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The metabolic syndrome and cancer: is the metabolic syndrome useful for predicting cancer risk above and beyond its individual components?

Short running title: The metabolic syndrome and cancer risk

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Abstract

Aims The metabolic syndrome (MetS) is a risk factor for cancer. However, it is not known if the MetS confers a greater cancer risk than the sum of its individual components, which components drive the association, or if the MetS predicts future cancer risk.

Materials and Methods We linked 20,648 participants from the Australian and New Zealand Diabetes and Cancer Collaboration with complete data on the MetS to national cancer registries and used Cox proportional hazards models to estimate associations of the MetS, the number of positive MetS components, and each of the five MetS components separately with the risk for overall, colorectal, prostate and breast cancer. Hazard ratios (HR) and 95% confidence intervals (95%CI) are reported. We assessed predictive ability of the MetS using Harrell's c-statistic.

Results The MetS was inversely associated with prostate cancer (HR 0.85; 95% CI 0.72—0.99). We found no evidence of an association between the MetS overall, colorectal and breast cancers. For those with five positive MetS components the HR was 1.12 (1.02-1.48) and 2.07 (1.26—3.39) for overall, and colorectal cancer, respectively, compared with those with zero positive MetS components. Greater waist circumference (WC) (1.38; 1.13—1.70) and elevated blood pressure (1.29; 1.01—1.64) were associated with colorectal cancer. Elevated WC and triglycerides were (inversely) associated with prostate cancer. MetS models were only poor to moderate discriminators for all cancer outcomes.

Conclusions We show that the MetS is (inversely) associated with prostate cancer, but is not associated with overall, colorectal or breast cancer. Although, persons with five positive components of the MetS are at a 1.2 and 2.1 increased risk for overall and colorectal cancer, respectively, and these associations appear to be driven, largely, by elevated WC and BP. We also demonstrate that the MetS is only a moderate discriminator of cancer risk.

Background

The metabolic syndrome (MetS) is defined by a group of metabolic risk factors that have a tendency to cluster together in one individual – obesity (particularly central obesity), hypertension, dyslipidaemia and insulin resistance.(1, 2) These factors, separately and jointly, have been associated with several chronic diseases, in particular cardiovascular disease (CVD)(3) and type 2 diabetes.(4) There is emerging evidence that the MetS may also be important in the development of some cancers.(5)

A recent meta-analysis reported that the MetS is associated with low to modest increased risks for colorectal, post-menopausal breast, bladder, pancreas, endometrium and liver cancers, (5) but for prostate cancer, evidence is conflicting. Some studies report an increased risk,(6) others report a decreased risk,(7) and others report no association with the MetS.(5) Mechanisms linking the MetS and cancer are not well understood. The association may partially be explained by the presence of obesity, and overt hyperglycaemia, both of which have been repeatedly associated with increased risks for some common cancers and a decreased risk for prostate cancer.(8, 9) There is also some evidence to suggest that elevated blood pressure (BP) is associated with an increased cancer risk (10) while high-density lipoprotein (HDL) cholesterol have been shown to have an inverse association with cancer(11). It is not yet known whether the strength of the association between the MetS and cancer is greater than the sum of its individual components, which individual components may be driving this association, or whether the MetS is a useful predictor of future cancer risk.

Using a large pool of prospective studies, we report the risks for overall, and the three most common site-specific cancers, colorectal, prostate and breast cancer associated with the components of the MetS, both separately and jointly. We additionally investigate whether the MetS is a useful measure for discriminating cancer risk.

Methods

Study population

The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC) is a pooled cohort comprising 18 prospective studies in Australia and New Zealand with data on 153,025 men and women. All included cohorts were comprised of adults, except Fremantle Diabetes Study (FDS), a diabetes cohort which also included some

adolescents with type 1 diabetes. Details of sampling procedures, study designs, and methods for each of the studies have been described.(12) In brief, investigators of cohort studies conducted in the region from 1983 onwards with data on diabetes and the MetS, and with a minimum sample size of 1,000 were invited to participate in the ANZDCC study. For the current analysis, we included studies that had collected data on all five MetS components in order to determine MetS status (5 cohorts; n= 59,630). We further excluded participants with missing data on any of the five MetS components (n=37,392); a cancer diagnosis prior to their baseline date (n=905); and missing data on smoking and education status (n=305). A total of 20,468 participants (men=9,437; women=11,031) with complete data were included in the final data analysis.

Data Linkage

The ANZDCC cohort was linked to the *Australian Cancer Database* (ACD), a register of all primary, malignant cancers diagnosed in Australia since 1982, and the *National Death Index* (NDI). Linkage was performed by the Australian Institute of Health and Welfare (AIHW) and the Western Australian Data Linkage Unit (FDS only) using first name, second name, last name, gender, and date of birth.(13) Cancer status of the cohort was determined until 31 December 2008 for the Australian Diabetes Obesity and Lifestyle Study (AusDiab), Crossroads Undiagnosed Disease Study (CUDS) and the North West Adealaide Health Study (NWAHS); 31 August 2010 for the Melbourne Collaborative Cohort Study (MCCS); and 31 October 2012 for FDS. We set a match link rate of 97.70% (true matches/correct links) with link accuracy of 97.92% (1.08% expected to be false positive links). 27% of links underwent clerical review, performed by AIHW. This match link rate has shown to be a reliable cut-off in similar studies.(14) Cancer was defined using the International Classification of Disease 10th Revision (ICD-10) codes as follows: overall cancer (C00-C97, D45-D46, D47.1, D47.3); colorectal (C18-C20); prostate (C61); breast (C50).

Definition of covariates

All participants were measured for weight, height, waist circumference (WC), BP; fasting plasma glucose, serum HDL cholesterol and triglycerides by trained staff adhering to standardised protocols at baseline. Information on education and smoking status was collected by questionnaires. These risk factors were harmonized across

studies to reflect common categories as follows: smoking (current smoker, ex-smoker, never-smoker; education (high school or lower, above high school).

Definition of the metabolic syndrome

The MetS was defined according to the current harmonized definition, Table 1.(2)

Statistical Analysis

Individuals were followed from baseline date to census date of data linkage, date of death or date of cancer diagnosis, whichever occurred first. Incidence of cancer was defined as the first occurrence of cancer or death from cancer if that was the first time the cancer had been reported. For site-specific cancers, individuals with a diagnosis of a cancer at a site other than the one under consideration were censored at their date of diagnosis.

Differences in baseline characteristics were assessed using Pearson's chi-square test for proportions, Student's t-test for means from approximately continuous distributions and Wilcoxon's rank sum test for skewed data. Heterogeneity of studies was assessed by conducting a meta-analysis using a random effects model and statistical heterogeneity was estimated by the I^2 statistic.(15) Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (95%CI) of cancer incidence associated with the MetS, the number of positive components of the MetS and the five component elements of the MetS. Proportional hazards assumptions were satisfied as assessed with graphs of log-log plots of the relative hazards by time for discrete variables and by scaled Schoenfeld residuals. All models were adjusted for sex, smoking, education and study cohort with age as the time scale. Sensitivity analyses were performed excluding the first two years of follow up, and excluding FDS.

To ascertain the best predictor of cancer incidence, we assessed the predictive capacity (discrimination) of models using Harrell's c-statistic. The models considered were: age and sex; MetS; the number of positive components for MetS; all individual MetS components in continuous form: all individual MetS components according to cut-offs. The c-statistic estimates the probability of concordance between predicted risk and the

observed order of events from a randomly selected pair of participants while accounting for censored data.(20) A score of 1.0 indicates perfect discrimination and 0.5 indicates poor discrimination. The c-statistic and 95% CI's from each model were estimated and compared with the MetS model using the `somersd` package and `lincom` commands, respectively, in STATA (version 12.1, (StataCorp, College Station, TX, USA), as described elsewhere.(16) All models were adjusted for age and sex using follow-up time as the time scale.

This study was approved by the Alfred Health Human Research Ethics Committee (HREC), the Australian Institute for Health and Welfare HREC and the Western Australian Department of Health HREC.

Results

Those included in the MetS analysis (n=20,468) were younger, less likely to be current smokers and had attained a higher level of education compared with those who were not excluded (n=132,557), Supplementary Table 1. Over a median follow-up of 8.5 years 2,827; 468; 651 and 549 cancers were identified for overall, colorectal, prostate and breast cancer, respectively. Baseline characteristics of the study population, by cancer and MetS status, are shown in Table 2. In brief, those who developed cancer were more likely to be men, older, less likely to be never smokers and have completed high school and more likely to manifest the MetS and its components, excluding triglycerides, compared with those who did not develop cancer. Similar patterns were observed among those with a diagnosis of the MetS as compared with those who did not have the MetS at baseline.

Information on the MetS and its components, by study, are shown in Supplementary Table 2. Similar proportions of participants with positive MetS components were observed across cohorts, except for FDS, a sample of people with diabetes, for which proportions were higher. No significant heterogeneity across studies was found (I^2 = 12.6%).

Overall, the MetS was not associated with an increased risk of overall, or breast cancer, Table 3, and there was a non-significant borderline association with colorectal cancer, p=0.067. Associations for overall and colorectal cancer were similar in men and women. A reduction in risk of prostate cancer, was observed for the MetS (HR 0.85, 95% CI: 0.72 –0.99). The HRs rose as the number of positive components rose, such that those with five

positive MetS components were 1.12 (1.02 – 1.48) and 2.07 (1.26–3.39) times more likely to develop overall, and colorectal cancers, respectively, compared with those with no positive MetS components, p_{trend} = 0.275 and p_{trend} = 0.006 for overall and colorectal cancer, respectively (Figure 1). There was an inverse association between the number of MetS components present and incident prostate cancer risk (p_{trend} = 0.005). No significant relationship with breast cancer was observed for the number of MetS components. Excluding the first two years of follow up and excluding FDS had little effect on the magnitude of HR estimates (data not shown).

Of the five MetS components, WC was associated with an increased risk for colorectal cancer (1.38, 1.13-1.69) that was stronger in men (1.58, 1.19-2.10) compared with women (1.22, 0.91-1.65) and a decreased risk for prostate cancer 0.77 (0.66-0.91) (Table 4). Elevated BP was associated with an increased risk for overall cancer in men only (1.16, 1.02-1.33). Elevated BP was also associated with an increased risk for colorectal cancer (1.29, 1.01-1.64) with HRs higher for men than women, 1.38 vs 1.24, though analyses by sex were non-significant. Elevated triglycerides was protective against prostate cancer (0.78, 0.66-0.93) and elevated FPG and low HDL were not associated with any of the cancers.

C-statistics comparing prediction models were similarly moderate across all models for overall, colorectal, prostate and breast cancers with c-statistics ranging from 0.60 to 0.76 (Table 5). Models of age and sex had greater discriminative ability than the MetS for overall cancer, p=0.027(Supplementary Table 3). Models using the number of positive MetS components performed better than the MetS for the prediction of prostate and breast cancers, and models of all MetS components in continuous form and as cut-offs performed better than the MetS for the prediction of prostate cancer.

Discussion

Using a large pooled cohort of Australian adults, we show that the MetS is inversely associated with prostate cancer, but is not associated with overall, colorectal or breast cancer. Individuals who manifest all five components of the MetS are at a 1.2 and 2.1 times increased risk for overall and colorectal cancer, respectively, compared with those who have none. Elevated WC and BP are associated with a 1.4 and 1.3 times increased risk for colorectal cancer, respectively, and elevated WC and triglycerides are associated with decreased risks for

prostate cancer. FPG was not associated with an increased risk for any cancer outcome. In discriminatory analysis, we show that all models were moderate discriminators but there was no clear driver for prediction of cancer.

Comparisons with literature

Our null findings of an association between the MetS and overall, breast and colorectal cancer were unexpected. For colorectal cancer, our risk estimate of 1.20 (0.99-1.45) for men and women combined is similar to those published in the meta-analysis by Esposito et al which estimated a 1.25 (1.19-1.32) and 1.34 (1.09-1.64) increased risk for men and women, respectively, with MetS defined in various ways, compared with those without MetS.(5) Our borderline non-significant finding might be due to the limited power in our study sample or a real null finding. The same meta-analyses concluded that women with MetS also have a 52% increased risk of post-menopausal breast cancer, but no association with total breast cancer.(5) For the current study we combined pre-and post menopausal breast cancer as effect estimates between pre-and post menopausal breast cancer were not materially different (data not shown). The lack of significant findings here may be explained by a relatively young age of women at baseline with a mean age of 52 years. Previous studies have also shown no association between the MetS and breast cancer in middle-aged women, unless the MetS has been present for three to five years (HR 1.84, 95% CI 1.12-3.01).(17) This suggests that the MetS may take time to manifest any deleterious effects on breast cancer development. For prostate cancer, we confirm previous studies that have shown the MetS to be protective such that men with MetS are approximately 15-25% less likely to develop prostate cancer compared with men without the MetS.(7) This is thought to be due to lower levels of circulating testosterone in overweight or obese men.(18) Future studies should explore these relationships by cancer grade as obese men are at a higher risk for more aggressive prostate cancers on diagnosis.(19)

Mechanisms linking the MetS and cancer are not well understood. In this study we have shown that high WC, a marker of visceral adiposity, is strongly associated with an increased risk for colorectal cancer. Visceral adiposity is an established risk factor for cancer, resulting in a chronic low-grade inflammatory state which contributes to production of inflammatory cytokines.(20) We have also shown that BP is associated with colorectal cancer risk. High BP has shown to be associated with cancer by some studies,(21) but data are conflicting. The Physician's

Health Study showed that BP was not associated with an increased risk for colorectal cancer, though obesity and diabetes were.(22) It is possible that the association between high BP and cancer may, in part, be due to reverse causality whereby cancer gives rise to high BP.(10) But in our study we excluded the first two years of follow-up and this did not materially change our results. The other key component thought to drive the association between the MetS and cancer is insulin resistance whereby levels of insulin-like growth factors (IGF) are influenced by circulating insulin levels. Increasing insulin leads to decreased levels of IGF-binding proteins 1 and 2, thus increasing the bioavailability of IGF, which in turn is thought to promote cell cycle progression and inhibition of apoptosis.(23) Unexpectedly, hyperglycaemia was not associated with overall, colorectal, breast or prostate cancers in our study. This may be because insulin resistance is more strongly associated with cancers of the pancreas, liver and endometrium, for which we were underpowered to investigate.

The utility of the MetS as a marker for future disease risk has been questioned in recent years. Commonly, the MetS has been a useful tool for predicting risk of CVD and type 2 diabetes. As the MetS is associated with cancer it seems intuitive that the MetS could also be used to predict an individual's risk of future cancer. On the other hand, studies of CVD have shown that while the MetS is strongly associated with increased risks for CVD, it is not a strong discriminator of CVD and therefore is not good at ranking people in terms of a future cardiovascular event.(24) To our knowledge, we are the first group to explore the utility of the MetS as a discriminator of cancer risk. Here, we find that the MetS is not a useful way of deciding who is or is not likely to get cancer. While people with the MetS are at a greater risk for certain cancers, the MetS is not likely to be a useful tool for predicting cancer risk in a clinical setting.

Strengths and weaknesses

Our study combined data from five large Australian population-based studies to investigate the association between MetS, individuals MetS components and risk of some common cancers. While studies have investigated the discriminative ability of MetS for CVD(24) this is the first time it has been assessed in terms of cancer risk. There are several limitations to this study that should be acknowledged. First, a large proportion of the ANZDCC population was excluded due to missing data on one or more of the MetS component variables. We assessed selection bias across a range of demographics and showed that those who were included in the study were more

likely to be younger, never smokers and better educated than those who were not included. This may, therefore, limit the generalisability of our results. Second, because of our strict inclusion criteria that excluded any participant with missing data, it is possible that we were underpowered to detect true associations between the MetS and cancer, should they exist, and therefore increased our chance of type II errors. Third, the diagnosis of MetS was made on the basis of a single measure at a cross-sectional time point. It is possible, however, that the trajectory of MetS components, such as anthropometric measures and the duration of abnormalities, may influence cancer risk over time. Last, this is a pooled collaborative analysis and even though we did have lifestyle data such as physical activity and diet in some studies, these data were collected too differently across studies to derive sensible harmonized categories. Therefore, we could not further adjust our analyses for potential confounding effects of physical activity, diet and alcohol in a meaningful way.

Conclusions

This large pooled collaborative study has shown that the MetS is associated with a decreased risk for prostate cancer but is not associated with an increased risk for overall, colorectal or breast cancer. We have shown that those with five positive components of MetS are at a 1.2 and 2.1-fold increased risk for overall and colorectal cancer, respectively, and these associations appear to be driven, largely, by elevated WC and BP. We have also demonstrated that the MetS is only a moderate predictor of cancer risk and, thus, do not present strong evidence for the use of MetS in a clinical setting as a useful means for assessing an individual's risk for cancer. It may be more effective to identify high risk individuals who might benefit from targeted treatment and prevention of high WC and BP to decrease future cancer risk.

Conflicts of Interest

None declared

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Authors' contributions

JLH, BBiomedsci(hons), (Baker IDI Heart and Diabetes Institute; Monash University) and MS, MBBS, (Baker IDI Heart and Diabetes Institute; Monash University) wrote the manuscript, had full access to all the data, and conducted the analyses. JES, FRACP, (Baker IDI Heart and Diabetes Institute; Monash University), and DJM, PhD, (Baker IDI Heart and Diabetes Institute; Monash University) contributed to conceptualisation, discussion and reviewed/edited manuscript. DJM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the collaboration and reviewed the manuscript and approved the final version.

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Figure legends

Figure 1 Hazard ratios for cancer, with 95% confidence intervals, by the number of positive components of the metabolic syndrome. *Significant linear trend, $p<0.05$

Table 1 Criteria for a diagnosis of the metabolic syndrome

Component	Cut-off Points
Any three of:	
Elevated waist circumference	Europid: men≥94cm; women: ≥80cm South Asian and Chinese: men≥90 cm; women≥80 cm Japanese: men≥90 cm; women≥80 cm OR Body Mass Index≥30kg/m^2
Raised triglycerides	≥1.7 mmol/L
Reduced HDL-C	Men: <1.0 mmol/L; Women: <1.3 mmol/L
Raised blood pressure	Systolic ≥130 and/or diastolic ≥85mmHg OR antihypertensive therapy (self-report)
Raised fasting plasma glucose	≥5.6mmol/L OR previously diagnosed diabetes (defined by self-report or anti-hyperglycaemic medication)

Table 2 Baseline characteristics of participants according to cancer status and metabolic syndrome (MetS) status.

	Cancer status			Metabolic Syndrome status		
	Cancer	No cancer	p-value	MetS	No MetS	p-value
N	2,827	17,641		7,923	12,545	
Men (%)	53.8	44.9	<0.001	53.4	41.5	<0.001
Mean Age	61.1(10.7)	51.3(14.2)	<0.001	57.6 (12.7)	49.5 (14.1)	<0.001
Age range	14-91	11-96				
Education						
High school or lower	71.6	62.5	<0.001	71.4	59.0	<0.001
Above high school	28.4	37.5		28.6	41.0	
Smoking						
Never smoker	49.9	52.9		47.6	55.6	
Ex-smoker	37.4	30.1	<0.001	36.1	27.9	<0.001
Current smoker	12.7	17.0		16.3	16.4	
Metabolic syndrome variables						
Metabolic syndrome positive	47.7	37.3	<0.001			
WC (high risk)	64.8	62.8	0.043	93.3	44.0	<0.001
FPG (high risk)	47.6	32.2	<0.001	67.6	13.3	<0.001
BP (high risk)	73.6	51.7	<0.001	84.3	36.0	<0.001
HDL (high risk)	31.2	28.4	0.002	57.0	10.9	<0.001
TRIG (high risk)	31.0	29.9	0.240	64.0	8.7	<0.001
WC (men) (cm)	98.0(11.3)	97.6(11.9)	0.243	103.9 (10.4)	92.6 (10.3)	<0.001
WC (women) (cm)	86.0(13.7)	86.4(14.0)	0.316	96.7 (12.3)	81.2 (11.6)	<0.001
FPG (mmol/L)	6.1(1.9)	5.7(1.7)	<0.001	6.6 (2.3)	5.3 (1.0)	<0.001
Systolic BP (mmHg)	140.8(21.0)	130.8(20.1)	<0.001	142.5 (19.7)	125.7 (18.2)	<0.001
Diastolic BP (mmHg)	77.0(12.2)	73.6(12.2)	<0.001	78.7 (12.0)	71.2 (11.5)	<0.001
HDL cholesterol (mmol/L)	1.3(0.4)	1.4(0.4)	<0.001	1.2 (0.3)	1.5 (0.4)	<0.001
TRIG (mmol/L)†	1.3 (0.9,1.9)	1.2 (0.9, 1.8)	<0.001	1.9 (1.4,2.6)	1.0 (0.8, 1.3)	<0.001

Data are means(SD) or proportions; †Median (25^{th}, 75^{th} percentile); Abbreviations: WC: Waist Circumference; FPG: Fasting Plasma Glucose; BP: Blood Pressure; HDL: High Density Lipoproteins; TRIG: Triglycerides. Cut-off points for high risk by MetS component are detailed in Table 1

Table 3 Hazards ratios (HR) and 95% confidence intervals (95%CI) of the association between the metabolic syndrome and cancer

	N events	Person-years	HR (95%CI)*
All cancer (total)	2,827	187,794	1.01 (0.94-1.10)
All cancer (men)	1,520	85,669	1.05 (0.94-1.16)
All cancer (women)	1,307	103,125	1.03 (0.92-1.17)
Colorectal (total)	468	187,620	1.20 (0.99-1.45)
Colorectal (men)	242	84,609	1.22 (0.94-1.59)
Colorectal (women)	226	103,011	1.20 (0.91-1.60)
Prostate	651	84,582	0.85 (0.72-0.99)
Breast	549	102,992	1.00 (0.83-1.20)

Model adjusted for sex (in models of total population), smoking, education and study name with age as the time scale

Table 4 Hazards ratios (HR) and 95% confidence intervals (CI) for the association between individual components of the metabolic syndrome and cancer

	N	Person-years	WC	FPG	BP	HDL	Trig
All cancer (total)	2,827	187,794	1.02 (0.94-1.10)	1.00 (0.92-1.08)	1.07 (0.98-1.17)	1.06 (0.98-1.15)	1.00 (0.92-1.09)
All cancer (men)	1,520	84,669	1.05 (0.95-1.18)	1.01 (0.90-1.12)	1.16 (1.02-1.33)	1.07 (0.95-1.19)	1.02 (0.91-1.13)
All cancer (women)	1,307	103,124	1.03 (0.91-1.16)	1.02 (0.90-1.16)	1.06 (0.93-1.21)	1.07 (0.95-1.21)	1.06 (0.93-1.20)
Colorectal (total)	468	20,468	1.38 (1.13-1.70)	1.01 (0.83-1.24)	1.29 (1.01-1.64)	1.19 (0.97-1.45)	1.09 (0.89-1.34)
Colorectal (men)	242	84,609	1.58 (1.19-2.10)	0.86 (0.65-1.13)	1.38 (0.96-1.99)	1.13 (0.85-1.48)	1.18 (0.90-1.54)
Colorectal (women)	226	103,011	1.22(0.91-1.65)	1.24 (0.93-1.64)	1.24 (0.89-1.73)	1.29 (0.97-1.72)	1.01 (0.74-1.39)
Prostate	651	84,582	0.77 (0.66-0.91)	0.91 (0.79-1.04)	1.05 (0.88-1.25)	0.89 (0.76-1.04)	0.78 (0.66-0.93)
Breast	549	102,992	1.00 (0.84-1.20)	0.91 (0.75-1.11)	1.03 (0.86-1.25)	0.89 (0.73-1.09)	0.97 (0.78-1.21)

Abbreviations: WC: waist circumference; FPG: fasting plasma glucose; BP: blood pressure; HDL: high-density lipoprotein cholesterol; Trig: triglycerides. Effect estimates adjusted for sex (in models of total population), smoking and education with age as the timescale. HRs compare those at high risk for each component, compared with those not at high risk.

Table 5 Discrimination of cancer for five prediction models

	Harrell's c statistic (95% CI)				
	Metabolic Syndrome	Age and sex	Continuous MetS components	Number of MetS components	Component cut-offs
All cancer	0.69 (0.69-0.71)	0.70 (0.69-0.71)*	0.70 (0.69-0.71)	0.70 (0.69-0.71)	0.70 (0.69-0.71)
Colorectal	0.75 (0.73-0 .77)	0.75 (0.73-0.77)	0.75 (0.73-0.76)	0.75 (0.73-0.77)	0.75 (0.73-0.77)
Prostate	0.76 (0.74-0.77)	0.75 (0.74-0.77)†	0.76 (0.75-0.78)*	0.76 (0.75-0.77)*	0.76 (0.75-0.78)*
Breast	0.61 (0.59-0.63)	0.60 (0.58-0.62)†	0.60 (0.58-0.62)	0.62(0.60-0.64)*	0.60 (0.58-0.62)

*c-statistics significantly greater than MetS model, determined by estimating the differences in c-statistics, $p<0.05$ (Supplementary Table 3).†METS better. All MetS models adjusted for age and sex

Supplementary Table 1 Baseline characteristics of participants included in MS analysis compared to those who were not

	Inclusion status		
	Not included	Included	p-value
N	132,557	20,468	
Men	45.4	46.1	0.053
Age	57.8±14.5	55.8±13.2	<0.001
Smoking			
Never smoker	49.9	50.4	
Ex smoker	35.7	35.7	<0.05
Current smoker	14.4	13.9	
Education			
High school or lower	65.9	64.8	
Above high school	34.1	35.2	<0.001

Data are means ± SD or proportions

Supplementary Table 2 Baseline characteristics and follow-up data by study

	Australian Diabetes Obesity and Lifestyle Study	Crossroads Undiagnosed Study	Fremantle Diabetes Study	Melbourne Collaborative Cohort Study	Northwest Adelaide Health Study	Total
N	10,376	1,634	1,247	3,806	3,675	20,468
Year of baseline examination	1999-2000	2001-2002	1993-1996	1991-1994	1999-2000;2002-2003	1993-2003
Median follow-up (years)	8.7	6.8	14.9	16.6	8.1	8.5
% Men	45.0	44.3	49.6	47.1	47.6	46.1
Age (years)	51.0±14.2	52.3±15.5	62.2±13.1	57.2±8.5	49.5±16.0	52.7±14.2
Education (above high school)	37.1	25.2	11.7	27.5	55.2	36.2
Smoking (ever smoker)	45.0	49.1	55.3	43.6	55.4	47.5
WC (high risk)	61.4	72.4	81.6	52.0	69.7	63.1
FPG (high risk)	31.0	21.1	100.0	42.9	17.4	34.4
BP (high risk)	46.9	56.6	88.0	69.8	49.2	54.7
HDL (high risk)	24.7	24.9	64.6	28.6	29.7	28.8
TRIG (high risk)	31.4	28.7	55.9	20.8	27.8	30.1
MetS	35.3	35.1	88.3	38.9	32.6	38.7
N cancer events	831	94	295	1,356	251	2,827

Data are means ± SD or proportions. Abbreviations: WC: Waist Circumference; FPG: Fasting Plasma Glucose; BP: Blood Pressure; HDL: High Density Lipoproteins; TRIG: Triglycerides. Cut-off points for high risk by MetS component are detailed in Table 1

Supplementary Table 3 Coefficients and p-values for the difference in c-statistics between each model discriminative ability for cancer outcomes, as compared to METS

	Coefficients and p-values							
	Age and sex		Continuous variables		Number of MetS components		Component cut-offs	
	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value
All cancer	-0.0013	0.027	0.0054	0.213	-0.0001	0.868	-0.0001	0.616
Colorectal	-0.0006	0.597	0.0036	0.109	-0.0001	0.940	0.0006	0.754
Prostate	0.0032	<0.01	-0.0078	<0.001	-0.0038	<0.01	-0.0056	<0.001
Breast	0.0062	<0.05	0.0020	0.678	-0.0172	<0.01	0.0056	0.228

Note: A negative coefficient denotes that the model mentioned is a better discriminator than the METS model; a positive coefficient denotes that the METS model is a better. All MetS models adjusted for age and sex discriminator

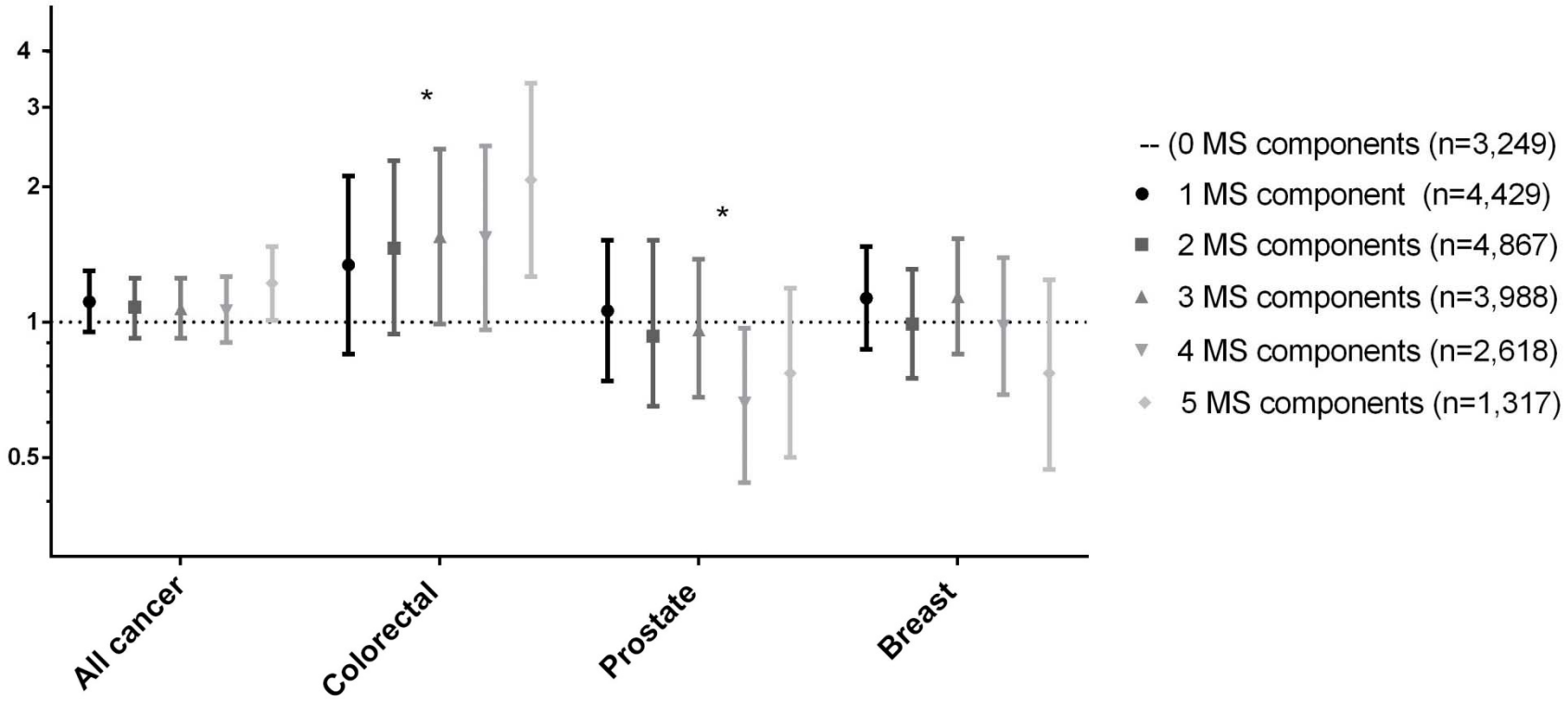

Figure 1 Hazard ratios for cancer, with 95%confidence intervals, by the number of positive components of the metabolic syndrome. *Significant linear trend, *P*<0.05