RESEARCH COMMUNICATION

The Impact of Modifiable Risk Factors on Mortality from Prostate Cancer in Populations of the Asia-Pacific Region

Asia Pacific Cohort Studies Collaboration[1]*

Abstract

Mortality from cancer of the prostate is increasing in the Asia-Pacific, when much of this region is undergoing a transition to a Western lifestyle. The role that lifestyle factors play in prostate cancer appears limited, but existing data mainly are from the West. We conducted an individual participant data analysis of 24 cohort studies involving 320,852 men (83% in Asia). Cox proportional hazard models were used to quantify associations between risk factors and mortality from prostate cancer. There were 308 deaths from prostate cancer (14% in Asia) during 2.1 million person-years of follow-up. The age-adjusted hazard ratio (95% confidence interval; CI) for men with body mass index (BMI) 28 kg/m^2 or more, compared with below 25, was 1.55 (1.12 - 2.16); no such significant relationship was found for height or waist circumference. The BMI result was unchanged after adjustment for other variables, was consistent between Asia and Australia/New Zealand (ANZ) and did not differ with age. There was no significant relationship with diabetes, glucose or total cholesterol ($p \geq 0.18$). Smoking, alone, showed different effects in the two regions, possibly due to the relative immaturity of the smoking epidemic in Asia. In ANZ, the multiple-adjusted hazard ratio for an extra 5 cigarettes per day was 1.12 (95%CI: 1.03 - 1.22), whereas in Asia it was 0.77 (0.56 - 1.05). Body size is an apparently important determinant of prostate cancer in the Asia-Pacific. Evidence of an adverse effect of smoking is conclusive only in the predominantly Caucasian parts of the region.

Key Words: Prostate cancer - obesity - smoking - Asia-Pacific

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Introduction

Cancer of the prostate is the second leading cause of internal malignancy among men worldwide, with an annual incidence of 679,000 cases, and an annual mortality load of 220,000 deaths, making it the sixth leading cause of cancer mortality among men (Perkin et al., 2002). It is a cancer predominantly of the elderly, with three-quarters of cases occurring in men over the age of 65 years (Stewart and Kleihues, 2003). There are substantial ethnic differences in both incidence and mortality rates between regions, with the highest rates found in North America and Western Europe and the lowest rates occurring in Asian populations (Gronberg, 2003). Data for the past 30 years indicate that mortality from prostate cancer is increasing in certain parts of the world, including Asia, particularly in Japan, China and Singapore (Hsing and Devesea, 2001), suggesting that environmental and lifestyle factors may have an aetiological role in prostate cancer, and hence may provide potential targets for future intervention (Stewart and Kleihues, 2003).

Relatively little is known about possible modifiable causes of prostate cancer. Some, but not all, studies have suggested that cigarette smoking (Levi and LA Vecchia, 2001; Hickey et al., 2001; Rodriguez et al., 1997), cholesterol (Kneket et al., 1988; Eichholzer et al., 2000; Bravi et al., 2006), high fat diets (Kolonel et al., 1981) and excess body weight (Rodriguez et al., 2001) might all be associated with increased risk of mortality from prostate cancer. A recent meta-analysis of prospective cohort studies (Bonovas et al., 2004) has, by comparison, suggested that diabetes might actually be protective against prostate cancer. However, the size of this reported association was small equating to an approximate 10% reduction in the relative risk of prostate cancer among individuals with diabetes compared with those without, and this may be explained by residual confounding.

Most of the prospective studies that have investigated the environmental and physiological factors associated with prostate cancer have been conducted among predominantly Caucasian populations (Rodriguez et al., 1997; 2001). Increasing life expectancy and urbanization (Lopez et al.,2006), exemplified by the high prevalence of cigarette smoking (Liu et al.,1998) and increasing prevalence of obesity (Seidell,2000), across large parts of Asia, provides the rationale for exploring the nature of the associations between putative risk factors and mortality from prostate cancer in a large prospective

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database of populations of the Asia-Pacific Region, The Asia Pacific Cohort Studies Collaboration (APCSC).

Patients and Methods

The APCSC comprises a large number of prospective cohort studies and was established to provide reliable evidence about the relationships between a variety of modifiable risk factors and the incidence of major causes of death among populations in the Asia-Pacific region. Details of study identification, data collection and event verification in the Asia Pacific Cohort Studies Collaboration (APCSC) are described elsewhere (Zhang et al., 1999; Woodward et al., 2006). Briefly, studies were included if they had continued follow-up for at least 5,000 person-years and had recorded vital status at the end of follow-up. Studies were excluded if entry was dependent upon a particular condition or risk factor. Mortality was classified according to the 9th Revision of the International Classification of Diseases (ICD): Prostate cancer was selected as ICD 185. Studies were classified as Asian if their participants were recruited from mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan or Thailand; and ANZ if from Australia or New Zealand.

All data on cigarette smoking (Woodward et al., 2005) were based on self-reporting at the time of entry into one of the included studies; smoking status was recorded as current, former or never-smoker. In addition, 15 studies recorded the average number of cigarettes per day for smokers; groups of <20 and ≥20 cigarettes for categorical analysis.

Within most studies in the APCSC, there was no distinction made between type-1 and type-2 diabetes, and hence the analyses included all individuals with diabetes recorded at study baseline on the basis of self-report (Woodward et al., 2003) or elevated blood glucose (Lawes et al,2004), or both. Using the values for height and weight measured at study baseline, body mass index (BMI) (Ni Mhurchu et al., 2004) was computed as weight in kilograms divided by height squared (kg/m^2). Four studies additionally recorded waist circumference. At recruitment, data were also collected on current medications, and several risk factors, including blood pressure (Lawes et al., 2003), and cholesterol (Zhang et al., 2003).

Analyses used individual participant data and were restricted to men aged ≥20 years at enrolment. Cox proportional hazard models, stratified by study and adjusted for age, were used to estimate hazard ratios and 95% confidence intervals (CIs) associated with risk factors both before and after adjustment for other risk factors. Associations between continuously distributed variables and prostate cancer were assessed by obtaining the hazard ratios and 95% CIs for a standard increment in each variable. Dose-response associations were explored by categorizing study participants into equal thirds of continuous distributions. Due to the limited number of events among the studies that had information on waist circumference, we did not examine the dose-response association between waist circumference and prostate cancer. Statistical heterogeneity between region (Asia v ANZ) was examined by adding interaction terms to the Cox model. Only, if evidence of significant regional interactions were found were the associations shown separately for Asia and ANZ. An equivalent procedure was used for age.

Results

Data from 24 studies with information on 320,852 men (83% in Asia) with a mean age of 46 years and a median follow-up of 6.8 years, were included in the analysis. Study populations from Asia were younger (44 vs. 54 years),

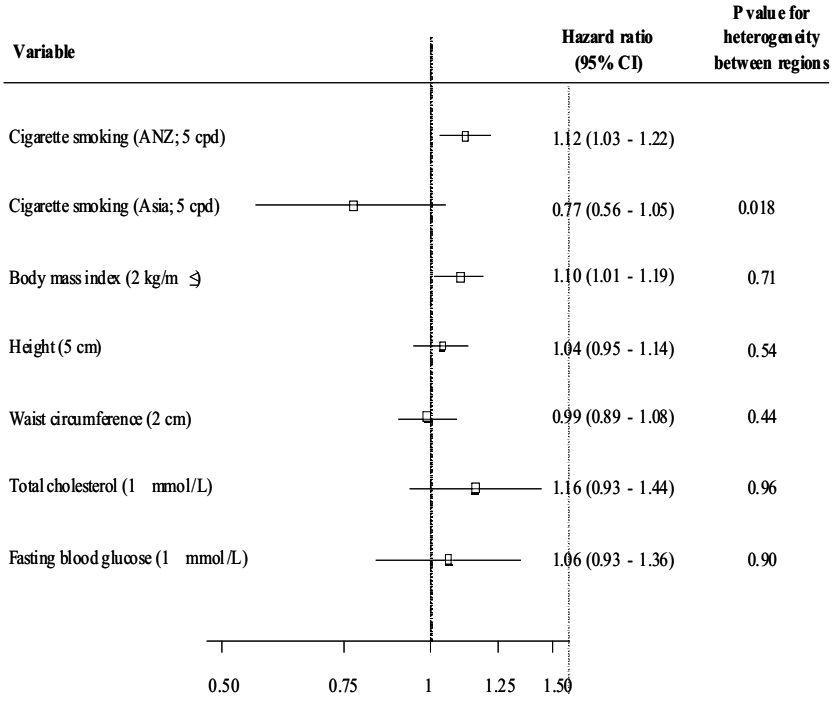

Figure 1. Multiple-adjusted Hazard Ratios and 95% Confidence Intervals for the Associations between Known and Putative Risk Factors for Mortality from Prostate Cancer in Asia and ANZ. Cpd= cigarettes per day

Table1. Study Characteristics at the Baseline

Country	Study	Baseline	No. of subjects	Mean age (years)	Diabetes (%)	Median FU (years)	PC Deaths	Current Smokers(%)	Mean CPD	Mean BMI
Australia	Busselton	1966-81	3,745	45.4	4.0	24.7	76	44	19	24.9
Australia	Canberra-Queanbeyan	1990-91	385	76.3	7.4	7.9	16	13	-	-
Australia	Longitudinal Study of Aging	1992-93	841	79.1	9.6	3.7	9	8	16	25.9
Australia	Melbourne	1990-94	16,951	55.3	7.1	8.5	68	15	22	27.2
Australia	National Heart Foundation	1989-90	4551	43.5	2.2	8.4	9	27	21	25.9
Australia	Newcastle	1983-94	1,953	52.1	4.8	8.5	10	28	20	27.1
Australia	Perth WA AAA	1978-94	5,294	44.8	2.0	14.4	27	30	20	25.1
Australia	Screenees	1996-99	12,203	72.2	11.6	3.2	41	11	14	26.9
NZ	Fletcher Challenge	1992-94	7,430	43.1	2.5	5.8	9	26	15	26.7
ANZ	Subtotal	1966-99	54,353	53.9	6.3	7.6	265	20	20	26.6
China	Guangzhou Occupational	1985-98	130,587	41.9	10.6	7.2	5	60	15	22.4
China	Seven Cities Cohorts	1987	4,916	53.6	1.0	2.7	1	57	-	22.3
China	Six Cohorts	1982-86	10,336	44.6	-	8.4	1	76	-	21.1
China	Xi'an	1976	1,124	45.1	-	19.7	1	54	14	-
Hong Kong	Hong Kong	1985-91	1,273	78.1	7.9	2.5	5	29	13	21.6
Japan	Akabane	1985-86	813	54.5	3.3	11.0	2	62	23	22.2
Japan	Hisayama	1961	698	55.4	-	21.6	1	76	-	21.5
Japan	Miyama	1988-90	477	60.8	8.0	6.6	2	58	21	21.8
Japan	Saitama	1986-90	1,368	55.3	2.1	10.0	8	63	22	22.2
Japan	Shibata	1977	995	56.7	1.3	20.0	3	72	20	22.0
Japan	Shirakawa	1974-79	2,120	47.4	1.0	17.1	5	70	-	21.3
Singapore	Singapore Heart	1982-97	1,186	41.2	12.9	14.4	1	40	-	23.1
S.Korea	KMIC	1992	106,743	44.9	10.0	4.0	5	58	-	23.5
Taiwan	CVDFACTS	1988-96	2,558	48.8	3.2	5.8	2	48	-	23.6
Taiwan	Kinmen	1993-97	1,305	62.2	7.3	2.9	1	50		22.9
Asia	Subtotal	1961-98	266,499	44.1	9.2	6.8	43	60	16	23.1
Total		1961-99	320,852	45.9	8.4	6.8	308	53	17	24.0

NZ=New Zealand; ANZ=Australia and New Zealand; BMI = body mass index; CPD=cigarettes per day for current smokers; FU = follow-up; PC=prostate cancer Note: blank denotes no data available

had a lower mean BMI (23.1 vs. 26.6 kg/m^2), and a higher prevalence of both diabetes (9.2% vs. 6.3%) and current cigarette smoking (60 vs. 20%) compared with ANZ populations (Table 1). Overall, there were 308 deaths from prostate cancer (86% in ANZ) during 2,108,843 person-years of follow-up.

Among individuals over the age of 65 years the risk of dying from the neoplasm was 37 times that of those less than 55 years of age (HR 37.3; 95% CI: 24.0 – 58.1). The association was approximately linear in that for every extra 10 years of age, the relative risk of mortality from prostate cancer was fourfold: HR 3.94 (95% CI 3.33 – 4.60). The age-standardized mortality rates for prostate cancer differed between the regions and were considerably higher in ANZ: 5 per 100,000 person-years in Asia vs. 28 per 100,000 person-years in ANZ.

Cigarette smoking and mortality from prostate cancer

The association between cigarette smoking and prostate cancer differed between the two regions (p for interaction=0.018; Figure 1) and hence the estimates are reported separately for ANZ and Asia. In age-adjusted analyses, after exclusion of former smokers, current smokers in ANZ had a 60% greater risk (HR 1.63 [95% CI 1.10 - 2.43]) of mortality from prostate cancer compared with never smokers, and this was unaffected by adjustment for BMI and diabetes (HR 1.67 [95% CI 1.12 - 2.45]). Every extra five cigarettes smoked per day was associated with a 10% greater risk of mortality from prostate cancer in men from ANZ (Figure 1). Among men in Asia, there was a lack of evidence of a direct association between smoking and prostate cancer which was most likely due to the small number of events upon which this analysis was based (n=26) (HR 0.57 [95% CI 0.24 – 1.32]; Figure 1). There was no evidence that the overall strength of the association between smoking and mortality from prostate cancer differed with age in either of the two regions (p>0.1 in both regions).

Body anthropometry and mortality from prostate cancer

None of the associations between measures of body size with prostate cancer differed between the two regions (p for interaction>0.40 in all instances; Figure 1) and hence a pooled estimate is reported. There was a positive and significant relationship between BMI and the risk of mortality from prostate cancer such that a 2kg/m^2 higher

Table 2. Hazard Ratios and 95% Confidence Intervals for The Associations between Anthropometric and Biochemical Risk Factors and Mortality from Prostate Cancer in Men from Asia and ANZ

Covariate	No. of subjects	No. of deaths	Adjusted for age, sex & study HR (95% CI)	Multiple-adjusted HR (95% CI)
BMI (kg/m_)				
<25*	109,334	91	1	1[a]
25-28	43,470	88	1.37 (1.00-1.87)	1.38 (1.01-1.89)
≥28	21,565	80	1.55 (1.12-2.16)	1.55 (1.11-2.17)
Height (cm)				
≤168*	63,250	80	1	1[a]
168-173	66,674	94	1.26 (0.92-1.73)	1.28 (0.93-1.76)
≥174	42,457	81	1.14 (0.81-1.60)	1.16 (0.83-1.63)
Total cholesterol (mmol/L)				
<5.2*	92,789	69	1	1[b]
5.3-6.1	42,577	71	1.25 (0.88-1.76)	1.24 (0.88-1.75)
≥6.2	21,863	65	1.21 (0.84-1.74)	1.20 (0.83-1.73)
Fasting blood glucose (mmol/L)				
<5.5*	88,377	24	1	1[c]
5.5-5.9	16,803	25	1.24 (0.70-2.22)	1.21(0.68-2.18)
≥6.0	14,743	25	1.32 (0.74-2.36)	1.19(0.66-2.18)

* Reference group; a Adjusted for smoking and diabetes; b Adjusted for diabetes and BMI; c Adjusted for smoking and BMI

BMI was associated with a 10% greater risk of death from this condition in men from both Asia and ANZ: HR 1.10 (95% CI: 1.01 - 1.19; Figure 1). Compared with men who were considered to be within the "normal" weight range (i.e. BMI <25 kg/m²), men who were substantially overweight (BMI >28 kg/m²) had a 50% greater risk of dying from prostate cancer (Table 2). The association was independent of the potential confounding effects of diabetes and smoking, with no evidence of an interaction with age (p=0.14). Waist circumference, which is more accurate measure of central obesity compared with BMI, was not associated with prostate cancer in these populations (Figure 1). There was a non-significant positive association with height such that a 5 cm increment in height was associated with a 4% (95% CI -5% to 14%) greater risk of mortality from prostate cancer in men from both ANZ and Asia.

Metabolic variables and mortality from prostate cancer

As the associations between neither diabetes and total cholesterol with prostate cancer differed between the two regions (p for interaction >0.90 in both instances; Figure 1) only pooled estimates are reported. There was some evidence to suggest that total cholesterol was positively associated with risk of mortality from prostate cancer, although the relationship did not attain conventional levels of significance (p = 0.21) (Figure 1). A 1 mmol/L higher total cholesterol was compatible with a 16% (95% CI -7% - 44%) greater risk of mortality from prostate cancer, which was unaffected by adjustment for smoking, diabetes or BMI. There was no evidence of any interaction with age (p=0.35). In these analyses, there was no evidence of an association between diabetes (HR 1.25 [95% CI 0.81 – 1.92]) or blood glucose (Figure 1) with risk of mortality from prostate cancer in men from either Asia or ANZ. Previous studies had suggested that a protective effect of diabetes on prostate cancer was only apparent several years after diabetes had been diagnosed. In the current study, length of study follow-up was used as a proxy for duration of diabetes, but there was no evidence of a temporal association; in those individuals with study follow-up <3 years the multiple adjusted HR for the association between diabetes and prostate cancer was 1.04 (95% CI 0.47 – 2.30) vs. 1.36 (95% CI 0.81 – 2.27) in those with follow up >3 years.).

Discussion

The primary finding from this large meta-analysis of prospective cohorts within populations of the Asia Pacific Region was that of a direct association between BMI and risk of mortality from prostate cancer. The magnitude of the association was such that a 2 kg/m² increment in BMI – which is equivalent to an approximate 6 kg higher weight – was associated with a 10% greater risk of mortality from the neoplasm. The association was observed in men from both Asia and ANZ and was independent of the possible confounding effects of diabetes and cigarette smoking. This current finding is consistent with that reported by a recent meta-analysis (Macinnis and English, 2006) of more than 50 observational studies with information on nearly 70,000 prostate cancer events. In that review, an overall relative risk of prostate cancer of 1.05 (95% CI 1.01 - 1.08) per 5 kg/m² increment in BMI was reported, with a subgroup analysis showing a stronger association among men presenting with advanced stages of the disease (RR 1.12 per 5 kg/m²). Interestingly, there was no evidence that waist circumference was associated with prostate cancer in either the current study or the aforementioned review, the latter being more adequately powered to address this issue. In comparison, there was some evidence from the current study to suggest a weak (albeit non-significant) positive association between stature and risk of mortality from prostate cancer in men from both Asia and ANZ, of the magnitude of 4% higher risk per 5 cm increment in height. Previously, the evidence of an association between height and prostate cancer has been ambiguous. For example, several investigations including the large Cancer Prevention Study-II (CPS-II) (Rodriguez et al., 2001), have not shown an association

between height and prostate cancer, whereas a systematic review (Gunnell et al., 2001) reported that compared with short men, tall men had between a 20 to 40% greater risk of prostate cancer, although the association was substantially attenuated after adjustment for ethnicity and socioeconomic factors. More recently, the large meta-analysis (Macinnis and English, 2006) reported a small but significant direct association such that a 10 cm increment in height was associated with a 5% greater risk of prostate cancer.

Cigarette smoking has been inconsistently reported to be associated with prostate cancer, depending on the outcome used. Most prospective cohort studies that used incident prostate cancer as the outcome reported no association between current smoking and prostate cancer, whereas many of the studies that used death from prostate cancer as the outcome observed a positive relationship, compatible with a 30% greater risk among smokers compared with non-smokers (Hickey et al.,2001; Rodriguez et al., 1997). Data from the current study are in agreement with such estimates as current smokers had an increase in risk of mortality from prostate cancer of approximately 60% compared with never-smokers, although the association was only observed among smokers from ANZ. Unfortunately, despite the large sample size, there were an insufficient number of events, due to the younger age of the cohorts and short duration of follow up, for reliable detection of an association between smoking and prostate cancer among men in Asia, a finding common to other published studies among Asian men. For example, data from previous cohort and case-control studies in Chinese and Japanese men have generally observed weak, but non-significant, associations between smoking and prostate cancer (Hickey et al., 2001). It is conceivable that the relative immaturity of the smoking epidemic in Asia compared with Western countries, combined with a potentially greater degree of under-or misdiagnosis of prostate cancer in Asia, may have underestimated any effects of smoking on mortality from prostate cancer.

Both positive and inverse associations between total cholesterol levels and prostate cancer have been reported, but most of the data have come from case-control or small cohort studies that may have been unduly influenced by chance (Eichholzer et al., 2000; Bravi et al., 2006). Most recently, a large case-control study (Bravi et al., 2006) reported that a positive association between cholesterol and prostate cancer risk was age-dependent and apparent only in men aged over 65 years. Data from the current study, which is by far the largest prospective study that has explored this relationship, suggested a positive trend between total cholesterol and mortality from prostate cancer but there was no evidence of an interaction with age. However, the magnitude of the association was small (and non-significant), and hence compatible with the effects of residual confounding or possibly chance. Furthermore, a recent meta-analysis of randomized controlled trials of statin therapy (Dale et al.,2006) showed no evidence that cholesterol-lowering had any impact on the risk of various site-specific cancers, including prostate cancer. Overall, the evidence of an association between total cholesterol and mortality from prostate cancer is weak.

Diabetes is considered to be a risk factor for certain site-specific cancers such as pancreatic cancer (Huxley et al, 2005), but its relationship, if any, with prostate cancer is less clear. A recent meta-analysis of observational studies (Bonovas et al., 2004) with information on more than 9000 events suggested a weak, protective, effect of diabetes of around 10% lower risk of prostate cancer among men with diabetes compared with those without. In the current study, there was no evidence to suggest a protective effect of either diabetes, or blood glucose levels, on the risk of mortality from prostate cancer among men from Asia or ANZ. Nor was there evidence of a time-dependent effect as has previously been reported. For example, data from CPS-II (Rodriguez et al., 2005), which included information on over 5000 incident prostate cancers, suggested that men with diabetes were a third less likely to develop prostate cancer, but only among those who had been diagnosed with diabetes for more than three years. In men in whom diabetes had only recently been diagnosed (less than three years) the risk of prostate cancer was reported to be (non-significantly) higher. It remains unclear however, whether any apparent protective effect of diabetes on the risk of prostate cancer is due to competing risks. As prostate cancer is primarily a condition of old-age, it is possible that death due to diabetes-related cardiovascular conditions occurs before manifestation of any antagonistic effects that diabetes may have on the tumour.

Mechanisms

Most of the mechanisms speculated to mediate the associations between height, smoking and diabetes with prostate cancer involve circulating levels of hormones, predominantly, insulin-like growth factor-I (IGF-1), testosterone and androstenedione. Cell division in the prostate gland is controlled by testosterone and early prostate cancer is sensitive to androgens. In turn, these are elevated by cigarette smoking (Coffey, 1979; Dai et al, 1988). However, in a review of the evidence between smoking and prostate cancer, studies have generally been inconsistent with regards to the effect of smoking on androgen levels (Hickey et al., 2001). In contrast to smoking diabetes is suggested to exert its protective effect by inhibiting production of testosterone, which is supported by the observation from several studies of a step-wise decrease in mean levels of testosterone with increasing blood glucose levels (Barrett-Connor et al., 1990; Fushimi et al., 1989; Madsbad et al., 1986). However, a meta-analysis of prospective studies (Eaton et al., 1999) found no evidence of a difference in the average serum concentrations of testosterone and other androgens, between men with prostate cancer and controls. This raises questions about the importance of androgens in the aetiology of prostate cancer, and hence the mechanisms underlying any associations between smoking, diabetes and the neoplasm. There is speculation that a positive association between stature and prostate cancer may reflect exposure to high levels of IGF-I in puberty, the time when the prostate develops. This

hypothesis holds that tall men have been exposed to higher levels of IGF-I and other growth-promoting factors during puberty, compared with short men, which in turn is thought to stimulate epithelial division in the prostate and subsequent risk of disease in later life (Smith et al., 1995; Giovannucci et al., 1997).

There are several limitations to our study. The analyses were largely based on self-reported cigarette consumption, which may have introduced a bias towards null. Although the majority of studies recorded anthropometric variables at baseline, measurement error would have been present, especially for waist circumference, which is more cumbersome to measure than either weight or height. The individual studies used different methods to verify mortality from prostate cancer. These methods will have varied over time, and therefore the lack of standardization could have had some unpredictable effect on our results. Finally, the data from the Asian cohorts is limited, and a longer follow up is needed to yield more reliable results for Asian populations.

In summary, there is good evidence that men who are overweight have a small, but significantly higher risk of mortality from prostate cancer in both Asia and ANZ. Although cigarette smoking was inconsistently associated with prostate cancer between the two regions, possibly due to insufficient statistical power to detect any small effect of smoking among Asian men, the association observed in ANZ should be robust. Population-wide approaches that reduced the prevalence of these risk factors could have a significant impact on reducing mortality from prostate cancer as well as on other chronic conditions in populations of the Asia-Pacific Region.

Appendix

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