858</td><td>0.953</td></tr>
</table>
For g(t) = t, p-value = 0.39
<table>
<tr><th colspan="7">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th></tr>
<tr><td>neoadj</td><td>1</td><td>-1.37131</td><td>1.70419</td><td>0.6475</td><td>0.4210</td><td>0.254</td></tr>
<tr><td>na_lnt</td><td>1</td><td>-0.22187</td><td>0.59477</td><td>0.1392</td><td>0.7091</td><td>0.801</td></tr>
</table>
For g(t) = ln(t), p-value = 0.71</td><td>With p-values > 0.05, we fail to reject the null hypothesis. This suggests the PH assumption is met for neoadjuvant therapy when using both g(t) = t and g(t)=ln(t)</td></tr>
<tr><td>DECISION</td><td colspan="2">With non-overlapping log-log survival curves, non-statistically significant interactions with time (g(t)=t and g(t)=ln(t)), and a GOF test with an associated p-value of 0.40, it is reasonable to conclude that the PH assumption is met for neoadjuvant therapy</td></tr>
</table>

<table>
<tr><th colspan="3">Evaluating the Proportional Hazards Assumption for Chemotherapy</th></tr>
<tr><th>METHOD</th><th>RESULTS</th><th>NOTES</th></tr>
<tr><td>Graphical</td><td> 
</td><td>As the lines are roughly parallel, the PH assumption does not appear to be violated</td></tr>
<tr><td>Goodness-of-fit</td><td>
<table>
<tr><th colspan="2">Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations</th></tr>
<tr><th></th><th>sh_ch</th></tr>
<tr><td>timerank
Rank for Variable followUpinMon</td><td>-0.03457
0.7302
102</td></tr>
</table>
p-value = 0.73
</td><td>With a p-value > 0.05 at 0.73, we fail to reject the null hypothesis and conclude the goodness-of-fit test for chemotherapy suggests that the PH assumption is met</td></tr>
<tr><td>Time-dependent covariates</td><td>
<table>
<tr><th colspan="8">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th><th>Label</th></tr>
<tr><td>chemo_Cat</td><td>1</td><td>-0.90943</td><td>0.35910</td><td>6.4135</td><td>0.0113</td><td>0.403</td><td>Chemotherapy categorized. 0=No, 1=Yes, 2=Discordant Care</td></tr>
<tr><td>ch_t</td><td>1</td><td>-0.00459</td><td>0.01059</td><td>0.1880</td><td>0.6646</td><td>0.995</td><td></td></tr>
</table>
For g(t) = t, p-value = 0.66
<table>
<tr><th colspan="8">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th><th>Label</th></tr>
<tr><td>chemo_Cat</td><td>1</td><td>-0.48205</td><td>0.59392</td><td>0.6588</td><td>0.4170</td><td>0.618</td><td>Chemotherapy categorized. 0=No, 1=Yes, 2=Discordant Care</td></tr>
<tr><td>ch_lnt</td><td>1</td><td>-0.19128</td><td>0.19485</td><td>0.9638</td><td>0.3262</td><td>0.826</td><td></td></tr>
</table>
For g(t) = ln(t), p-value = 0.33
</td><td>With p-values > 0.05, we fail to reject the null hypothesis. This suggests the PH assumption is met for chemotherapy when using both g(t) = t and g(t)=ln(t)</td></tr>
<tr><td>DECISION</td><td colspan="2">With roughly parallel log-log survival curves, non-statistically significant interactions with time (g(t)=t and g(t)=ln(t)), and a GOF test with an associated p-value of 0.73, it is reasonable to conclude that the PH assumption is met for chemotherapy</td></tr>
</table>

<table>
<tr><th colspan="3">Evaluating the Proportional Hazards Assumption for Radiation</th></tr>
<tr><th>METHOD</th><th>RESULTS</th><th>NOTES</th></tr>
<tr><td>Graphical</td><td> 
</td><td>As the lines are roughly parallel, the PH assumption may not be violated</td></tr>
<tr><td>Goodness-of-fit</td><td>
<table>
<tr><th colspan="2">Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations</th></tr>
<tr><th></th><th>sh_rd</th></tr>
<tr><td>timerank</td><td>0.18926</td></tr>
<tr><td>Rank for Variable followUpinMon</td><td>0.0532</td></tr>
<tr><td></td><td>105</td></tr>
</table>
p-value = 0.053
</td><td>With a p-value > 0.05, we fail to reject the null hypothesis and conclude the goodness-of-fit test for radiation suggests that the PH assumption is met</td></tr>
<tr><td>Time-dependent covariates</td><td>
<table>
<tr><th colspan="8">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th><th>Label</th></tr>
<tr><td>rad_Cat</td><td>1</td><td>-1.42264</td><td>0.34849</td><td>16.6654</td><td><.0001</td><td>0.241</td><td>Radiation categorized. 0=No, 1=Yes, 2=Discordant Care</td></tr>
<tr><td>rd_t</td><td>1</td><td>0.01864</td><td>0.00956</td><td>3.7997</td><td>0.0513</td><td>1.019</td><td></td></tr>
</table>
For g(t) = t, p-value = 0.51
<table>
<tr><th colspan="8">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th><th>Label</th></tr>
<tr><td>rad_Cat</td><td>1</td><td>-2.66001</td><td>0.73997</td><td>12.9223</td><td>0.0003</td><td>0.070</td><td>Radiation categorized. 0=No, 1=Yes, 2=Discordant Care</td></tr>
<tr><td>rd_lnt</td><td>1</td><td>0.58508</td><td>0.22570</td><td>6.7197</td><td>0.0095</td><td>1.795</td><td></td></tr>
</table>
For g(t) = ln(t), p-value = 0.01
</td><td>With p-values of 0.51 and 0.01, we, overall, reject the null hypothesis. This suggests the PH assumption is not met for radiation when using g(t)=ln(t) and may be met using g(t) = t</td></tr>
<tr><td>DECISION</td><td colspan="2">With roughly parallel log-log survival curves, non-statistically significant interactions with time (g(t)=t), and a GOF test with an associated p-value of 0.053, it is reasonable to conclude that the PH assumption not met for radiation</td></tr>
</table>

<table>
<tr><th colspan="3">Evaluating the Proportional Hazards Assumption for surgery after adjusting for age</th></tr>
<tr><th>METHOD</th><th>RESULTS</th><th>NOTES</th></tr>
<tr><td>Goodness-of-fit</td><td>
<table>
<tr><th colspan="2">Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations</th></tr>
<tr><th></th><th>sh_sx</th></tr>
<tr><td>timerank</td><td>-0.03930
0.6849
109</td></tr>
<tr><td>Rank for Variable followUpinMon</td><td></td></tr>
</table>
p-value = 0.69
</td><td>With a p-value > 0.05 at 0.69, we fail to reject the null hypothesis and conclude the goodness-of-fit test for surgery after adjusting for age suggests that the PH assumption is met</td></tr>
<tr><td>Time-dependent covariates</td><td>
<table>
<tr><th colspan="7">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th></tr>
<tr><td>ageDxNum</td><td>1</td><td>0.09498</td><td>0.00820</td><td>134.1640</td><td><.0001</td><td>1.100</td></tr>
<tr><td>sx</td><td>1</td><td>-1.23572</td><td>0.26900</td><td>21.1033</td><td><.0001</td><td>0.291</td></tr>
<tr><td>sx_t</td><td>1</td><td>0.02892</td><td>0.00815</td><td>12.6018</td><td>0.0004</td><td>1.029</td></tr>
</table>
For g(t) = t, p-value = 0.0004
<table>
<tr><th colspan="7">Analysis of Maximum Likelihood Estimates</th></tr>
<tr><th>Parameter</th><th>DF</th><th>Parameter Estimate</th><th>Standard Error</th><th>Chi-Square</th><th>Pr > ChiSq</th><th>Hazard Ratio</th></tr>
<tr><td>ageDxNum</td><td>1</td><td>0.09373</td><td>0.00814</td><td>132.4857</td><td><.0001</td><td>1.098</td></tr>
<tr><td>sx</td><td>1</td><td>-2.90556</td><td>0.57899</td><td>25.1839</td><td><.0001</td><td>0.055</td></tr>
<tr><td>sx_lnt</td><td>1</td><td>0.83112</td><td>0.18269</td><td>20.6972</td><td><.0001</td><td>2.296</td></tr>
</table>
For g(t) = ln(t), p-value < 0.001
</td><td>With p-values < 0.001, we reject the null hypothesis. This suggests the PH assumption is not met for surgery after adjusting for age when using both g(t) = t and g(t)=ln(t)</td></tr>
<tr><td>DECISION</td><td colspan="2">With statistically significant interactions with time (g(t)=t and g(t)=ln(t)), and a GOF test with an associated p-value of 0.001, it is reasonable to conclude that the PH assumption is not met for surgery after adjusting for age at diagnosis</td></tr>
</table>

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