RESEARCH COMMUNICATION

Risk Factors for Prostate Cancer in Universiti Kebangsaan Malaysia Medical Centre: A Case-Control Study

Mohd Nizam Subahir[1], Shamsul Azhar Shah[1]*, Zulkifli Md Zainuddin[2]

Abstract

Introduction: In Malaysia, prostate cancer is ranked 6th among male cancer and expected to increase in the future. Several factors have shown to be related to prostate cancer such as sociodemographic, lifestyle, diet, occupational exposure, medical and health status. This is the first time a similar study was conducted in Malaysia to recognize the risk factors for prostate cancer patients who came for treatment at Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Methods: Prostate cancer cases diagnosed between 2003 and 2008 which met with the inclusion criteria were included in the study. One hundred and twelfth (112) pairs of cases and controls matched by age and ethnicity were analysed. McNemar Odds Ratios (OR_M) were calculated using McNemar Calculator software for univariate analysis while conditional logistic regression was used for multivariate analysis, both using SPSS version 12.0. Results: Most of the prostate cancer patients (68.8%) that came for treatment in UKMMC were above 70 years old. The majority were Chinese (50.0%) followed by Malay (46.4%) and Indian (3.6%). Multivariate analysis showed cases were more likely to have a first-degree relative with a history of cancer (OR= 3.77, 95% CI= 1.19-11.85), to have been exposed to pesticides (OR= 5.57, 95% CI= 1.75-17.78) and consumed more meat (OR= 12.23, 95% CI= 3.89-39.01). Significantly reduced risks of prostate cancer were noted among those consuming more vegetables (OR= 0.12, 95% CI= 0.02-0.84), more tomatoes (OR= 0.35, 95% CI= 0.13-0.93) and those who had frequent sexual intercourse (OR= 0.44, 95% CI= 0.19-0.96). Conclusion: Some lifestyle and occupation factors are strong predictors of the occurrence of prostate cancer among patients in UKMMC. More importantly, with the identification of the potentially modifiable risk factors, proper public health intervention can be improved.

Key Words: Prostate cancer - case-control study - risk factors - Malaysia

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Introduction

Although prostate cancer ranked 6th among male cancer in Malaysia, it is expected to increase in the future with an increasing ageing population 60-year and above which will increase to 3.4 million in year 2020 compare with 1.03 million in 1991 (NCR, 2002). At the same time more exposure to carcinogen agent in the environment and greater awareness of the disease lead to increasing diagnosis (Hass et al., 1997). Even the incidence of this cancer is consider low as other Asian country, our incidence pattern will approach that developed countries such as United State and Canada.

Interestingly the age specific incidence rate in Chinese (15.7 per 100,000) and Indian (11.5 per 100,000) in Malaysia were already higher than in Shanghai, China (2.3 per 100,000) and Madras, India (7.9 per 100,000). While Chinese who migrates to Hawaii and Los Angeles the ASR will increase to 62.9 and 20.2 subsequently. It shows that environmental and genetic factors may play an important role to prostate cancer (NCR, 2002) and may need some public health intervention.

It causes remain poorly understood but recently many evidence correlate the incidence of prostate cancer with multiple factors such as genetic, occupation, diet, hormonal disturbances, sexual activity and sexual transmitted disease (O'Reilly, 1999).

This study is important because this is the first time it's done in Malaysia to recognize the risk factors for prostate cancer. Using sample and data from prostate cancer patient which follow-up in UKMMC, we examined the relationship between prostate cancer and smoking, alcohol consumption, diet, family history of cancer, physical activity, sexual activity, occupation and certain medical problem. Examining these risk factors will be useful in identifying risk factors for planned studies of environmental exposures and prostate cancer within this study population. More importantly, identifying risk factors that are common and potentially modifiable, and even modestly increase the odds of developing prostate cancer, may have important public health consequences.

Materials and Methods

UKMMC is one of the most advanced teaching hospitals in Malaysia and acts as a referral centre for many

*[1]Department of Community Health, [2]Department of Sugery, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia *For Correspondence: shamsulazharshah@yahoo.com*

diseases. The case-control component of this study is hospital-based with cases identified from registered patients with a histopathologically confirmed diagnosis of primary prostate cancer from 2003 till 2008. We decided to exclude prostate cancer patients who were not Malaysian citizens, had dementia and had secondary type prostate cancer. This study was approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia in April 2008.

Controls were patients who came to the UKMMC for other disease which is never diagnosed as prostate cancer during this study period from June 2008 till November 2008. Controls could only be chosen if the screening test showed no symptom of prostate problem or PSA in normal range (0-4 ng/ml). Patients who already undergone biopsy and proven not to have malignancy also were eligible.

Subjects were randomly selected to achieve a one-to-one case control and matched according their age and ethnic. Our analyses were performed on 112 prostate cancer cases and 112 controls. Subjects were interviewed face to face by researcher and 2 trained personnel they gave their consent and done in the wards or clinics during their appointment date.

The relationship between tobacco use and prostate cancer risk was assessed for the following aspects of smoking behavior: average number of cigarettes smoked daily, years since quitting, years of cigarette smoking and cigarette pack-years. The number of alcoholic drinks consumed calculated by summing the subject's responses about consumption of beer, wine and any other alcoholic drinks. The criteria used were taken at least one stick per day for smoking and at least one drink per week for alcohol consumption for at least six months (Ji et al., 2002). Demographic variables examined included education, marital status and household income.

We examined the risk of prostate cancer by consumption levels of meat, fish, tomato, vegetables, and fruit. An estimate of total weekly frequency intake for each individual using a modified validated dietary questionnaire form (Suzana et al., 2000).

History of sexual activities were examined based on had or not sexual intercourse, frequency of sexual intercourse per week and number of partner. We decided to examine only heterosexual intercourse. For odds ratio (ORM) analysis we categorized the frequency of sexual intercourse into two, not frequent (if never had sexual intercourse or had not more than two time per week).and frequent (if had sexual intercourse three time or more per week). While for the partner of sexual intercourse was divided into low (if had not more than one partner) and high (if had two or more partners) according to Health Interview Study of Men, 1993-1996 (Rosenblatt et al., 2001).

We also examined the history of medical and health problem of the respondent base on their report whether they had disease such as hyperlipideamia, benign prostate hyperplasia (BPH), sexual transmitted disease (syphilis and gonorrhea) or any other medical problem. Family history of prostate cancer or any other cancer was also asked at this section.

The physical activity component asked about their routine daily works and exercise during the young age till retirement before prostate cancer confirmation. To investigate the relationship between physical activity and prostate cancer we separate the analysis of routine daily work and exercise. For ORM analysis we decided to categorized the routine daily works into sedentary level (if do more office work) and strenuous level (if do more fieldwork). While exercise which is any activity used major body muscles for at least 20 to 30 minutes (CDC, 2008) was divided into frequent (if exercise at least 3 times per week) and not frequent (if exercise less than 3 times per week).

Occupational exposure examined history of their main occupation and history of exposure to pesticide. Main occupation categorized to Blue-Collar (use more physical energy to perform job such as labourer) and White-Collar (use more thinking energy such as professional field) based on definition by Kamus Dewan (2002). While exposure to pesticide used based on respondent report whether had or not exposed.

Body Mass Index (BMI) was categorized as Obese (≥27.5kg/m_) and Not Obese (≤27.4 kg/m_) adapted from the Clinical Practice Guideline on Management of Obesity Ministry of Health Malaysia (MOH, 2003).

The relation between risk factors and prostate cancer was examined using software of McNemar Calculator to calculate the odds ratio (ORM) (Graphpad.com, 2008) and for conditional logistic regression using the software SPSS version 12.0 to calculate the adjusted odds ratio.

Results

There were 112 pairs subjects enrolled. For ethnic groups, 56 (50%) were Chinese, 52 (46.4%) were Malays and 4 (3.6%) were Indian. Majority of the case equal or more 70 years old (68.8%) and sudden increase of cases from 60-69 years old (25.0%) to age range of 70-79 years old (55.3%). The youngest age was 50 and the oldest was 86 years old while mean was 71.7 and median 72.0.

Table 1 shows the McNemar Odds Ratio (ORM) and related 95% confidence intervals for prostate cancer with sociodemographic, lifestyle, diet, medical problem and occupational exposure with different frequency. It was found that family history of cancer, frequent intake of meat within one week and history of occupational exposure to pesticide were statistically increase risk factors for prostate cancer. While history of frequent practice of sexual intercourse, exercise and strenuous physical activity were significantly reducing risk same as shown by frequent intake of vegetables, fruits and tomatoes. However, in term of sociodemographic, medical problem and other lifestyle factors such as smoking and alcohol consumption, no significant risk were found.

Table 2 shows the adjusted odds ratio from conditional logistic regression model for prostate cancer. Multivariate analysis showed that frequent intake of vegetables (OR 0.120, 95%CI: 0.017-0.840), tomatoes (OR 0.354, 95%CI: 0.135-0.927), and high frequency of sexual intercourse (OR 0.435, 95%CI: 0.197-0.963) significantly reduced risk to prostate cancer. While factors of family history of cancer (OR 3.768, 95% CI: 1.199-11.846) exposed to

Table 1. McNemar Analysis of Study Variables

Variable	Cases	Control	OR	95% CI	P value
Education					
Low (+)	30 (26.7)	20 (17.9)	0.69	(0.37-1.26)	0.25
High (-)	29 (25.9)	13 (11.5)			
Income RM					
≤1500 (+)	61 (54.5)	17 (15.2)	0.68	(0.35-1.31)	0.28
≤1500 (-)	25 (22.3)	9 (8.00)			
Married					
No (+)	4 (3.6)	12 (10.7)	0.80	(0.34-1.83)	0.70
Yes (-)	15 (13.4)	81 (72.3)			
Family Cancer					
Yes (+)	4 (3.60)	20 (17.8)	2.87	(1.62-7.99)	0.02*
No (-)	7 (6.30)	81 (72.3)			
Smoking					
Yes (+)	37 (33.0)	30 (26.8)	1.11	(0.64-1.94)	0.79
No (-)	27 (24.1)	18 (16.1)			
Alcohol					
Yes (+)	11 (9.80)	25 (22.3)	1.25	(0.67-2.37)	0.55
No (-)	20 (17.9)	56 (50.0)			
Sexual Intercourse					
Yes (+)	106 (94.6)	2 (1.80)	0.50	(0.04-3.85)	0.68
No (-)	4 (3.60)	0 (0.0)			
Frequency Sexual Intercourse					
Low (+)	36 (32.1)	41 (36.7)	0.46	(0.25-0.82)	0.007*
High (-)	19 (17.9)	16 (14.3)			
Sexual Interc. Partner					
Low (+)	98 (87.5)	7 (6.30)	0.86	(0.24-2.98)	1.00
High (-)	6 (5.4)	1 (0.9)			
Hyperlipidemia					
Yes (+)	26 (23.2)	30 (26.8)	1.11	(0.64-1.94)	0.79
No (-)	27 (24.1)	29 (25.9)			
BPH					
Yes (+)	17 (15.2)	34 (30.4)	1.17	(0.69-1.99)	0.61
No (-)	29 (25.9)	32 (28.6)			
Other Medical Problem					
Yes (+)	94 (83.9)	7 (6.30)	0.70	(0.23-2.00)	0.63
No (-)	10 (8.9)	1 (0.90)			
Occupation Collar					
Blue (+)	64 (57.1)	17 (15.2)	1.53	(0.80-3.00)	0.22
White (-)	26 (23.2)	5 (4.50)			
Pesticide Exposure					
Yes (+)	9 (8.0)	24 (21.4)	2.40	(1.11-5.62)	0.03*
No (-)	10 (8.40)	69 (61.6)			
Exercise Frequent?					
No (+)	76 (67.8)	22 (19.6)	0.41	(0.67-0.93)	0.03*
Yes (-)	9 (8.00)	5 (4.50)			
Daily Work Activity					
Sedentary (+)	21 (18.8)	44 (39.3)	0.55	(0.32-0.92)	0.02*
Strenuous (-)	24 (21.4)	23 (20.5)			
Vegetables					
Frequent (+)	89 (79.5)	4 (3.6)	0.21	(0.05-0.63)	0.004*
Infrequent (-)	19 (16.9)	0 (0.0)			
Fruits					
Frequent (+)	80 (71.4)	8 (7.1)	0.36	(0.14-0.85)	0.018*
Infrequent (-)	22 (19.6)	2 (1.8)			
Tomatoes					
Frequent (+)	4 (3.6)	13 (11.6)	0.41	(0.20-0.80)	0.007*
Infrequent(-)	32 (28.6)	63 (56.2)			
Meat					
Frequent (+)	6 (5.4)	46 (41.1)	5.75	(2.69-14.1)	0.001*
Infrequent (-)	8 (7.1)	52 (46.4)			
Fish					
Frequent (+)	95 (84.8)	5 (4.5)	0.42	(0.12-1.27)	0.15
Infrequent (-)	12 (10.7)	0 (0)			
BMI					
Obese (+)	6 (5.4)	19 (16.9)	1.06	(0.52-2.13)	1.00
Not Obese (-)	18 (16.1)	69 (61.6)			

Data are numbers and (%); *significant at p< 0.05

Table 2. Conditional Logistic Regression Model for Prostate Cancer

Risk Factor	ß	SD	Wald	P	OR (95% CI)
Pesticide Exposure					
No					1.0
Yes	1.718	0.592	8.419	0.004*	5.57 (1.74-17.8)
Daily Work Activity					
Sedentary					1.0
Strenuous	-0.440	0.354	1.546	0.214	0.64 (0.32-1.29)
Family History Carcinoma					
No					1.0
Yes	1.327	0.584	5.154	0.023*	3.77 (1.20-11.8)
Sexual Intercourse Frequency					
Low					1.0
High	-0.832	0.405	4.217	0.04*	0.44 (0.20-0.96)
Vegetable Consumption					
Not Frequent					1.0
Frequent	-2.120	0.993	4.560	0.033*	0.12 (0.02-0.84)
Fruit Consumption					
Not Frequent					1.0
Frequent	0.108	0.694	0.024	0.876	1.11 (0.29-4.34)
Tomato Consumption					
Not Frequent					1.0
Frequent	-1.039	0.491	4.470	0.035*	0.35 (0.14-0.93)
Meat Consumption					
Not Frequent					1.0
Frequent	2.511	0.588	18.242	0.001*	12.2 (3.89-39.0)
Exercise					
Not Frequent					1.0
Frequent	-0.205	0.628	0.106	0.745	0.82 (0.24-2.79)

*significant at p< 0.05; SD, standard error

pesticide (OR 5.572, 95%CI 1.746-17.780) and frequent intake of meat (OR 12.232, 95% CI: 3.892-39.013) significantly increased risk to prostate cancer.

Discussion

The ethnic group and age distribution among patient in this study group is almost similar to that of the second report of National Cancer Registry (NCR, 2003) where majority equal or more 50% is above 70 years old. Because, when a men become older the most pathologically transform organ is prostate (Grover & Martin, 2002). Therefore, the risk of prostate cancer will increase as long as become older. There was no association found in this study between sociodemographic factor (education, income and married) and prostate cancer. This result is consistent with other studies such as Lee et al. (1988) and Villeneuve et al. (1999).

Family history of other cancer was found increase risk for prostate cancer consistent with other studies (Villeneuve et al., 1999; Freindenreich et al., 2004). While relation of family history of prostate cancer cannot be shown as denominator for ORM is 0 and the value become infinity because no control sample had family history of prostate cancer even there was 9 from case sample.

Frequent sexual intercourse from lifestyle factors was found to be associated with prostate cancer gave protective effect till 57%. Even this result is inconsistent with Rosenblatt et al. (2001) but Leitzman et al.(2004) found that frequent ejaculation ≥ 21 times per month compared to those who had only 4-7 times will significantly reduced

risk for prostate cancer with Multivariate Relative Risk 0.67 (95%CI: 0.51-0.89). The possibility is frequent sexual intercourse and ejaculation will reduce and stabilize testosterone hormone level and therefore reduce risk of prostate cancer.

Smoking was here not found to be associated with prostate cancer, consistent with other studies (Lee et al., 1998; Roman et al., 2000; Kamel et al., 2006). Same also as alcohol consumption consistent with study done by Hiat et al (1994) and Ronquist et al (2004). According to Dennis and Hayes (2001) someone will increase risk of prostate cancer if alcohol consumption more than 7 times per day while from this study mean of alcohol consumption only 0.38 and maximum 2 times per day.

There was no association found in this study between history of medical problem with prostate cancer. For BPH it is consistent with other studies (Hiat et al., 1994; Weinmann et al., 2004) while for hyperlipidaemia it is inconsistent with the study done by Bravi et al (2006). Even the meta-analysis performed by Taylor et al. (2005) found that sexual transmitted disease increase risk for prostate cancer but Hiat et al (1994) found no association between gonorrhea and prostate cancer. Ronquist et al (2004) found no association between prostate cancer with other disease such as diabetes mellitus, ischemic heart disease, heart failure and hypertension.

The present study found an association between history of exposure to pesticides with prostate cancer. This result is consistent with the results of Meyer et al (2006) and Alavanja et al (2003). Pesticide content such as glyphosate isopropylamine and paraquat even not yet proven as carcinogen but have potential, because it can effect immune system, disturbing hormone level and DNA mutation (De Ross 2008).

There was an association found in this study between exercise and strenuous level works activity reduce risk for prostate cancer till 59% and 45% but multivariate analysis shown no association. This result is consistent with Friendenreich et al (2004) and Villeneuve et al (1994) for daily work activity and Zhu et al (2004) for exercise.

About diet factors, frequent intake of vegetables was found to reduce risk for prostate cancer consistent with other studies (Cohen et al., 2000; Kamel et al., 2006). There is a dispute about the relationship between fruits intake and prostate cancer as mention by Global Review for Fruits and Prostate Cancer Risk. There was no consistency between fruits intake and prostate cancer, and therefore no concrete result can be taken (Chan & Giovannuci, 2001). In the present study this relationship was not observed in multivariate analysis. Frequent intake of tomatoes consumption was found reduced risk for prostate cancer consistent with the study done by Mills et al. (1989) and Giovannuci et al. (1995) but Kamel et al. (2006) no found any significant association. While frequent consumption of meats was found significantly increase risk to prostate cancer consistent to case control study done by Lee et al. (1998) but was not found by Alavanja et al. (2003), and for factor of frequent intake of fish no association was found with prostate cancer in this study even consistent with Villeneuve et al. (1999) and Kamel et al.(2006) but different with study done by Augustsson et al (2003) where consumption of fish more than 3 times per week will significantly reduce the risk of prostate cancer.

Several limitation that usually occur in hospital-based case control studies been identified. First, study subjects did not represent all cases within the population. Second, some selection bias may be present as control groups were limited to the hospital patients. It would have been better if the control were from the general population. Third, information bias usually happens in the case-control study. Lastly, confounding bias may occur among the variables in the study although the effect was controlled through multivariate analysis.

The present study suggests that some lifestyle and occupation factors are strong predictors of the occurrence of prostate cancer. More importantly the identification of the potentially modifiable risk factors, proper public health intervention can be improved such as encourage public to frequent intake of vegetables and tomatoes and educate farmer to be careful in use of pesticide.

References

Alavanja MCR, Samanic C, Dosemeci M, et al (2003). Use of agriculture pesticide and prostate cancer risk in the agricultural health study cohort. *Am J Epidemiol*, **157**, 800-14.

Augustsson KM, Michaud DS, Rimm EB, et al (2003). A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev*, **12**, 64-7.

Bravi F, Scotti L,BosettiC, et al (2006). Sel- reported history of hypercolesterolemia and gallstone and the risk of prostate cancer. *Ann Oncol*, **17**, 1014-7.

CDC (2008). http://www.cdc.gov/physicalactivity/everyone/guidelines/adults.html [14 Jun 2008].

Chan, J.M. and Gionannuci, E.L. 2001. Vegetables, Fruits, Associated Micronutrients and Risk of Prostate Cancer. Epidemiologic Reviews. John Hopkins University Bloomberg School of Public Health

Cohen, J., Kristal, A. And Stanford, J. (2000). Fruits and vegetables intakes and Prstate Cancer Risk. J Natl Cancer Inst 92: 61-68

Dennis LK Hayes R.B. 2001. Alcohol and Prostate Cancer. Epidemiologic review by the Johns Hopkins University Bloomberg School of Public Health. Vol. 23, No. 1.

De Roos AJ (2008). Research on Long Term Health Effect of Pesticide. Fred Hutchinson Cancer Centre.

Freindenreich CM, McGregor SE, Courneya KS, Angyalfi SE, Elliot FG (2004). Case-control study of lifetime total physical activity & prostate cancer risk. *Am J Epidemiol*, **159**, 740-9.

Giovannuci E, Ascherio A, Rimm E, Wigo PA (1995). Intakes of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst*, **87**, 1767-76.

Grover LP, Martin FL (2002). The initiation of breast and prostate cancer. *Carcinogenesis*, **23**, 1095-102.

Haas GP, Sakr WA (1997). Epidemiology of prostate cancer. *CA Cancer J Clin*, **47**, 273-87.

Hiatt RA, Armstrong MA, Klatsky AL, Sidney S (1994). Alcohol consumption, smoking, and other risk factors and prostate cancer in large health plan in Carlifornia (United States). *Cancer Causes Control*, **5**, 66-72.

Ji BT, Dai Q, Gao YT, et al (2002). Cigarette and alcohol consumption and the risk of cancer in Shanghai, China. *Eur J Cancer Prev*, **11**, 237-44.

Kamel NM, Tayel SE, El Abbady AA, Khasab SS (2006). Risk of cancer prostate - a case control study. *J Egypt Public Hlth Assoc*, **81**, 143-63.

Kamus Dewan (2002). Edisi ke-3. Kuala Lumpur: Dewan Bahasa dan Pustaka.

Lee MM, Wang RT, Hsing AW, et al (1998). Case control study of diet and prostate cancer in China. *Cancer Causes Control*, **9**, 545-52.

Lietzman MF, Platz EA, Stampfer MJ, Willet CW, Giovannuci E (2004). Ejaculation frequency and subsequent risk of prostate cancer. *JAMA*, **291**, 1578-86.

Meyer ET, Coker AL, Sanderson M, Symanski E (2006). A case-control study of farming and prostate cancer in African-American and Caucasian Men. *Occup Environ Med*, **10**, 1136.

Mills P, Beeson W, Philip R, Fraser GE (1989). Cohort study of diet lifestyle and prostate cancer in Adventist Men. *Cancer*, **64**, 598-604

Ministry of Health Malaysia. 2003. Clinical Practice Guideline on Management of Obesity.

National Cancer Registry Malaysia. 2002. The First Report of Cancer Incidence in Malaysia.

National Cancer Registry Malaysia. 2003. Second Report of Cancer Incidence in Malaysia.

O'Reilly, P.H. 1999. Aetiology and Pathology of Prostate Cancer. www.pjonline.com/noticeboard/credit1999/199903_aetiology.pdf [18 Ogos 2007]

Roman JM, Bou R, Romea S, et al (2000). Dietary fat intake and prostate cancer risk : a case-control study in Spain. *Cancer Causes Control*, **11**, 679-85.

Ronquist G, Rodriguez LAG, Ruigomez A, et al (2004). Associatain Between Captopril, Other Anti Hypertensive drugs and risk of prostate cancer. *The Prostate*, **58**, 50-6.

Rosenblatt KA, Wicklund, KG, Stanford JL (2001). Sexual factors and the risk of prostate cancer. *Am J Epidemiol*, **153**, 1152-8.

Suzana S, Earland J, Suriah AR (2000). Validation of dietary history questionnaire against a 7-D weighed record for estimating nutrien intake among rural elderly Malays. *Malay J Nutr*, **6**, 33-4.

Taylor ML, Mainous AG, Wells BJ (2005). Prostate cancer and sexually transmitted disease: A meta analysis. *Clin Res Methods Fam Med*, **37**, 506-12.

Villeneuve PJ, Johnson KC, Kreiger N, Mao Y (1999). Risk factors for prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System. *Cancer Causes Control*, **10**, 355-67.

Weinmann S, Boe KR, Glass AG, Weiss NS (2004). Prostate cancer screening and mortality : A case-control study (United States). *Cancer Causes Control*, **14**, 133-8.

Zhu K, Lee I-M, Sesso HD, et al (2004). History of diabetes mellitus and risk of prostate cancer in physicians. *Am J Epidemiol*, **159**, 978-82.