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Risk of prostate cancer specific death in men with baseline metabolic aberrations treated with androgen deprivation therapy for biochemical recurrence

S. M. Rudman¹, K. P. Gray², J. L. Batista^{3,4}, M. J. Pitt⁴, E. L. Giovannucci^{3,4,5}, P. G. Harper¹, M. Loda⁴, L. A. Mucci^{3,4}, and C. J. Sweeney^{6,7}

¹Department of Oncology, Guy's & St Thomas' NHS Foundation Trust, London, UK

²Dept. of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard School of Public Health, Boston, USA

³Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School Boston, USA

⁴Department of Epidemiology, Harvard School of Public Health, Boston, USA

⁵Department of Nutrition, Harvard School of Public Health, Boston, USA, Center for Molecular Oncologic Pathology, Dana Farber Cancer Institute, Boston, USA

⁶Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute, Boston, USA

⁷Harvard Medical School, Boston, USA

Abstract

Objectives—To investigate the association of host metabolic factors and the metabolic syndrome on prostate cancer specific death (PCSD) and overall survival (OS) in patients treated with androgen deprivation therapy (ADT) for biochemically recurrent disease.

Patients and Methods—The analysis included 273 prostate cancer patients treated with ADT for rising PSA after surgery or radiotherapy. Patients were assessed for the presence of diabetes, hypertension, dyslipidaemia, and obesity prior to the commencement of ADT and using ATPIII criteria for the presence of the composite diagnosis of metabolic syndrome (MS). Competing risks regression model assessed associations of time to PCSD with the metabolic conditions, while multivariable Cox regression model assessed associations of OS with MS and metabolic conditions.

Results—During a median follow-up of 11.6 years, 157 (58%) patients died, of which 58 (21%) died of prostate cancer. At the start of ADT the median age was 74 (range=46, 92) years, the median PSA was 3.0 ng/mL. MS were observed in 31% patients; hypertension (68%) and

Corresponding Author: Dr. Christopher J Sweeney, Lank Center for Genitourinary Oncology, Dana Farber Cancer Institute, Harvard Medical School, 450 Brookline Avenue, D1230, Boston, MA 02215, Tel: +1617 6324524, christopher_sweeney@dfci.harvard.edu.

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dyslipidaemia (47%) were the most common metabolic conditions. No association of PCSD and MS status was observed. Patients with hypertension tended to have a higher cumulative incidence of PCSD compared to those without hypertension (sub-distribution hazards ratio HR=1.59 (95%CI 0.89, 2.84; p-value=0.11) though not statistically significant. Patients with MS had an increased risk of death from all causes (HR=1.56, 95%CI: 1.07, 2.29; p=0.02) when compared with patients without MS; as did patients with hypertension (HR=1.72, 95% CI: 1.18-2.49; p=0.004).

Conclusions—No association of prostate cancer specific death and metabolic syndrome was observed in this cohort of men receiving ADT for biochemically recurrent prostate cancer. Patients with MS were associated with an increased risk of death from all causes and a similar effect was also observed for prostate cancer patients with hypertension alone.

Keywords

Prostate cancer; metabolic syndrome; hypertension; androgen deprivation therapy; biochemical recurrence; competing risks

Introduction

ADT is important for both high risk localized and metastatic prostate cancer. In advanced disease whilst nearly all respond to therapy, most tumours will eventually develop resistance to ADT with recurrent growth despite castrate levels of serum testosterone. Results from NCIC PR.7 reported that men treated with either continuous or intermittent ADT for biochemical recurrence had a median overall survival of 9 years and the estimated 7-year prostate cancer death rate was 15%¹.

After initiation of ADT, many men develop well documented constitutional metabolic changes which are similar to MS including insulin resistance. However, unlike MS, LHRH agonist-associated changes include changes in subcutaneous fat mass, HDL cholesterol, and adiponectin, but do not alter the waist-to-hip ratio, blood pressure, or C-reactive protein level^{2,3}. The risk of these changes to patients who are often exposed to the effects of hypogonadism for years has been extensively studied and lead to increased incidence of insulin resistance and possibly cardiovascular disease⁴.

However the impact on response to ADT by the presence of these metabolic conditions prior to commencement of ADT remains largely unknown. This is particularly relevant considering the current global obesity epidemic which is associated with more patients having diagnoses of metabolic co-morbidities such as hypertension, dyslipidaemia and diabetes or impaired glucose tolerance at the time of prostate cancer diagnosis. To date the number of patients meeting the criteria for the cluster of disorders comprising the MS continues to rise and is estimated to be up to 30% of the population in the USA⁵. Several studies considering the effect of these co-morbidities have shown both reduced survival and poorer prostate cancer outcomes for patients^{6,7}.

To our knowledge, only one study to date has evaluated the association of these co-morbidities on the efficacy of ADT for the treatment of metastatic or biochemically recurrent prostate cancer. This retrospective study of 82 patients from the Veteran's

Administration (VA) cohort found a significant difference in median time to PSA progression of 16 versus 36 months among men with and without MS respectively⁸ suggesting that MS may be a risk factor for the development of early castration resistant prostate cancer (CRPC).

To assess the association of metabolic co-morbidities with PCSD and OS for patients treated with ADT, patients with biochemically recurrent prostate cancer after surgery or radiation therapy treated with ADT were identified from both the Health Professionals Follow up Study (HPFS) and the previously described VA cohort. The individual data from the two groups provided a reasonable sample size to assess the association of these conditions on PCSD and OS for patients with the prostate cancer disease state of biochemical recurrence post definitive local therapy.

Patients and methods

A combined database analysis of prostate cancer patients treated with ADT for biochemically recurrent disease from the HPFS and the VA cohorts were used. The HPFS cohort was initiated in 1986 and includes over 50,000 men initially without a cancer diagnosis. During follow-up to March 2014 when the database was queried more than 6000 men have been diagnosed with prostate cancer (confirmed through medical records and pathology reports). Following a prostate cancer diagnosis, participants complete further cancer specific questionnaires bi-annually. We identified 209 prostate cancer patients treated with ADT alone for biochemically recurrent disease without evidence of metastatic disease after radical prostatectomy (RP) or radiation therapy (RT) for whom data were available to assess the presence or absence of the following conditions; diabetes, hypertension, hypercholesterolaemia, hypertriglyceridaemia, and obesity around the time of starting ADT. Similarly, 64 patients from the original VA cohort with biochemically recurrent disease only were identified by chart review fulfilling these criteria. The two cohorts formed the analytic cohort of 273 patients

Host factors were defined based on the following criteria: hypertension (systolic BP 140mmHg and/or diastolic BP 90mmHg on two out-patient visits (VA) or self-reported high blood pressure and/or use of blood pressure-lowering medications (HPFS); obesity (BMI > 30 kg/m² – used for VA cohort or waist circumference >102 cm or waist-hip circumference ratio > 0.9 or BMI > 30 kg/m² –used for HPFS cohort; hypertriglyceridaemia (>150 mg/dl on two fasting tests (VA) or self-report of elevated triglycerides (HPFS); fasting high density lipoprotein (HDL) <40 mg/dl (VA) or self-report of low HDL, high cholesterol, statin use, or other cholesterol-lowering medications (HPFS); fasting glucose >110mg/dl (two outpatient morning values whilst not on glucocorticoids (VA) or self-reported diabetes (HPFS). The ATP III criteria was used to define the presence or absence of MS where information on the measureable components was available and by accepting surrogate self reports as above when not. The presence of these conditions among men was assessed up to 26 months prior to the commencement of ADT and up to 2 months post ADT start. (This broad time interval facilitated assessment of the metabolic status of as many patients as possible). All data was ascertained from either electronic medical records (VA cohort) or a combination of patient self-report and electronic medical record (HPFS cohort). The authors

acknowledge that using surrogate markers for the MS criteria identified a cohort of patients with a metabolic syndrome - like condition, not the classic definition of MS. (This will be referred to as MSC hereafter).

Men were followed from date of initiation of ADT to either of the following endpoints: 1) time to PCSD defined as time to death with prostate cancer to death from other causes as competing risk events or censored at last follow-up visit. Death from prostate cancer was confirmed from death certificates or reports from family members. 2) OS, defined as time from start of ADT to death from any cause or censored at date last known alive (in HPFS – March 2014; in VA cohort – February 2010; in the absence of an event time was censored at last follow-up visit).

Statistical analysis

Patient characteristics were descriptively summarized using median, range or interquartile range (IQR) for continuous variables or numbers with proportion for categorical variables. The association with MSC status was evaluated using Chi-square test for categorical variables and Wilcoxon test for continuous variables. The primary analyses assessed the associations of time to PCSD with MSC status using a competing risks regression model⁹ as subjects who died of other causes were no longer at risk for dying from prostate cancer. The method assessed the associations with MSC on the cumulative prostate cancer death probability over time in the presence of death from other causes (as competing risks), with estimates of sub distribution hazard ratio (HR) and 95% confidence interval (CI); the model adjusted for cohort (VA or HPFS) effect and potential relevant clinical factors including race, tumor stage, definitive local therapy, biopsy Gleason Score, age at the start of ADT and PSA level at diagnosis or the start of ADT, respectively. The distribution of time to PCSD according to MSC was estimated using the cumulative incidence function.¹⁰ Similarly, the associations of time to PCSD with individual metabolic conditions were assessed as secondary analyses and were estimated using the cumulative incidence function.¹⁰

Multivariable Cox proportional hazards model¹¹ was used to assess the association of OS with the presence or absence of MSC as well as metabolic conditions with estimates of hazard ratio (HR) and 95% CI. The model was adjusted for potential relevant aforementioned patient or clinical factors and stratified by cohort (VA or HPFS) due to the potential differences in socioeconomic status in the patient populations. Secondary analyses assessed the associations for patients in the two cohorts respectively. The proportional hazards assumption was assessed using Schoenfeld residuals without deviation. The distribution of OS according to MSC status were estimated using the Kaplan-Meier method.

All reported P-values were two-sided. No multiple comparison adjustments were used. The analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC) and R 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval and review was obtained from the Harvard School of Public Health, Health Professionals Follow up Study board and Indianapolis VA Medical Center.

Results

Patient population

A total of 273 patients (64 from VA and 209 from HPFS cohort) treated with ADT for biochemically recurrent prostate cancer are included in this analysis. The patient characteristics are summarized in Table 1. The median age at ADT initiation was 74 years, and the majority of patients were non-African American (93%). The median PSA at diagnosis was 12 (IQR=7-21) ng/mL, 18% of patients had a biopsy Gleason Score >7, 56% of patients received RT as their definitive local therapy and median PSA at the start of ADT was 3.0 (IQR=1.2-9.5) ng/mL.

Overall 68% of patients had hypertension, 47% dyslipidaemia, 31% hypertriglyceridaemia, 22% obesity and 15% impaired glucose tolerance. 31% of patients met the criteria for MSC and within this group only 3 patients had MSC without hypertension (Table 1). Patients with MSC were slightly younger (median age 72 years) compared to patients without MSC (median age 74 years), ($p=0.07$). PSA at ADT start was also higher for patients with MSC compared to those without (5.0 versus 2.6 ng/mL) ($p=0.006$). All other evaluated patient characteristics were similar according to MSC status.

Associations of disease outcomes with patient characteristics

The median follow up for the cohort was 11.6 years. There were 157 (58%) deaths, 47 (56%) patients with MSC and 110 (58%) patients without MSC respectively. 58 (21%) of patients died of prostate cancer; the proportion dying from prostate cancer were 20% (17/84 cases) and 22% (41/189 cases) with and without MSC group respectively (Table 1).

No association of PCSD and clinical factors of race, tumor stage, type of local therapy (radiotherapy versus surgery), age or PSA at diagnosis or ADT start were observed (Table S1). However, age at ADT start, PSA at diagnosis and tumor stage were potentially associated with OS, in particular, older patients (>78 years) had an increased risk of death from any causes [HR = 3.1 (95% CI: 1.89, 5.08); $p<0.001$] when compared with patients ≤ 69 year. (Table S2).

Associations of disease outcome with metabolic syndrome and metabolic conditions

Using the sub-distribution regression model that adjusted for cohort effect as well as potential relevant clinical factors (using cutoff $p<0.2$ from the univariate analysis (Table S1)), no statistically significant associations of time to PCSD with MSC or individual metabolic conditions, were observed. (Table 2) However a trend towards an increased risk of PCSD was observed for patients with hypertension (HR 1.59 95%CI 0.89, 2.84). Figure 1 A and B show the cumulative incidence function according to the metabolic conditions.

Using a Cox regression model that stratified by cohort effect as well as adjusting for potential relevant clinical factors (using cutoff of $p<0.2$ from the univariate analysis (Table S2), the presence of MS was associated with 56% increased risk of death from any cause (HR=1.56, 95%CI: 1.07, 2.29; $p=0.02$) when compared with patients without MSC (Table

3). The Kaplan-Meier estimates for the distribution of OS according to MSC status are shown in Figure 2.

For patients with metabolic co-morbidities, those with hypertension had an increased risk of death from any cause (HR=1.72, 95% CI: 1.18, 2.49, $p=0.004$) (Table 3). In addition, patients with MSC including hypertension as a component had a significant increased risk of death from any cause (HR=2.02, 95% CI: 1.29, 3.17; $p=0.002$) when compared with patients without MSC nor HTN. No statistically significant differences in OS were seen for the other metabolic conditions analyzed.

Discussion

This study examined the association of metabolic co-morbidities on PCSD and OS in prostate cancer patients commencing ADT therapy for biochemically recurrent disease after local therapy. Our analysis confirmed prior observations that patients with more comorbidities (those patients meeting the criteria for MSC) had a significantly increased risk of death from any cause. The competing risks analysis method assessed the probability of PCSD whilst accounting for death from other causes, and no sufficient evidence of difference in risk of PCSD for patients with and without MSC were observed. When assessing the individual MS components a trend towards increased risk of PCSD was observed in the hypertension group (HR=1.59, 95% CI: 0.89-2.84).

This study combined patients with biochemically recurrent disease from the initially reported VA cohort with data from prostate cancer patients in the HPFS study with the same stage of disease. Whilst the combined analysis benefited from the larger sample size, some heterogeneity in the cohorts was observed with the VA cohort having a greater preponderance of comorbid illnesses and MSC - 52% for VA) compared to 24% for HPFS. The VA cohort may represent a lower socioeconomic demographic than those in the HPFS cohort. It was also noted that the VA cohort had a higher risk of death from any cause and PCSD than the HPFS cohort. The authors acknowledge this heterogeneity in addition to the low number of prostate cancer deaths and the reliance on retrospective patient reports and chart reviews are limitations of the study. However, it is worth noting, that the median survival in the NCIC PR-7 phase 3 study in the same disease setting was 9 years for all comers and in the present series it is 12.2 years for those without MSC and 6.2 years for those with MSC. The percentage of men who died of prostate cancer was 15% in NCIC trial and in this series was slightly higher at 21%. This consistency supports the contention that our combined population is representative of the outcomes in prostate cancer patients in the same setting treated with ADT. As such it supports the plausibility of the findings and provides guidance and rationale for a prospective evaluation of the association of MSC with prostate cancer specific mortality and OS.

The interpretation of the association of MSC status on PCSD is complicated by a higher rate of non prostate cancer deaths associated with MSC associated conditions potentially reducing the impact of MSC by dying from a co-morbid illness before a prostate cancer death. In other words, patients with biochemical only relapse have median OS of about 9 years¹, putting them at ongoing risk from MSC associated co-morbidities especially

cardiovascular risks. This observation is supported by the ratio of prostate cancer deaths in this population (n=58) compared to a substantial number of deaths from other causes (n=99).

Of note, hypertension was associated with a trend towards poor survival with prostate cancer as well as death from all causes. Hypertension is known to be associated with poorer OS^{12, 13} but it is not clear why it may be associated with prostate cancer mortality. The exact biological mechanisms that lead to these associations are unknown although evidence of links between the neural microenvironment (which may be linked to hypertension) mediating prostate cancer progression have been suggested¹⁴.

This study adds to an emerging body of biological and clinical data implicating patient's metabolic health and prostate cancer incidence and clinical outcomes. There is a strong correlation between low testosterone levels and the development of MS¹⁵ and the replacement of testosterone is associated with an improvement in insulin resistance, central obesity and dyslipidaemia¹⁶. It is possible that prostate cancers arising from men with lower testosterone may be less dependent on androgens and may therefore become androgen independent more rapidly. Another potential explanation is that the presence of MSC is a surrogate for poor health habits such as smoking and lack of exercise. Whilst there is currently a paucity of data in this area the study by Keto and co-workers⁷ looked at the effect of obesity on a similar cohort of prostate cancer patients. This study found that higher BMI was associated with a trend for greater risk of progression to castrate resistant prostate cancer and towards prostate cancer specific death.

Population studies have also shown an association between IGF-1, its binding proteins and the risk of prostate cancer^{17,18} and elevated IGFBP-1 has been associated with shorter time to castration resistant prostate cancer (CRPC) and OS in men with metastatic disease treated with ADT¹⁹. The latter is contended to be due to increased IGFBP-1 leading to increased transport of IGF-1 into the cell.²⁰ Preclinical data has also shown that ADT plus IGFR inhibition was more effective than ADT or IGFR inhibition alone in prostate cancer xenograft models²¹. To date, however clinical trials of IGFR inhibitors in unselected CRPC and hormone sensitive patients have been disappointing^{22, 23, 24}. In addition lifestyle modifications including increased physical activity and smoking cessation have been shown to result in weight reduction and an associated reduction in the risk of developing diabetes²⁵, dyslipidaemia²⁶ and decreased risk of prostate cancer mortality in men diagnosed with non-metastatic prostate cancer²⁷.

In conclusion, no evidence for an association between a shorter time to death from prostate cancer and the presence of MS related co-morbidities at the time of starting ADT for androgen dependent biochemically recurrent prostate cancer was observed. However trends toward an association of the MS component hypertension was observed supporting the hypothesis that metabolic status at the time of commencement of ADT may be important for prostate cancer disease control. These findings support the conduct of studies to assess whether strategies to improve metabolic health and manage hypertension can decrease death from prostate cancer and earlier deaths from non-cancer causes associated with MSC and its associated components. In addition the presence of MSC and hypertension were both associated with an increased risk of death from any causes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Cumulative incidence of prostate cancer specific death (PCSD) according to (A) metabolic syndrome (MS), and (B) MS factors of HTN status, with HR estimate, 95%CI from competing risk regression model that adjusted for cohorts and relevant clinical factors

Figure 2.

Kaplan Meier plots of Overall survival (OS) according to metabolic syndrome (MS) status, with HR estimate, 95%CI and Wald test P-value from Cox proportional hazards model stratified by cohorts (VA vs. HPFS) and adjusted for potential clinical factors.

Table1

Patient characteristics by metabolic syndrome (MS) status (N=273)

Characteristics		Total (N=273)	No MS (N=189)	MS (N=84)	P- value*
Follow-up years, Median (95%CI)		11.6(10.4,12.5)	12.2(11.1,14.2)	6.2(5.9,12.5)	
Cohorts, N(%)	VA cohort	64(23)	31(16)	33(39)	<0.0001
	HPFS cohort	209(77)	158(84)	51(61)	
Race, N(%)	Non-Black	253(93)	176(93)	77(92)	0.802
	Black	20(7)	13(7)	7(8)	
PSA at diagnosis (ng/mL)	Median (IQR)	12 (7,21)	10 (7,19)	12 (7,25)	0.301
	Mean (SD)	18.3(23.8)	16.0(14.4)	23.2(36.4)	
Clinical stage at diagnosis, N(%)	T1	124(46)	82(44)	42(50)	0.285
	T2	106(39)	80(43)	26(31)	
	T3	31(11)	19(10)	12(14)	
	N1	10(4)	6(3)	4(5)	
	Unknown/Missing	2	2	0	
Biopsy Gleason Score, N(%)	<7	111(45)	75(45)	36(45)	0.982
	=7	90(37)	60(36)	30(38)	
	>7	44(18)	30(18)	14(18)	
	Unknown/Missing	28	24	4	
Definitive local therapy, N(%)	Radical Prostatectomy	121(44)	84(44)	37(44)	1
	EBRT or Brachytherapy	152(56)	105(56)	47(56)	
Age at ADT start (years)	Median (IQR)	74 (69,78)	74 (70,79)	72 (68,76)	0.072
	[Min, Max]	[46,92]	[48,92]	[46,87]	
PSA at ADT start (ng/mL)	Median (IQR)	3.0 (1.2,9.5)	2.6 (1.0,7.8)	5.0 (1.8,22.8)	0.006
	Mean (SD)	34.37(130.77)	28.59(122.19)	47.66(148.68)	
Metabolic factors					
Obesity **, N(%)		59(22)	21(11)	38(45)	<0.0001
Hypertension, N(%)		185(68)	104(55)	81(96)	<0.0001
Dyslipidemia, N(%)		128(47)	62(33)	66(79)	<0.0001
Hypertriglyceridemia, N(%)		85(31)	19(10)	66(79)	<0.0001
Impaired glucose tolerance, N(%)		42(15)	10(5)	32(38)	<0.0001
Analysis events					
All death, N(%)		157(58)	110(58)	47(56)	
Prostate cancer death, N(%)		58(21)	41(22)	17(20)	

IQR: interquartile range ; SD= standard deviation, EBRT= External beam radiotherapy; ADT=androgen deprivation therapy; PSA=Prostate-Specific Antigen

Waist circumference >102 cm, or waist-hip; circumference ratio>0.9 (for HPFS cohort)

* Wilcoxon Test or Chi-Square Test when appropriate,

** Obesity: BMI>30 kg/m² for VA cohort; BMI>30 kg/m²,

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Table 2

Association of prostate cancer specific death (PCSD) with Metabolic Syndrome (MS) status (Yes vs. No).

	Overall ^a			VA cohort ^b			HPFS cohort ^b		
	N (events)	HR(95%CI)	p-value	N (events)	HR (95%CI)		N (events)	HR (95%CI)	
Metabolic syndrome									
Metabolic syndrome	84(17) vs. 189(41)	1.04(0.58,1.87)	0.9	33(7) vs. 31(2)	2.62(0.54,12.71)		51(10) vs. 158(39)	0.93(0.47,1.86)	
MS components									
Obesity	59(13) vs. 214(45)	1.02(0.55,1.88)	0.95	21(5) vs. 43(4)	2.17(0.62,7.65)		38(8) vs. 171(41)	0.85(0.41,1.77)	
Hypertension (HTN)	185(41) vs. 88(17)	1.59(0.89,2.84)	0.11	58(9) vs. 6(0)	-		127(32) vs. 82(17)	1.54(0.84,2.82)	
Dyslipidemia	128(25) vs. 143(33)	0.81(0.48,1.37)	0.43	24(4) vs. 38(5)	1.26(0.32,5.04)		104(21) vs. 105(28)	0.79(0.45,1.39)	
Hypertriglyceridemia	85(13) vs. 185(45)	0.58(0.31,1.1)	0.10	38(7) vs. 23(2)	1.81(0.39,8.46)		47(6) vs. 162(43)	0.45(0.19,1.03)	
Diabetes	42(10) vs. 231(48)	1.14(0.56,2.34)	0.71	19(4) vs. 45(5)	1.67(0.41,6.72)		23(6) vs. 186(43)	1.07(0.46,2.48)	
MS+HTN status									
MS=No, HTN=No (ref)	85(17)	1		5(0)	1		80(17)	1	
MS=No, HTN=Yes	104(24)	1.56(0.81,2.99)	0.18	26(2)	-		78(22)	1.55(0.79,3.05)	
MS=Yes, HTN=Yes	81(17)	1.43(0.7,2.91)	0.32	32(7)	-		49(10)	1.27(0.57,2.84)	

N(Events)=total number of patients(number of prostate cancer deaths). HR: Hazard Ratio; CI=confidence interval

^aCompeting risk regression model[11] adjusted for cohort groups (HPFS vs. VA), and potential relevant clinical factors

^bCompeting risk regression model [11] adjusted for potential relevant clinical factors of PSA at diagnosis.

Table 3

Association of all death with metabolic syndrome (MS) status (Yes vs. No) and metabolic components

	Overall ^a			VA cohort ^b		HPFS cohort ^b	
	N (events)	HR (95%CI)	p-value	N(events)	HR (95%CI)	N(events)	HR(95%CI)
Metabolic syndrome							
Metabolic syndrome	84(47) vs. 189(110)	1.56(1.07,2.29)	0.02	33(19) vs. 31(5)	4.03(1.3,12.54)	51(28) vs. 158(105)	1.3(0.84,2.02)
MS components							
Obesity	59(37) vs. 214(120)	1.06(0.7,1.6)	0.79	21(12) vs. 43(12)	1.72(0.65,4.53)	38(25) vs. 171(108)	0.91(0.56,1.49)
Hypertension (HTN)	185(104) vs. 88(53)	1.72(1.18,2.49)	0.004	58(23) vs. 6(1)	6.69(0.73,61.15)	127(81) vs. 82(52)	1.61(1.1,2.36)
Dyslipidemia	128(71) vs. 143(85)	1.31(0.93,1.83)	0.12	24(11) vs. 38(12)	1.98(0.77,5.06)	104(60) vs. 105(73)	1.23(0.85,1.78)
Hypertriglyceridemia	85(41) vs. 185(115)	1.05(0.69,1.6)	0.81	38(18) vs. 23(5)	1.23(0.4,3.76)	47(23) vs. 162(110)	0.94(0.58,1.52)
Diabetes	42(27) vs. 231(130)	1.33(0.86,2.05)	0.20	19(11) vs. 45(13)	2.22(0.92,5.34)	23(16) vs. 186(117)	0.99(0.58,1.69)
MS+HTN status							
MS=No, HTN=No (ref)	85(52)	1		5(1)	1	80(51)	1
MS=No, HTN=Yes	104(58)	1.5(0.99,2.28)	0.06	26(4)	3(0.27,33.35)	78(54)	1.54(1.01,2.36)
MS=Yes, HTN=Yes	81(46)	2.02(1.29,3.17)	0.002	32(19)	9.02(0.97,84.09)	49(27)	1.68(1.03,2.77)

N(Events)=total number of patients(number of deaths); HR: Hazard Ratio; CI=confidence interval

^a: Multivariable Cox regression model stratified by cohorts (HPFS vs. VA) and adjusted for potential significant clinical factors

^b: Multivariable Cox regression model adjusted for potential significant clinical factors