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Hemoglobinopathies and Adverse Cancer-Related Outcomes

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Despite long-term research efforts to identify a cohesive explanation of racial disparities in cancer outcomes, evidence remains mixed. Disparities persist in randomized clinical trials, suggesting that inherited factors contribute to differential outcomes. Hemoglobin variants represent a heretofore unstudied inherited prognostic factor, the most prevalent of which is sickle cell trait (SCT). SCT is disproportionally prevalent in African American/Blacks (AA/Bs) (~8%) compared to non-Hispanic whites (NHWs) (<0.1%). Case report evidence suggests SCT interacts with the tumor microenvironment and rigors of cancer treatment, inducing adverse outcomes. We identified 162,357 older cancer patients (75,633 breast; 86,904 prostate) diagnosed 2007-2013 using the SEER-Medicare linked database. AA/B and NHW patients were grouped by hemoglobinopathy status (AA/B+, AA/B-, NHW-) and three-way propensity score weighting was performed to evaluate treatment completion, occurrence of adverse events, and survival. A total of 371 AA/B+ patients were analyzed, compared to 17,303 AA/B- and 144,863 NHW-. At diagnosis, AA/B+ were more likely than AA/B- and NHW- to have multiple comorbidities including cerebrovascular disease, diabetes, and chronic renal failure. After propensity score weighting, no significant association was observed in treatment completion status between AA/B+ and AA/B-. Among treated patients, however, AA/B+ status was associated with increased risk of experiencing one or more adverse event compared to both AA/B- (HR: 1.15, 95% CI: 1.07 – 1.24) and NHW- (HR: 1.18, 95% CI: 1.10 – 1.26). While hazards models failed to reveal significant differences across study groups, the magnitude of the associations with

mortality in relation to either treatment completion or adverse events varied by hemoglobinopathy status. Among AA/B+ who completed treatment, those who experienced one or more adverse events had more than five times the mortality risk compared to those with no adverse events (HR: 5.56, 95% CI: 4.70 – 6.58) whereas the estimated mortality risk among AA/B- and NHW- patients were approximately three-fold. Among patients who failed to complete treatment, however, the adverse event-mortality relationship was similar across groups. This study, to our knowledge, provides the first analytical evidence of SCT and other hemoglobinopathies as prognostic biomarkers in cancer, acting as important effect modifiers of the association between treatment completion, adverse events, and mortality.

Hemoglobinopathies and Adverse Cancer-Related Outcomes

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1.0 Introduction

1.1 Background

1.1.1 Racial disparities in cancer outcomes

Cancer is the leading cause of death in the United States (US) among men and women ages 40-79 and the second-leading cause of death in the US overall, accounting for 23% of all deaths and over 550,000 deaths annually.[1] Compared to non-Hispanic Whites (NHW), the African American/Black (AA/B) population experiences 22.3% and 12.6% higher all-site cancer mortality rates for men and women, respectively; AA/B women are 40% more likely to die from breast cancer than NHW women in the US, and AA/B men are more than twice as likely to die from prostate cancer than NHW men.[1] Despite the steady decline in cancer mortality rates since the 1990s in all groups, largely attributed to the introduction of improved cancer therapies and screening techniques[2], racial disparities persist.[3] The largest racial disparities in cancer-specific mortality have persisted for over three decades within breast and prostate cancer, the two most prevalent cancers among AA/B women and men, respectively.[3] Further, the survival gap has increased between AA/B and NHW breast cancer patients[1,3], hence, novel questions are warranted.[4]

Established and putative explanatory factors of racial disparities in cancer outcomes reflect a complex interplay across three major domains[5]: 1) macroenvironment level; 2) individual environment level; and, 3) biologic levels such as cellular biomarkers and inherited genetic variants.[5] Applying this multilevel approach to disparities research for cancer outcomes has highlighted interactions among and between macroenvironment factors such as geography and latent discriminatory policies and practices that reduce access to and completion of high quality cancer care with local/individual factors such as socioeconomic deprivation,

comorbidities, and lower rates of healthcare utilization.[6-8] Despite an extensive body of research documenting these contributions to outcome disparities, a composite analysis of randomized clinical trials (RCTs) from the Southwest Oncology Group (SWOG) reported that racial disparities in breast and prostate cancer survival remained after controlling for clinical presentation (e.g., stage, histology, and tumor characteristics) among patients with similar eligibility requirements who received uniform therapy.[9] These findings suggest that unmeasured factors, such as genetic status, may be associated with persistent outcome disparities.[10]

Specifically, our current investigation focuses on the prognostic role of a prevalent inherited genotype in the AA/B population, sickle cell trait (SCT), which to date has not been the object of a systematic investigation in cancer outcomes. This topic was prompted by a recent report of multiple cases with SCT and sickle cell disease (SCD) who experienced various adverse events during systemic chemotherapy or whose tumors exhibited increased hypoxia.[11] SCT is the most common genetic mutation of hemoglobin worldwide; in the US, the prevalence of SCT is comparatively high in the AA/B population at 8.0% compared to < 1.0% of NHWs.[12] Additional hemoglobinopathies are included in this investigation as described later.

SWOG findings also could be explained by residual confounding due to differences in tumor clinicopathology. For example, in an analysis of 373,563 women diagnosed with invasive breast cancer from 2004 to 2011 in the Surveillance, Epidemiology, and End Results (SEER) 18 registries database, AA/B women with small tumors (less than or equal to 2 cm) were more likely to present with lymph node metastases (24.1% vs. 18.4%, respectively, $p < .001$) and distant metastases (1.5% vs. 1.0%, respectively, $p < .001$) compared to NHW women.[13] Population-based gene expression profiling of intrinsic breast cancer subtypes has revealed a

much higher prevalence of aggressive basal-like[i] tumors among premenopausal AA/B woman compared to postmenopausal AA/B and non-AA/B women of all ages, and a lower prevalence of less aggressive luminal A[ii] tumors.[14] In spite of these differences, however, the incidence of more aggressive tumor subtypes has not accounted for worse breast-cancer specific survival in AA/B women compared to NHW women, particularly among women with stage I disease.[13,14] Further, evidence from an RCT examining long-term follow-up of adjuvant taxane therapy in approximately 5,000 (8% AA/B) women with stage II and III breast cancer suggested that even among patients with more favorable ER positive disease, AA/B women were at higher risk of recurrence and experienced worse overall survival after adjustment for obesity, disease stage, and treatment adherence.[15] Since AA/B women diagnosed with breast cancer exhibit greater intratumor genetic heterogeneity compared to NHW women, it could be that overall genomic instability, epigenetic changes, or some other inherited influence(s) are contributing more aggressive and/or treatment resistant disease.[16] Whether the presence of SCT or other inherited hemoglobinopathies play a role in tumor metastasis and treatment resistance is unknown.

Studies of genetic variation in drug metabolizing genes across populations have reported reduced cancer survival[17] in relation to certain genotypes, and can serve as a general model for studying the impact of SCT and other inherited hemoglobinopathies on clinical outcomes.[18] Adverse drug responses may materialize as lower tumor response rates and increased systemic toxicity, which can lead to non-standard dose adjustments, treatment discontinuation, and worse survival. For example, hematologic toxicity (i.e. leukopenia and anemia) from chemotherapeutic antimetabolites such as 5-fluorouracil (5-FU) is significantly more prevalent in AA/B patients

[i] Basal-like: estrogen receptor (ER) negative, progesterone receptor (PR) negative, human epidermal growth factor receptor-2 (HER2) negative, cytokeratin 5/6 positive, and/or HER1 positive.
[ii] Luminal A: ER positive and/or PR positive, HER2 negative.

compared to NHWs, likely attributable to higher prevalence of dihydropyrimidine dehydrogenase (DPD)[iii] deficiency (8% in AA/B compared to 2.8% in NHW).[18,19] DPD deficiency is thought to be the result of germline polymorphisms in a host of genes with greater population frequencies in AA/Bs compared to NHWs and other genetic ancestries. Other chemotherapeutic adverse drug responses that could be due to differences in genetic ancestry and are more likely among AA/B compared to NHW include cardiotoxicity from anthracyclines[18,20], cisplatin-induced nephrotoxicity, and lower maximum tolerable dose.[20,21] Predicted adverse events related to SCT and other hemoglobinopathies are discussed in detail in section 1.1.4, and the biologic plausibility is proposed in section 1.1.5.

Despite the documented history of racial disparities in cancer outcomes in the US and evidence for distinct chemotherapy-related toxicities between AA/B and NHW cancer patients, there is no available research outside of a collection of case reports regarding the impact of inherited hemoglobinopathies on cancer related adverse drug response and outcomes.[11] In a secondary analysis of the large SEER-Medicare claims database, we will evaluate if there is an association between sickling hemoglobinopathies and adverse events in cancer patients and if these events contribute to racial disparities in cancer survival.

1.1.2 Epidemiology of hemoglobinopathies: Sickle cell trait and sickle cell anemia

Sickling hemoglobinopathies are the result of mutations that occur in the beta globin gene, one component of the hemoglobin (Hb) protein.[22] SCT (commonly abbreviated HbAS) is a monogenic inherited heterozygous single base pair substitution (p.Glu7Val, rs334) in the Beta globin (HBB) gene on chromosome 11. Red blood cells (RBCs) of SCT carriers generally

[iii] DPD is the rate-limiting enzyme of 5-FU catabolism[18,19]

contain 35-40% abnormal hemoglobin (HbS), but this proportion is not static either within or between individuals with SCT.[22-24] SCT is prevalent in approximately 1 in 12 (8%) AA/B in the US and the incidence of SCT is 25 times higher in AA/B compared to NHW, and 10 times higher compared to Hispanics.[12] Sickle cell anemia (SCA, commonly abbreviated HbSS) is the most common genetic disorder of SCD and occurs through homozygous inheritance of the p.Glu7Val mutation in HBB. SCD has an estimated prevalence of approximately 1 in 365 AA/B in the US, compared to approximately 1 in 16,000 Hispanics, and less than 0.1% in the NHW population.[25] For individuals with SCD, conditions of either local or systemic deoxygenation can cause abnormal beta globin to polymerize hemoglobin within RBCs thus disturbing RBC shape and ease of circulation with a propensity to adhere to the endothelium.[22]

1.1.3 Epidemiology of hemoglobinopathies: Thalassemia disorders

Thalassemia disorders and associated variants in the US are characterized by mutations in either alpha or beta globin genes that result in reduced or absent production of hemoglobin. The prevalence of thalassemia in the US is increasing and is driven primarily by increased immigration from affected regions in Asia and Arab countries.[26,27] Among newborns screened in California, the prevalence of the beta-thalassemia variant Hb H represents over 80% of thalassemic conditions.[26] Similarly, Hb E (the second most common hemoglobin variant in the world after SCT[28]) is often co-inherited with Hb H and is most commonly prevalent among individuals from Cambodian and Thai/Laotian ancestry, respectively.[29] Thalassemia disorders are prevalent around the world with estimated ranges from 5 to 40% across Western Africa, the Eastern Mediterranean, Middle East, and Southeast Asia.[30]

1.1.4 Clinical complications associated with hemoglobinopathies

Clinical manifestations of SCD are a consequence of the accumulation of rigid sickled RBCs that adhere to the vascular endothelium and obstruct blood flow, triggering both hemolysis and vaso-occulsive "sickling crises" from tissue hypoxia, enhanced apoptosis, tissue necrosis, and organ damage.[22] Complications of sickling crises include severe intermittent pain, susceptibility to infection, stroke, organ failure, and early death.[31] Historically, SCT has been considered a benign condition that confers a protective effect against malaria, but recent evidence suggests that SCT may be related to numerous health conditions.[32] In addition to exercise-related sudden death, some adverse health complications associated with SCT include renal medullary carcinoma, hematuria, renal papillary necrosis, hyposthenuria, splenic infarction, and exertional rhabdomyolysis.[33,34] Known factors associated with rare but clinically significant adverse outcomes include hypoxemia, acidosis, and dehydration; most of which are often encountered during periods of intense exercise, under extreme heat, or at high altitudes.[35] The proposed pathophysiological mechanisms through which individuals with SCT experience exertional injury and death include slight decrease in RBC deformability, increase of whole blood viscosity, oxidative stress, and systematic inflammation.[36] It should be noted, however, that the magnitude of these responses is less than that observed among individuals with SCA.[36]

Recent large observational cohort studies have revealed additional adverse associations with SCT. For example, a cross-sectional analysis across four dialysis centers in three North Carolina counties found that SCT was twice as common among AA/B with end-stage renal disease (ESRD) compared with the general AA/B population (15% vs. 7%, $p<0.001$).[37] Subsequently, Naik et al. (2014), in a pooled analysis of 15,000 AA/B from five population-based cohorts found a positive association between SCT and chronic kidney disease (CKD)

within each cohort.[38] Another prospective study of AA/B adults (mean age of SCT carriers: 53; SD: 6) found a positive association between SCT and stroke, with increased risk observed after controlling for demographics and traditional cerebrovascular risk factors.[39] In a prospective cohort of AA/B followed from 1987 through 2011 in the Atherosclerosis Risk in Communities Study, the adjusted hazard ratios of venous thromboembolism and pulmonary embolism were 1.50 (95% CI: 0.96 – 2.36) and 2.05 (95% CI: 1.12 – 3.76), respectively, for participants with SCT compared to those without SCT.[40] The characterization of adverse events associated with SCT continues to evolve, with a focus on impact on morbidity as well as clinical mechanisms of disease.

In contrast to sickling hemoglobinopathies, the range of different clinical phenotypes represented in thalassemia disorders is less heterogeneous; the most common complication of both alpha- and beta-thalassemia is anemia with or without evidence of hemolysis.[22] Individuals with only one deletion of the four alpha-globin genes generally do not exhibit any adverse clinical phenotype; individuals with two alpha-globin deletions, however, may experience anemia without hemolysis. Serious complications of thalassemias include infection, osteoporosis, and heart and liver disease due to iron overload from receipt of regular blood transfusions.[41] The presence of alpha thalassemia in individuals with SCT has been shown to modify the concentration of sickle hemoglobin in RBCs and exacerbate ischemic-reperfusion injury leading to renal disease.[42] More recently, renal dysfunction in patients with thalassemia without concomitant SCT or SCA has been documented, posited to be caused by hypoxia, anemia and iron-mediated toxicity.[43,44] In a sample of 216 individuals primarily presenting with variants of beta thalassemia, Quinn et al. (2011) documented albuminuria in 59% of patients, as well as renal hyperfiltration and hypercalciuria in approximately one-third of patients.[45]

1.1.5 Biologic plausibility underlying hemoglobinopathies and cancer outcomes

We posit that the mechanisms that trigger sickling and vaso-occlusion in individuals with SCD may be responsible for similar processes, at both the tumor and systemic levels, in SCT carriers undergoing cancer therapy. In SCD, conditions of low oxygen in the blood (i.e., hypoxia) play a central role in the cycle of RBC deoxygenation and sickling, as well as the promotion of inflammation and angiogenesis.[46,47] For example, despite a lack of systematic population-based studies, both animal and case-report evidence suggest that provocation of RBC sickling within or near the tumor microenvironment among cancer patients with SCT may be related to hypoxia, an adverse tumor feature found in 50-60% of locally advanced solid tumors.[11,48,49] At the systemic level, a putative mechanism for hypoxic-related induction of sickling in the SCT patient with cancer may be the physiologic rigors of systemic chemotherapy, general anesthesia admitted during surgery, and local radiotherapy [11,48-51]

It is biologically plausible that RBC sickling is associated with hypoxia and subsequent angiogenesis in the tumor microenvironment, resulting in tumor progression and/or reduced sensitivity to systemic chemotherapy. In the tumor microenvironment, hypoxia can be caused by inadequate blood flow in tissues, an increase in diffusion distances with tumor expansion, and reduced oxygen transport capacity of the blood subsequent to anemia.[52] Under these conditions, hypoxia inducible factors (HIFs) accumulate and activate genes that express protein products related to oxygen delivery, angiogenesis, and glycolysis—all of which are related to an increase in tumor cell survival, growth, and metastasis.[52] In analysis of 40 patients ages 5 to 32 with renal medullary carcinoma (RMC), a hypoxic tumor found almost exclusively in young patients with SCT, Swartz et al. found diffuse expression of HIF and vascular endothelial growth factor (VEGF), a key protein involved in angiogenesis.[53]

In addition to promoting tumor growth and metastasis, hypoxia is also related to direct and indirect resistance to radiotherapy and chemotherapy.[54] First, many anticancer drugs exhibit decreased cytotoxicity at low oxygen concentrations and are therefore less effective within a hypoxic tumor microenvironment.[55] Second, hypoxia promotes proliferation of cells with diminished apoptotic potential, specifically those with p53 mutations.[56] Third, poor blood flow associated with an impaired vasculature can lead to diminished distribution of chemotherapeutic agents into the tumor.[55]

In individuals with either SCD or SCT, the molecular mechanism through which resistance to malaria occurs is thought to involve a higher rate of heme release from sickled versus normal hemoglobin[57] which might be of relevance to tumoral hypoxia. Free heme induces heme oxygenase-1 (HO-1), responsible for the oxidative degradation of cellular heme.[58] HO-1 overexpression is prevalent in many solid tumors and is associated with reduced sensitivity to chemotherapy, advanced disease stage, and poor prognosis.[58,59] Promoted by overexpression of HO-1, murine melanoma models with SCD experienced accelerated tumor angiogenesis, tumor growth, and metastatic potential three weeks after melanoma tumor inoculation compared to wild type mice.[60] In addition, tumors from SCD mice were marked by frequent microvascular occlusion. Terman et al. (2013) demonstrated rapid adherence of sickled RBCs but not normal RBCs to tumor vasculature, also characterized by vaso-occulsion.[61]

In addition to plausible interactions between hemoglobinopathies and the hypoxic tumor microenvironment leading to adverse outcomes in cancer, associations between hemoglobinopathies and sub-clinical or clinical comorbid conditions such as renal dysfunction and chronic kidney disease may interact to induce adverse cancer outcomes. In individuals with SCD, hypoxia-induced sickling in the renal medulla results in a dose-dependent relationship with

kidney injury in the form of glomeruloscleriosis and proteinuria.[38,62] Naik et al. (2014) observed approximately 6% of incident chronic kidney disease was attributable to SCT, with additional associations with decline in estimated glomerular filtration rate (eGFR), and albuminuria.[38] Among individuals with transfusion-independent beta-thalassemia, renal dysfunction and disease can develop via anemia and increased intestinal iron absorption triggered by ineffective erythropoiesis. Chronic hypoxia of tubular cells lead to endothelial and epithelial injury, glomerulosclerosis, kidney fibrosis, and an ultimate decline in eGFR.[43,44] In cancer patients, acute renal failure and chronic kidney disease are associated with survival in patients with cancer, through limited ability to withstand aggressive therapies due to dose adjustments in chemotherapeutic agents excreted primarily by the kidneys.[63,64]

Overall, we hypothesize that the increased physiologic stressors, specifically sustained tumor hypoxia and sickling events, in cancer patients with inherited hemoglobinopathies, is positively associated with a more malignant cancer phenotype and treatment resistance, potentially leading to lower rates of treatment completion, increased rates of adverse events, and worse overall survival.

1.1.6 SCT and public health research agenda

A 2010 workshop of The National Heart, Lung, and Blood Institute (NHLBI) of the NIH as well as a 2009 working meeting of CDC via request from the Sickle Cell Disease Association of America have provided information and guidelines regarding health implications of SCT, gaps in current public health research, and frameworks for future research initiatives.[32] Similarly, the American Society of Hematology (ASH) recently published a set of sickle cell research priorities which included unanswered questions regarding the contribution of SCT to health outcomes.[65]

From a historical perspective, early efforts to conduct sickle cell screening were marred by issues of discrimination, stigma, and poor or inadequate counseling.[32] In the early 1970s, race-based newborn screening programs were instituted in 34 US states, targeting AA/B individuals exclusively. In 1981, a young woman in North Carolina brought a federal case against the local Burke County Health Department and Department of Social Services after being erroneously diagnosed with SCT during a prenatal care visit and coerced to undergo unwanted sterilization.[66] In other instances, individuals with SCT were denied health and life insurance, faced employment discrimination, and denied entry into the armed forces.[67,68] A lack of public awareness combined with inconsistent health education programs persists into the present and may often result in messages delivered to SCT carriers and their families that increase stigma and anxiety.[32] Since 2010, the National Collegiate Athletic Association (NCAA) has required all athletes at Division I and II schools to be tested (with an 'opt-out' provision for students who can show proof of a prior test or who are willing to sign a waiver of liability) for SCT.[69] The NCAA has worked with the American College of Sports Medicine (ACSM) to formulate guidelines and establish a research agenda to study the relationship between physical exertion and SCT, but organizations such as ASH have publicly opposed the testing and disclosure of SCT status, instead recommending universal interventions for all athletes to reduce exertion-related injury and death, following policy implemented by the US Army.[70]

Despite the controversy surrounding SCT screening among athletes, universal newborn screening for hemoglobinopathies regardless of race has been mandated in all 50 states and the District of Columbia since May 1, 2006.[71] Beginning with New York in 1975, other states gradually adopted universal screening for hemoglobinopathies, but variation continues to exist in the types of hemoglobinopathies screened for, the techniques used for screening, and the

counseling offered to families. No standardized medical language ontology or data collection techniques are integrated across states, and only New York, Texas, Washington, and California perform molecular testing as a routine part of their screening protocols.[71,72] The staggered and non-uniform implementation of universal screening for hemoglobinopathies has resulted an estimated 84% of the adult population with SCT and other hemoglobinopathy variants currently unaware of their status.[73-76] Further, only an estimated 37% of families are notified of SCT from newborn screening follow-up, likely due to the fact that many screening programs have no protocols for ensuring positive results for SCT are received.[76]

Even with the advent of adequate genetic counseling programs, the dearth of information available regarding the potential health consequences of SCT will still leave families uncertain about best health practices. The NIH, CDC, and ASH have all highlighted the issue of limited population-based research assessing adverse health outcomes associated with SCT, and have recommended studies that employ databases with sufficient population size to analyze these associations.[77] From the perspective of cancer outcomes research, it may be appropriate for investigations to include all hemoglobinopathies in addition to SCT, since it is possible that mechanisms leading to adverse cancer events in patients with SCT may be similar for other hemoglobin variants.[77] One major unanswered question proposed by ASH is whether hemoglobin variants interact with other genes or gene products to ameliorate or worsen other conditions[65], which can be practically appended to the challenge in cancer therapeutics research in determining whether SCT or other hemoglobin variants interact with specific oncogenic mutations or exhibit response within malignant tumor environments.

1.2 Preliminary Research

The absence of population-based studies among individuals with hemoglobinopathies has made it difficult to confidently predict associations with cancer outcomes. In addition to a published collection of case reports documenting an association between SCT and cancer outcomes[11], Dr. Swede conducted a chart review on a sample of 94 breast cancer patients from the Connecticut Tumor Registry (CTR).

We identified 14 breast cancer patients (12 AA/B versus 2 NHW cases) (1998-2013) (ICD-9 codes: 174.x; ICD-O-3 codes: C50.0–C50.9) about whom also was reported a status of SCT or SCD (ICD-9 codes: 282.5, 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69) from the Yale-New Haven Hospital system (including the Hospital of Saint Raphael) in Connecticut. An age- and race-matched sample of breast cancer patients without a report of sickling hemoglobinopathy diagnosis (n = 40 AA/B and n = 40 NHW controls) also was identified. Demographic and clinical information was abstracted from each patient's medical chart, including medical history.[78] Breast surgery, radiation, and chemotherapy regimens, as well as any complications/adverse events related to each treatment also were recorded. Adverse events potentially related to SCT were defined as one or more of the following: mild joint pain (diffuse or specific), severe joint pain (diffuse or specific), renal insufficiency, renal failure, deep vein thrombosis, cerebrovascular event (stroke), emergency room visit, hospitalization, and early treatment discontinuation.[79,80]

Median follow-up was shorter for AA/B SCT+ cases (46 months) compared to AA/B SCT- controls (88 months) and NHW SCT- controls (99 months). Five of 14 SCT+ cases died during follow-up (35.7%), compared to 32.5% (n = 13) for AA/B SCT- controls and 15.0% (n = 6) for NHW SCT- controls. Of the 5 SCT+ cases who died, the cause of death was associated

with sickle cell disorder for only 1 patient. A summary of demographic and clinical characteristics is provided in Table 1.1. Since this preliminary investigation did not have sufficient power to detect true differences if they exist between groups of patients, statistical tests of significance were not performed. The proportion of AA/B women who experienced at least one adverse event from any treatment (surgery, radiation, chemotherapy) was similar between SCT+ and SCT- patients (64.3% and 63.2%, respectively) and nearly 50% higher than in NHW SCT- patients (35.9%), as seen in Figure 1.1.

A comparison of complications by treatment modality (surgery, radiation, and chemotherapy) suggest that a higher proportion of AA/B SCT+ breast cancer patients undergoing surgery, radiation, or chemotherapy, respectively, experienced adverse events compared to AA/B SCT- and NHW SCT- patients. Of the 12 AA/B SCT+ patients who had surgery, 58.3% (n = 7) experienced one or more adverse event, of which 1 was potentially associated with SCT. Of the 38 AA/B SCT- patients who had surgery, 31.6% (n = 12) experienced one or more adverse event, of which 2 were potentially associated with SCT. Of the 38 NHW SCT- patients who had surgery, 15.8% (n = 6) experienced one or more adverse event, none of which were potentially associated with SCT.

Of the six AA/B SCT+ that had radiation therapy, 83.3% (n = 5) experienced one or more adverse event. Of the 29 AA/B SCT- patients that had radiation therapy, 37.9% (n = 11) experienced one or more adverse event (Table 1.2). Of the 25 NHW SCT- that had radiation therapy, 12.0% (n = 3) experienced one or more adverse event. No patients experienced an adverse event potentially associated with SCT. Of the 8 AA/B SCT+ patients who had chemotherapy, 75.0% (n = 6) experienced one or more adverse event, of which 4 were potentially associated with SCT. Of the 29 AA/B SCT- patients who had chemotherapy, 58.6%

(n = 17) experienced one or more adverse event, of which 3 were potentially associated with SCT. Of the 22 NHW SCT- patients who had chemotherapy, 31.8% (n = 7) experienced one or more adverse event, 1 of which was potentially associated with SCT. The potential sickling-related adverse events experienced following surgery and chemotherapy were hospitalization, treatment discontinuation, joint pain, and deep vein thrombosis (AA/B SCT+ only, n = 2). Overall, a descriptive presentation of results suggests that SCT+ breast cancer patients experience a larger proportion of potentially unique complications that carry with them clinical implications for treatment protocols.

1.3 Research Plan

1.3.1 Conceptual model

Based on the biologic plausibility of an association between SCT (and potentially other hemoglobinopathies) and adverse cancer outcomes, our conceptual model proposes an increase in tumor hypoxia among patients with SCT who are diagnosed with cancer. The sustained tumor hypoxia resulting from the cycle of RBC deoxygenation and sickling is positively associated with an aggressive tumor phenotype and resistance to radiation and chemotherapy, ultimately leading to lower rates of treatment completion, increased adverse events, and worse survival (Figure 1.2).

1.3.2 Specific Aims

In a sample of AA/B patients diagnosed with breast (female only) or prostate cancer with diagnosed hemoglobinopathies (AA/B +, n= 371) and a propensity score-weighted sample of patients without diagnosed hemoglobinopathies (AA/B -, n= 17,303; NHW-, n= 144,863), we pursued the following primary analyses:

Aim 1. Describe demographic and clinical characteristics of the three study groups (AA/B+, AA/B-, NHW-) such as age, comorbidities, AJCC 6th edition stage, histology, survival time, and treatment received by cancer site (breast, prostate).

Aim 2. Compare treatment completion (yes/no) across the three study groups by cancer site (breast, prostate) and stage.

Aim 3. Compare rates of specific adverse events (e.g., hospitalization, neutropenia, acute renal dysfunction, anemia, deep vein thrombosis, joint pain, cardiotoxicity) across the three patient groups after receipt of treatment.

Aim 4. Estimate differences in survival across the three patient groups (all-cause, site-specific, and competing-risk mortality).

2.0 Methods

2.1 Database

We used patient-level information from Medicare claims linked to population-based cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI). The SEER program collects cancer incidence, vital status, and clinicopathological data for patients and tumors from 18 geographic registries covering approximately 28% of the US population, including 26% (n = 9,975,844) of the AA/B population.[81] Contributing to the SEER program are nine states (New Mexico, Hawaii, Utah, Iowa, Connecticut, Greater California, Kentucky, Louisiana, New Jersey), five metropolitan areas (Metro Atlanta with a sample of rural Georgia, San Francisco-Oakland and San Jose-Monterey, Los Angeles, Seattle, Detroit), and the Alaska Native Tumor Registry. The SEER program is the gold-standard source of population-based cancer information in the US comprising patient demographics, clinical and diagnostic information (primary site, morphology, stage at diagnosis), and survival data.[81] Vital status for overall and cause-specific mortality are reported to SEER by the National Center for Health Statistics.[82] Quality control studies

(casefinding, reabstracting/recoding, reliability studies) are conducted in SEER areas annually and consistently demonstrate a standard for case ascertainment at 98%.[82]

Medicare is a federally funded fee-for-service single-payer health insurance program available to individuals in the US age 65 or older, people under age 65 with certain disabilities, and people with end-stage renal disease (ESRD).[83] As is the case in most analyses of SEER-Medicare data, our investigation is limited to the population 65 years or older because the Medicare population under 65 years is not representative of the general population (only comprised of disabled individuals and those with ESRD).[83] Medicare beneficiaries receive Part A hospital insurance which helps cover inpatient care and skilled nursing facilities, as well as hospice and home health care. Most Medicare beneficiaries also receive Part B medical insurance which helps cover provider services (doctors, nurse practitioners, physical and occupational therapists) and outpatient care. Part D prescription drug insurance helps cover prescription drug costs, and Part C (Medicare Advantage Plans) coverage consists of private health plans (i.e. HMOs) instead of Part A and Part B insurance. All Medicare beneficiaries are entitled to Part A hospital insurance, but there are monthly premiums associated with Part B and Part D coverage.[84] Original Medicare (Part A and Part B) has existed in some form since 1965, with the introduction of Part C in 1997, and Part D in 2006.[83,84]

The linkage between the SEER program and Medicare (SEER-Medicare) is performed by the NCI and the Centers for Medicare and Medicaid Services (CMS) via matching individual identifiers (social security number, name, sex, date of birth) in the SEER program to Medicare's master enrollment file.[83] The linkage has been completed nine times since 1991 and most recently in 2016. Approximately 93% of people 65 years or older identified in the SEER program are found in the Medicare enrollment file.[83] The full SEER-Medicare database consists

of multiple files, one of which is SEER program data while the others are Medicare files. Table 2.1 provides an overview of the SEER-Medicare data files requested and used for our research.

The SEER-Medicare database also includes information on a 5% random sample of Medicare beneficiaries residing in SEER program areas without a diagnosis of cancer to serve as a control group (SUMDENOM file in Table 2.1). Medicare files are available for this control group as well as demographic information, and are used in this research to compare comorbidity profiles in groups with cancer versus those without cancer.[83]

Since SEER-Medicare data are previously collected and de-identified, The University of Connecticut Health Institutional Review Board determined that this research did not constitute human subjects research and was exempt from review.

2.2 Cohort Selection

We identified individuals with a diagnosis of breast (female) or prostate cancer from 2007 to 2013 for inclusion in this investigation. We chose to restrict analysis to breast and prostate cancer because these cancers are the highest incident cancers in both the AA/B and NHW populations[1] and because they exhibit large and persistent disparities in cancer-specific mortality between AA/B and NHW patients.[3] We included patients for which female breast or prostate cancer was the first or only primary tumor. For breast cancer patients, we included only patients with histology consistent with epithelial origin. We included patients age 66 years or older in order to calculate comorbidities up to one year prior to cancer diagnosis. The cohort was limited to patients with a known month and year of diagnosis, not diagnosed on an autopsy report or diagnosis to ensure availability of follow-up information. We also required patients to have continuous Part A and B coverage from at least one year before through at least one year

after cancer diagnosis; we excluded patients with HMO coverage because no Medicare claims are available in the SEER-Medicare database for these patients.[83] We constructed three study groups based on race and a diagnosis of SCT or other hemoglobinopathy:

1. AA/B patients with a hemoglobinopathy diagnosis (AA/B+)
2. AA/B patients with no hemoglobinopathy diagnosis (AA/B-)
3. NHW patients with no hemoglobinopathy diagnosis (NHW-)

The complete cohort selection criteria diagrams for breast and prostate cancer are available in Appendix A. A total of 163,532 patients met the clinical selection criteria consisting of breast (female only) (n = 76,135; 46.6%) and prostate cancer (n = 87,397; 62.2%). Of the breast cancer patients, 6,919 (9.1%) were AA/B and 187 (2.7%) were found to have had at least one claim for a hemoglobinopathy. Of the prostate cancer patients, 10,755 (12.3%) were AA/B and 184 (1.7%) had at least one claim for a hemoglobinopathy. A total of 995 NHW patients (n = 502 breast cancer; n = 493 prostate cancer) with a hemoglobinopathy diagnosis were removed from primary analyses, but select sensitivity analysis including this group is presented in Appendix D. The final sample size for the study cohort was 162,537 patients (n = 75,633 breast cancer; n = 86,904 prostate cancer).

2.3 Data Elements

2.3.1 Hemoglobinopathies

We identified patients in the SEER-Medicare database with an International Classification of Disease (ICD-9) diagnostic code for any hemoglobinopathy (ICD-9: 282.4 – 282.7) over the course of the entire study period (2006-2014) (Table 2.2). A total of 18 distinct ICD-9 diagnosis codes were identified as hemoglobinopathies, which were further grouped into

four subcategories: sickle cell trait, sickle cell disease, thalassemia, and other hemoglobinopathies.

2.3.2 Demographic and clinical covariates

Patient characteristics incorporated into various analyses included: age at diagnosis, race (AA/B or NHW), year of diagnosis (2007 to 2013), geographic residence (SEER registry area), urban/rural residence, median household income (measured at the census tract and ZIP code levels), education (percentage of adults without a high school degree from census tract and ZIP code levels), marital status (married, single, other), and Charlson Comorbidity Index (CCI) score[85,86] (0, 1, ≥2). Tumor characteristics included in the SEER dataset are: AJCC 6th edition stage, tumor size (cm), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated), Gleason score (prostate cancer only), histological type (ductal, lobular, other) (breast cancer only), number of positive lymph nodes[iv], estrogen receptor status[v] (breast cancer only), and progesterone receptor status[vi] (breast cancer only).

Using a validated macro provided by the NCI, the CCI score was calculated from a weighted list of 16 conditions based on their respective hazard ratio of death within 1 year of cancer diagnosis[87]: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, cirrhosis, dementia, paralysis, diabetes, diabetes with sequelae, chronic renal failure, moderate to severe liver disease, rheumatologic disease, ulcers, connective tissue disorders, and AIDS. The CCI score is

[iv] Collaborative Stage (CS) Regional Nodes Examined
[v] Collaborative Stage (CS) Site-Specific Factor 1
[vi] CS Site-Specific Factor 2

calculated based on diagnoses for which associated medical claims appears from one year prior to cancer diagnosis through one month prior to cancer diagnosis.

2.3.3 Treatment regimen – breast cancer[vii]

A complete list of diagnosis and treatment codes for breast cancer is available in Appendix B.

Surgery

Surgery was defined from Medicare inpatient, outpatient, and carrier claims (ICD-9 procedure codes and HCPCS codes) for mastectomy or breast-conserving surgery (BCS) (including partial mastectomy or lumpectomy) received within six months of initial diagnosis.

Radiation

Radiation therapy was defined from Medicare outpatient and carrier claims (ICD-9 diagnosis and procedures codes, HCPCS codes, revenue center codes[91]) for external beam radiotherapy, intensity modulated radiotherapy, or brachytherapy received within nine months of initial diagnosis.

Chemotherapy

Chemotherapy was defined from Medicare inpatient, outpatient, carrier, and DME claims (ICD-9 diagnosis and procedure codes and HCPCS codes). Time to adjuvant chemotherapy was defined as days from the most definitive resection of the primary site to the first administration of chemotherapy. Length of adjuvant chemotherapy was defined as the number of months between the first and last claims indicating the use of chemotherapy, with the standard length

[vii] We identified surgery and radiation therapy from both SEER data and Medicare claims[88,89] and identified chemotherapy from Medicare claims.[90]

defined as 24 weeks or six months. For breast cancer patients with estrogen receptor positive and progesterone receptor positive disease, we also identified the use of hormone therapy using HCPCS codes.

2.3.4 Treatment regimen – prostate cancer

A complete list of diagnosis and treatment codes for prostate cancer is available in Appendix B.

Surgery

Surgery was defined from Medicare inpatient, outpatient, and carrier claims (ICD-9 procedure codes and HCPCS codes) for prostatectomy, laparoscopic radical prostatectomy with robotic assistance, with or without pelvic lymph node dissection received within 12 months of initial diagnosis.

Radiation

Radiation therapy was defined from Medicare outpatient and carrier claims (ICD-9 diagnosis and procedures codes, HCPCS codes, revenue center codes[91]) for external beam radiation, brachytherapy, image-guided radiation, stereotactic radiosurgery, or proton beam radiation therapy received within 12 months of initial diagnosis; for men who received surgery, receipt of radiation therapy was examined within 12 months of initial diagnosis or within nine to 12 months of surgery.[92,93]

Androgen Deprivation Therapy (ADT)

ADT was defined from Medicare outpatient and carrier claims (ICD-9 diagnosis and procedures codes, HCPCS codes, revenue center codes[91]) for orchiectomy and gonadotropin-

releasing hormone (GnRH) agonist received in combination with radiation therapy (within 12 months of initial diagnosis or within nine to 12 months of surgery).

2.3.5 Outcomes

Treatment Completion

Treatment completion was broadly defined based on National Comprehensive Cancer Network (NCCN) guidelines for breast and prostate cancer, respectively.[94,95] For stage I or II breast cancer, definitive surgical therapy was defined as receipt of BCS or mastectomy within six months of initial diagnosis, and receipt of radiation after surgery within nine months of initial diagnosis.[96] For stage I or II breast cancer patients who received chemotherapy, completion of adjuvant chemotherapy was defined as five consecutive months with at least one chemotherapy claim.[97,98] For Stage III breast cancer, treatment completion was defined as BCS or mastectomy, with radiation therapy following surgery, and adjuvant chemotherapy or hormone therapy (same guidelines as above). In breast cancer patients with HER2 positive receptor status, receipt of trastuzumab (Herceptin) and pertuzumab (Perjeta) was required for treatment to be defined as complete.[94] For stage IV breast cancer patients, treatment completion was defined as receipt of five consecutive months with at least one chemotherapy claim. For stage 0 breast cancer patients with ductal carcinoma in situ (DCIS), treatment completion was defined as receipt of BCS or mastectomy within six months of initial diagnosis. Breast cancer patients with stage 0 lobular carcinoma in situ (LCIS) and patients with unknown stage were excluded from analysis of treatment completion. For breast cancer patients who received surgery and who were indicated to receive chemotherapy, time from surgery to chemotherapy was calculated for each study group.

For prostate cancer, stage I cancer (T1 or T2a), treatment completion was defined as receipt of a prostate-specific antigen (PSA) blood test or prostate biopsy, radiation therapy, or prostatectomy within 12 months of initial diagnosis. For stage II cancer (T2b and T2c), treatment completion was defined as receipt within 12 months of initial diagnosis of radical prostatectomy with pelvic lymph node dissection or radiation therapy and receipt of ADT. For stage III cancer (T3), treatment completion was defined as radical prostatectomy and/or receipt of ADT or receipt of radiation therapy, or radical prostatectomy with receipt of PSA testing or prostate biopsy. Finally, for stage IV cancer, treatment completion was defined as any combination of therapy for stage III, with the addition of ADT therapy alone.[95]

Adverse Events

Adverse events were defined as specific clinical complications requiring hospitalization known to be associated with hemoglobinopathies including hematuria, renal papillary necrosis, acute chest syndrome, anemia, ischemia, thrombocytopenia, hyposthenuria, splenic infarction, rhabdomyolysis, hyphema, venous thromboembolism, priapism, leg ulcers, cholelithiasis, and stroke.[34] We also included other adverse events known to be associated with receipt of chemotherapy: infections, fever, nausea, leukopenia, diarrhea, dehydration/electrolyte abnormality, malnutrituion, malaise/fatigue, fractures, headaches, pulmonary conditions, disorders of lipid metabolism, diabetes, blood transfusion, nephrotoxicity, and cardiac events.[99]

In addition, we defined adverse events as those putatively related to sickle cell trait and other hemoglobinopathies based on case report evidence up to 12 months after cancer diagnosis. Adverse events included emergency room (ER) visits, neutropenic fever, shortness of breath, severe chest pain, diffuse body aches, hemiplegia, renal toxicity, hepatic toxicity, hemolysis,

severe back pain, myalgia, generalized joint pain, multiorgan failure, respiratory distress, hypoxia, dyspnea, mechanical ventilation, pulmonary embolism, vaso-occulsive crisis, and mucositis.[33,34,79]

A dichotomous indicator was created for each adverse event, and the total number of adverse events was calculated for each of the three study groups. A complete list of adverse event codes is available in Appendix B.

Mortality and Survival Time

Vital status is captured in SEER data and cause of death (COD) was categorized as site-specific (breast or prostate cancer) or other COD. Survival time was measured from the date of diagnosis until death or December 31, 2015 (end of follow-up). For site-specific survival, patients were censored if they were alive at the end of the study period or died of causes other than breast or prostate cancer, respectively. For competing risks survival, patients were censored if they were alive at the end of the study period and considered to have died from a competing cause if the cause of death was not breast or prostate cancer.

2.4 Statistical Analysis

2.4.1 Descriptive analyses

For each cancer site (breast and prostate), demographic and clinical patient characteristics were categorized (see section 2.3.2) and frequency distributions of categorical variables were compared in combined analysis using chi-square tests across the three comparison groups: AA/B+, AA/B-, NHW-. ANOVA (Kruskal Wallis non-parametric method) was performed for continuous variables across the three study groups.

2.4.2 Propensity score weighting

As in any observational study, the demographic, clinical, and treatment characteristics among AA/B+, AA/B-, and NHW- patients could be unequally distributed, resulting in a selection bias not fully controlled in multivariable 'adjusted' analyses. Hence, three-way propensity score weighting was performed for each cancer site (breast, prostate) to create similarly situated (i.e. balanced) comparison groups for subsequent estimation of treatment completion, adverse events, and survival. The generalized boosted model (GBM), a non-parametric machine-learning classifier with multiple iterative regression trees (10,000) was used to estimate the propensity score for each of the three comparison indicators using the *twang* package and *mnps()* function in R Studio v3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).[100] Separate GBMs were fitted to each comparison group and the probability of being in the AA/B+ group was estimated, adjusting for the aforementioned demographic and clinical characteristics, stratified by treatment completion status (i.e. two separate propensity score analyses performed among those who completed treatment and those who did not complete treatment; only stratified in estimation of adverse events and survival analysis). Inverse probability of treatment weighting (IPTW) was used to calculate the 'average treatment effect', or the average effect of having a hemoglobinopathy on a particular outcome.[100] Covariate balance was evaluated graphically (box plots showing the distribution of propensity score by group), as well as using the standardized population mean differences of <20% (Appendix C). Any imbalanced covariates still remaining after propensity score weighting were evaluated for clinical meaning and if differences were determined to be modest, they were included in doubly robust estimation.[100]

2.4.3 Power calculation

Based on the study cohort size of 162,537, with 371 total AA/B+ (n_B) patients, the sampling ratio for comparisons with 17,303 AA/B- patients (n_A) is represented as, $k_1 = \frac{n_A}{n_B} = 46.6$. The sampling ratio for comparisons with 144,863 NHW- patients (n_X) is represented as, $k_2 = \frac{n_X}{n_B} = 390.5$. Assuming a 25% baseline treatment failure rate, 50% baseline adverse event rate, and 5% mortality rate, our study will have sufficient power to analyze a range of effect size differences in outcomes:

	1%	5%	10%	15%	25%	50%	75%
Treatment failure	.051	.085	.190	.356	.734	.998	.999
Adverse event	.054	.161	.488	.828	.998	1.00	1.00
Mortality	.030	.061	.124	.219	.472	.930	.997

2.4.4 Estimation of treatment completion

Receipt of treatment and treatment completion status were compared across study groups (AA/B+, AA/B-, NHW-) using chi-square tests. Unadjusted and multivariable modified Poisson regression with robust error variance[101] was first performed to estimate the relative risk of chemotherapy treatment completion across study groups. Adjusted models accounted for demographic and clinical covariates (see section 2.3.2). Second, Poisson regression with robust error variance using the propensity weighted study cohort was applied to estimate the association between hemoglobinopathies and treatment completion.

2.4.5 Estimation of adverse events

Adverse events (yes vs. no) requiring hospitalization were compared across the three study groups (AA/B+, AA/B-, NHW-) using chi-square tests. Adverse events were characterized individually and, in order to account for small sample size, within each of the three groups: 1) adverse events potentially related to hemoglobinopathies based on case report evidence, 2) other adverse events potentially related to hemoglobinopathies, and 3) Other adverse events requiring hospitalization. Unadjusted and multivariable modified Poisson regression with robust error variance was first performed to estimate the relative risk of being hospitalized for any adverse event across the study groups. Adjusted models accounted for demographic and clinical covariates (see section 2.3.2). Second, modified Poisson regression with robust error variance using the propensity weighted study cohort was applied to estimate the association between hemoglobinopathies and adverse events, stratified by treatment completion status.

2.4.6 Survival analysis

The propensity score weighted study cohort was used to generate Kaplan-Meier curves for overall, site-specific, and competing risk survival. Cox proportional hazard regression using the propensity score weighted study cohort was applied to estimate the association between study group and overall-, cancer-specific, and competing risks survival. Patients were required to live up to six months after initial diagnosis to allow patients to survive long enough to initiate and/or complete treatment. Effect modification of the association between treatment completion and mortality by the occurrence of one or more adverse event and by study group was tested to investigate the potentially divergent mechanisms across study groups through which treatment completion and adverse events were associated with survival.

All statistical tests were two-sided with a significance level of $\alpha = 0.05$. As mentioned in section 2.4.2, propensity score weighting was performed in R Studio v3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

3.0 Results

3.1 Study Cohort

3.1.1 Patient characteristics

Of the 162,537 patients included in the analytic sample (Table 3.1), 75,633 (46.53%) were breast cancer patients and 86,904 (53.47%) were prostate cancer patients. Median age was 72 (IQR: 69 to 78) for AA/B+, 72 (IQR: 69 to 78) for AA/B-, and 74 (IQR: 69 to 79) for NHW-. A larger proportion of AA/B+ and AA/B- resided in metro areas (88.68% and 87.75%, respectively) compared to NHW- (81.43), omnibus p <.001. AA/B+ and AA/B- were more likely to be diagnosed with stage IV disease (9.97% and 8.71%, respectively) compared to NHW- patients (6.46%, omnibus p <.001). Among breast cancer patients, AA/B+ and AA/B- women were more likely to have tumors ≥4 cm, more likely to have poorly differentiated (grade 3) tumors, and more likely to have estrogen and progesterone receptor negative tumors compared to NHW- women (omnibus p <.001). Among prostate cancer patients, less than 1% of all patients (n = 845) had Gleason scores from 2 to 4; 56.09% (n=48,744) had scores from 5 to 7; and, 36.81% (n=31,990) had Gleason scores from 8 to 10. Significant differences across the three study groups were observed for all variables included in Table 3.1.

When analysis of variables listed in Table 3.1 was restricted to a comparison between AA/B+ and AA/B- patients, only two significant differences (data not shown) emerged: SEER

Registry Area (p =.008) in that AA/B+ were more likely to reside in the Midwest and less likely to reside in the South compared to AA/B-); and, the Charlson Comorbidity Index (CCI) score (36.66% of AA/B+ had a CCI score ≥3 compared to 22.97% for AA/B-; p <.001).

We estimated the prevalence of specific hemoglobinopathies in the analytic study cohort, prior to excluding NHW+ patients (n = 995). As seen in Appendix D, the proportion of patients with any hemoglobinopathy was 2.10% (n = 371 of 17,674) for AA/B patients and 0.68% (n = 995 of 145,858) for NHW patients. Overall, the prevalence of every hemoglobinopathy disorder/variant was more common among AA/B patients compared to NHW patients. Among AA/B patients, SCT was the most prevalent hemoglobinopathy. The prevalence of SCT was 0.78% (n = 137 of 17,674) for AA/B patients and 0.03% (n = 40 of 145,858) for NHW patients. These estimates varied somewhat by cancer type for AA/B patients; the prevalence of SCT was 1.11% (n = 77 of 6,919) among AA/B breast cancer patients compared to 0.56% (n = 60 of 10,755) among AA/B prostate cancer patients. The most prevalent hemoglobinopathy among NHW patients was "other hemoglobinopathies" comprising hemoglobin C and hemoglobin E disease.

To ensure that the prevalence estimates of hemoglobinopathies in our analytic study cohort were not subject to selection bias, we estimated the prevalence of hemoglobinopathies in the SEER-Medicare database prior to having applied exclusions to create the analytic study cohort (e.g., requirement to be age 66 or older in order to have co-morbidity data in the preceding year and continuous fee-for-service coverage from one year prior through one year after cancer diagnosis), and found no appreciable difference in prevalence estimates (<0.1% difference) (data not shown).

The distribution of the CCI score by study group is depicted in Figure 3.1. We found that AA/B+ patients had significantly higher mean CCI scores (2.30, 95% CI: 2.08 to 2.52) compared to AA/B- patients (1.54, 95% CI: 1.51 to 1.56) and NHW- patients (1.01, 95% CI: 1.00 to 1.02), respectively (omnibus p <.001). A larger proportion of AA/B- (37.38%) and NHW- (41.01%) patients had no comorbidities diagnosed in the 12 months prior to cancer diagnosis compared to AA/B+ patients (22.91%), while a larger proportion of AA/B+ patients had a CCI score of five or more (16.44%) compared to AA/B- (7.67%) and NHW- (5.93%) patients (Figure 3.1).

Regarding specific comorbidities (Table 3.2), statistically significant (all p <.05) differences were observed by study group among each of the selected comorbidities (e.g., myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, paralysis, diabetes, diabetes with sequelae, chronic renal failure, moderate to severe liver disease, ulcers, connective tissue disorders, AIDS). When analysis was restricted to comparisons between AA/B+ vs. AA/B- patients (Table 3.2), we found that AA/B+ patients were more likely than AA/B- to have a history in the 12 months prior to diagnosis of myocardial infarction (2.96% vs. 1.46%), congestive heart failure (20.75% vs. 12.60%), cerebrovascular disease (18.06 vs. 13.73%), chronic obstructive pulmonary disease (COPD) (23.72% vs. 17.91%), diabetes (55.53% vs. 38.81%), diabetes with sequelae (22.10% vs. 12.81%), chronic renal failure (25.34% vs. 14.08%), ulcers (3.50% vs. 1.78%), and connective tissue disorders (6.20% vs. 3.24%).

3.1.2 Treatment receipt

Receipt of treatment was stratified by tumor site. For breast cancer patients (Table 3.3), a total of 65,162 (86.16%) of patients received surgery. Rates of breast-conserving surgery (BCS)

were lower among AA/B+ (47.59%) and AA/B- (45.81%) patients compared to NHW- patients (57.3%) (omnibus p <.001), but there were no statistically significant differences between AA/B+ and AA/B- patients in receipt of surgery or the type of breast surgery, regardless of AJCC stage or CCI Score. A similar pattern was observed for radiation therapy, in that both AA/B+ and AA/B- were less likely to receive radiation therapy compared to NHW- (44.39% for AA/B+, 41.25% for AA/B-, 50.12% for NHW-, omnibus p <.001), yet no statistically significant difference was observed between AA/B+ and AA/B-. The rate of receipt of any chemotherapy was slightly higher among AA/B+ (31.02%) and AA/B- (29.96%) breast cancer patients compared to NHW- (25.87%) patients (omnibus p <.001), but again, no significant differences emerged between AA/B+ and AA/B- patients. Less than 5.0% of patients within each study group received neoadjuvant chemotherapy.

Among prostate cancer patients (Table 3.4), a total of 61,760 (71.07%) patients received initial curative therapy, defined as receipt of prostatectomy, radiation, ADT, or chemotherapy within 180 days of diagnosis. AA/B- were less likely than NHW- to receive initial curative therapy (67.51% vs. 71.56%, respectively, p <.001), but rates for AA/B+ (70.11%) did not differ significantly from the other two study groups. A total of 16,561 (19.06%) of patients received prostatectomy (including laparoscopic radical prostatectomy with robotic assistance). Rates of surgery were significantly higher in AA/B- (13.59%) and AA/B+ (12.21%) compared to NHW- (20.02%) (p <.001), but there was no statistically significant difference between AA/B+ and AA/B- patients. No significant differences in receipt of radiation therapy were observed between the study groups (p =.53). Overall, 29,699 (34.17%) prostate cancer patients received ADT within 12 months of diagnosis; AA/B- were slightly more likely to receive ADT compared to NHW- (35.99% vs. 33.91%, respectively, p <.001), but AA/B+ patients (39.67%) did not differ

significantly in receipt of ADT compared to the other two study groups. Finally, the rate of receipt of chemotherapy within 12 months of diagnosis was significantly higher among AA/B+ (42.93%) and AA/B- (37.14%) compared to NHW- (35.32%) (p =.03 and p <.001, respectively), but again, no significant differences emerged between AA/B+ and AA/B- patients (p =.10).

3.2 Treatment Completion

Of the 75,633 breast cancer patients included in the study cohort, a total of 71,078 (93.98%) patients had sufficient data on stage at diagnosis to determine whether treatment was completed based on NCCN guideline criteria. For prostate cancer, a total of 81,325 (93.58%) patients had sufficient data on stage at diagnosis to determine whether treatment was completed based on NCCN guideline criteria. Therefore, a total of 152,403 patients were evaluated for treatment completion by stage.

Among breast cancer patients, AA/B+ and AA/B- patients had lower rates of treatment completion compared to NHW- (44.38% vs. 45.40% vs. 52.84%, respectively, omnibus p <.001) (Table 3.5). This pattern remained consistent when treatment completion was stratified by stage. Stage II breast cancer AA/B+ patients were marginally less likely than AA/B- stage II breast cancer patients to complete treatment (22.92% vs 34.81%, p = .08). Cell sizes <11 for AA/B+ with stage III and stage IV breast cancer prevented comparison with AA/B- and NHW- patients.

Among prostate cancer patients, AA/B+ and AA/B- patients had slightly lower overall rates of treatment completion compared to NHW- (75.74% vs. 74.90% vs. 77.46%, respectively, omnibus p <.001), driven by the high completion rates in patients with stage I (T1 and T2a) disease (Table 3.6). For stage II cancer, AA/B+ and AA/B- patients were less likely to complete treatment compared to NHW- (37.04% vs. 33.47% vs. 43.52%, respectively, omnibus p <.001).

Cell sizes <11 for AA/B+ with stage III and stage IV breast cancer prevented comparison with AA/B- and NHW- patients, but AA/B- experienced dramatically lower rates of treatment completion compared to NHW- patients (stage III AA/B-: 43.37% vs. NHW-: 64.75%, p <.001; stage IV AA/B-: 59.40% vs. NHW-: 71.92%, p <.001).

Table 3.7 displays the unadjusted and adjusted (both multivariable adjusted and propensity score weighted) relative risk of incomplete treatment by study group for all patients and stratified by tumor site. In unadjusted analysis, AA/B+ and AA/B- breast cancer patients had significantly higher risk of incomplete treatment compared to NHW- patients; this effect remained significant among AA/B- patients in multivariable adjusted analysis (RR: 1.05, 95% CI: 1.043 – 1.08, p <.001), but was attenuated and did not remain significant in propensity score weighted analysis (RR: 1.01, 95% CI: 0.96 – 1.05, p = .82). Pairwise comparisons between AA/B+ and AA/B- patients revealed no significant differences in adjusted risk of treatment completion, overall or by tumor site (data not shown).

AA/B- prostate cancer patients were significantly less likely to complete treatment compared to NHW- patients in unadjusted, multivariable adjusted, and propensity score weighted analysis (propensity score weighted RR: 1.17, 95% CI: 1.12 – 1.22, p <.001), but no statistically significant differences in risk of incomplete treatment were observed between AA/B+ vs. NHW- patients (Table 3.7). Pairwise comparisons between AA/B+ and AA/B- patients revealed no significant differences in adjusted risk of treatment completion, overall or by tumor site (data not shown). Details and diagnostic assessment of the propensity score weighted analysis are presented in Appendix C.

3.3 Adverse Events

Patients who received treatment were evaluated for the incidence of adverse events requiring hospitalization during follow-up (Table 3.8). A total of 69,531 (91.9%) breast cancer patients and 65,505 (75.4%) prostate cancer patients received treatment after cancer diagnosis, defined as receipt of any surgery[viii], radiation, chemotherapy, hormone therapy, or ADT. Over half of the breast cancer patients who received no treatment were diagnosed as stage IV or with unknown stage, and approximately 60% of the prostate cancer patients were received no treatment were diagnosed as stage I (T1 or T2a), where watchful waiting or active surveillance (PSA test and/or prostate biopsy) is recommended, particularly for older patients with expected survival <20 years.[95]

Overall, 89,479 treated patients (66.26%) experienced at least one adverse event requiring hospitalization; nearly half of all treated patients had an emergency room visit (n = 64,165; 47.52%). Of the 81,797 patients who received surgery, 9,969 (12.19%) experienced an adverse event within 90 days; AA/B+ (15.64%) and AA/B- (14.37%) patients were more likely to experience an adverse event following surgery compared to NHW- (11.99%) patients (omnibus p <.001), but there was no significant difference between AA/B+ and AA/B- patients (p= .63). A similar trend was observed for adverse events occurring within 6 months following receipt of chemotherapy or ADT (Table 3.8). When adverse events were categorized into three groups (known associations with hemoglobinopathies, putative associations with hemoglobinopathies, known toxicity associated with cancer therapy) (Table 3.8, Figure 3.2), we observed that AA/B+ had a significantly higher proportion of adverse events in all three categories compared to both AA/B- and NHW- patients (each p <.001). In addition, AA/B+

[viii] Breast cancer: receipt of BCS or mastectomy within 6 months of diagnosis; Prostate cancer: receipt of prostatectomy within 12 months of diagnosis.

patients had a significantly higher proportion of emergency room visits compared to NHW- patients, and a marginally significantly higher proportion of emergency room visits compared to AA/B- patients (p =.065).

Among all treated patients, AA/B+ had increased propensity score weighted risk of experiencing one or more adverse event compared to both AA/B- (RR: 1.15, 95% CI: 1.07 – 1.24, p <.001) and NHW- (RR: 1.18, 95% CI: 1.10 – 1.26, p <.001) (Table 3.9). The magnitude and significance of this relationship was similar for breast and prostate cancer patients (Table 3.9).

Among breast cancer patients who completed treatment (Table 3.10), the risk of experiencing one or more adverse event requiring hospitalization or an emergency room visit was 1.18 times higher for AA/B+ patients vs. NHW- (multivariable adjusted 95% CI: 1.06 – 1.32, p =.002; propensity score weighted 95% CI: 0.98 – 1.42; p=.084). Likewise, AA/B+ patients also were 1.17 times more likely than AA/B- to have experienced an adverse event requiring hospitalization or ER visit (multivariable adjusted 95% CI: 1.05 – 1.31, p =.004; propensity score weighted 95% CI: 0.97 – 1.41, p=.098). In contrast, no significant differences in risk of hospitalization were observed between AA/B- and NHW- patients.

For prostate cancer patients who completed treatment (Table 3.10), a statistically increased risk of an adverse event requiring hospitalization or ER visit was observed in all analyses for AA/B+ patients compared to NHW- and AA/B- patients. Specifically, the propensity score weighted risk of experiencing one or more adverse events was 1.22 times greater for AA/B+ vs. NHW- (95% CI: 1.09 – 1.36, p <.001). The propensity score weighted risk of experiencing one or more adverse events was 1.17 times greater for AA/B+ vs. AA/B- (95% CI: 1.06 – 1.31, p =.003) for prostate cancer patients who completed treatment. AA/B- patients

were at small but significantly increased risk for adverse events compared to NHW, in both propensity score weighted (RR: 1.04, 95% CI: 1.01 – 1.07, p =.020) and multivariable adjusted (RR: 1.05, 95% CI: 1.03 – 1.07, p <.001) analysis.

Among breast cancer patients who did not complete treatment (Table 3.11), AA/B+ patients had increased propensity score weighted risk of adverse events compared to both NHW- (RR: 1.14, 95% CI: 1.01 – 1.26, p =.018) and AA/B- (RR: 1.13, 95% CI: 1.02 – 1.25, p =.024) patients. No statistically significant differences were observed between AA/B- and NHW- patients in adjusted analysis.

Among prostate cancer patients who did not complete treatment (Table 3.11), AA/B+ patients had increased multivariable adjusted risk of adverse events compared to both NHW- (RR: 1.18, 95% CI: 1.06 – 1.31, p =.002) and AA/B- (RR: 1.15, 95% CI: 1.03 – 1.28, p =.009), but these effects did not remain statistically significant in propensity score weighted analysis. No statistically significant differences were observed between AA/B- and NHW- patients in adjusted analysis.

3.4 Survival

3.4.1 Mortality and Kaplan-Meier Survival Curves

Median follow-up time was 53 months (IQR: 33 - 77) and 59 months (IQR: 37 - 82) for breast and prostate cancer patients, respectively. Of those surviving to the end of the study period, median follow-up time was significantly different across study groups in both cancer sites. That is, for surviving breast cancer patients, median follow-up time was 59.5 months (IQR: 45 to 85) for AA/B+, 60 months (IQR: 40 to 81) for AA/B-, and 62 months (IQR: 42 to 83) for NHW-. For corresponding prostate cancer patients, median follow-up time was 68 months (IQR: 47 to 88) for AA/B+, 65 months (IQR: 46 to 86) for AA/B-, and 67 months (IQR: 47 to 88) for NHW-. It is unlikely that differences in follow-up time among surviving patients across study groups represent clinically meaningful difference in the adequacy of the follow-up time.

Regarding mortality among breast cancer patients, 57 AA/B+ (30.48%), 6,732 AA/B- (36.41%), and 19,230 NHW- (27.99%) patients died during the study period (omnibus p <.001) (Table 3.12). AA/B- were more likely to die from both breast cancer and competing causes compared to NHW (p <.001), but no significant differences were observed between AA/B+ and NHW- or between AA/B+ and AA/B-. Overall, 2-year and 5-year survival differed only between AA/B- and NHW- patients (Table 3.12).

Among prostate cancer patients (Table 3.12), a total of 75 AA/B+ (40.76%), 3,310 AA/B- (31.31%), and 19,507 NHW- (25.62%) patients died during the study period (omnibus p <.001). Furthermore, pairwise comparisons revealed that the rate of AA/B+ mortality was higher than both AA/B- (p =.006) and NHW- (p <.001) groups. Regarding cause-specific death, proportionately more AA/B+ patients died from prostate cancer (n = 17, 9.24%) compared to NHW (n = 4,201, 5.52%, p =.004) and AA/B- patients (n= 783, 6.98%), but the AA/B+ vs.

AA/B- difference did not reach statistical significance (p =.10). Similarly, proportionately more AA/B+ patients died from other causes (n = 58, 31.52%) compared to NHW (n = 15,306, 20.10%), p <.001) and AA/B- patients (n= 2,572, 24.33%, p =.013).

Two-year and 5-year survival rates (Table 3.12) were significantly higher (all p <.001) among NHW- prostate cancer patients (2-year: 92.74%, 5-year: 79.90%) compared to both AA/B- (2-year: 90.06%; 5-year: 74.59%, respectively) and AA/B+ patients (2-year: 87.43%, 5-year: 67.95%, respectively). In contrast, no statistically significant differences were observed between AA/B+ and AA/B- patients. Unadjusted and propensity score weighted Kaplan-Meier curves illustrating the aforementioned 2-year and 5-year survival patterns per outcome (i.e., all-cause, cancer-specific, and non-cancer deaths) are presented for breast cancer (Figure 3.3) and prostate cancer (Figure 3.4).

3.4.2 Cox Proportional Hazards Survival Analyses

The propensity scores generated for use in Cox proportional hazards models included demographic characteristics (age, year of diagnosis, marital status, SEER region, income, and education) as well as stage, CCI score, and number of positive lymph nodes. For breast cancer patients, additional covariates were tumor grade, tumor size, histology, estrogen receptor status, progesterone receptor status, and HER2 receptor status. For prostate cancer patients, the propensity score model included Gleason score.

While the propensity score weighted hazards models failed to reveal significant differences in mortality risk across study groups, the magnitude of the associations with mortality in relation to either treatment completion (no vs. yes) or adverse events (≥1 vs 0) significantly varied by hemoglobinopathy status Specifically, as depicted in Figure 3.5, the risk

of mortality among AA/B+ patients was 1.29 (95% CI: 1.23 – 1.36, p <.001) times greater among those who failed to complete treatment compared to those who completed treatment, yet the relative difference in mortality was greater in both AA/B- and NHW- groups (HR: 2.05, 95% CI: 1.96 – 2.15, p <.001); HR: 2.32, 95% CI: 2.22 – 2.43, p <.001; respectively).

Regarding adverse events and mortality (Figure 3.6), the risk of mortality among AA/B+ patients was 4.78 (95% CI: 4.23 – 5.41, p <.001) times greater among patients experiencing one or more adverse event compared to those who did not experience an adverse event. Unlike the trend for treatment completion analyses, however, the adverse event-mortality effect was attenuated significantly among both AA/B- (HR: 3.28, 95% CI: 3.06 – 3.51, p <.001) and NHW- patients (HR: 3.16, 95% CI: 2.96 – 3.37, p <.001). Compared to NHW-, AA/B+ had a 1.13 (95% CI: 1.08 – 1.18) times higher risk of mortality if they completed treatment and experienced 1 or more adverse event. Compared to AA/B-, AA/B+ had a 1.11 (95% CI: 1.06 – 1.16) times higher risk of mortality if they completed treatment and experienced 1 or more adverse event.

4.0 Discussion

4.1 Summary of Key Findings

In this retrospective cohort study of patients diagnosed with breast (female) and prostate cancer from 2007 to 2013 in the SEER-Medicare linked database, we found that AA/B patients diagnosed with hemoglobinopathies experienced higher rates of adverse outcomes compared to similarly situated AA/B and NHW cancer patients not diagnosed with hemoglobinopathies. Specifically, we found that compared to AA/B- and NHW- patients, AA/B+ patients experienced increased risk of one or more adverse event requiring hospitalization following treatment initiation, and the risk of mortality was significantly higher among AA/B+ patients who experienced one or more adverse event compared to AA/B- and NHW- patients who experienced one or more adverse event.

We observed significant differences across patient, clinical, and tumor characteristics by study group, but apart from SEER region and CCI score, these differences were driven by race; AA/Bs, regardless of hemoglobinopathy status, were more likely to be diagnosed with cancer at younger ages (66 – 74), reside in a metro area, have a lower median household income, not married, and diagnosed with stage IV disease. Among breast cancer patients, AA/Bs had larger tumors ≥4 cms (breast cancer), poorly differentiated grade tumors (breast cancer), and had higher proportions of estrogen and progesterone receptor status negative cancers.

The observed differences between AA/B+ and AA/B- revealed that AA/B+ patients were more likely to reside in the Midwest and less likely to reside in the South compared to AA/B- patients. In addition, AA/B+ patients had a significantly lower proportion of CCI scores of 0, and significantly higher proportion of scores of 4 and 5 or more, compared to NHW- and AA/B-. When differences in individual comorbidities were compared across study groups, myocardial

infarction, congestive heart failure, diabetes, diabetes with sequelae, chronic renal failure, and ulcers were significantly more common not only among AA/B+ compared to NHW-, but among AA/B+ compared to AA/B- as well. When differences across comorbidities were further divided across specific hemoglobinopathy groups (SCT, SCD, thalassemia, other), we found that SCT was primarily responsible for the observed group differences. Finally, NHW patients who appeared in the dataset as having a hemoglobinopathy (NHW+) did not follow the same trend (Appendix D).

While no statistically significant differences were found in the adjusted risk of treatment completion between AA/B+ cancer patients compared to NHW- or AA/B- patients, respectively, we found that AA/B- prostate cancer patients had an estimated 17% increased risk (95% CI: 12% to 22%, p <.001) of incomplete treatment compared to NHW- patients. It is possible that the AA/B+ study group lacked the statistical power needed to detect a true effect if it existed. Irrespective of power considerations, no statistically nor clinically meaningful differences emerged between AA/B+ vs. AA/B- in regards to treatment completion, which could reflect actual clinical practice, or could be an artifact of how treatment completion was defined in our analysis.

The overall proportion of adverse events requiring an emergency room visit or hospitalization experienced among patients who initiated treatment was significantly higher among AA/B+ compared to both NHW- and AA/B-. Approximately 28% of all AA/B+ patients experienced 3 or more adverse events, compared to only 15% and 13% in AA/B- and NHW-, respectively. In addition, AA/B+ patients were significantly more likely to experience adverse events known or putatively known to be associated with hemoglobinopathies as well as other chemotherapy-related adverse events. The adjusted risk of experiencing one or more adverse

event was approximately 14% higher for AA/B+ compared to both AA/B- and NHW- breast cancer patients who failed to complete treatment; while this effect was not significant among prostate cancer patients who failed to complete treatment, a 17% and 22% increased risk of one or more adverse event was observed for AA/B+ prostate cancer patients who did complete treatment compared to AA/B- and NHW- patients, respectively. The relative risk of adverse events was marginally increased among AA/B+ compared to AA/B- and NHW- breast cancer patients who completed treatment (17% and 18%, respectively). When the requirement for having initiated treatment was removed and adverse events were explored in the entire study population (n = 162,537), AA/B+ had 17% increased risk of experiencing one or more adverse event compared to NHW- (95% CI: 10% to 26%, p <.001) and a 15% increased risk compared to AA/B- (95% CI: 8% to 24%, p <.001). This effect remained consistent when adverse events were isolated to inpatient hospitalizations, suggesting that AA/B+ cancer patients are not only more likely to experience a larger proportion of adverse events, but also more severe adverse events compared to AA/B- and NHW- patients across the entire spectrum of cancer care.

To test the underlying assumption that adverse events were treatment-related and not just due to existing comorbidities or an unobserved confounding factor, we examined the risk of adverse events, stratified by CCI score (Figure 4.1). Among patients with no comorbidities, AA/B+ patients experienced 35% increased risk of experiencing one or more adverse event compared to NHW- (95% CI: 15% to 60%). This trend was attenuated (e.g., 18% (95% CI; 6% to 30%) for CCI=1; 26% (95% CI: 16% to 38%) for CCI=2; 6% (1% to 28%) for CCI=3; 4% (1% to 14% for CCI=4), but remained significant across CCI Scores, and was proportionately higher than the association between AA/B- compared to NHW- across CCI Scores from 0 to 2. (Figure 4.1).

In propensity score weighted survival analysis, no apparent overall survival differences emerged between AA/Bs (independent of hemoglobinopathy status) and NHW-. When we explored potential factors through which each study group experienced mortality, however, treatment completion and adverse events were identified as significant effect modifiers. Specifically, while patients in all three study groups who experienced at least one adverse event were far more likely to die compared to those with no reported events, the relative difference in mortality was highest within the AA/B+ patient group. In contrast, when comparing mortality risk among AA/B+ patients who did not complete treatment versus those who did, the relative difference was the lowest among the three study groups. A coherent explanation for these divergent patterns of effect modifications might be that while AA/B+ patients might be just as likely to fail to complete treatment as AA/B- and NHW- patients, the specific reasons for discontinuation among AA/B+ patients confer a greater risk of mortality. By extension, we posit that the higher risk of AA/B+ patients to experience one or more adverse events suggests that these events are comparatively deadlier to AA/B+ compared to AA/B- and NHW- patients. Our findings suggest, therefore, that occurrence of an adverse event poses a more serious threat to mortality than does not completing treatment.

This interpretation also is supported by the variation in the magnitude of the interaction between treatment completion and adverse events across the study groups (Figure 4.2). Among AA/B+ patients who completed treatment, those who experienced one or more adverse events had more than five times the risk of dying than those for whom there were no reports of adverse events whereas the estimated relative risks of mortality among AA/B- and NHW- patients were about three-fold. Among patients who failed to complete treatment, however, the relative risks of

mortality for patients experiencing one or more adverse events was similar across groups (HRs of 2.64 to 3.28 with overlapping 95% CIs.

4.2 Consistency with Existing Evidence and Biologic Plausibility

This research presents the first observational, population-based study investigating the association between inherited hemoglobinopathies and cancer outcomes, and as such there is limited existing evidence to compare for consistency. On a broad scale, studies investigating racial disparities in cancer outcomes can be used as a benchmark to compare the magnitude of treatment completion, adverse events, and survival outcomes. Our results can also be put into context with other observational studies measuring the impact of SCT and other hemoglobinopathies on a variety of chronic conditions and diseases including chronic kidney disease[38], stroke[39], and pulmonary embolism[40]. Existing evidence for the association between hemoglobinopathies and cancer outcomes is limited to a collection of case reports published by Swede et al. in 2014[11] and the preliminary chart review conducted using the CTR (See Section 1.2). Our results are consistent with case report evidence among patients with SCT, SCD, and other combinations of hemoglobin variants who were diagnosed with cancer and receiving therapy, which revealed instances of painful crises and other adverse effects requiring hospitalization including neutropenia, pulmonary embolism, renal toxicity, respiratory distress, and multi-organ failure. Our results are also consistent with findings from a preliminary chart review in breast cancer patients undergoing treatment which suggested that women with SCT experienced a higher proportion of total adverse events compared to women without SCT.

The biologic mechanisms underlying the association between hemoglobinopathies and cancer-related adverse events are not well defined, but we propose that cancer patients with inherited hemoglobinopathies, particularly SCT, are at increased risk for adverse events when

exposed to physiologic stressors. Stressors in the form of existing tumor hypoxia, surgery, radiotherapy, or systemic chemotherapeutic agents may lead to RBC sickling, vaso-occulsive crises, and a host of additional complications. Evidence from case reports and *in vivo* animal studies suggest that intravascular sickling within the tumor microenvironment may be promoted by acidosis and results in increased hypoxia. Sickle cells are considered in the literature as a site-specific contrast agent due to their propensity to preferentially accumulate in the tumor vasculature through impaired blood flow and oxygenation, but this may ultimately result in vascular hemolysis, vaso-occulsion, and further hypoxia and organ damage.[102] Via upregulation of HIF-1, hypoxia induces expression of genes that drive tumor growth (by promoting angiogenesis), proliferation, and metastatic potential.[103] Pretreatment tumor hypoxia is a known prognostic factor for survival after treatment with radiation alone or in combination with surgery or chemotherapy, and combined treatments are demonstrably less effective in hypoxic tumors.[104] From a mechanistic perspective, hypoxia confers treatment resistance by inhibiting apoptosis and producing quiescent, stem-cell like cell fractions least affected by anticancer treatments targeting rapidly proliferating cells. In addition to disrupting the cellular environment, the hypoxic microenvironment facilitates tumor growth via angiogenesis, leading to suppression of anti-tumor immune cells and escape from immune surveillance.[103] Multiple studies have found sickled RBCs target the hypoxic tumor vascular microenvironment and subsequently include vaso-occlusion, autohemolysis leading to endothelial injury.[60,61] In a small study comparing 10 SCD vs. 10 wild-type mice, the tumor growth rate was accelerated in SCD mice compared to wild-type, enhanced by HO-1 activity and angiogenesis.[60]

In addition to tumor hypoxia, we propose the associations between hemoglobinopathies and other conditions including chronic kidney disease, diabetes, and pulmonary embolism play a

role in the occurrence of adverse events requiring hospitalization among cancer patients. While our results suggested that AA/B+ have increased risk of adverse events compared to NHW-and AA/B- across CCI scores, there is evidence to suggest that the specific type of comorbidity may impact outcomes. For example, the prevalence of comorbid diabetes in our study was significantly higher among AA/B+ (55.5%) compared to AA/B- (38.8%) and NHW- (24.3%). In the epidemiological literature, diabetes has been found to be associated with significantly higher all-cause mortality across all types of cancer, and higher cancer-specific mortality in patients diagnosed with cancer of the breast, endometrium, and colorectum.[105,106] The association between diabetes and cancer mortality persists even after adjustment for age, BMI, physical activity, and other dietary factors.[107] From a biological perspective, the association between diabetes and cancer mortality could be explained indirectly via the shorter overall life expectancy among individuals with diabetes.[108] More direct associations include hyperglycemia, and to a lesser extent, impaired immune function and/or pro-inflammatory conditions, known to be associated with tumor cell proliferation and survival.[107,109]

In addition to diabetes, recent observational studies have documented independent associations between SCT and chronic kidney disease[38], stroke[39], ESRD[37], and pulmonary embolism[40]. Among patients with no comorbidities in our study, we found that the risk of experiencing a pulmonary embolism or venous thromboembolism was significantly higher among AA/B+ compared to both AA/B- and NHW-, but did not find any significant increase in the risk of renal failure or stroke in AA/B+ compared to AA/B- or NHW-. We did find, however, that AA/B+ had an increased risk of heart failure and other cardiovascular complications, as well as anemia, pain, respiratory dysfunction, and emergency room visits compared to AA/B- and NHW- (Appendix D). A recent meta-analysis of 4 different US population-based cohorts

concluded that the presence of SCT was not associated with an increased risk of heart failure or alterations in cardiac structure or function[110], so further investigation may be warranted to better understand the relationship between hemoglobinopathies and cardiovascular-related events in the context of cancer. For thromboembolism, the coagulation pathway is activated by elevated levels of d-dimers and monocytes in SCT carriers, which in turn poses an increased risk of vaso-occlusive crises among patients with sickle cell disease.[111] Dirix et al. (2002) found that plasma levels of d-dimers are associated with cell proliferation and tumor growth, metastatic potential, and shorter overall survival in breast cancer patients. Our results provide indirect evidence to support the association between hemoglobinopathies and thromboembolism in the setting of cancer, and suggest that the development of thrombosis may reflect the presence of a biologically more aggressive cancer that in turn leads to a worse prognosis. Further exploration into the potential pathways through which SCT and thromboembolism interact to impact cancer outcomes may be important for understanding the overall burden of thrombosis in cancer, given that cancer patients account for 20% of all patients with venous thromboembolism and thrombosis is believed to account for 9% of all cancer-related deaths.[112]

4.3 Strengths and Limitations

The utilization of SEER-Medicare database is the greatest strength of this study, as it is a population-based cancer database that contains information on hemoglobinopathy diagnosis from medical claims. Data from SEER has the benefit of very low loss to follow-up and contains detailed tumor characteristics and cause of death. The Medicare database provides a near 100% linkage to individuals appearing in the SEER program, which increases the external validity of the study in regards to generalizability of the results to the US elderly population.

The primary limitation regarding the use of administrative claims to identify hemoglobinopathies is the potential for misclassification bias; in the general population, many individuals with hemoglobinopathy variants, particularly SCT, are unaware of their status. This is reflected in the low prevalence of SCT and other hemoglobinopathies in our study cohort, particularly for AA/B (1.74% for hemoglobinopathies; 0.63% for SCT), where the population prevalence is estimated to be approximately 8% and has been confirmed in other observational studies investigating the association between SCT and health outcomes.[38] Further, it is likely that a proportion of patients in our study were incorrectly classified as not having a hemoglobinopathy, since diagnosis depended on having a claim for the condition. This limitation, however, would bias our comparisons between AA/B+ and AA/B- study groups towards the null.

Another limitation in this observational study is the potential for selection bias and confounding by unobserved variables such as performance status (e.g. activities of daily living status, functional status, and patient quality of life) used to summarize ability of a patient to tolerate aggressive treatment, current smoking status, body mass index, various metabolic functions, and treatment dose adjustments. For example, it is possible that patients with hemoglobinopathies and associated conditions (i.e. renal failure) are subject to more dose adjustments during cancer therapy compared to patients without hemoglobin variants[113], which could bias results either away from or towards the null. Based on our hypothesis that increased tumor hypoxia is the primary mechanism through which patients with hemoglobinopathies experience worse clinical outcomes, another important limitation of this study is the absence of tumor hypoxia assessment. Since our diagnosis data are based on administrative claims, it is likely that we underestimated comorbidities even though we captured comorbidity claims during

the 12 months prior to diagnosis. Our study was also limited to individuals ages ≥66 and those with continuous Medicare Part A and B/non-HMO coverage, potentially limiting the overall generalizability of results to the entire older adult population, although there is evidence to suggest comparable diagnosis and treatment characteristics between managed care and fee-for-service plans.[114]

Finally, this study lacked adequate sample size and power to investigate the association between hemoglobinopathies and adverse cancer-related outcomes in individuals with genetic ancestry other than AA/B and NHW, specifically individuals with Southeast Asian and Middle Eastern ancestry. The increase among immigrant populations in the US from Asian and Arab countries with high prevalence of hemoglobinopathies suggest our results may be applicable to other races, but our study did not have sufficient sample size to perform these analyses. Further, in many studies that deliberately investigate cancer outcomes in racial minorities, Asian populations are often grouped together, potentially masking certain effects that could be associated with hemoglobinopathies. A recent SEER study found that South Asian and "other Asian" (Asian Indian, Pakistani, Filipino, Thai, Vietnamese, Laotian) women exhibit more aggressive breast cancer, similar to the magnitude experienced by AA/Bs, when compared to Japanese Asian groups.[13]

4.4 Future Research Directions

The present study has documented the clinical profile of AA/B+ cancer patients in comparison to AA/B- and NHW- patients as well as revealed associations between hemoglobinopathy status and treatment completion, adverse events, and mortality. Given the nature of observational data analysis, in combination with the relatively limited existing research

into the association between hemoglobinopathies and adverse cancer outcomes, our results have generated additional hypotheses for future exploration. The framework for our interpretation was based on hypothesis-driven results suggesting that AA/B+ status and the occurrence of adverse events acted to modify the effect of treatment completion on mortality. Specifically, we observed that AA/B+ patients who completed treatment had proportionately increased risk of death compared to those who failed to complete treatment. This exaggerated effect was not observed in AA/B- or NHW- patients. Furthermore, the increased risk of death for AA/B+ who completed treatment also was increased among patients who experienced one or more adverse event. One explanation for this result is that AA/B+ patients exposed to extended treatment leading to completion were subject to more severe physiologic stressors that resulted in a larger proportion of adverse events. It is likely the case, however, that adverse events also inform whether treatment is completed. In the latter situation, adverse events act not only to moderate the association between treatment completion and mortality, but also confound the association between treatment completion and mortality.

Outside of the current investigation using the SEER-Medicare database, there are opportunities to conduct similar studies using a variety of analytical techniques in additional databases. In their investigation into the association between SCT and chronic kidney disease, Naik et al. (2014) pooled data across five large, prospective, US population-based cohorts (ARIC, JHS, CARDIA, MESA, WHI)[ix], resulting in more than 15,000 AA/B individuals overall and 1,248 individuals with SCT (prevalence ranged from 6.3% to 9.3% among study cohorts).[38] Identification of SCT was ascertained through custom genotyping, exome sequencing, and imputation. While it is not possible to obtain genotyping data ('gold standard') for the SEER-

[ix] ARIC: Atherosclerosis Risk in Communities Study; JHS: Jackson Heart Study; CARDIA: Coronary Artery Risk Development in Young Adults; MESA: Multi-Ethnic Study of Atherosclerosis; WHI: Women's Health Initiative

Medicare cohort, we are currently investigating natural-language processing as a tool to abstract hemoglobinopathy status from clinical notes that would appear in an electronic medical record (EHR). While clinical notes are not as sensitive as genomic profiling data for determining SCT or other hemoglobinopathy status, they are more likely to be available in clinical settings for a larger proportion of the population overall compared to genotype data, and they are more likely to produce more accurate estimates of hemoglobinopathy prevalence compared to medical claims. Although universal newborn screening for hemoglobinopathies has only been in effect in the US since 2006, an increasing proportion of the population are becoming aware of their status. It will be of great importance for clinical health providers to ethically ascertain hemoglobinopathy status from patients to ensure this information is available in EMRs.

In addition to having genotype data available for identifying SCT status, Naik et al. utilized pooled data across research cohorts. Upon receiving approval from both the NCI and Mayo Clinic, we will have the ability to pool data in a similar manner in order to increase the overall power of future investigations. In addition to SEER-Medicare and Mayo Clinic databases, we are also exploring the ability to link to other prospective cohorts or EMRs with tumor registry data. The WHI was utilized by Naik et al. to analyze the association between SCT and chronic kidney disease; we have proposed to use the WHI data in a similar manner to assess cancer outcomes.

The Mayo Clinic database signifies two additional important future directions for investigating the relationship between hemoglobinopathies and cancer related adverse events. First, since the Mayo Clinic data comes from a tumor registry linked to an EMR and does not rely solely on claims for identification of hemoglobinopathies, analysis will not be limited to patients age ≥65. Second, the Mayo Clinic data contains data on other cancer sites in addition to

breast and prostate cancer. The SEER-Medicare database has this information available as well, but each cancer site needs to be requested separately and comes with an additional fee. While breast and prostate cancer represent excellent exemplar cancer sites due to their high prevalence in the population and the large outcome disparities observed between AA/B and NHW patients, there is evidence to suggest other solid tumors may be more sensitive to the adverse effects of hypoxia (i.e. head and neck cancer, cervical cancer). In addition, outcome disparities by race are not limited to breast and prostate cancer—disparities are documented across cancer sites including cancer of the colorectum, stomach, lung and bronchus, ovary, cervix, and uterine corpus.[1]

4.5 Translational Implications

Despite overall improvements in cancer-specific mortality rates since the 1990s in all groups, largely attributed to the introduction of improved cancer therapies and screening, racial disparities in outcomes persist between AA/B and NHW populations.[1] While SCT has been historically considered a benign condition not associated with decreased life expectancy, a growing number of clinical complications have been found to be associated with SCT. Our study adds adverse cancer outcomes to the list of complications associated with SCT and other inherited hemoglobinopathies known to have a higher prevalence in AA/B populations. At present, hemoglobinopathies are not established as a clinically relevant prognostic indicator among patients with cancer, and therefore providers have no reason to obtain information from patients regarding their status. From a translational perspective, it will be important for providers to communicate with patients regarding the potential risks and treatment considerations associated with carrier status. Despite universal newborn screening in the US, survey estimates suggest that only 16% of the adult population with SCT is aware of their status.[115] This fact is

reflected in the prevalence estimates of hemoglobinopathies in our study cohort. Assuming an 8% prevalence of SCT, only 10% of AA/B patients expected to have SCT had claims and were therefore likely aware of their status (7% for prostate cancer patients and 13.9% for breast cancer patients).

In the preliminary CTR chart review, breast cancer patients were informed of their SCT carrier status after a complication occurred. In the SEER-Medicare study cohort, approximately 60% of patients had a claim for a hemoglobinopathy after diagnosis. Claims are an imperfect proxy for the timing of when a patient learns about her/his hemoglobinopathy status, but it suggests and perhaps confirms that a majority of cancer patients are informed of their hemoglobinopathy status after cancer diagnosis. Based on this information, health care providers may be responsible for taking initiative to communicate with patients about whether they have a hemoglobinopathy, and potentially to screen individuals who have immigrated from or have ancestry from an area with a high prevalence of SCT or thalassemia. Overall, the timing of a hemoglobinopathy claim did not appear to be associated with treatment completion or vital status in the SEER-Medicare cohort.

Results from this study prompt a number of translational science research questions. First, a deeper understanding of the potential histologic differences in the tumor microenvironment between patients with hemoglobinopathies and those without will elucidate associations between hypoxia and intratumoral sickling. In a case report documenting intratumoral sickling in a patient with cervical cancer and sickle cell trait, Milosevic et al. (2001) obtained a punch biopsy of the tumor which confirmed moderately differentiated invasive squamous cell carcinoma, with extensive RBC sickling and severe hypoxia.[48] The amplification cycle of tumor hypoxia and RBC sickling leading to enhanced tumor growth and reduced

sensitivity to radiation and chemotherapy has important clinical implications regarding modified treatment and monitoring plans. Results from our observational study provide indirect evidence to suggest that hemoglobinopathies influence the occurrence of adverse events and patient mortality, but further histologic study of cancers in individuals with SCT is warranted. In addition to SCT, it is worthwhile to consider additional hemoglobinopathies as well to determine if a similar mode of action appears across a range of hemoglobinopathies.

Overall, results from this retrospective observational research study represent the first formal population-based study of SCT and other hemoglobinopathies as an adverse prognostic factor in older adults with cancer. In his 2015 State of the Union Address, President Barack Obama announced a new Precision Medicine Initiative, "…to bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalized information we need to keep ourselves and our families healthier".[116] The concept of precision medicine focuses specifically on cancer, aiming to gain insight into inherited genetic variations that drive disease prevention, treatment, prognosis, and outcomes on a population scale.[116] The present investigation of the prognostic influence of inherited hemoglobin variants and their subsequent contribution to racial disparities in cancer outcomes falls perfectly into the framework of precision medicine. This framework also provides a roadmap to future studies measuring the pharmacogenomics for SCT carriers with cancer, allowing treatment dose, intensity, and overall plan to be tailored for each individual patient, thereby giving this patient population the greatest chance to reduce morbidity and improve survival outcomes.

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Tables

Table 1.1. CTR Preliminary chart review: Demographic and clinicopathological characteristics by study group

	Clinical Phenotype			
Characteristics	**AA/B SCT + (n = 12)**	**NHW SCT + (n = 2)**	**AA/B SCT - (n = 40)**	**NHW SCT - (n = 40)**
Median follow-up, months (IQR)	46 (30 - 115)	62 (53 - 71)	88 (44 - 138)	99 (60 - 133)
Age at diagnosis, mean (SD)	55.5 (12.9)	46.0 (6.4)	53.5 (9.8)	54.6 (11.3)
Stage				
0	1 (8.3)	1 (50.0)	4 (10.0)	1 (2.5)
I	5 (41.7)	1 (50.0)	10 (25.0)	13 (32.5)
II	3 (25.0)	--	20 (50.0)	16 (40.0)
III	3 (25.0)	--	6 (15.0)	7 (17.5)
IV	--	--	--	2 (5.0)
BMI, mean (SD)	33.5 (7.1)	25.2 (0.0)	32.8 (10.0)	29.4 (8.3)
Vital status				
Alive	8 (66.7)	1 (50.0)	27 (67.5)	34 (85.0)
Dead	4 (33.3)	1 (50.0)	13 (32.5)	6 (15.0)
Smoking history				
Never	8 (66.7)	0 (0.0)	22 (55.0)	17 (42.5)
Former	3 (25.0)	0 (0.0)	12 (30.0)	16 (40.0)
Current	1 (8.3)	1 (50.0)	4 (10.0)	5 (12.5)
NOS	0 (0.0)	1 (50.0)	2 (5.0)	2 (5.0)
Number of comorbid conditions (CCI[a] Score)				
0	1 (8.3)	0 (0.0)	2 (5.0)	2 (5.0)
1	3 (25.0)	0 (0.0)	6 (15.0)	7 (17.5)
2+	6 (50.0)	1 (50.0)	17 (42.5)	9 (22.5)
missing	3 (25.0)	1 (50.0)	15 (37.5)	22 (55.0)
Family history of cancer	3 (25.0)	0 (0.0)	19 (47.5)	11 (27.5)

[a] Charlson Cormorbidity Index

Table 1.2. Breast cancer patients who experienced adverse events during or after cancer therapy

	Treatment modality[a]		
	Surgery n (%)	**Radiation n (%)**	**Chemotherapy n (%)**
AA/B SCT+ (n=12)			
No. received	12 (100)	6 (50.0)	8 (66.7)
Any AE	7 (58.3)	5 (83.3)	6 (75.0)
Potential sickling-related AE	1 (8.3)	0 (0.0)	4 (50.0)
AA/B SCT- (n=40)			
No. received	38 (95.0)	29 (72.5)	29 (72.5)
Any AE	12 (31.6)	11 (37.9)	17 (58.6)
Potential sickling-related AE	2 (5.3)	0 (0.0)	3 (10.3)
NHW SCT- (n=40)			
No. received	38 (95.0)	25 (62.5)	22 (55.0)
Any AE	6 (15.8)	3 (12.0)	7 (31.8)
Potential sickling-related AE	0 (0.0)	0 (0.0)	1 (4.5)

AE: adverse event; SCT: sickle-cell trait

[a]Patients who received more than one modality are counted in each category

Table 2.1. SEER-Medicare data files[83]

File Name	Years Included	File Summary	Diagnosis/Procedure Codes
Patient entitlement and diagnosis summary file (PEDSF)	2007-2013	• SEER data • Medicare HMO and entitlement (month/year)	SEER coding
Summarized denominator file for non-cancer cases (SUMDENOM)	2006-2014	• 5% random sample of Medicare beneficiaries residing in SEER areas without a diagnosis of cancer • Medicare HMO and entitlement (month/year)	None
Medicare analysis and procedure file (MEDPAR)	2006-2014	• Part A coverage • 100% Medicare hospitalizations with one record per hospitalization	ICD-9 diagnosis and HCPCS† procedures
Outpatient	2006-2014	• Part B coverage • 100% Medicare outpatient claims with multiple procedures for the same date of service	HCPCS and revenue center procedures
Carrier - Physician/supplier (NCH)	2006-2014	• Part B coverage • 100% Physician/Provider claims for single date of service	ICD-9 diagnosis and HCPCS procedures
Hospice	2006-2014	• Part B coverage • 100% of claims for one or more dates	ICD-9 diagnosis codes
Home Health Agency (HHA)	2006-2014	• Part A/Part B coverage • 100% of claims for one or more dates	ICD-9 diagnosis codes

File Name	Years Included	File Summary	Diagnosis/Procedure Codes
Durable Medical Equipment (DME)	2006-2014	• Part B coverage • 100% of claims for one or more dates	ICD-9 diagnosis and HCPCS codes

† *HCPCS: Health Care Common Procedure Classification System*

Table 2.2. Hemoglobinopathy Codes used to Identify Diagnosed Patients

Disorder/Variant	ICD-9
Thalassemia	282.4
Sickle-cell beta thalassemia	282.41
	282.42
Alpha thalassemia	282.43
Beta thalassemia	282.44
Delta-beta thalassemia	282.45
Beta thalassemia trait	282.46
Hemoglobin E-beta thalassemia	282.47
Other thalassemia variants	282.49
Sickle-cell trait	282.5
Sickle-cell disease	282.6
Other sickle-cell variants	282.61
	282.62
	282.63
	282.64
Sickle-cell anemia without crisis	282.68
Sickle-cell anemia with crisis	282.69
Other hemoglobinopathies	282.7
Hemoglobin C disease	282.7
Hemoglobin E disease	282.7

Table 3.1. Demographic and clinicopathological characteristics by study group

	Total (n = 162,537)		AA/B+ (n = 371)		AA/B- (n = 17,303)		NHW- (n = 144,863)		p-value[c]
	n	%	n	%	n	%	n	%	
Median Follow-up time (months), IQR	56	35 - 80	52	33 - 78	53	32 - 77	57	35 - 80	<.001
Tumor site									
Breast (female only)	75,633	46.53	187	50.40	6,732	38.91	68,714	47.43	<.001
Prostate	86,904	53.47	184	49.60	10,571	61.09	76,149	52.57	
Age									
66-74	89,954	55.34	233	62.80	10,554	61.00	79,167	54.65	<.001
75 to 84	55,910	34.40	106	28.57	5,335	30.83	50,469	34.84	
≥85	16,673	10.26	32	8.63	1,414	8.17	15,227	10.51	
Year of diagnosis									
2007	26,794	16.48	64	17.25	2,723	15.74	24,007	16.57	
2008	25,163	15.48	47	12.67	2,650	15.32	22,466	15.51	
2009	23,852	14.67	57	15.36	2,591	14.97	21,204	14.64	
2010	23,199	14.27	45	12.13	2,509	14.50	20,645	14.25	.017
2011	23,285	14.33	70	18.87	2,480	14.33	20,735	14.31	
2012	20,379	12.54	39	10.51	2,269	13.11	18,071	12.47	
2013	19,865	12.22	49	13.21	2,081	12.03	17,735	12.24	
SEER Registry Area									
Northeast	34,750	21.38	72	19.41	3,471	20.06	31,207	21.54	
Midwest	20,769	12.78	76	20.49	2,599	15.02	18,094	12.49	<.001
South	45,492	27.99	146	39.35	8,007	46.28	37,339	25.78	
West	61,526	37.85	77	20.75	3,226	18.64	58,223	40.19	
Urban/Rural Residence									
Metro	133,473	82.12	329	88.68	15,183	87.75	117,961	81.43	<.001
Nonmetro	29,064	17.88	42	11.32	2,120	12.25	26,902	18.57	
Median Household Income ($), IQR	59,701	43.1 - 82.4	39,289	27.2 - 54.2	40,415	28.5 - 56.7	61,701	45.5 - 84.6	<.001
Median % Without HS Education, IQR	9.95	5.37 - 18.17	20.25	12.15 - 27.15	18.28	11.06 - 26.16	8.97	4.92 - 15.63	<.001

Table 3.1 (con't).

	Total (n = 162,537)		AA/B+ (n = 371)		AA/B- (n = 17,303)		NHW- (n = 144,863)		p-value[c]
	n	%	n	%	n	%	n	%	
Marital Status									
Married	88,895	54.69	150	40.43	6,903	39.89	81,842	56.50	
Not married	57,235	35.21	180	48.52	8,246	47.66	48,629	33.57	<.001
Other	16,407	10.09	41	11.05	1,974	11.41	14,392	9.93	
Charlson Comorbidity Score									
0	71,354	43.90	85	22.91	6,467	37.38	71,354	49.26	
1-2	55,175	33.95	150	40.43	6,861	39.65	55,175	38.09	<.001
≥3	18,334	11.28	136	36.66	3,975	22.97	18,334	12.66	
AJCC Stage									
0	11,811	7.27	34	9.16	1,157	6.69	10,620	7.33	
I	31,473	19.36	67	18.06	2,125	12.28	29,281	20.21	
II	87,111	53.59	190	51.21	10,242	59.19	76,679	52.93	<.001
III	10,735	6.60	21	5.66	1,073	6.20	9,641	6.66	
IV	10,903	6.71	37	9.97	1,507	8.71	9,359	6.46	
Unknown	10,504	6.46	22	5.93	1,199	6.93	9,283	6.41	
Number of positive lymph									
0	49,746	30.61	108	29.11	3,834	22.16	45,804	31.62	
1-3	9,723	5.98	19	5.12	991	5.73	8,713	6.01	
>4	4,184	2.57	13	3.50	475	2.75	3,696	2.55	<.001
No nodes examined	94,427	58.10	215	57.95	11,445	66.14	82,767	57.13	
Unknown	4,457	2.74	16	4.31	558	3.22	3,883	2.68	

Table 3.1 (con't).

	Total (n = 162,537)		AA/B+ (n = 371)		AA/B- (n = 17,303)		NHW- (n = 144,863)		p-value[c]
	n	%	n	%	n	%	n	%	
Tumor characteristics - breast									
Tumor Size (cm)a									
0-2	41,715	55.15	91	48.66	3,060	45.45	38,564	56.12	<.001
2.1-3	22,274	29.45	64	34.22	2,226	33.07	19,984	29.08	
≥4	4,510	5.96	17	9.09	639	9.49	3,854	5.61	
Unknown	7,134	9.43	15	8.02	807	11.99	6,312	9.19	
Histology[a]									
Ductal	61,831	81.75	160	85.56	5,526	82.09	56,145	81.71	<.001
Lobular	7,931	10.49	11	5.88	584	8.67	7,336	10.68	
Other	5,871	7.76	16	8.56	622	9.24	5,233	7.62	
Grade[a]									
Well differentiated (1)	16,800	22.21	30	16.04	1,072	15.92	15,698	22.85	<.001
Moderately differentiated (2)	30,735	40.64	62	33.16	2,522	37.46	28,151	40.97	
Poorly differentiated (3)	19,171	25.35	65	34.76	2,133	31.68	16,973	24.70	
Undifferentiated (4)	933	1.23	n/a[d]	n/a	72	1.07	861	1.25	
Unknown	7,994	10.57	n/a	n/a	933	13.86	7,031	10.23	
Estrogen Receptor Status[a]									
Positive	59,251	78.34	130	69.52	4,749	70.54	54,372	79.13	<.001
Negative	10,077	13.32	40	21.39	1,328	19.73	8,709	12.67	
Unknown	6,305	8.34	17	9.09	655	9.73	5,633	8.20	
Progesterone Receptor Status[a]									
Positive	50,537	66.82	113	60.43	3,978	59.09	46,446	67.59	<.001
Negative	18,009	23.81	56	29.95	2,045	30.38	15,908	23.15	
Unknown	7,087	9.37	18	9.63	709	10.53	6,360	9.26	

Table 3.1 (con't).

	Total (n = 162,537)		AA/B+ (n = 371)		AA/B- (n = 17,303)		NHW- (n = 144,863)		p-value[c]
	n	%	n	%	n	%	n	%	
Tumor Characteristics - prostate									
Gleason Score[b]									
Well-differentiated, 2-4	845	0.97	n/a	n/a	110	1.04	734	0.96	<.001
Moderately-differentiated, 5-7	48,744	56.09	103	55.98	5,770	54.58	42,871	56.30	
Poorly-differentiated, 8-10	31,990	36.81	63	34.24	3,959	37.45	27,968	36.73	
Unknown	5,325	6.13	n/a	n/a	732	6.92	4,576	6.01	

Notes:

[a]breast cancer only

[b]prostate cancer only

[c]Chi-square test for categorical data and Kruskal-Wallis one-way ANOVA for continuous variables

[d]values n/a suppressed due to cell size n<11

Table 3.2. Distribution of selected comorbidities in the Charlson Comorbidity Index (CCI) by study group

	AA/B+ (n = 371)		AA/B- (n = 17,303)		NHW- (n = 144,863)		p-value[b]	AA/B+ vs. AA/B- p-value*
Selected comorbidities (yes)	n	%	n	%	n	%		
Myocardial infarction*	11	2.96	252	1.46	1,767	1.22	<.001	.018
Congestive heart failure*	77	20.75	2,181	12.60	11,547	7.97	<.001	<.001
Peripheral vascular disease	42	11.32	1,934	11.18	10,880	7.51	<.001	.930
Cerebrovascular disease*	67	18.06	2,375	13.73	17,041	11.76	<.001	.017
COPD*[a]	88	23.72	3,099	17.91	24,467	16.89	<.001	.004
Dementia	10	2.70	482	2.79	2,384	1.65	<.001	.917
Paralysis	n/a[d]	n/a	196	1.13	643	0.44	<.001	.177
Diabetes*	206	55.53	6,716	38.81	35,231	24.32	<.001	<.001
Diabetes with sequelae*	82	22.10	2,217	12.81	8,785	6.06	<.001	<.001
Chronic renal failure*	94	25.34	2,437	14.08	10,182	7.03	<.001	<.001
Moderate-severe liver disease	n/a	n/a	43	0.25	231	0.16	.019	.336
Ulcers*	13	3.50	308	1.78	1,672	1.15	<.001	.014
Connective tissue disorders*	23	6.20	561	3.24	4,364	3.01	<.001	.002
AIDS	n/a	n/a	60	0.35	74	0.05	<.001	.140

Notes:

*Statistically significant difference between AA/B+ vs. AA/B-

[a]Chronic obstructive pulmonary disease

[b]Chi-square test

[d]values n/a suppressed due to cell size n<11

Table 3.3. Breast cancer treatment receipt characteristics by study group

Receipt of Breast Cancer Treatment[a]	Total (n = 75,633)		AA/B+ (n = 187)		AA/B- (n = 6,732)		NHW- (n = 68,714)		p-value[b]
	n	%	n	%	n	%	n	%	
Surgery									
Breast-conserving surgery (BCS)	42,545	56.25	89	47.59	3,084	45.81	39,372	57.30	<.001
Mastectomy	22,617	29.90	63	33.69	2,196	32.62	20,358	29.63	
No initial surgery	10,471	13.84	35	18.72	1,452	21.57	8,984	13.07	
Radiation therapy (RT)									
Yes	37,300	49.32	83	44.39	2,777	41.25	34,440	50.12	<.001
No	38,333	50.68	104	55.61	3,955	58.75	34,274	49.88	
Receipt of chemotherapy									
Yes	19,849	26.24	58	31.02	2,017	29.96	17,774	25.87	<.001
No	55,784	73.76	129	68.98	4,715	70.04	50,940	74.13	
Combined therapy (yes)									
BCS+RT	31,287	41.37	63	33.69	2,194	32.59	29,030	42.25	<.001
Mastectomy+RT	4,203	5.56	12	6.42	384	5.70	3,807	5.54	.749
BCS+RT+Chemotherapy	6,915	9.14	15	8.02	533	7.92	6,367	9.27	.001
Mastectomy+RT+Chemotherapy	2,392	3.16	n/a	n/a	208	3.09	2,180	3.17	.678

[a]Treatment received within 9 months of diagnosis

[b]Chi-square test

Table 3.4. Prostate cancer treatment receipt characteristics by study group

	Total (n = 86,904)		AA/B+ (n = 184)		AA/B- (n = 10,571)		NHW- (n = 76,149)		p-value[c]
Receipt of Prostate Cancer Treatment	n	%	n	%	n	%	n	%	
Initial curative therapy[a]									
Yes	61,760	71.07	129	70.11	7,136	67.51	54,495	71.56	<.001
No	25,144	28.93	55	29.89	3,435	32.49	21,654	28.44	
Prostatectomy[b]									
Yes	16,561	19.06	25	13.59	1,291	12.21	15,245	20.02	<.001
No	70,343	80.94	159	86.41	9,280	87.79	60,904	79.98	
Radiation Therapy (RT)[b]									
Yes	39,638	45.61	81	44.02	4,872	46.09	34,685	45.55	
No	47,266	54.39	103	55.98	5,699	53.91	41,464	54.45	.528
Androgen Deprivation Therapy (ADT)[b]									
Yes	29,699	34.17	73	39.67	3,804	35.99	25,822	33.91	<.001
No	57,205	65.83	111	60.33	6,767	64.01	50,327	66.09	
Chemotherapy[b]									
Yes	30,904	35.56	79	42.93	3,926	37.14	26,899	35.32	
No	56,000	64.44	105	57.07	6,645	62.86	49,250	64.68	<.001

[a]Receipt of surgery, radiation, or ADT within 180 days of diagnosis

bTreatment received within 12 months of diagnosis

[c]Chi-square test

Table 3.5. Treatment completion for breast cancer patients by stage and study group

Completion of Breast Cancer Treatment (yes)[a]	Total[a] (n = 71,078)		AA/B+ (n = 178)		AA/B- (n = 6,287)		NHW- (n = 64,613)		p-value[c]
	n	%	n	%	n	%	n	%	
Stage									
I (n= 31,343)	17,399	55.51	34	50.75	1,081	51.21	16,284	55.83	<.001
II (n= 18,774)	7,936	42.27	11	22.92	645	34.81	7,280	43.15	<.001
III (n= 3,263)	601	18.42	n/a	n/a	45	6.62	556	10.85	.001
IV (n= 4,145)	635	15.32	n/a	n/a	70	13.01	563	15.67	.278
Total	37,077	52.16	79	44.38	2,854	45.40	34,144	52.84	<.001

[a]Number of breast cancer patients with sufficient stage at diagnosis information to be included in analysis of treatment completion

[c]Chi-square test

Table 3.6. Treatment completion for prostate cancer patients by stage and study group

Completion of Prostate Cancer Treatment (yes)[a]	Total[a] (n = 81,325)		AA/B+ (n = 169)		AA/B- (n = 9,822)		NHW- (n = 71,334)		p-value[c]
	n	%	n	%	n	%	n	%	
Stage									
I (n= 52,519)	49,797	94.82	104	96.30	6,309	92.08	43,384	95.23	<.001
II (n= 25,676)	10,906	42.48	20	37.04	884	33.47	10,002	43.52	<.001
III (n= 2,141)	1,344	62.77	n/a	n/a	85	43.37	1,258	64.75	<.001
IV (n= 989)	694	0.70	n/a	n/a	79	59.40	612	71.92	.012
Total	62,741	77.15	128	75.74	7,357	74.90	55,256	77.46	<.001

[a]Number of prostate patients with sufficient stage at diagnosis information to be included in analysis of treatment completion

[c]Chi-square test

Table 3.7. Risk of incomplete treatment by study group and cancer site

Study group	Unadjusted RR	(95% CI)	p-value	Adjusted RR[a]	(95% CI)	p-value	PS weighted RR[b]	(95% CI)	p-value
All patients									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.21	1.19 - 1.23	<.001	1.11	1.09 - 1.13	<.001	1.09	1.06 - 1.13	<.001
AA/B+	1.13	1.00 - 1.27	.049	1.05	0.94 - 1.17	.393	1.03	0.89 - 1.18	.737
Breast cancer									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.16	1.13 - 1.20	<.001	1.05	1.03 - 1.08	<.001	1.01	0.96 - 1.05	.816
AA/B+	1.19	1.01 - 1.40	.038	1.10	0.96 - 1.27	.159	1.00	0.82 - 1.21	.974
Prostate cancer									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.22	1.19 - 1.25	<.001	1.17	1.14 - 1.20	<.001	1.17	1.12 - 1.22	<.001
AA/B+	1.07	0.90 - 1.27	.451	1.04	0.89 - 1.21	.627	1.14	0.84 - 1.27	.737

Note : Relative Risk (RR) estimated using modified Poisson regression with robust error variance

[a]Adjusted for age, year of diagnosis, SEER region, metro residence, maritial status, income, CCI score, stage, number of positive lymph nodes, adverse events after surgery or chemotherapy; Prostate cancer model adjusted for age, year of diagnosis, SEER region, metro residence, maritial status, income, CCI score, stage, number of positive lymph nodes, adverse events after surgery or ADT

[b]Further adjusted for adverse events 30 days after surgery or 180 days after chemotherapy

Table 3.8. Adverse events by study group

	Total[a] (n = 135,036)		AA/B+ (n = 309)		AA/B- (n = 13,563)		NHW- (n = 121,164)		p-value
	n	%	n	%	n	%	n	%	
TOTAL	135,036		309		13,563		121,164		
Number of adverse events									
0	45,557	33.74	46	14.89	3,750	27.65	41,761	34.47	<.001
1	45,972	34.04	93	30.10	4,657	34.34	41,222	34.02	
2	26,008	19.26	84	27.18	3,076	22.68	22,848	18.86	
≥3	17,499	12.96	86	27.83	2,080	15.34	15,333	12.65	
Adverse event within 90 days of surgery[b]									
Yes	9,969	12.19	28	15.64	946	14.37	8,995	11.99	<.001
No	71,828	87.81	151	84.36	5,637	85.63	66,040	88.01	
Adverse event within 180 days of chemotherapy or ADT[c]									
Yes	10,171	19.73	34	24.64	1,373	22.49	8,764	19.34	<.001
No	41,375	80.27	104	75.36	4,731	77.51	36,540	80.66	
Adverse events known to be associated with hemoglobinopathies[d]									
Yes	15,402	11.41	69	22.33	1,708	12.59	13,625	11.25	<.001
No	119,634	88.59	240	77.67	11,855	87.41	107,539	88.75	
Adverse events putatively associated with hemoglobinopathies[e]									
Yes	19,083	14.13	78	25.24	2,200	16.22	16,805	13.87	<.001
No	115,953	85.87	231	74.76	11,363	83.78	104,359	86.13	
Adverse events associated with chemotherapy toxicity[f]									
Yes	34,467	25.52	126	40.78	4,010	29.57	30,331	25.03	<.001
No	100,569	74.48	183	59.22	9,553	70.43	90,833	74.97	
Emergency room visit									
Yes	64,165	47.52	176	56.96	7,116	52.47	56,873	46.94	<.001
No	70,871	52.48	133	43.04	6,447	47.53	64,291	53.06	

[a]n = 135,036 patients received treatment (any surgery, any radiation, any chemotherapy, ADT)

[b]n = 81,797 patients received surgery

[c]n = 51,546 patients received chemotherapy or ADT

[d]Hematuria, renal papillary necrosis, acute chest syndrome, anemia, myocardial infarction, thrombocytopenia, hyposthenuria, deep vein thromboembolism, splenic infarction, rhabdommyolysis, hyphema, priapism, leg ulcers, cholelithiasis, stroke

[e]Neutropenia, shortness of breath, pain, hemiplegia, renal toxicity, hepatic toxicity, hemolysis, organ failure, respiratory dysfunction/dyspnea

[f]Infection, fever, mailaise, leukopenia, fracture, pulmonary, cardiac events, blood transfusion, hypercholesterolemia, nephritis, adverse events of antineoplastic and immunosuppressive drugs

Table 3.9. Risk of one or more adverse event requiring hospitalization or emergency room visits

Study group	Unadjusted RR	(95% CI)	p-value	Adjusted RR[a]	(95% CI)	p-value	PS weighted RR	(95% CI)	p-value
All patients									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.10	1.09 - 1.12	<.001	1.03	1.02 - 1.05	<.001	1.03	1.01 - 1.06	<.001
AA/B+	1.30	1.24 - 1.36	<.001	1.16	1.11 - 1.22	<.001	1.23	1.15 - 1.31	<.001
AA/B+ vs. AA/B-	1.18	1.12 - 1.23	<.001	1.12	1.07 - 1.18	<.001	1.19	1.11 - 1.27	<.001
Breast cancer									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.11	1.09 - 1.13	<.001	1.02	0.99 - 1.03	.061	1.02	0.99 - 1.05	0.12
AA/B+	1.29	1.22 - 1.38	<.001	1.14	1.07 - 1.22	<.001	1.20	1.08 - 1.33	<.001
AA/B+ vs. AA/B-	1.16	1.09 - 1.24	<.001	1.12	1.05 - 1.20	<.001	1.17	1.06 - 1.30	.002
Prostate cancer									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.10	1.08 - 1.12	<.001	1.05	1.04 - 1.07	<.001	1.04	1.01 - 1.07	<.001
AA/B+	1.30	1.21 - 1.40	<.001	1.18	1.10 - 1.26	<.001	1.25	1.14 - 1.36	<.001
AA/B+ vs. AA/B-	1.19	1.10 - 1.27	<.001	1.12	1.04 - 1.20	.002	1.20	1.10 - 1.30	<.001

Note : Relative Risk (RR) estimated using modified Poisson regression with robust error variance

[a]Adjusted for age, year of diagnosis, SEER region, metro residence, maritial status, income, education, CCI score, stage, number of positive lymph nodes

Table 3.10. Risk of one or more adverse event requiring hospitalization or emergency room visit among patients who completed treatment

Study group	Unadjusted RR	(95% CI)	p-value	Adjusted RR[a]	(95% CI)	p-value	PS weighted RR	(95% CI)	p-value
All patients									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.11	1.09 - 1.13	<.001	1.03	1.01 - 1.05	.001	1.03	1.00 - 1.05	.041
AA/B+	1.35	1.26 - 1.45	<.001	1.19	1.11 - 1.28	<.001	1.21	1.10 - 1.33	<.001
AA/B+ vs. AA/B-	1.21	1.13 - 1.30	<.001	1.16	1.08 - 1.24	<.001	1.17	1.07 - 1.29	<.001
Breast cancer									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.10	1.08 - 1.13	<.001	1.01	0.98 - 1.04	.568	1.01	0.96 - 1.05	.721
AA/B+	1.35	1.21 - 1.49	<.001	1.18	1.06 - 1.32	.002	1.18	0.98 - 1.42	.084
AA/B+ vs. AA/B-	1.22	1.10 - 1.35	<.001	1.17	1.05 - 1.31	.004	1.17	0.97 - 1.41	.098
Prostate cancer									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.11	1.09 - 1.14	<.001	1.05	1.03 - 1.07	<.001	1.04	1.01 - 1.07	.020
AA/B+	1.35	1.24 - 1.48	<.001	1.20	1.10 - 1.31	<.001	1.22	1.09 - 1.36	<.001
AA/B+ vs. AA/B-	1.22	1.11 - 1.34	<.001	1.14	1.04 - 1.25	.003	1.17	1.06 - 1.31	.003

Note : Relative Risk (RR) estimated using modified Poisson regression with robust error variance

[a]Adjusted for age, year of diagnosis, SEER region, metro residence, maritial status, income, education, CCI score, stage, number of positive lymph nodes

Table 3.11. Risk of one or more adverse event requiring hospitalization or emergency room visit among patients who did not complete treatment

Study group	Unadjusted RR	(95% CI)	p-value	Adjusted RR[a]	(95% CI)	p-value	PS weighted RR	(95% CI)	p-value
All patients									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.07	1.06 - 1.09	<.001	1.01	1.00 - 1.03	.159	1.00	0.96 - 1.02	.487
AA/B+	1.24	1.16 - 1.32	<.001	1.12	1.05 - 1.20	.004	1.13	1.02 - 1.25	.009
AA/B+ vs. AA/B-	1.15	1.07 - 1.23	<.001	1.11	1.03 - 1.18	.004	1.14	1.02 - 1.29	.016
Breast cancer									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.09	1.07 - 1.11	<.001	1.01	0.99 - 1.03	.192	1.01	0.97 - 1.04	.721
AA/B+	1.20	1.11 - 1.30	<.001	1.09	1.00 - 1.19	.040	1.14	1.01 - 1.26	.018
AA/B+ vs. AA/B-	1.10	1.01 - 1.19	.025	1.08	0.99 - 1.18	.084	1.13	1.02 - 1.25	.024
Prostate cancer									
NHW-	1.00	--	--	1.00	--	--	1.00	--	--
AA/B-	1.06	1.03 - 1.09	<.001	1.02	0.99 - 1.05	.123	0.96	0.91 - 1.01	.137
AA/B+	1.31	1.17 - 1.47	<.001	1.18	1.06 - 1.31	.002	1.11	0.89 - 1.38	.348
AA/B+ vs. AA/B-	1.24	1.10 - 1.39	<.001	1.15	1.03 - 1.28	.009	1.15	0.93 - 1.44	.190

Note : Relative Risk (RR) estimated using modified Poisson regression with robust error variance

[a]Adjusted for age, year of diagnosis, SEER region, metro residence, maritial status, income, education, CCI score, stage, number of positive lymph nodes

Table 3.12. Survival characteristics by study group and cancer site.

	AA/B+ (n = 371)		AA/B- (n = 17,303)		NHW- (n = 144,863)		*p* -value
Outcome	n	%	n	%	n	%	
Breast cancer							
Survival, median (IQR), months	52	(33 - 78)	47	(29 - 72)	53	(33 - 77)	<.001
Vital status							
Alive	130	69.52	4,281	63.59	49,484	72.01	<.001
Dead	57	30.48	2,451	36.41	19,230	27.99	
Cause of death							
Breast cancer	17	29.82	886	36.02	5,447	28.33	<.001
Other/unknown	40	70.18	1,565	63.62	13,783	71.67	
2-year survival, % (95% CI)	89.89	(84.43 - 93.51)	87.71	(86.88 - 88.50)	91.65	(91.44 - 91.86)	<.001
5-year survival, % (95% CI)	75.85	(68.13 - 81.94)	69.04	(67.76 - 70.29)	77.01	(76.65 - 77.36)	<.001
Prostate cancer							
Survival, median (IQR), months	52	(34 - 77.5)	55	(34 - 79)	59	(38 - 82)	<.001
Vital status							
Alive	109	59.24	7,261	68.69	56,642	74.38	<.001
Dead	75	40.76	3,310	31.31	19,507	25.62	
Cause of death							
Prostate cancer	17	22.67	738	22.30	4,201	21.54	<.001
Other/unknown	58	77.33	2,572	77.70	15,306	78.46	
2-year survival, % (95% CI)	87.43	(81.54 - 91.54)	90.06	(89.46 - 90.62)	92.74	(92.55 - 92.93)	<.001
5-year survival, % (95% CI)	67.95	(59.78 - 74.81)	74.59	(73.66 - 75.49)	79.90	(79.56 - 80.21)	<.001

Figures

Figure 1.1. Proportion of breast cancer patients experiencing any complications/adverse events or potential sickling adverse event following treatment (surgery, radiation, or chemotherapy).

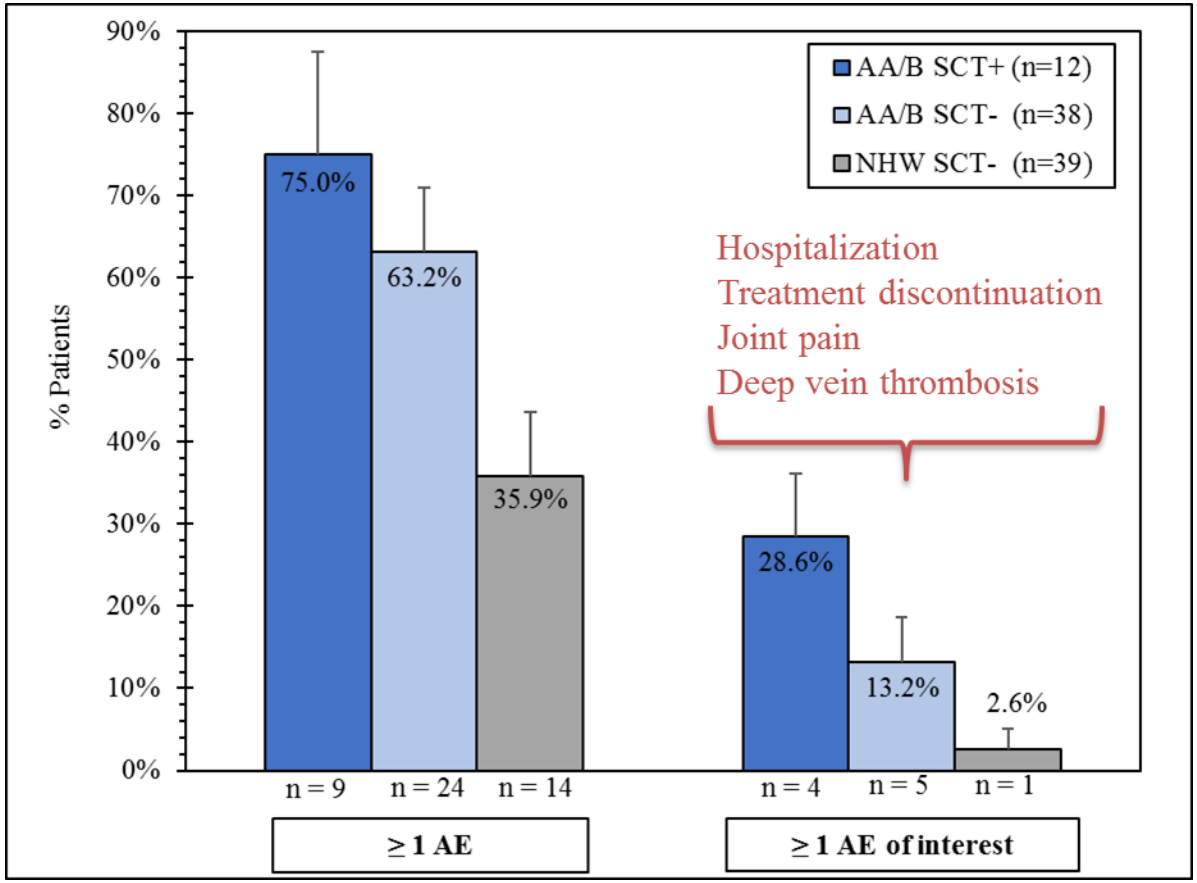


Figure 1.2. Conceptual Model

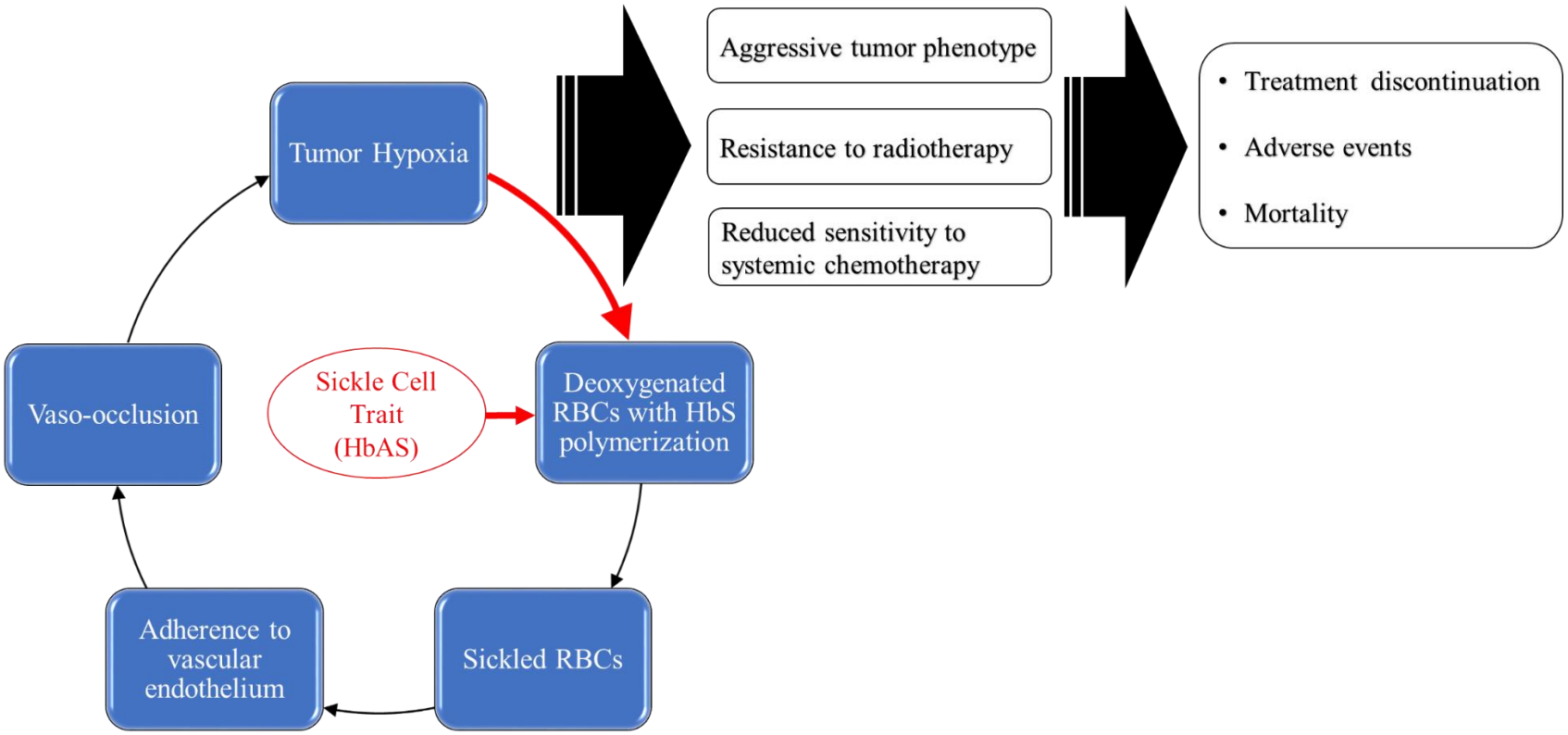


Figure 3.1. Distribution of comorbidities by study group

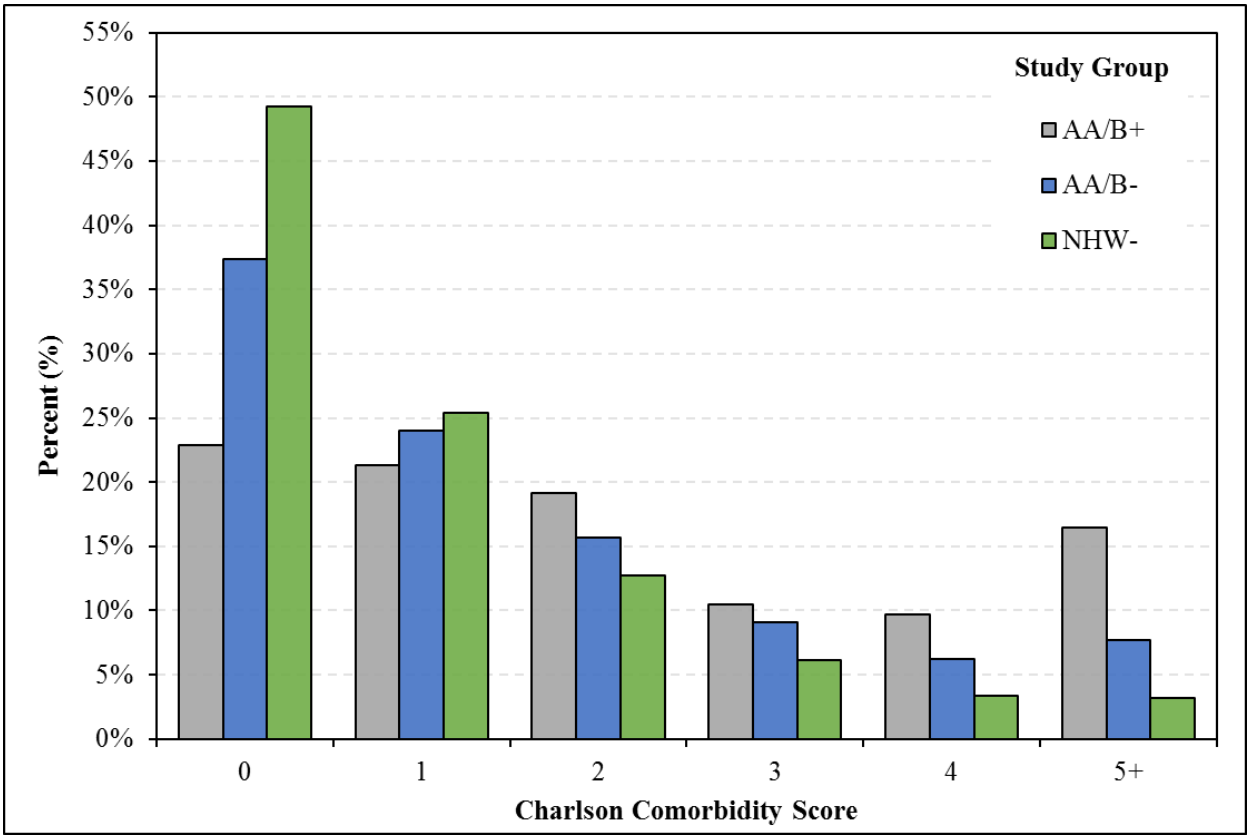
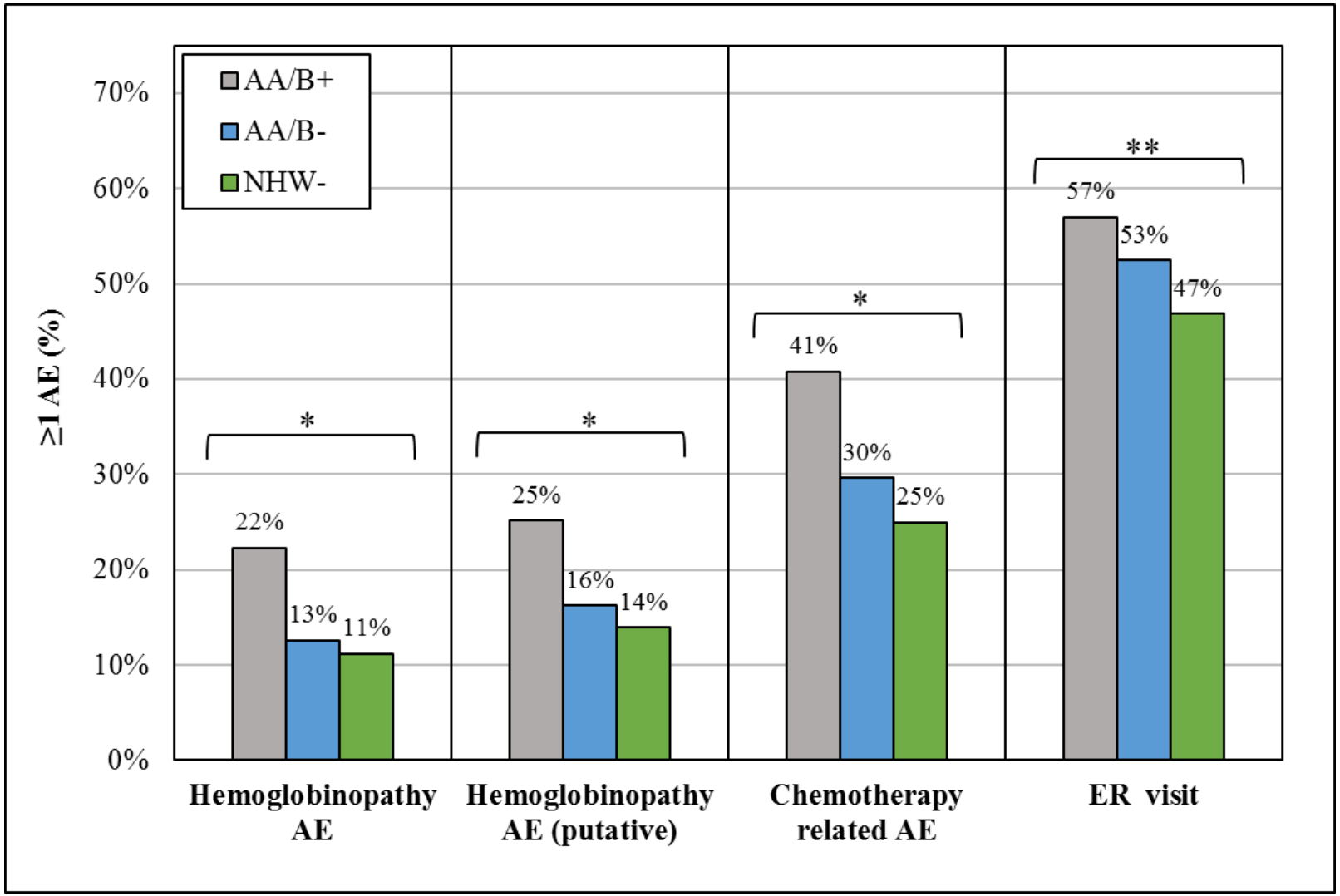


Figure 3.2. Distribution of Adverse Events (AEs) by category and study group



*Pairwise comparisons between AA/B+ vs. AA/B- and NHW-, respectively, p <.001
**Pairwise comparison between AA/B+ vs. AA/B-, p =.065; between AA/B+ vs. NHW-, p <.001

Figure 3.3. Kaplan-Meier all-cause (top row), breast-cancer specific (middle row) and competing risk (bottom row) survival curves by study group for unadjusted (left panels) and propensity score weighted (right panels) breast cancer patients.

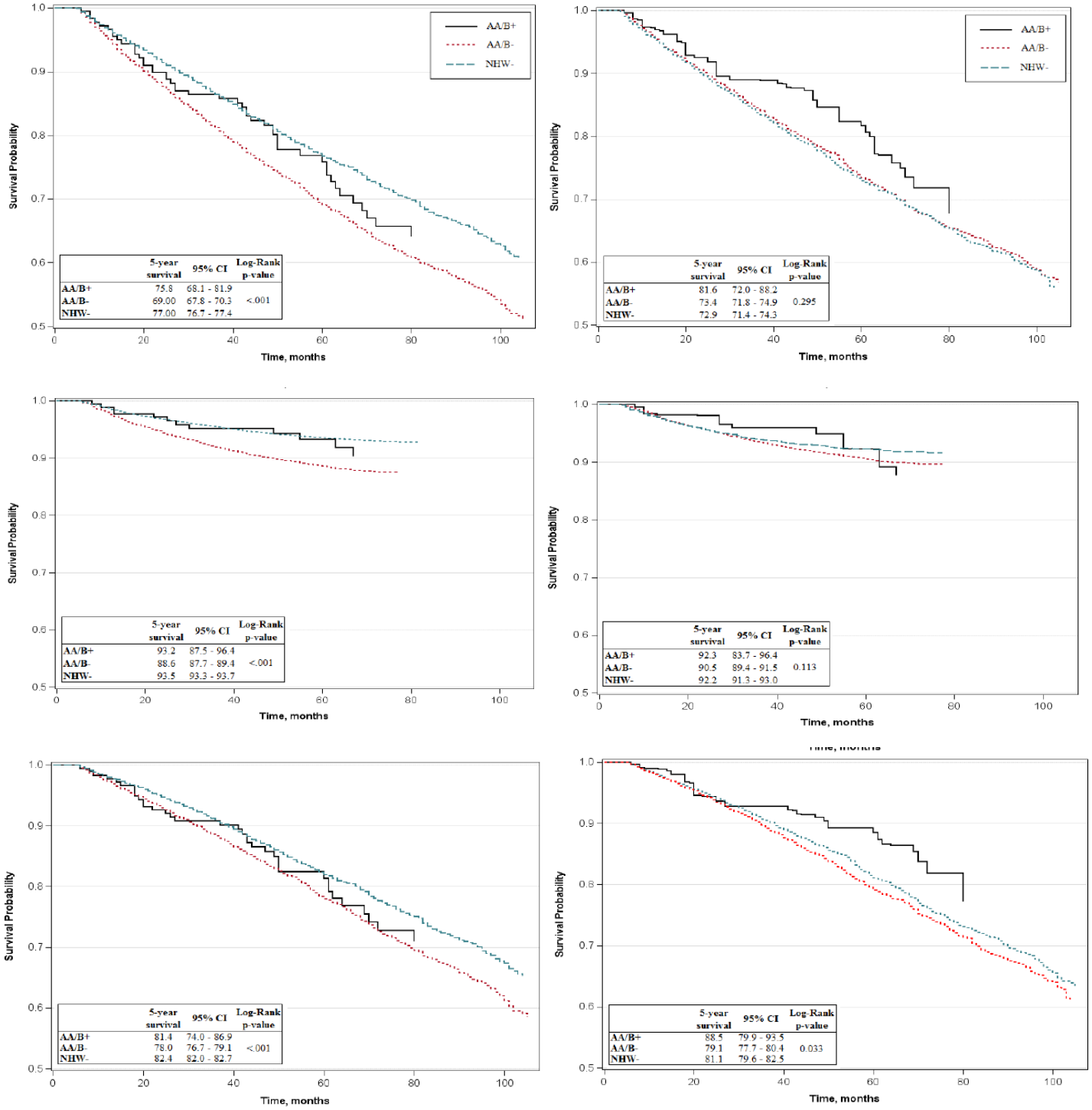


Figure 3.4. Kaplan-Meier all-cause (top row), prostate-cancer specific (middle row) and competing risk (bottom row) survival curves by study group for unadjusted (left panels) and propensity score weighted (right panels) prostate cancer patients.

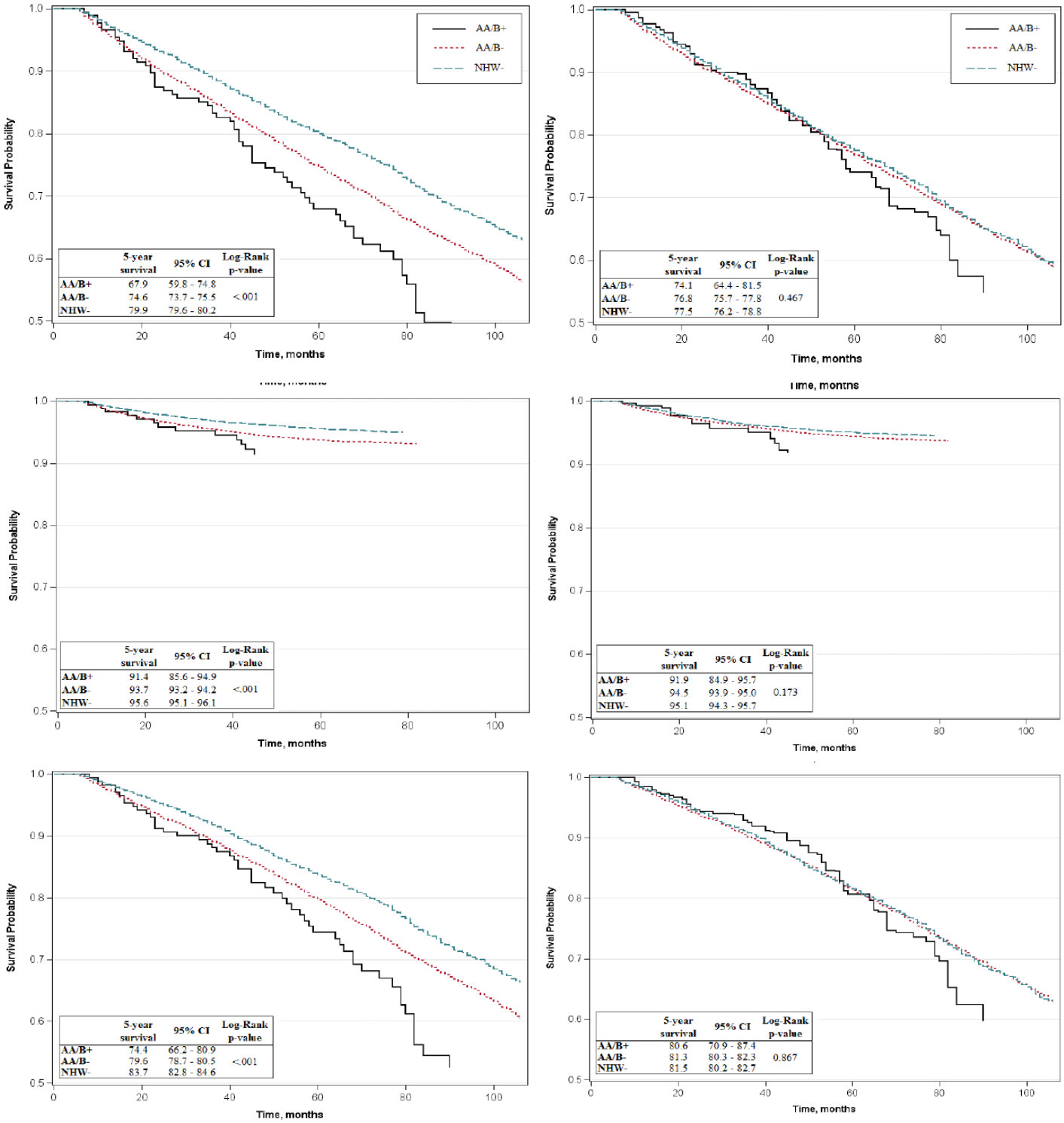


Figure 3.5. Propensity score weighted hazard ratios (HRs) for death among breast and prostate cancer patients who failed to complete treatment by study group.

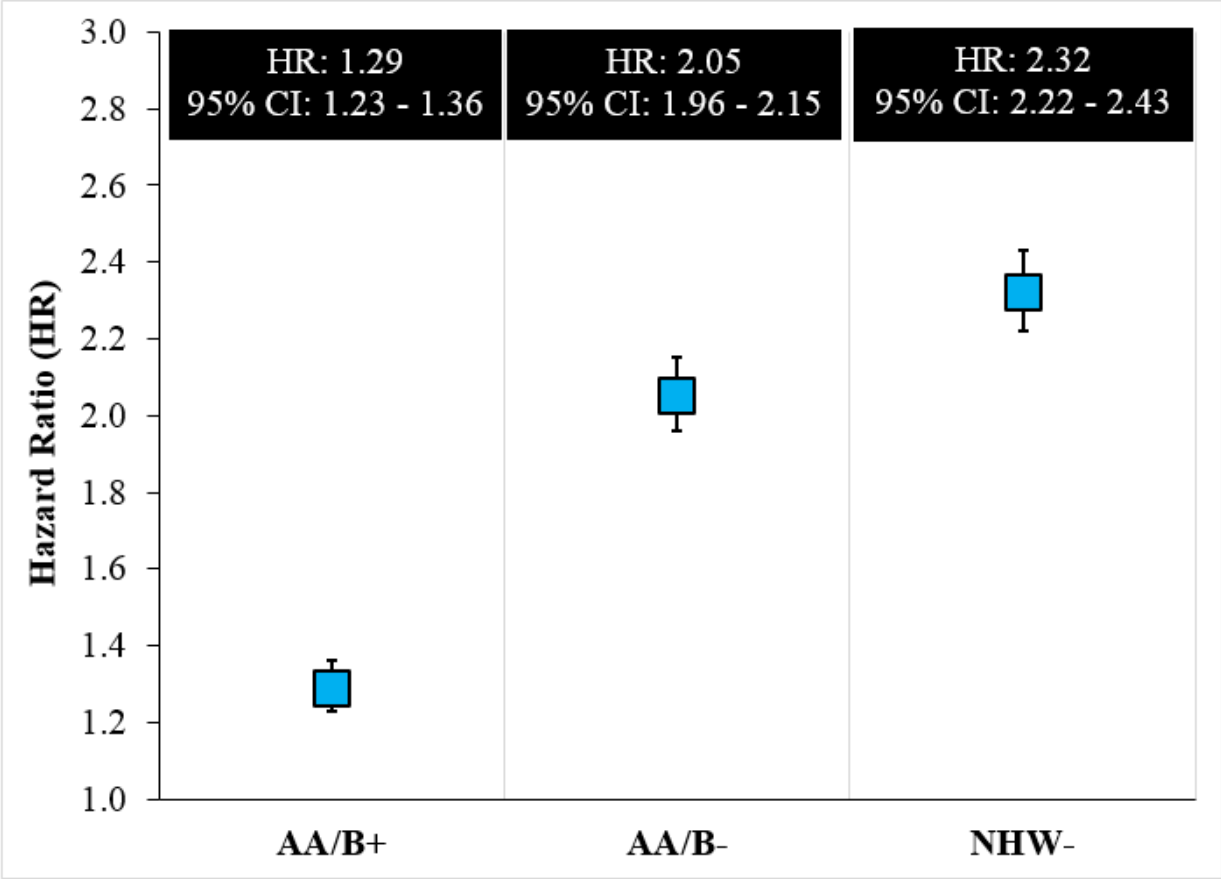


Figure 3.6. Propensity score weighted hazard ratios (HRs) for death among breast and prostate cancer patients who experienced one or more adverse event by study group.

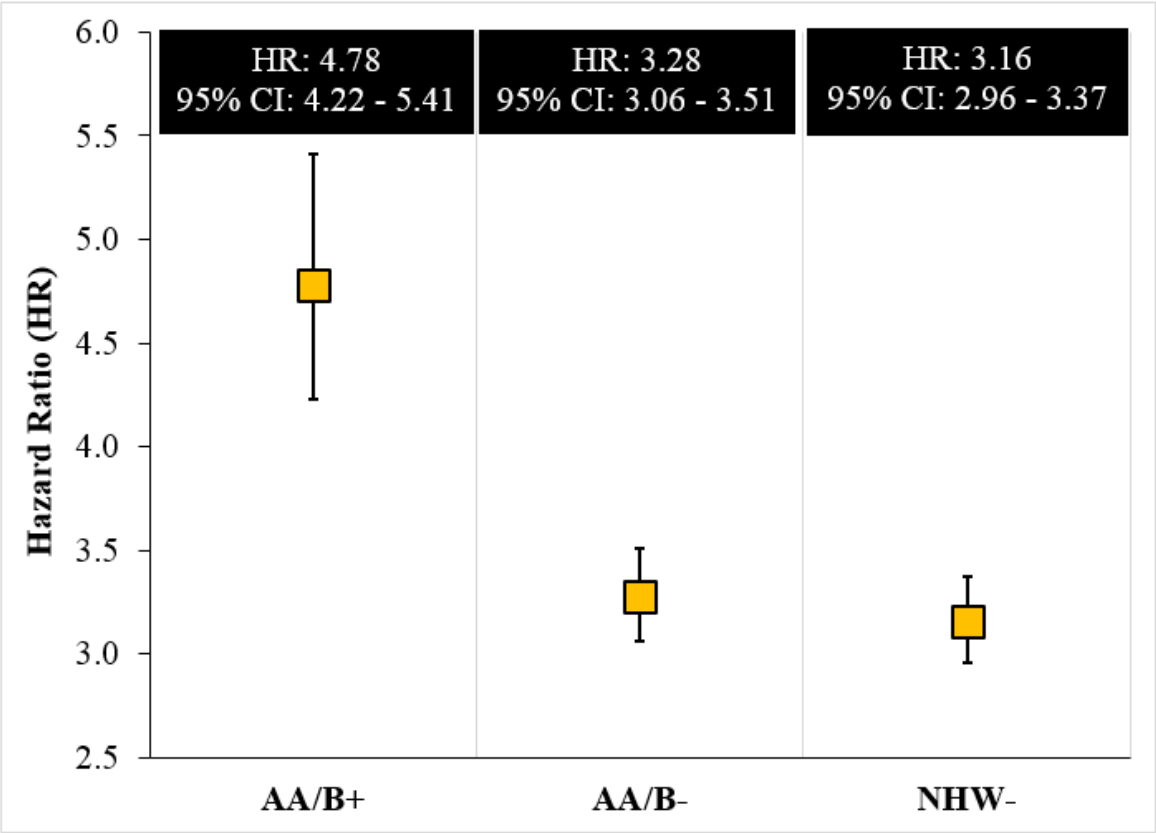


Figure 4.1. Risk of one or more adverse event requiring hospitalization or emergency room visit by CCI Score.

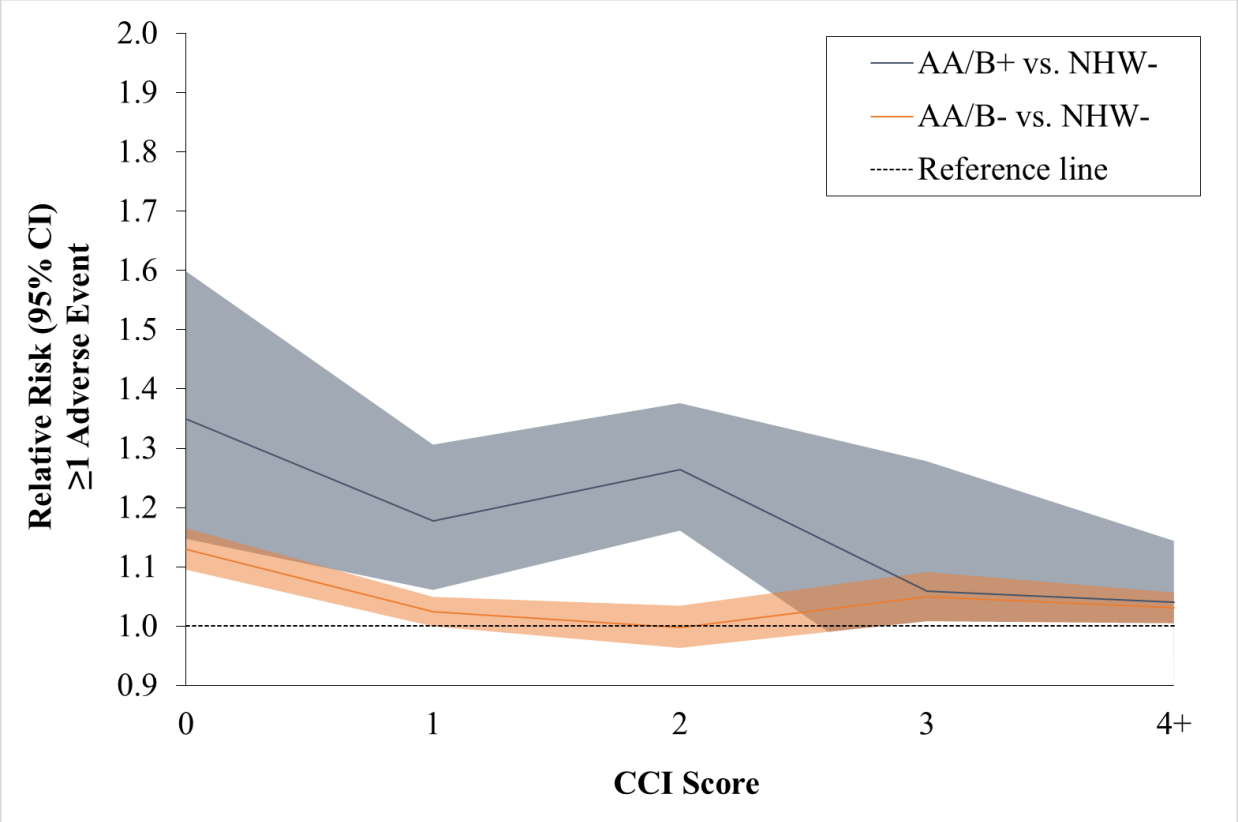
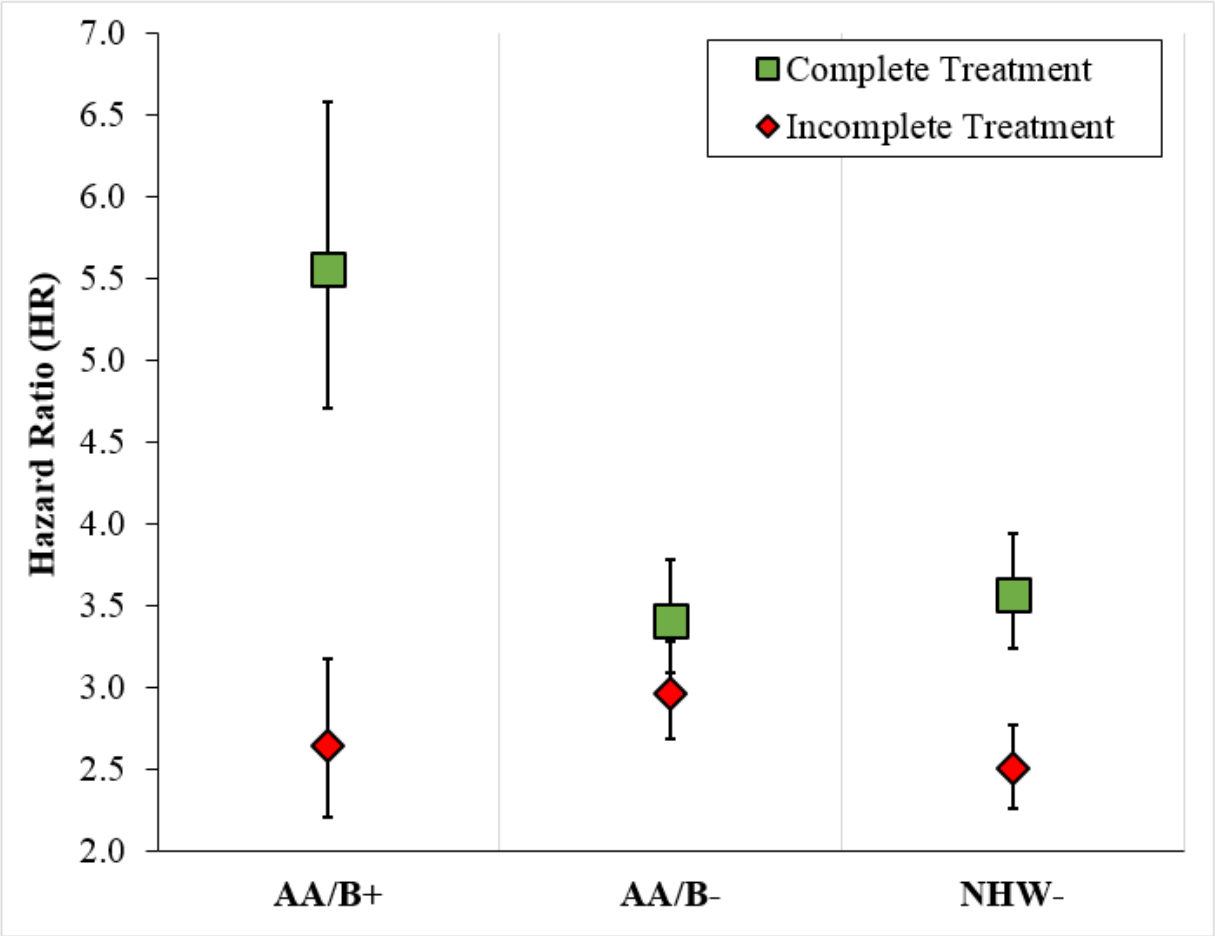
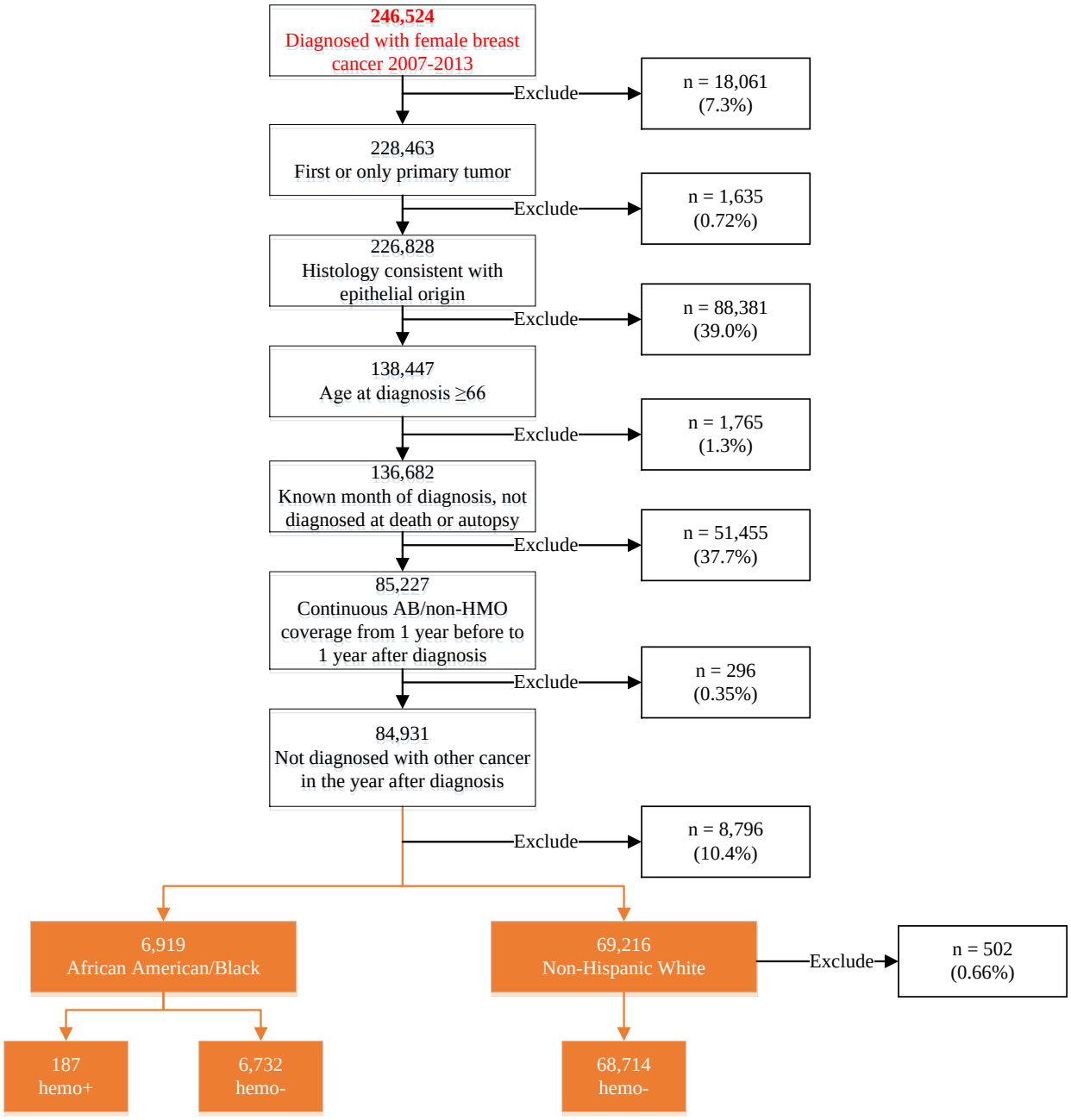


Figure 4.2. Propensity score weighted hazard ratios (HRs) for death among breast and prostate cancer patients who experienced one or more adverse event by treatment completion status and study group.

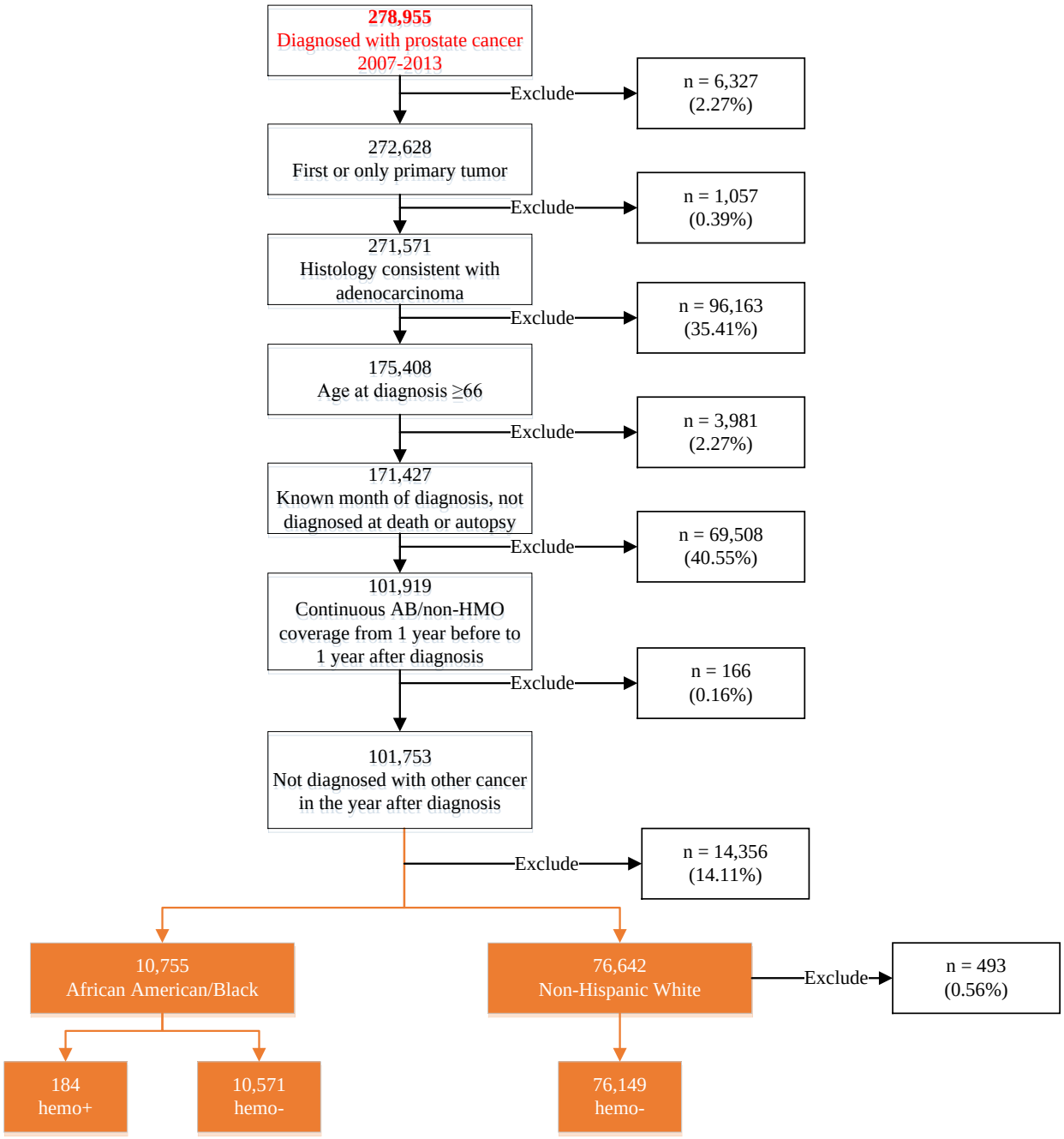


Appendices

Appendix A1. Cohort Selection Criteria – Breast Cancer



Appendix A2. Cohort Selection Criteria – Prostate Cancer



Appendix B1. Diagnosis and Treatment Codes – Breast cancer

	Healthcare Common Procedure Coding System	**International Classification of Diseases, 9th revision**
Diagnosis		
Malignant neoplasm of female breast		174.0 - 174.9 C500 – C509 (ICD-O-3) 26000 (ICD-O-3 recode)
Surgery		
Mastectomy	19180, 19182, 19200, 19220, 19240, 19303, 19304, 19305, 19306, 19307	85.41, 85.42, 85.43, 85.44, 85.45, 85.46, 85.47, 85.48
Breast-conserving surgery	19110, 19120, 19125, 19126, 19160, 19162, 19301, 19302	85.20, 85.21, 85.22, 85.23, 85.25
Radiation		
External beam radiotherapy	77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416	V58.0, V67.1 (administration)
Intensity modulated radiotherapy	77301, 77418, 0073T, G0174	
Brachytherapy	77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77799, 0182T, 19296, 19297, 19298, C9714, C9715	
Chemotherapy		
Agents & administration	J9000-J9999, J0640, J8530, J8600, J8610, J8999, J8510, J8520, J8521, 96400-96549, Q0083-Q0085	992.5, V58.1, V66.2, V67.2, V07.51 (CEN: 0331, 0332, and 0335)

Appendix B2. Diagnosis and Treatment Codes – Prostate cancer

	Healthcare Common Procedure Coding System	**International Classification of Diseases, 9th revision**
Diagnosis		
Malignant neoplasm of prostate		185.0 C619 (ICD-O-3) 28010 (ICD-O-3 recode)
Surgery		
Prostatectomy	55801, 55810, 55812, 55815, 55821, 55831, 55840, 55842, 55845	60.3, 60.4, 60.5, 60.62, 60.69, 60.61 (local excision of lesion of prostate)
Laparoscopic Radical Prostatectomy (robotic assistance)	55866	
Radiation		
External beam radiotherapy	77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416	92.21 – 92.29
Intensity-modulated radiation therapy	77301, 77418, 0073T, G0174	
Image-guided radiation therapy	77421, 76950, 77014, 76370, C9722	
Brachytherapy	77326, 77328, 76873, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77799, G0256, G0261,	
Stereotactic Radiosurgery	G0251, G0339, G0340, 0082T, 77373	
Proton beam radiation therapy	77520, 77522, 77523, 77525	
Androgen Deprivation Therapy		

	Healthcare Common Procedure Coding System	**International Classification of Diseases, 9th revision**
orchiectomy	54520, 54521, 54522, 54535, 54690, 54530	62.4, 62.41, 62.42
Hormone therapy	49510, 11980, J9202 (goserelin), J9217, J9218, J9219, J1950, C9430, (leuprolide), J3315 (Triptorelin pamoate), C9216, S0165, (Abarelix), S0175 (Flutamide), S9560	
Chemotherapy		
Agents & administration	J9000-J9999, J0640, J8530, J8600, J8610, J8999, J8510, J8520, J8521, 96400-96549, Q0083-Q0085	992.5, V58.1, V66.2, V67.2, V07.51 (CEN: 0331, 0332, and 0335)

Appendix B3. Adverse Event Codes

Adverse Event	**ICD-9 Code**
Anemia	281, 283, 284, 285
Thrombocytopenia	287.4, 287.5
Leukopenia	288.5
Neutropenia	288.0
Infections/fever	001.0–139.8, 780.6, 99.85
Dehydration	276.5
Nausea/vomiting/diarrhea/fatigue/headache	780.0, 780.52, 787.0, 787.91, 564.5, 780.4, 784.0, 346
Renal toxicity, renal failure (including chronic kidney disease)	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 588.0, V42.0, V45.1, 583.6, 585, 586, V56, 584
Deep vein thrombosis	444, 445, 451, 452, 453
Pulmonary embolism	415
Other pulmonary conditions	416-417, 518.0–518.89
Emergency Room (ER) visit	99281 – 99285 (HCPCS)
Adverse effect of systemic therapy	E933.1
Shortness of breath	786.05
Severe chest pain	786.5
Diffuse body aches, severe back pain, myalgia, artharalgia	724.8, 729.10, 729.1, 719.4
Hemiplegia	342
Hepatic toxicity	573.9, 572.8, 570, 573.3
Hemolysis	283
Multiorgan failure	995.94
Respiratory distress/dyspnea	518.81, 786.0
Hypoxia	799.02

Adverse Event	**ICD-9 Code**
Mechanical ventilation	96.7
Vaso-occlusive crisis	282.62
Mucositis	528.0, 112.0, 101
Hematuria	599.7
Renal papillary necrosis	584.7
Acute chest syndrome	517.3
Hyposthenuria	593.89
Splenic infarction	289.59
Rhabdomyolysis	728.88
Complicated hyphema	364.41
Priapism	607.3
Leg ulcers	707.25
Gallstones/cholelithiasis, cholecystitis	574, 575
Stroke	433-435
Myocardial infarction	410.0-413.9
Blood transfusion	V58.2, 99.03, 99.04
Cardiomyopathy/hypertension/heart failure	398.91, 401.0-4.05.9, 422.90, 425.4, 425.9, 428
Unspecified diseases of blood and blood-forming organs	289.9

Appendix C. Propensity Score Weighting and Balance Diagnostics

```
#############################################################################################################
library(twang)
library(survey)

#BREAST
set.seed(1)
bmnps <- mnps(hemo_cat ~ agecat + YRDX1 + mar_cat + seer_reg + stage + ln_pos + PCHRLSON + income_q +
              hs_q + breast_grade + breast_hist + her2 + estrogen + progesterone + t_size,
              data = breast1,
              estimand = "ATE",
              verbose = FALSE,
              stop.method = c("es.mean","ks.mean"),
              n.trees = 10000)

plot(bmnps, plots=1, subset = "es.mean")
plot(bmnps, plots=2, subset = "es.mean")
plot(bmnps, plots=3, subset = "es.mean")

#export summary table of balance diagnostics
breastBT <- as.data.frame(bal.table(bmnps, es.cutoff = 0.1))
write.csv(breastBT, file = "breastBT.csv")

#get weights and export to .csv
breast1$w <- get.weights(bmnps,stop.method = "es.mean")
write.csv(breast1, file = "bmnps.csv")

#############################################################################################################

#PROSTATE
set.seed(1)
pmnps <- mnps(hemo_cat ~ agecat + YRDX1 + mar_cat + seer_reg + stage + ln_pos + PCHRLSON + income_q +
              hs_q + gleason + pros_stg,
              data=prostate1,
              estimand="ATE",
              verbose = FALSE,
              stop.method = c("es.mean","ks.mean"),
```

```
              n.trees = 10000)

plot(pmnps, plots=1, subset = "es.mean")
plot(pmnps, plots=2, subset = "es.mean")
plot(pmnps, plots=3, subset = "es.mean")

#export summary table of balance diagnostics
prosBT <- as.data.frame(bal.table(pmnps, es.cutoff = 0.1))
write.csv(prosBT, file = "prostateBT.csv")

#get weights and export to .csv
prostate1$w <- get.weights(pmnps,stop.method = "es.mean")
write.csv(prostate1, file = "pmnps.csv")
##############################################################################################################
```

Figure C1. Summarized absolute standardized mean difference (ASMD) after 10,000 generalized boosted regression (GBM) model iterations for breast (left) and prostate (right) samples.

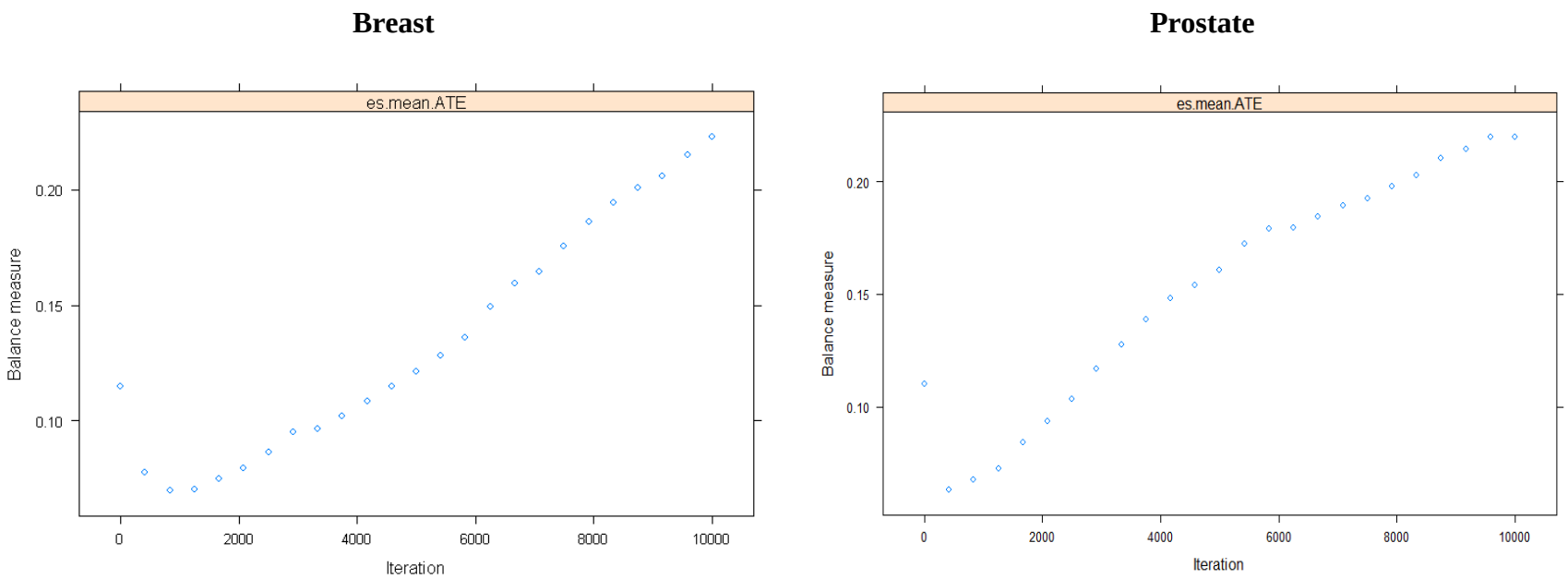


Figure C2. ASMD plots assessing maximum pairwise covariate balance after weighting by study group for breast (left) and prostate (right) samples.

Note: solid circle indicates statistically significant difference between unweighted and weighted ASMD.

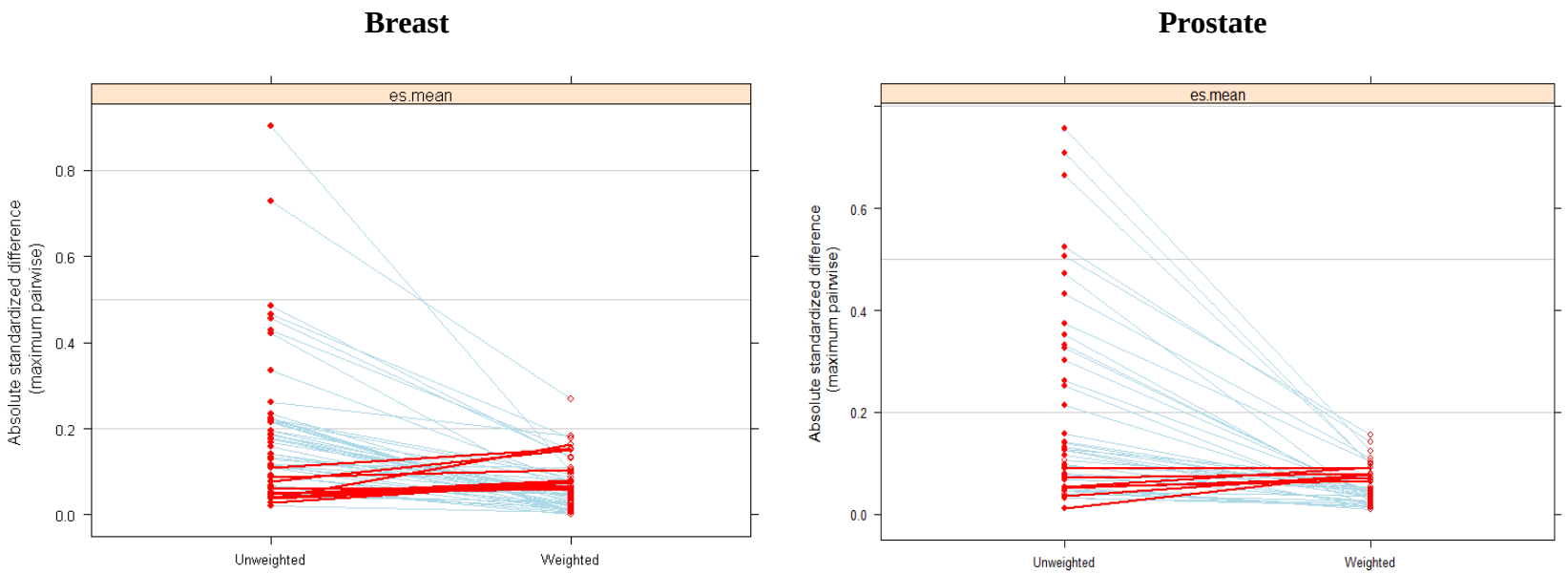


Figure C3. Box plots of estimated propensity score overlap by study group for breast (left) and prostate (right) samples.

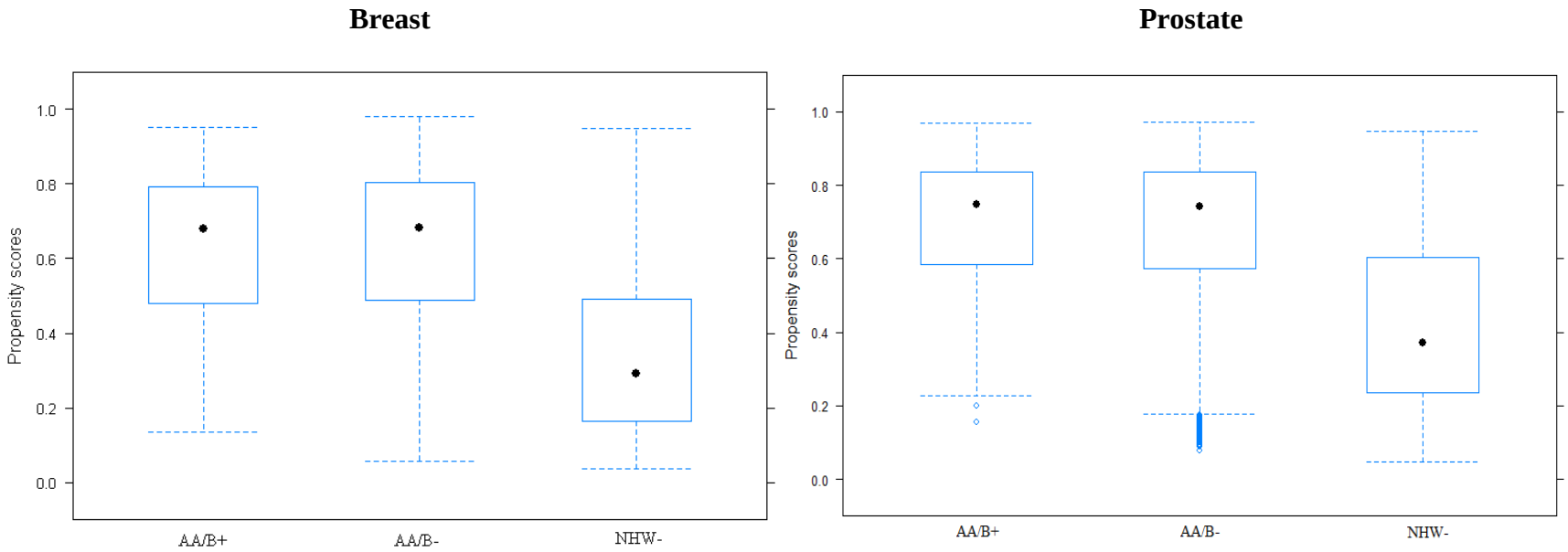


Table C1a. Maximum ASMD and minimum p-values remained >.10 across all pairwise comparisons for each covariate after weighting, breast cancer sample.

Group 1	Group 2	variable	mean1	mean2	pop.sd	std.eff.sz	p	stop.method
AA/B+	AA/B-	agecat:1	0.595	0.505	0.5	0.181	0.100	es.mean
AA/B+	AA/B-	agecat:3	0.081	0.129	0.34	0.143	0.100	es.mean
AA/B+	AA/B-	YRDX1:2010	0.104	0.14	0.347	0.104	0.718	es.mean
AA/B+	AA/B-	YRDX1:2013	0.19	0.14	0.346	0.142	0.718	es.mean
AA/B+	AA/B-	mar_cat:1	0.29	0.343	0.477	0.11	0.297	es.mean
AA/B+	AA/B-	mar_cat:2	0.665	0.601	0.491	0.13	0.297	es.mean
AA/B+	AA/B-	seer_reg:4	0.228	0.294	0.459	0.143	0.456	es.mean
AA/B+	AA/B-	income_q:1	0.444	0.34	0.471	0.221	0.391	es.mean
AA/B+	AA/B-	hs_q:1	0.083	0.127	0.344	0.129	NA	es.mean
AA/B+	AA/B-	hs_q:5	0.39	0.305	0.455	0.188	NA	es.mean
AA/B+	AA/B-	hs_q:6	0	0	0	NA	NA	es.mean
AA/B+	AA/B-	breast_grade:4	0	0.011	0.107	0.102	0.423	es.mean
AA/B+	AA/B-	her2:1	0.019	0.055	0.224	0.164	0.056	es.mean
AA/B+	NHW-	agecat:1	0.595	0.504	0.5	0.182	0.090	es.mean
AA/B+	NHW-	agecat:3	0.081	0.132	0.34	0.15	0.090	es.mean
AA/B+	NHW-	YRDX1:2010	0.104	0.14	0.347	0.105	0.696	es.mean
AA/B+	NHW-	YRDX1:2013	0.19	0.136	0.346	0.154	0.696	es.mean
AA/B+	NHW-	mar_cat:1	0.29	0.354	0.477	0.134	0.201	es.mean
AA/B+	NHW-	mar_cat:2	0.665	0.591	0.491	0.151	0.201	es.mean
AA/B+	NHW-	seer_reg:4	0.228	0.309	0.459	0.177	0.275	es.mean
AA/B+	NHW-	income_q:1	0.444	0.317	0.471	0.27	0.185	es.mean
AA/B+	NHW-	income_q:5	0.092	0.137	0.341	0.132	0.185	es.mean
AA/B+	NHW-	hs_q:1	0.083	0.139	0.344	0.165	NA	es.mean
AA/B+	NHW-	hs_q:5	0.39	0.288	0.455	0.224	NA	es.mean
AA/B+	NHW-	hs_q:6	0	0	0	NA	NA	es.mean
AA/B+	NHW-	breast_grade:4	0	0.012	0.107	0.109	0.368	es.mean
AA/B+	NHW-	her2:1	0.019	0.053	0.224	0.155	0.067	es.mean

Table C1b. Maximum ASMD and minimum p-values remained >.10 across all pairwise comparisons for each covariate after weighting, prostate cancer sample.

Group 1	Group 2	variable	mean1	mean2	pop.sd	std.eff.sz	p	stop.method
AA/B+	AA/B-	seer_reg:3	0.438	0.385	0.485	0.108	0.405	es.mean
AA/B+	AA/B-	seer_reg:4	0.208	0.268	0.445	0.134	0.405	es.mean
AA/B+	AA/B-	stage:0	0	0	0	NA	NA	es.mean
AA/B+	AA/B-	stage:99	0.048	0.078	0.269	0.109	NA	es.mean
AA/B+	AA/B-	hs_q:1	0.083	0.123	0.334	0.12	0.693	es.mean
AA/B+	NHW-	seer_reg:3	0.438	0.385	0.485	0.109	0.311	es.mean
AA/B+	NHW-	seer_reg:4	0.208	0.278	0.445	0.155	0.311	es.mean
AA/B+	NHW-	stage:0	0	0	0	NA	NA	es.mean
AA/B+	NHW-	stage:99	0.048	0.077	0.269	0.106	NA	es.mean
AA/B+	NHW-	income_q:1	0.394	0.335	0.475	0.124	0.638	es.mean
AA/B+	NHW-	income_q:4	0.117	0.154	0.358	0.103	0.638	es.mean
AA/B+	NHW-	hs_q:1	0.083	0.13	0.334	0.142	0.531	es.mean
AA/B-	NHW-	stage:0	0	0	0	NA	NA	es.mean

Appendix D. Select Sensitivity Analysis including NHW+ patients

Table D1. Frequency distribution for hemoglobinopathies in the SEER-Medicare study cohort

	Total (n = 163,532)				Breast cancer (n = 76,135)				Prostate cancer (n= 87,397)			
	AA/B (n = 17,674)		NHW (n = 145,858)		AA/B (n = 6,919)		NHW (n = 69,216)		AA/B (n= 10,755)		NHW (n = 76,642)	
Disorder/Variant	n	%	n	%	n	%	n	%	n	%	n	%
Sickle Cell Trait	137	0.78	40	0.03	77	1.11	18	0.03	60	0.56	22	0.03
Sickle Cell Disease	89	0.50	85	0.06	42	0.61	43	0.06	47	0.44	42	0.05
Thalassemia	94	0.53	371	0.25	54	0.78	192	0.28	40	0.37	179	0.23
Other Hemoglobinopathies	96	0.54	520	0.36	44	0.64	262	0.38	52	0.48	258	0.34
Total[a]	371	2.10	995	0.68	187	2.70	502	0.73	184	1.71	493	0.64

[a]Some patients diagnosed with ≥1 hemoglobinopathy variant

Table D2. Prevalence of CCI Score by study group

	AA/B+		AA/B-		NHW-		NHW+	
CCI Score	n	%	n	%	n	%	n	%
0	85	22.9%	6,467	37.4%	71,354	49.3%	408	41.0%
1	79	21.3%	4,152	24.0%	36,753	25.4%	259	26.0%
2	71	19.1%	2,709	15.7%	18,422	12.7%	145	14.6%
3	39	10.5%	1,567	9.1%	8,938	6.2%	64	6.4%
4	36	9.7%	1,080	6.2%	4,821	3.3%	60	6.0%
5+	61	16.4%	1,328	7.7%	4,575	3.2%	59	5.9%
Total	371		17,303		144,863		995	

Table D3. Incidence of adverse events requiring hospitalization

	AA/B+		NHW+		p-value
	n	%	n	%	
Any hemoglobinopathy					
≥1 AE	290	84.30	714	74.69	<.001
Sickle Cell Trait					
≥1 AE	102	77.86	28	75.68	.779
Thalassemia					
≥1 AE	78	85.71	258	72.07	.007
Other hemoglobinopathies					
≥1 AE	77	88.51	373	74.60	.005