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14. ABSTRACT As more men live with their prostate cancer, they face increased risk of cardiovascular disease (CVD); this risk is intensified by treatment type, in particular androgen deprivation therapy (ADT). There is a paucity of data exploring the risk of CVD among minority men with prostate cancer overall or by treatment type. The purpose of this study is to examine race-specific CVD risk in men with prostate cancer, overall and by treatment type. 2000 prostate cancer cases (1000 each African American and Caucasian) were identified and have undergone medical chart review. Pre-diagnosis CVD was common (particularly hypertension). In crude analyses, there is an overall relationship between treatment type (ADT) and post-diagnosis incident CVD (Myocardial infarction [MI]). The majority of these associations were predominantly detected in the Caucasian sample, where ADT was associated with both MI and Type II Diabetes Mellitus. No significant ADT and CVD association was detected in the African-American sample. An unexpected inverse association between ADT and hypertension was detected in crude analyses; further analyses are underway to determine if this is largely due to unaccounted for confounding in the crude analyses. Thus, in our sample, it appears that ADT may have a race-specific association with the development of CVD following prostate cancer treatment. Additional analyses accounting for confounding and other important risk factors are underway.					
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Introduction

Racial differences in the overall health of men living with prostate cancer are an important but understudied area of research. As more men live with their prostate cancer, they face increased risk of cardiovascular disease (CVD) events; this risk is intensified by treatment type. There is a paucity of data exploring the risk of CVD among minority men with prostate cancer overall or by treatment type. As African Americans, in general, are less likely to have CVD risk factors under control and are more likely to experience CVD events, we are (1) examining if African-American men with prostate cancer are more likely to have worsening CVD risk factor profiles and more CVD events than Caucasian men with prostate cancer during a follow-up period of 5 years past diagnosis and (2) examining if androgen deprivation therapy for prostate cancer is associated with worsening CVD risk factor profiles and more CVD events during a follow-up period of 5 years past diagnosis, and to determine whether race modifies these associations. This is a retrospective cohort study of men newly diagnosed with prostate cancer at Henry Ford Health System between years 1998 and 2006. As men undergoing prostate cancer treatment interface with the medical care system, there are considerable opportunities to assess their CVD factor profiles. If African-American men with prostate cancer are more likely to have worsening CVD risk factor profiles and to experience CVD events than their Caucasian counterparts, this could reveal an important and modifiable opportunity to reduce a disparity in the overall health of men with prostate cancer. Although treatment type may be associated with CVD risk factor changes and events, few studies have examined this association specifically among African-Americans. Results from this investigation will be used to identify the need to

couple therapy with risk factor monitoring and will stimulate future research into potential underlying causes for these disparities.

Body

As outlined in the approved statement of work, the following tasks have been completed:

- obtained Human Subjects Regulatory Board Approval;
- obtained and maintained Henry Ford Health System (HFHS) Institutional Review Board Approval for Human Subject Research;
- created Access database for direct medical record abstraction data entry;
- created, piloted and revised medical record abstraction tool;
- created electronic cohort of 2,000 prostate cancer cases (1,000 each African-American and Caucasian);
- developed and implemented quality control procedures;
- on-going database management;
- patient addresses have been geocoded to determine neighborhood-level SES indicators
- Medical chart abstraction completed
- Final state and national death data search pending (to accommodate lag in state death data available to PI); death searches using local data (i.e. electronic medical record and tumor registry) has been completed
- Analysis of major cardiovascular outcomes underway (explained in detail below)

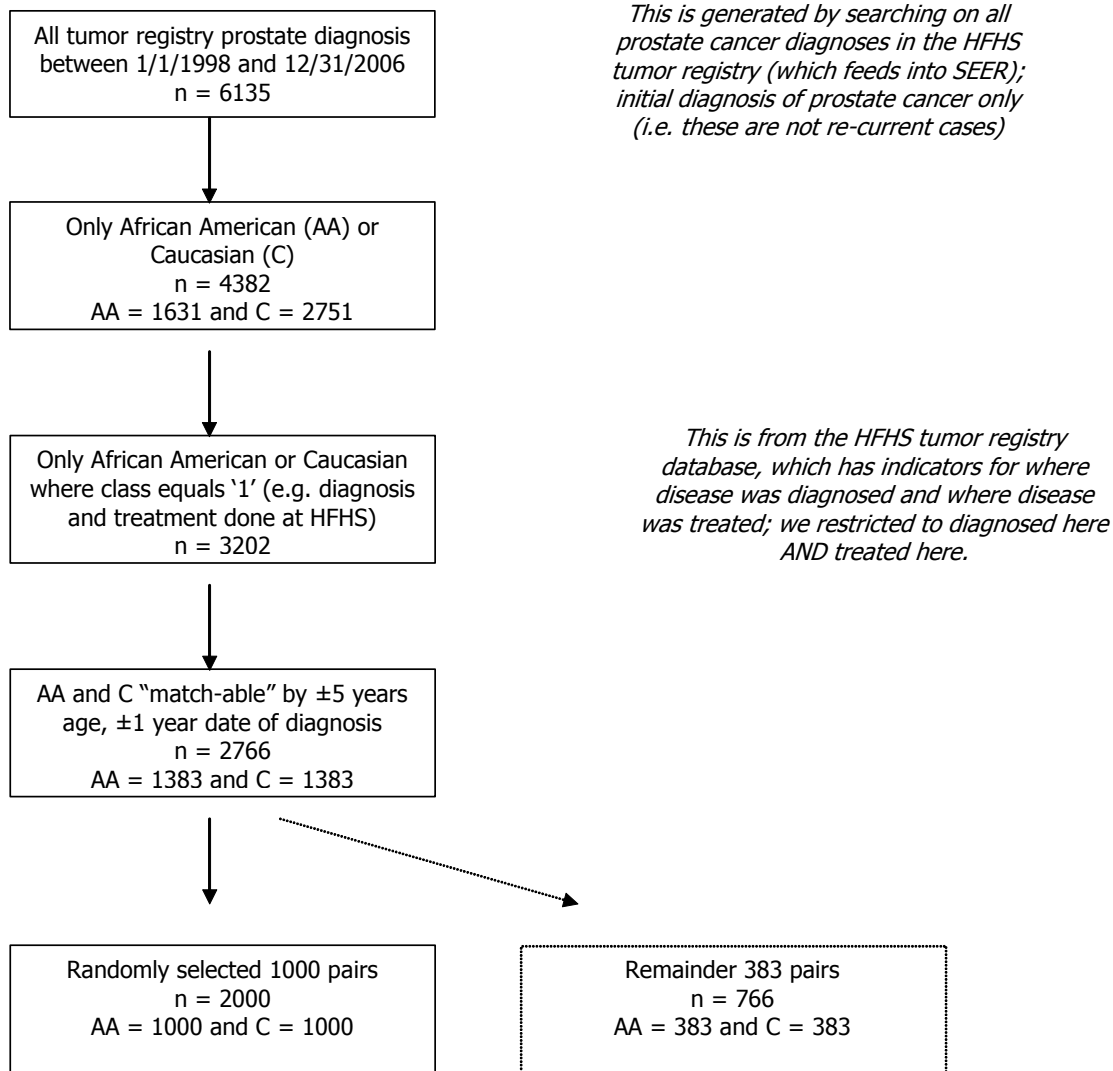
As described in the statement of work training activities include completing the following courses: Epid 787 “An Introduction to Multilevel Analysis in Public Health” at the University of

Michigan in July, 2010. This course covered analysis techniques that will be needed for analyzing the geocoded SES variables that are being collected for the current study. The PI also completed the following course: Epid 777 “Geographic Information Systems for Epidemiology” at the University of Michigan in July, 2011, which covered an analytic tool that is key to the SES component of this research. Additionally, the PI has regularly attended the HMORN Cancer Research Network annual meeting. The PI submitted and presented an abstract at the second Innovative Minds in Prostate Cancer Today (IMPACT) conference (March, 2011) and this poster is included in the appendix. The PI has also attended the 2012 Society of Epidemiological Research Meeting.

Study Cohort

The Henry Ford Health System (HFHS) provides medical care to between 20-30% of the metropolitan Detroit, MI population. All African-American and Caucasian cases of incident prostate cancer diagnosed between January 1, 1998 and December 31, 2006 were identified through the HFHS tumor registry. Cases were restricted to those classified in the tumor registry as having both the primary diagnosis and their initial treatment through HFHS. Date of diagnosis and age at diagnosis were electronically obtained. African-American and Caucasian prostate cancer cases were 1:1 frequency matched based on year of diagnosis (+/- 1 year) and age at diagnosis (+/- 5 years) to achieve 1000 matched pairs (2000 total men for data abstraction). The generation of the cohort is described in Figure 1.

Figure 1. Schematic of study cohort



Following generation of the cohort, all identified cases underwent detailed medical chart abstraction. The HFHS employs an electronic medical record, allowing us to obtain detailed information on the cases; paper records were requested on an as-needed basis to supplement electronically available data (only 22 (1.1%) charts were requested for this study).

Overall, the mean age of our cohort was 67.3±9.5 years; most men were married and the majority were retired (Table 1). We compared demographic characteristics of our study population by race (Table 1) using chi-square tests for discrete variables and t-tests for continuous variables. African-American cases were significantly less likely to be married but were significantly more likely to be residing in the city of Detroit at the time of diagnosis and to be a current smoker at the time of diagnosis.

Table 1. Demographic characteristics of Study Population, overall and by race

Characteristic at time of diagnosis	Overall	African-American	Caucasian	<i>P</i>*
N	2000	1000	1000	
Age (years)	67.3±9.5	66.9±9.8	67.7±9.1	0.061
Married/Living as Married	943 (47.2%)	444 (44.4%)	499 (49.9%)	0.014
Employment Status				
Retired	704 (35.2%)	358 (35.8%)	346 (34.6%)	
Employed (Full or Part time)	370 (18.5%)	196 (19.6%)	174 (17.4%)	0.251
Unknown/Missing/Other	926 (46.3%)	446 (44.6%)	480 (48.0%)	
Detroit resident	761 (38.1%)	706 (70.6%)	55 (5.5%)	<0.001
Current Smoker	232 (11.6%)	143 (14.3%)	89 (8.9%)	0.002

*Comparing African-American and Caucasian prostate cancer cases

The typical treatments used by the participants are described in Table 2. The most common treatment modalities were radiation therapy and hormonal therapy. Alternative treatments were identified for a small number of men, however, this is likely an underestimation

given that men might not report this to their clinician and/or it may not be recorded in the medical record. Similarly, orchiectomy was rarely used.

Table 2. Treatment characteristics* of Study Population, by race

	African-American	Caucasian
Radiation Therapy	279 (27.9%)	262 (26.2%)
Brachytherapy	21 (2.1%)	23 (2.3%)
Hormone Therapy	257 (25.7%)	183 (18.3%)
Orchiectomy	17 (1.7%)	12 (1.2%)
Prostatectomy	102 (10.2%)	115 (11.5%)
Alternative/Herbal Therapy	7 (0.7%)	15 (1.5%)

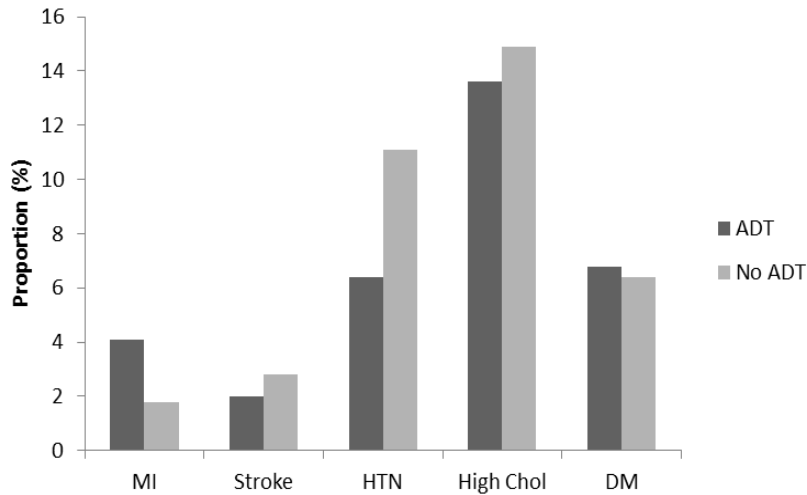
*Not Necessarily Mutually Exclusive

Preliminary Analysis of ADT and development of CVD and CVD risk factors

ADT is associated with the development of CVD and CVD risk factors. We examined the crude association of ADT with several major CVD and CVD risk factors (MI, stroke, hypertension, high cholesterol and type II diabetes mellitus). Analysis was restricted to physician-diagnosed documentation of these events. Chi-square tests were used to examine these associations overall and within race strata.

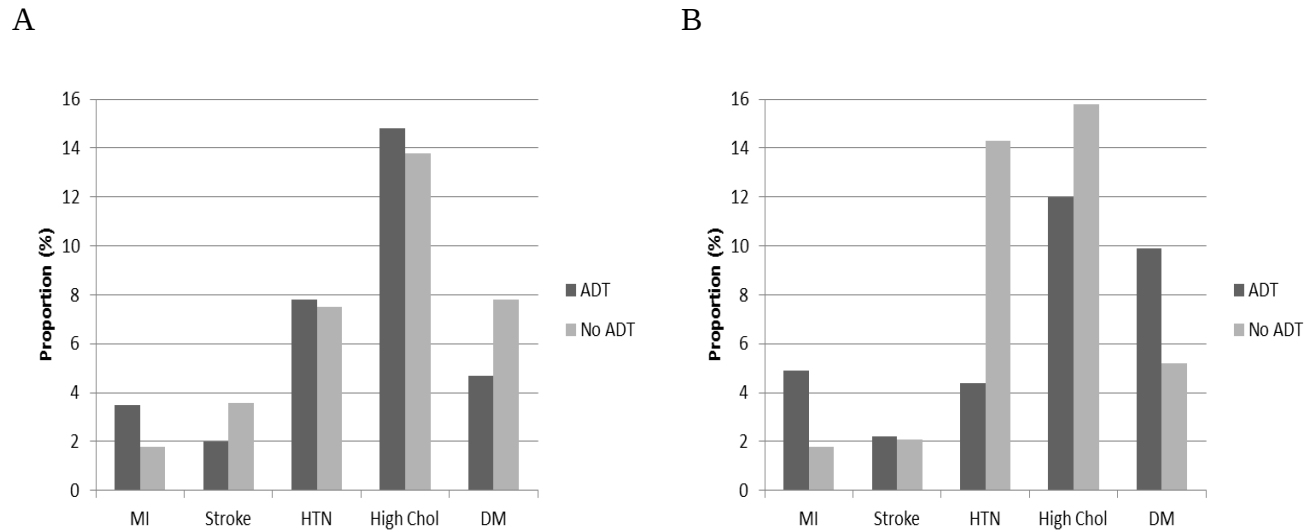
Overall, there was a significant crude association between ADT and development of incident MI post prostate cancer diagnosis ($P=0.019$); men treated with ADT were more likely to have developed an MI than men not treated with ADT (Figure 2). A statistically significant inverse association between ADT and development of incident hypertension was also detected ($P=0.007$). No association between ADT and stroke ($P=0.423$), hyperlipidemia ($P=0.548$) or type II diabetes mellitus ($P=0.787$) were detected in the overall sample.

Figure 2. Proportion of CVD events by ADT ever/never use in the overall sample; Myocardial Infarction (MI); Hypertension (HTN); High cholesterol (High Chol); Type II Diabetes Mellitus (DM).



There were differences, by race, in the association of ADT with incident CVD following prostate cancer diagnosis. Among African-American prostate cancer cases, there were no statistically significant associations of ADT with any CVD outcome (all $P > 0.1$; Figure 3A). In contrast, among Caucasian cases (Figure 3B), ADT was statistically significantly associated with MI ($P = 0.038$) and type II diabetes mellitus ($P = 0.040$) and was statistically significantly and inversely associated with hypertension ($P = 0.001$). Of note, with the exception of MI, the pattern of CVD outcome by ADT use was in the opposite direction comparing African-American to Caucasian prostate cancer cases (Figure 3A and 3B).

Figure 3. Proportion of CVD events by ADT ever/never use among (A) African-American and (B) Caucasian prostate cancer cases; Myocardial Infarction (MI); Hypertension (HTN); High cholesterol (High Chol); Type II Diabetes Mellitus (DM).



In our preliminary analyses, in crude models, ADT was associated with MI in the overall sample. By race, however, ADT was associated with MI and Type II Diabetes Mellitus only among Caucasian cases. These findings of an increased risk of ADT with MI and Type II Diabetes Mellitus are consistent with those found in other samples; importantly, we provide evidence for a potential race-specific impact of ADT on CVD risk. These preliminary findings should be cautiously interpreted, however, as we have not accounted for important confounding factors, such as age at diagnosis, pre-existing CVD and stage and/or grade of prostate cancer at diagnosis. Further, we found an unexpected and inverse association between ADT and hypertension in the overall and Caucasian sample. We believe that this association is most likely due to unaccounted for confounding; this will be addressed in future analyses.

Several limitations exist in this preliminary analysis that will be addressed in the next stages of analysis. We have initially focused on clinically documented mention of the occurrence of these events; we have additionally obtained laboratory and test result information on our entire cohort, which will allow us to create more robust definitions of disease, particularly for hypertension, high cholesterol and type II Diabetes mellitus. We are exploring the use of models that will allow us to estimate the trajectory or change in CVD risk factors over time (e.g. weight trajectories, blood pressure trajectories) which may better enable us to define pertinent risk groups for CVD outcomes. Finally, we have obtained detailed medication data on our cohort which will allow us to further expand definitions of CVD cases; these medications are in process of being categorized into indication groups.

Preliminary Analysis of race and ADT with time to events

In the previous analysis, we focused primarily on the development of events over the entire 5-year follow-up period. We have also applied a more robust approach of survival analysis to examine two of the major outcomes of interest, specifically, time-to-development of an MI and time-to-development of a stroke. Overall, mean follow-up time of prostate cancer cases was 47.9 ± 19.1 months; by race, mean follow-up time was 48.1 ± 19.2 months in Caucasian cases and 47.6 ± 19.0 months in African-American cases. There was no evidence of a racial difference in mean-follow-up time ($P=0.51$).

In all analyses described, time to event was defined as the difference in the date of event compared to the date of initial prostate cancer diagnosis in months; prostate cancer cases not experiencing the event of interest were either censored at the end of the follow-up time (5 years post-diagnosis or 60 months) or at the time, in months, of their last follow-up with the HFHS

health care system within that same 5 year post-diagnosis period. This included participants being censored due to death from other causes. There were 37 events of MI and 33 events of stroke over the follow-up period. Mean time to MI was 24.3 ± 18.7 months, ranging from <1 month post-diagnosis to 57 months post-diagnosis. Mean time to stroke was 28.8 ± 14.3 months, ranging from 1 month post-diagnosis to 50 months post-diagnosis.

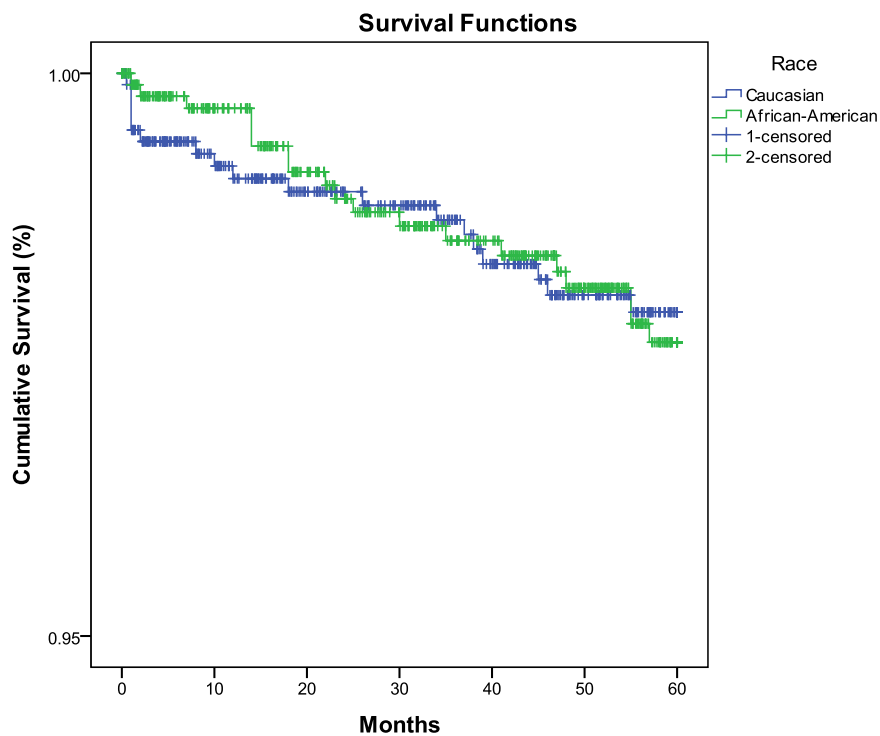
Statistical Methods

We employed Kaplan-Meier methods to estimate the univariable association of race with time-to-MI or time-to-stroke. We then fit multivariable Cox proportional regression models to examine the association of race with time-to-MI or time-to-stroke adjusted for the following covariates: age at prostate cancer diagnosis, residence (city of Detroit vs. elsewhere), marital status (married/living as married vs. other), employment status (employed vs. other) and current smoking.

Association of Race with Time-to-MI

Overall, there was no difference in time-to-MI between Caucasian and African-American prostate cancer cases ($P=0.861$) (Figure 4). There remained no significant association between race and time-to-MI after employing Cox regression models. Compared to African-American cases, Caucasian cases had a non-significant ($P=0.258$) hazard ratio (HR) for time to MI of 1.7 (95% CI HR: 0.66, 4.77) after adjusting for age at diagnosis, residence, marital status, employment status and current smoking. In this model, only age at diagnosis was significantly associated with time to MI ($P=0.013$); for every one-year increase in age, the HR for time to MI increased by 1.05 (95% CI HR: 1.01, 1.09).

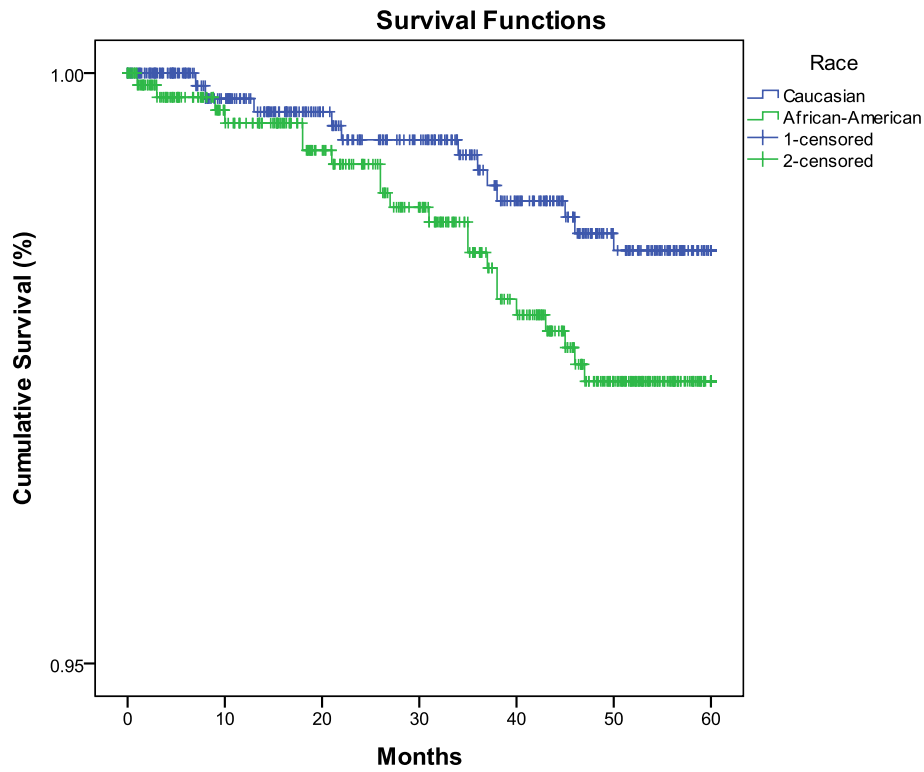
Figure 4. Kaplan-Meier survival curve of time-to-MI, presenting race-specific survival curves.



Association of Race with Time-to-Stroke

There was a moderately significant trend for increased risk of stroke among African-American men with prostate cancer compared to Caucasian men ($P=0.101$) (Figure 5). After adjusting for age at diagnosis, residence, marital status, employment status and current smoking, the association of race with time to stroke was no longer marginally significant ($P=0.120$). Compared to African-Americans, there was a 0.46 (95% CI HR: 0.18, 1.22) lower hazard for Caucasians for stroke. Only age at prostate cancer diagnosis was associated significantly with time to stroke ($P=0.005$); for every one year increase in age at diagnosis, there was a 1.06 (95% CI HR: 1.02, 1.11) greater hazard for stroke after adjusting for the other covariates.

Figure 5. Kaplan-Meier survival curve of time to stroke, presenting race-specific survival curves.



As described in the statement of work, we examined the association of ADT, overall and by race, with CVD outcomes, which is part of the analysis of aim 2: To examine if ADT is associated with worsening CVD risk factor profiles and more CVD events and to determine whether race modifies these associations.

Statistical Methods

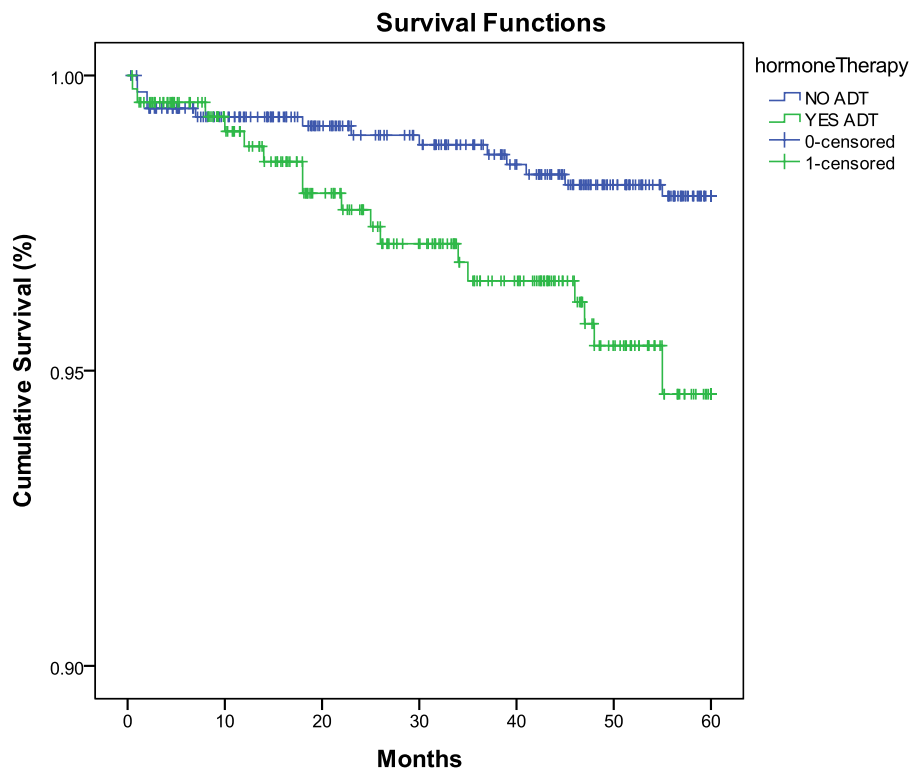
The statistical approach and definitions used are the same as above. Additionally, we defined ADT use as ever/never hormone therapy (as presented in Table 2). To examine if there were race-specific associations of ADT use on time-to-MI or stroke, we additionally employed Kaplan-Meier methods to explore the survival time for the four categories of race and ADT-use; Caucasians ever using ADT, Caucasians never using ADT, African Americans ever using ADT

and African Americans never using ADT. Cox models were fit with an ADT-by-race interaction term to formally test for a race-by-ADT effect of time to event and race-specific models were also fit to examine the magnitude of the association, if any, by race.

Association of ADT use with Time-to-MI, overall and by race

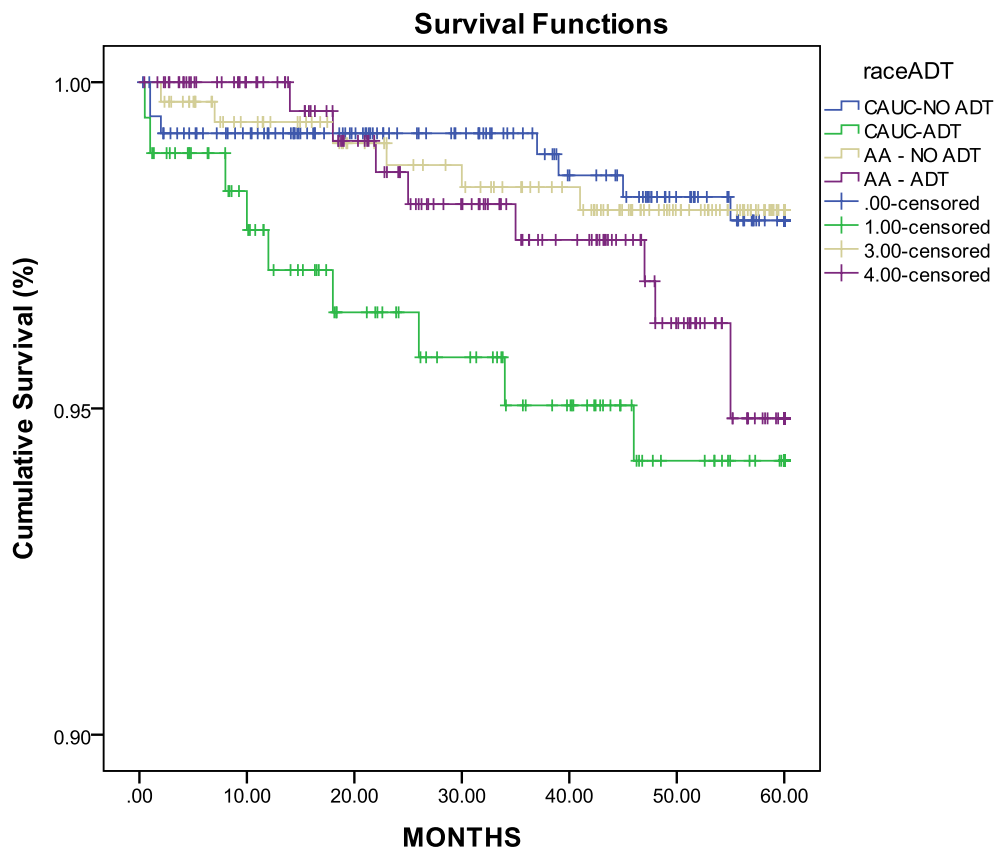
Overall, ADT was statistically significantly associated with time to MI ($P=0.01$) (Figure 6). In a Cox model exploring time-to-MI that adjusted for age at diagnosis, city of residence, marital status, employment status, current smoking and race, ADT use remained significantly associated with time to MI ($P=0.025$). Compared to never ADT users, ADT users had a 2.41 (95% CI HR: 1.12, 5.20) greater hazard of MI.

Figure 6. Kaplan-Meier survival curve of ADT-use with time to MI



We then explored the race-by-ADT association with time-to-MI. This association between ADT and time-to-MI remained significant ($P=0.044$) after accounting for race. As seen in Figure 7, ever use of ADT was associated with shorter time-to-MI among both Caucasian and African-American prostate cancer cases. In Cox regression models, we found no evidence of a race-by-ADT interaction ($P=0.89$) on time-to-MI. Stratifying by race, the association of ADT use with MI was similar (although no longer statistically significant) in each group. Among Caucasians, the association of ADT use with time to MI was 2.49 (95% CI HR: 0.88, 7.02; $P=0.085$) and among African Americans, the association of ADT use with time to MI was 2.30 (95% CI HR: 0.74, 7.20; $P=0.152$).

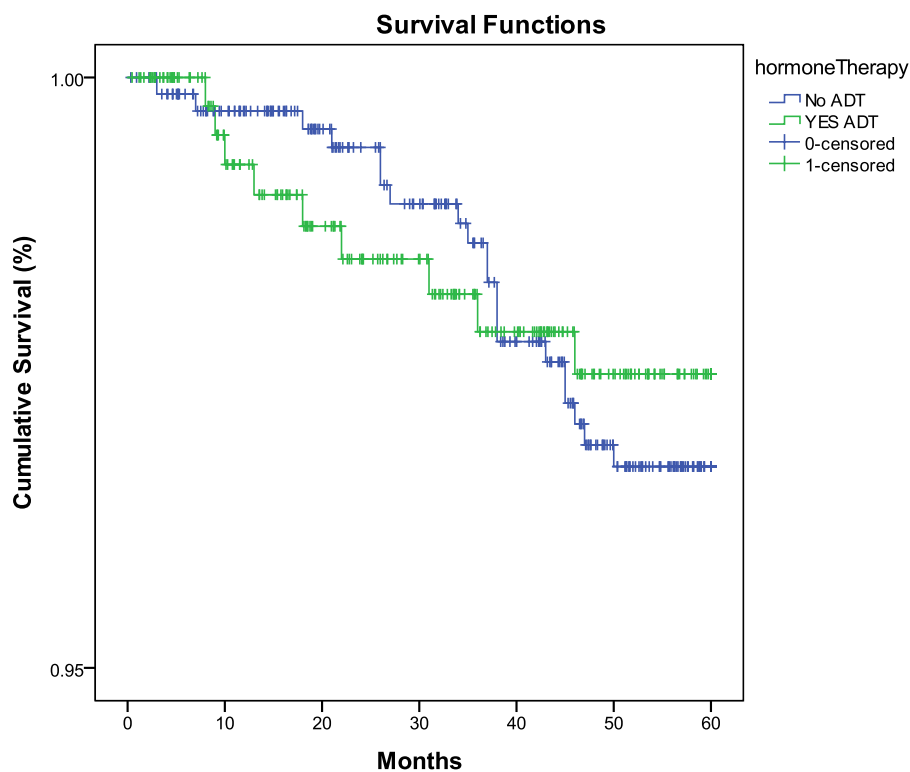
Figure 7. Kaplan-Meier survival curve of ADT-use with time-to-MI, by race



Association of ADT use with Time-to-stroke, overall and by race

There was no evidence that ADT use was associated with time-to-stroke ($P=0.659$); Figure 8. In the Cox model, this remained non-significant ($P=0.175$). Compared to non-ADT users, ADT users had a 0.57 lower hazard of stroke (0.24, 1.30) after adjusting for age at diagnosis, residence, marital status, employment status, current smoking and race.

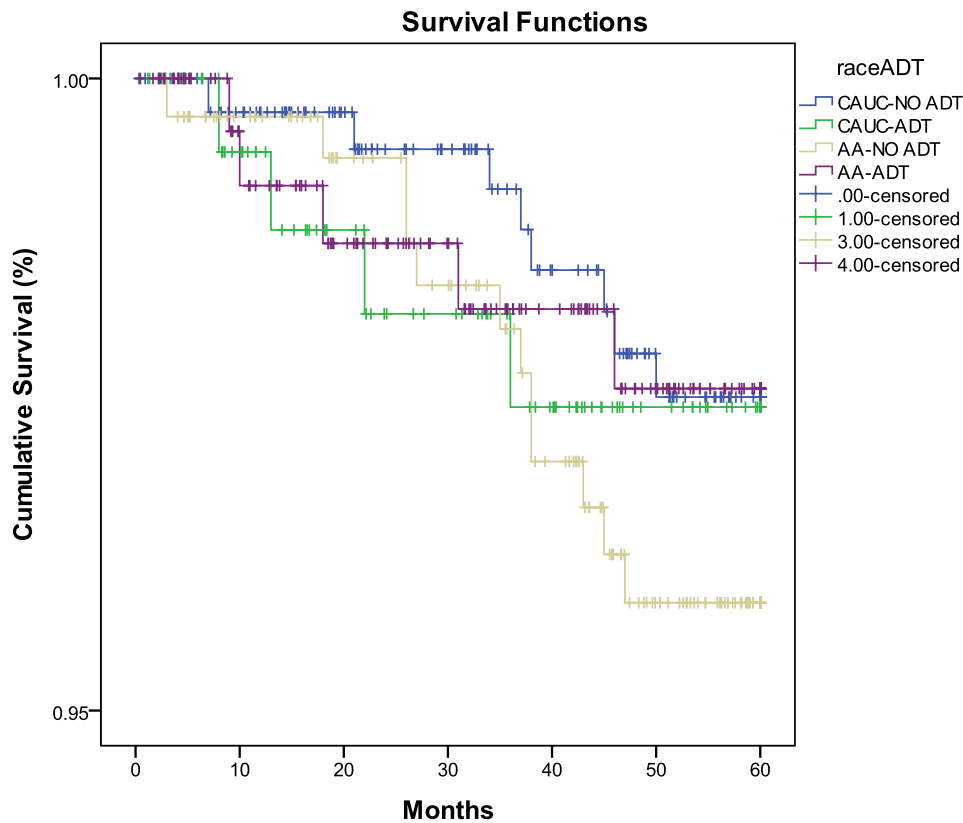
Figure 8. Kaplan-Meier survival curve of ADT-use with time-to-stroke



We then explored the race-by-ADT association with time-to-stroke. This remained non-significant ($P=0.643$); Figure 9. We similarly found no evidence for a race-by-ADT use interaction with time-to-stroke ($P=0.513$) in the multivariable Cox regression model. Stratifying by race, there was no evidence of an ADT – stroke association in Caucasians ($P=0.81$; HR=0.85

(95% CI HR: 0.24, 3.07)). There was similarly no statistically significant association in African Americans ($P=0.132$; HR = 0.42; 95% CI HR: 0.14, 1.30).

Figure 9. Kaplan-Meier survival curve of ADT-use with time to MI, by race



These analyses are being prepared for submission to a peer-reviewed journal.

Preliminary Analysis of ADT and Hyperlipidemia

As presented in the annual reports for this project, we have also examined the relationship of ADT use (ever/never) with total cholesterol level pre- and post-diagnosis (see poster in appendix). In cross-sectional studies, Androgen Deprivation Therapy (ADT) is associated with cholesterol levels¹ and ADT may also be associated with worsening risk factor profiles.²

Information on cholesterol levels 1 year prior to diagnosis to 5 years post-diagnosis and ADT use (ever/never) were obtained from electronic corporate data stores at HFHS. Linear mixed models were fit to examine whether there was a racial difference in change in cholesterol level, adjusting for first measured cholesterol, by ADT.

A total of 7,528 cholesterol measures were available. Pre-diagnosis, 1077 men (54%) had ≥ 1 cholesterol level measured and post-diagnosis, 1489 men (74%) had ≥ 1 cholesterol level measured. After diagnosis, there was a racial difference in number of men with cholesterol measures by ADT use ($P < 0.001$); among those ever using ADT, more African-American men had ≥ 1 cholesterol measure, while among those never using ADT, more Caucasian men had ≥ 1 cholesterol measure. After adjusting for first measured cholesterol, there was evidence for a race by ADT interaction with change in cholesterol level ($P = 0.06$). Compared to Caucasians never on ADT, both Caucasian and African-American men ever on ADT had an increase in cholesterol whereas African-American men never on ADT had a decrease in cholesterol (Table 3).

Table 3. Change in cholesterol level by Androgen Deprivation Therapy (ADT) and race

C / No ADT		AA / No ADT	C / ADT	AA / ADT	P
		Est (SE)	Est (SE)	Est (SE)	
Cholesterol	Ref	-1.33 (1.13)	1.64 (1.50)	2.52 (1.52)	0.0661

C, Caucasian; AA, African-American; Est, Estimate; SE, standard error

To our knowledge, this is the first investigation examining change in cholesterol levels by ADT use and race, adjusted for baseline cholesterol levels. Given that the 1-year pre-diagnosis

time frame only yielded 54% with a baseline cholesterol level, we obtained IRB approval to obtain the most recent pre-diagnosis cholesterol level not restricting to the 1 year time period, which improves our ability to adjust for baseline cholesterol levels in this cohort.

Individuals Supported by the Study

Andrea E. Cassidy-Bushrow, PhD

Roseanne Rose, RHIT

Nicole Woodward, RHIT

Anthony Wahlman, BS

Key Research Accomplishments

- Cholesterol profile of men with prostate cancer varies by race and treatment type. This abstract was submitted and accepted for poster presentation to the IMPACT meeting.

Reportable Outcomes

Cassidy-Bushrow, AE. Mahan, M. Rybicki BA. Cholesterol profile of men with prostate cancer varies by race and treatment type. 2011. Second Innovative Minds in Prostate Cancer Today (IMPACT) conference, Orlando, FL, March 2010.

Conclusions

In our study population of men with prostate cancer, we found preliminary evidence that ADT was associated with development of CVD, specifically MI and type II diabetes mellitus, in

a race-specific manner. The association of ADT with MI remained robust even after covariate adjustment. Additionally, as demonstrated by others, ADT was associated with an increase in overall cholesterol level. However, cholesterol monitoring overall was lacking among those ever on ADT, predominantly in the Caucasian group, demonstrating a potential gap in CVD risk factor monitoring in a high-risk group. Given that ADT increased cholesterol levels in both African American and Caucasian men with prostate cancer, guidelines for regular screening of men treated with ADT are warranted. Further analysis and manuscript development is underway.

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Appendices

Appendix 1. Poster presented at ImPACT meeting

