RESEARCH ARTICLE

Sun Exposure and the Risk of Prostate Cancer in the Singapore Prostate Cancer Study: a Case-control Study

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Abstract

Background: Most of the epidemiology studies on the effects of sun exposure and prostate cancer were conducted among the temperate countries of North America and Europe. Little is known about the influence on Asian populations. The purpose of current study was to evaluate any association of sun exposure with risk of prostate cancer in Chinese, Malays and Indians who reside in the tropics. Methods: The Singapore Prostate Cancer Study is a hospital-based case-control study of 240 prostate cancer incident cases and 268 controls conducted in Singapore between April 2007 and May 2009. Detailed information on outdoor activities in the sun, skin colour, sun sensitivity and other possible risk factors were collected in personal interviews. Cases were further classified by Gleason scores and TNM staging. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis, adjusted for age, ethnicity, education, family history of any cancers, BMI and skin colour. Results: We found that prostate cancer risk was increased in subjects with black/dark-brown eyes (OR 5.88, 95%CI 3.17-10.9), darker skin colour e.g. tan/dark brown/black (OR 7.62, 95%CI 3.41-17.0), frequent sunburn in lifetime (OR 4.30, 95%CI 1.7-11.2) and increased general sun exposure in adulthood per week (OR 2.03, 95%CI 1.09-3.81). The increased risk was consistent for high grade tumours and advanced stage prostate cancers. Conclusion: The findings from this study suggest that excessive sun exposure is a risk factor for prostate cancer in Asians.

Keywords: Case-control study - prostate cancer - risk factor - sun exposure

Asian Pacific J Cancer Prev, **13**, 3179-3185

Introduction

Prostate cancer is the commonest male cancer worldwide. Although many epidemiological studies have been conducted in the last few decades to determine the risk factors associated with prostate cancer, till dated the only known established factors are age, race and family history (Patel et al., 2009).

In the last decade, there were reports on the likely protective effect of sun exposure for prostate cancer, however these reports were not consistent (Bodiwala et al., 2003; John et al., 2005; Gilbert et al., 2009; Nair-Shalliker et al., 2011; Lin et al., 2012). Hanchette and Schwartz reported the association between sun exposure and risk of prostate cancer. They showed an inverse relationship between sun exposure and mortality rate from prostate cancer among White men in 3,073 counties in the United States of America (Hanchette et al., 1992). Since then there have been case-control, cohort and ecological studies that reported on the protective nature of sun exposure and prostate cancer (Gilbert et al., 2009; Gupta et al., 2009; Lin et al., 2012). Early reviews on this subject seem to suggest the protective nature of sun exposure to prostate cancer (Moon et al., 2005), other reports only suggested a weak protective effect. Gilbert et al reported a UK-wide nested case-control study, based on 1,020 prostate specific antigen-detected cases and 5,044 matched population controls and a systematic review with meta-analysis. They concluded that "Our data and meta-analyses provide limited support for the hypothesis that increased exposure to sun may reduce prostate cancer risk" (Gilbert et al., 2009).

All these studies were conducted among developed countries and most of the subjects were in the temperate countries of North America and Europe. Grant suggested that the protective effect of sunlight may not be so evident: "… the geographic variation for prostate cancer mortality rates differs from that for the 14 types of cancer with the strongest evidence for a beneficial role of ultraviolet-B and vitamin D" (Grant, 2010). By looking at the geographical mortality rate for prostate cancer in USA for White and Black males (1970-2004), it would appear that they don't correlate well (especially for Black males) with the sunlight exposure for the different states (Institute, 2004). However, in a recent Australian study, increasing weekend sun exposure increases prostate cancer risk (OR 5.55, 95%

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CI 2.94-10.5) in a high ambient solar UV environment (Nair-Shalliker et al., 2011).

To our knowledge, there are no reports on sun exposure and prostate cancer among Asian population. The aim of this study is to examine the association between sun exposure and pigment characteristics and risk of prostate cancer in an Asian population in Singapore which consisted of Chinese, Malays and Indians.

Materials and Methods

The study was approved by Institutional Review Board of the Singapore General Hospital where the study was conducted. It is one of the largest public tertiary hospitals in Singapore and draws in patients from different part of Singapore. Informed consent was given to all participants for the collection of information about pathology and/or access to medical records.

Selection of Cases

Eligible cases were males with incident carcinoma of the prostate, with biopsy or operative specimens diagnosed by pathologists (which accounted for 50% of prostate cancers among Singapore men). Cases were Singapore residence age 50 to 85 years, mentally alert and coherent, and were interviewed within 1 month of diagnosis of the disease.

Selection of Controls

Controls were selected from same hospital under other disciplines, with frequency matched by ethnic groups and ±5-years age groups on one-to-one ratio with cases. Patients who had a history of malignant disease were excluded.

Study Instrument

All subjects were interviewed in-person using a standardized questionnaire. Over the study period, two research staffs were responsible for data collection, and each interviewed both cases and controls. Training and supervision were carried out by the same investigator throughout. Interviewers were not blinded to case or control status, but possible observer bias was monitored by reviewing at random a sample of interviews conducted by each interviewer. None of the interviews were carried out solely with next-of-kin, but where necessary, relatives present with the subject at the time of interview were allowed to give information that was corroborated by the subject.

Detailed information on personal demographics, family history of cancer in the first degree relatives, pigment-related characteristics as well as general outdoor sun exposures (for both recreational and occupational purposes) were collected. Usual adult body weight (in kilogram) and height (in metre) (expressed as in Body Mass Index (BMI, kg/m^2)) and the hours spent on various levels of physical activities in the past one year were also recorded.

Subjects were asked about pigment-related questions on the eye colour (Black/Dark Brown, Light Brown) and the skin colour on the inner upper arm (White/Light Tan, Tan, Dark Brown/Black). Regarding the ultraviolet (UV) radiation related variables, the hours of spending outdoor activities were used as surrogate for UV exposure. "Outdoor" was defined as not under any shade between 9 am and 5 pm. Subjects were asked how many hours they spent outdoors on general activities including swimming, sailing, jogging, playing golf or tennis etc, on school days or weekends in childhood, and on working days or rest days in adulthood. The frequency of ever sunburn in lifetime were recorded, the unexposed group served as reference category.

The general physical activities in the past one year were also asked in terms of hours spent separately in vigorous activities, moderate activities, sitting or light activities, sleeping on weekdays and weekends. The physical activities were expressed as Metabolic Equivalent of Task (MET) per week.

Classification of prostate cancer cases

Prostate cancer was defined by Gleason score into two grades, called "High grade" (Gleason score ≥ 7) and "Low grade" tumour (Gleason score < 7). Using the TNM staging, we also grouped the cases into 2 categories, "Localized" (T1 or T2, N0, M0) and "Advanced" consisting of (a) M0, T3/T4 & N0; (b) T1-T4 with any N; (c) any T, any N, and (d) M1, M1b, M1c.

Measures of sun exposure were constructed for the statistical analysis: The total number of hours per week spent outdoors was calculated by adding the number of hours spent during the 5 weekdays (school days or working days) and 2 weekend days (i.e. maximum of 8 hours per day and 56 hours per week). Less than 30 minutes spent in outdoor per week was defined as reference category.

Statistical Analyses

An unconditional logistic regression model was used to estimate the odds ratio (OR) and its 95% confidence interval (CI) for the association between the outdoor UV exposure and the risk of prostate cancer.

Both current housing type and years of education are surrogates for social economic status. The education levels (never/1-6 years/7-10 years/>10years) is a better fit parameter in the model comparison, and thus included in the final model together with age (as continuous variable), ethnic group (Chinese/Malay/Indian/Others), family history of caner (yes/no) and BMI (as continuous variable). In examining the effect of sunburn and sun exposure, the model also adjusted for skin colour in addition to the other above mentioned variables. The exposure variables and possible confounders that are adjusted for in each of the modules are explained in the tables.

Continuous variables were categorized according to the distribution among control subjects, and the no exposure group was assigned as the reference category. Individuals with missing data for any variables were excluded for that analysis. All statistical tests were evaluated assuming a two-sided test at the 0.05 level of significance. Analyses were performed with STATA/SE 10.1 software (StataCorp, Texas 77845 USA, 1984-2009).

Table 1. Background Characteristics of Cases and Controls in the Singapore Prostate Cancer Study

Characteristics	Controls (n=268)		Case (n=240)		p-value[1]
	n	(%)	n	(%)	
Age					
50-59 years	102	(38.1)	43	(17.9)	<0.01
60-69 years	97	(36.2)	110	(45.8)	
70 years and above	69	(25.8)	87	(36.3)	
Ethnic					
Chinese	225	(84.0)	209	(87.1)	0.54
Malay	13	(4.9)	13	(5.4)	
Indian	23	(8.6)	13	(5.4)	
Others	7	(2.6)	5	(2.1)	
Housing					
HDB 1-3 room	73	(27.2)	40	(16.7)	<0.01
HDB 4+ room	154	(57.5)	112	(46.7)	
Private condominium	29	(10.8)	84	(35.0)	
Others	12	(4.5)	4	(1.7)	
Education					
Never	20	(7.5)	6	(2.5)	<0.01
1-6 years	89	(33.5)	55	(23.0)	
7-10 years	102	(38.4)	82	(34.3)	
>10 years	55	(20.7)	96	(40.2)	
Marital status					
Currently married	224	(83.9)	219	(91.6)	0.02
Separated/widowed etc	26	(9.7)	9	(3.8)	
Never married	17	(6.4)	11	(4.6)	
Family history of any cancer in the first degree relatives					
No	198	(79.5)	129	(56.3)	<0.01
Yes	51	(20.5)	100	(43.7)	
BMI (kg/m2)					
Quartile 1 (<22.0)	45	(24.5)	69	(32.6)	<0.01
Quartile 2 (22.0-24.9)	47	(25.5)	79	(37.3)	
Quartile 3 (25.0-27.9)	46	(25.0)	40	(18.9)	
Quartile 4 (≥28.0)	46	(25.0)	24	(11.3)	

n, number; [1]p-value from Chi-square test

Results

Subject characteristics

Of 293 prostate cancer cases that were approached, 247 consented for the study (response rate of 84.4%) and 240 completed questionnaire interview for current analysis. A total of 387 eligible controls were approached, 271 (response rate of 70.0%) consented to be interviewed. However, 1 withdrew post-consented and 2 did not complete the questionnaire, leaving 268 controls for this analysis. Control patients represented a wide range of conditions, of which 109 (40.7%) were diseases of the bones and joints in orthopaedic surgery department, 81 (30.2%) were admitted for general surgery department, and 70 controls had acute illnesses in the medicine department, and 8 (3.0%) with other reasons. The frequency of controls with 'bone and joints' problem spent an average of 3.8 hrs per week in the sun. Controls with no 'bone and joints' problems spent an average of 5.7 hrs per week. This difference is not significant.

Descriptive characteristics of the study population are presented in Table 1. Compared with the controls, the cases were significantly older (p<0.001). More cases lived in private housing (35.0% in cases versus 10.8% in controls), and had positive family history of any cancer in the first degree relatives (43.7% versus 20.5%). On the other hand, the BMI was higher in controls than the cases (p<0.001).

Table 2. Associations Between Pigment with Sun Sensitivities Characteristics of Prostate Cancer Cases and Hospital Controls

Category	Controls (n=268)		Case (n=240)		p-value[1]
	n	(%)	n	(%)	
Eye colour					
Black/dark brown	169	(63.5)	209	(89.3)	<0.01
Light brown	97	(36.5)	25	(10.7)	
Skin colour					
Very white/white	80	(29.9)	25	(10.7)	<0.01
Light tan	116	(43.3)	130	(55.6)	
Tan/dark brown/black	72	(26.9)	79	(33.8)	
Sunburn frequency					
Never	147	(57.4)	112	(48.5)	0.01
Seldom	70	(27.3)	56	(24.2)	
Occasionally	24	(9.4)	33	(14.3)	
Frequently	15	(5.9)	30	(13.0)	
Adult sun exposure					
<0.5 hours/week	188	(70.2)	131	(54.6)	0.01
0.5 to 10 hours/week	36	(13.4)	53	(22.1)	
10.1 to 56 hours/week	44	(16.4)	56	(23.3)	
Physical activities (MET/wk)					
Quartile 1 (≤222)	65	(24.3)	40	(16.7)	0.11
Quartile 2 (222.1-230.9)	66	(24.6)	57	(23.8)	
Quartile 3 (231.0-245.9)	69	(25.8)	64	(26.7)	
Quartile 4 (≥246)	68	(25.4)	79	(32.9)	

n, number; [1]p-value from Chi-square test

Table 3. Risk of Prostate Cancer and Pigment- and Sun Exposure-related Characteristics

Category	Crude OR		Adjusted OR	
	OR	95%CI	OR	95%CI
Pigment characteristics (model 1)				
Eye colour				
Light brown	1.00	Reference	1.00	Reference
Black/dark brown	4.80	2.96-7.79 ‡	5.88	3.17-10.9 ‡
Skin colour				
Very white/white	1.00	Reference	1.00	Reference
Light tan	3.59	2.14-6.00 ‡	4.43	2.26-8.69 ‡
Tan/dark brown/black	3.51	2.02-6.09 ‡	7.62	3.41-17.0 ‡
p-value for linear trend			<0.01	
Sunburn and related characteristics (model 2)				
Sunburn frequency				
Never	1.00	Reference	1.00	Reference
Seldom	1.05	0.68-1.61	1.30	0.71-2.39
Occasionally	1.80	1.01-3.22 †	2.27	0.96-5.35
Frequently	2.63	1.35-5.11 ‡	4.30	1.66-11.2 ‡
p-value for linear trend			<0.01	
Sun exposure in adulthood				
<0.5 hours/week	1.00	Reference	1.00	Reference
≥ 0.5 hours/week	1.96	1.36-2.82 ‡	1.87	1.13-3.11 †
0.5-10 hours/week	2.11	1.31-3.41 ‡	1.71	0.90-3.25
10.1-56 hours/week	1.83	1.16-2.87 ‡	2.03	1.09-3.81 †
p-value for linear trend			0.02	

OR, odds ratio; CI, confidence intervals; †p-value < 0.05; ‡p-value < 0.01; Model 1, multivariate regression model adjusted for age (continuous), ethnicity (4 categories), education (4 categories), family history of any cancers (yes/no), BMI (continuous; Model 2, multivariate regression model adjusted for age (continuous), ethnicity (4 categories), education (4 categories), family history of any cancers (yes/no), BMI (continuous), skin colour (3 categories)

Pigment and sun sensitivity characteristics

The associations between pigment with sun sensitivities

Table 4. Risk of Prostate Cancers and Pigment- and Sun Exposure-related Variables by Tumour Grade

Category	Controls (n=268)		Low grade[1] (n=89)				High grade[2] (n=150)			
	n	(%)	n	(%)	OR	95% CI	n	(%)	OR	95% CI
Pigment characteristics (model 1)										
colour										
Light brown	97	(36.5)	3	(3.5)	1.00	Reference	22	(15.0)	1.00	Reference
Black/dark brown	169	(63.1)	83	(96.5)	19.3	5.46-68.1 ‡	125	(85.0)	4.36	2.22-8.57 ‡
Skin colour										
Very white/white	80	(29.9)	8	(9.1)	1.00	Reference	17	(11.7)	1.00	Reference
Light tan	116	(43.3)	49	(55.7)	4.32	1.69-11.1 ‡	80	(55.2)	4.54	2.05-10.1 ‡
Tan/dark brown/black	72	(26.9)	31	(35.2)	8.80	2.96-26.1 ‡	48	(33.1)	8.01	3.10-20.7 ‡
p-value for linear trend					<0.01				<0.01	
Sunburn and related characteristics (model 2)										
Sunburn frequency										
Never	147	(57.4)	38	(44.7)	1.00	Reference	74	(51.0)	1.00	Reference
Seldom	70	(27.3)	24	(28.2)	1.77	0.80-3.94	31	(21.4)	1.06	0.52-2.19
Occasionally	24	(9.4)	12	(14.1)	1.85	0.60-5.75	21	(14.5)	1.85	0.70-4.87
Frequently	15	(5.9)	11	(12.9)	3.37	0.97-11.8	19	(13.1)	5.21	1.80-15.1 ‡
p-value for linear trend					0.04				<0.01	
Sun exposure in adulthood										
<0.5 hours/week	188	(70.1)	52	(58.4)	1.00	Reference	78	(52.0)	1.00	Reference
≥0.5 hours/week	80	(29.9)	37	(41.6)	1.39	0.70-2.75	72	(48.0)	2.07	1.17-3.68 †
0.5-10 hours/week	36	(13.4)	19	(21.4)	1.41	0.61-3.29	34	(22.7)	1.73	0.85-3.57
10.1-56 hours/week	44	(16.4)	18	(20.2)	1.36	0.58-3.21	38	(25.3)	2.44	1.20-4.96 †
p-value for linear trend					0.41				0.01	

[1]Low grade, Total Gleason score<7; [2]High grade, Total Gleason score ≥7; OR, odds ratio; CI, confidence intervals; †p-value<0.05, ‡ p-value<0.01; Model 1, multivariate regression model adjusted for age (continuous), ethnicity (4 categories), education (4 categories), family history of any cancers (yes/no), BMI (continuous); Model 2, multivariate regression model adjusted for age (continuous), ethnicity (4 categories), education (4 categories), family history of any cancers (yes/no), BMI (continuous), skin (3 categories) (Multivariate OR does not change after adjusted for physical activity or adult sun exposure hours)

Table 5. Risk of Prostate Cancers and Pigment- and Sun Exposure-related Variables by Tumour Stage

Category	Controls (n=268)		Localized stage[1] (n=181)				Advanced stage[2] (n=59)			
	n	(%)	n	(%)	OR	95% CI	n	(%)	OR	95% CI
Pigment characteristics (model 1)										
Eye colour										
Light brown	97	(36.5)	15	(8.5)	1.00	Reference	10	(17.5)	1.00	Reference
Black/dark brown	169	(63.1)	162	(91.5)	8.26	3.97-17.2 ‡	47	(82.5)	3.19	1.27-8.00 †
Skin colour										
Very white/white	80	(29.9)	19	(10.7)	1.00	Reference	6	(10.5)	1.00	
Light tan	116	(43.3)	101	(57.1)	4.35	2.12-8.92 ‡	29	(50.9)	4.56	1.33-15.6 †
Tan/dark brown/black	72	(26.9)	57	(32.2)	7.61	3.24-17.9 ‡	22	(38.6)	9.78	2.30-41.7 ‡
p-value for linear trend					<0.01				<0.01	
Sunburn and related characteristics (model 2)										
frequency										
Never	147	(57.4)	78	(45.1)	1.00	Reference	34	(58.6)	1.00	Reference
Ever	109	(42.6)	95	(54.9)	1.85	1.05-3.27 †	24	(41.4)	1.54	0.63-3.75
Seldom	70	(27.3)	44	(25.4)	1.40	0.74-2.67	12	(20.7)	1.05	0.36-3.05
Occasionally	24	(9.4)	30	(17.3)	2.47	1.02-5.97 †	3	(5.2)	0.48	0.06-3.57
Frequently	15	(5.9)	21	(12.1)	3.46	1.25-9.56 †	9	(15.5)	9.13	2.15-38.8 ‡
p-value for linear trend					0.01				0.02	
Sun exposure in adulthood										
<0.5 hours/week	188	(70.2)	97	(53.6)	1.00	Reference	34	(57.6)	1.00	Reference
≥0.5 hours/week	80	(29.9)	84	(46.4)	1.70	0.99-2.91	25	(42.4)	1.77	0.79-3.98
0.5-10 hours/week	36	(13.4)	45	(24.9)	1.71	0.88-3.32	8	(13.6)	0.80	0.26-2.50
10.1-56 hours/week	44	(16.4)	39	(21.6)	1.68	0.85-3.33	17	(28.8)	3.13	1.20-8.18 †
p-value for linear trend					0.08				0.03	

[1]Localized stage, (T1 or T2, N0, M0); [2]Advanced stage, (M0, T3/T4 & N0 or T1-T4 with any N or any T, any N, and M1, M1b, M1c); OR, odds ratio; CI, confidence intervals; †p-value<0.05, ‡p-value<0.01; Model 1, multivariate regression model adjusted for age (continuous), ethnicity (4 categories), education (4 categories), family history of any cancers (yes/no), BMI (continuous); Model 2, multivariate regression model adjusted for age (continuous), ethnicity (4 categories), education (4 categories), family history of any cancers (yes/no), BMI (continuous), skin (3 categories) (Multivariate OR does not change after adjusted for physical activity or adult sun exposure hours)

characteristics and prostate cancer are shown in Table 2. The cases had significantly more black/dark brown colour of the eyes compared to the controls (89.3% versus 63.5%), and the distribution of skin colours was also significantly darker for cases. The skin colour of Malays and Indians were much darker than Chinese, and consisted of about 13.5% of the controls and 10.8% of the cases. Likewise, the history of sunburn was more prevalent among cases (p=0.01). Higher proportions of cases were significantly spending more time in the adult weekly sun exposure (hours/week) categories compared to the controls.

On the univariate analysis, individuals with darker pigmentation and sun exposure in adult were associated with an increased risk for prostate cancer. Table 3 showed the crude and adjusted OR for pigment and sun sensitivity characteristics and adult sun exposure. The adjusted OR for eye colour of black/dark brown was 5.88 (95%CI 3.17-10.9) compared with light brown. There was an increased odd for prostate cancer with darker skin colour when compared with the very white/white subjects; from OR 4.43 (95%CI 2.26-8.69) for "Light Tan" to OR 7.62 (95%CI 3.41-17.0) in "Tan/Dark Brown/Black". This trend was significant (p<0.001).

Adult sun exposure was also associated with increased risk for prostate cancer (Table 3). Compared to those who never had sunburn in lifetime, there was an increased risk for prostate cancer, with increasing sunburn frequency for "Seldom" (OR 1.30; 95%CI 0.71-2.39), "Occasionally" (OR 2.27; 95%CI 0.96-5.35); and "Frequently" (OR 4.30; 95%CI 1.66-11.2) respectively. This trend was significant (p<0.001). Individuals with more than 10 hours of sun exposure per week in adulthood had an increased adjusted OR of 2.03 (95%CI 1.09-3.81) (p=0.017) compared to individuals with no sun exposure.

The association of skin colour between controls and low and high grade were fairly similar in term of the ORs (Table 4). There were significant trends and associations for sunburn frequency and sun exposure in adulthood; and also in high grade category. But for the low grade category, there were significant trends and association only for sunburn frequency.

The association of skin colour between controls and localized and advanced stages were fairly similar in term of the ORs. Sunburn frequency was associated with localized stage, and the trend was significant for frequency of sunburn. For advanced stage, only cases that "Frequently" got sunburn had significantly higher OR 9.13 (95%CI 2.15-38.8) compared to subjects who never had sunburn. With sun exposure in adulthood, significant associated was noted only in the advanced stage among those with >10 hours of exposure per week (Table 5).

Discussion

To our knowledge, this is the first epidemiologic study of sun exposure and risk of prostate cancer conducted in an Asian population. Our results from the Singapore Prostate Cancer Study indicated that pigment and sun sensitivity characteristics (i.e. sunburn frequency) and adult sun exposure are associated with an increased risk of prostate cancer; especially for the high grade tumour and advanced stage.

Compared with subjects with light brown eyes, individuals with eye colour of black/dark brown had a ~6-folded increased risk for prostate cancer. Likewise, compared with very fair skin colour, subjects with darker skin colour have significantly increase risk for prostate cancer respectively. From what we observed in this study, the skin colour of Malays and Indians were much darker than Chinese. Since we have already adjusted for ethnicity in the regression model, hence this observation is unlikely to be confounded by the ethnic distribution.

On the other hand, individuals with fairer skin would be more prone to frequent sunburn in lifetime and thus may avoid the sun which would translate to lower vitamin D production. In a large UK-wide nested case-control study based on 1,020 cases and 5,044 matched population controls, Gilbert et al reported that "Men with olive/brown skin had a significantly higher risk for prostate cancer (OR 1.47; 95%CI 1.00-2.17)". The authors suggested that "Olive/brown skin and a tendency not to burn (in other words, a person tans easily), may reflect lower exposure to ultraviolet light of the epidermal layers of the skin where vitamin D production is greatest, hence reducing cutaneous vitamin D synthesis" (Gilbert et al., 2009).

There have been reports on sun exposure conferring a protective effect on prostate cancer and the underlying mechanism is postulated to be related to vitamin D (Gupta et al., 2009). There are evidences to support that vitamin D can inhibit cell proliferation and promote apoptosis in vitro and the active form of vitamin D (i.e. 1,25-dihydroxyvitamin D) has anti-carcinogenic properties (IARC, 2008).

Melanin absorbs UV radiation and competes with formation of vitamin D3 (cholecalciferol). Subjects with black/dark brown eyes and individuals with darker skin colour would receive less UV-B, due to higher prevalence of melanin on skin, relatively low levels of vitamin D will be formed compared with fair skinned individuals under the same given time, unless exposure is prolonged or concentrated. Thus the degree of skin pigmentation may influence prostate cancer risk (Bodiwala et al., 2003). This explanation may be plausible in studies conducted in temperate countries where the level of UV radiation exposure varies considerably between summer and winter (Tuohimaa et al., 2004). This study was conducted in Singapore which is 80km north of the equator. Singapore received an average of 10-12 hours of daylight per day and the variation is very minimal from January to December. Thus it is very unlikely that the study subjects would not receive enough sun even for those with dark pigmented skins given the long hours of sun throughout the year in Singapore. We do not have a good hypothesis to explain this finding from our study. It is known that the highest prostate cancer incidence is in North America and Scandinavia, especially among the African-American men in the United States (Gupta et al., 2009). But skin pigmentation is probably not a good surrogate for race.

Tuohimaa et al study a cohort of 416,134 cases of skin cancer and 3,776,501 cases of non-skin cancer as a first cancer taken from 13 cancer registries from 11 countries

(Tuohimaa et al., 2007). They reported that standardised incidence ratios (SIR) for prostate cancer following non-melanoma skin cancer (excluding basal cell carcinoma) in sunny countries (Spain, Singapore and Australia) was 0.43 (95%CI 0.23-0.73), and less sunny countries (Canada, Slovenia, Scotland, Finland, Denmark, Iceland, Norway and Sweden) was 1.22 (95%CI 1.18-1.28). If non-melanoma skin cancers is a good surrogate for cumulative sun exposure, and sun exposure is protective against prostate cancer, it is difficult to understand why there is a significant different between sunny and less sunny countries.

The risk for low grade prostate cancer and high grade prostate cancer were fairly similar for eye and skin colours when compared with the controls (Table 4). Likewise, risks for localized and advanced groups were similar for eye and skin colours when compared with the controls (Table 5).

If skin pigmentation is a surrogate for sun exposure, there could be plausible explanation for this finding. Individuals who are out in the sun more frequently would develop darker complexion. If excessive sun is a risk factor, there would be significant association between prostate cancer and other sun related activities.

In this study, adult sun exposure is associated with increased risk for prostate cancer. There is an increase significant increasing trend for prostate cancer ($p<0.001$). Compared to "Never sunburn" group, the risk estimates for developing prostate cancer increases with increasing sunburn frequency. But if we examine this effect by grade of the tumour, only high grade prostate cancer was significantly associated with a 5-fold increase. With staging of prostate cancer, sunburn frequency was associated with localized and advanced stages compared to subjects who never had sunburn.

Sunburn may be more common among those who are not in the sun frequently, which would imply less vitamin D production. However, individuals who have lighter skin (more likely to have more vitamin D production) may be more prone to sunburn. Sunburn is a known risk factor for melanoma. Tuohimaa et al reported that SIR for prostate cancer following melanoma skin cancer in sunny countries (e.g. Spain, Singapore and Australia) was 1.20 (95%CI 1.10-1.30) and less sunny countries (e.g. Canada, Slovenia, Scotland, Finland, Denmark, Iceland, Norway and Sweden) was 1.31 (95%CI 1.23-1.40). There is no significant different between sunny and less sunny countries for prostate cancer among melanoma skin cancers suggesting that sunburn is associated with prostate cancer (Tuohimaa et al., 2007).

Compared to individuals with less than half an hour sun exposure per week, individuals who exposed under sun with more than 10 hours per week in adulthood have an ~2-time increased risk ($p=0.027$). When we analyzed by tumour grades and staging, this group of subjects were at significantly higher risk of developing high grade tumour at 2.4 times and advanced stage at 3.1 times. The findings from this study suggests that excessive sun exposure is a risk factor for developing more aggressive and advanced form of prostate cancer.

Our study is consistent with the recent Australian case-control study. Nair-Shalliker et al reported a positive association between reported personal sun exposure and risk of prostate cancer in a high ambient solar environment (Nair-Shalliker et al., 2011). Tuohimaa et al in a large 622 cases and 1,451 matched controls study in Finland and Norway reported a U-shaped relationship between serum 25-hydroxyvitamin D levels and prostate cancer. Both low (<19 nmol/l) and high (>80 nmol/l) 25(OH)-vitamin D serum concentrations are associated with higher prostate cancer risk (Tuohimaa et al., 2004). Suda et al first reported that active vitamin D promotes differentiation and inhibits tumour cells proliferation (Egan, 2006). Low vitamin D levels could increase one risk of developing prostate cancer. This observation has been reported in many studies (Polek et al., 2002; Moon et al., 2005).

Gilbert et al reported "… amongst men with prostate cancer, spending less time outside that was associated with a reduced risk of advanced cancer (OR 0.49; 95%CI 0.27-0.89) and high Gleason grade (OR 0.62; 95%CI 0.43-0.91), and men who burnt rarely/never had a reduced risk of advanced cancer (OR 0.71; 95%CI 0.47-1.08)" (Gilbert et al., 2009). Increased sun exposure may be a risk factor for prostate cancer. The explanation that Gilbert et al gave was increased sunlight exposure increased vitamin D serum levels and "raised levels of vitamin D may lead to increased 24-hydroxylase levels, an enzyme that decreases local synthesis of 1,25-dihydroxyvitamin D. 24-hydroxylase itself has been found to be cancer-inducing because it inactivates 1,25-dihydroxyvitamin D." Our findings are similar to that of Gilbert et al. They reported that sun exposure, measured by "Time spent outside (5-69 years)" were risk factors for high Grade (Gleason score ≥ 7) and advanced (T3-T4 and N1 or M1) prostate cancer (Gilbert et al., 2009).

The primary aim of this study was to evaluate the association of sun exposure and risk of prostate cancer in an Asian population living in the tropics. Its strengths are that data were collected using standardized techniques, with effort made to maintain comparability with previous questionnaires used in other populations. We are mindful of the limitations that are inherent in the retrospective nature of this study, and the limited sample size. Specifically, our risk estimates for Indians and Malays have wide confidence intervals and we were unable to make inferences about the effect of sun exposure on prostate cancer. The 70.0% participation rate in our hospital controls may introduce a selection bias, but it is unlikely that this is related to sun exposure in a way that would account for the associations observed. About 41% of our controls had 'bone and joints' problems. The concern may be that controls with this problem may not go out in the sun. There was no significant different in the average hours per week in the sun between controls with 'bone and joints' problem and those without the condition. We also acknowledge that reporting and recall bias could occur in this study, but as the hypothesis regarding sun exposure and prostate cancer risk is not known in the general population, we would expect such a misclassification to be non-differential. As sun exposure (and not vitamin D) was the primary exposure studied, we did not include dietary sources of vitamin D. This was

due to the relatively low intake of vitamin D-rich food sources in this population, and difficulties in obtaining accurate data on supplement intake, and we recognize that this limits the extent to which we can attribute our findings to a particular biologic mechanism.

In conclusion, we find that in this Asian population in the geographical region with high UV index, eye and skin pigmentation and outdoor sun exposure in adulthood are associated with the risk of developing prostate cancer. The finding of sun exposure is different from many reports that suggest sun exposure is protective. But there are reports with similar findings as this study. A larger study, in other similar context, across various populations may be needed to see if our findings can be replicated. Sun exposure may not be protective against prostate cancer in certain population groups.

Acknowledgements

This research was supported by National Medical Research Council, Singapore (NMRC/EDG/0008/2007). We are grateful to the medical boards, clinicians and other staff of the Singapore General Hospital for allowing us to include their patients. Special thanks to the field staff Miss Brenda Tse for coordinating the data collection and interviewing with Ms Janice Teo, and data entry personnel for their untiring efforts. Our appreciation is to all our participants for their contribution to this work. The authors declare no conflict of interest.

References

Bodiwala D, Luscombe CJ, French ME, et al (2003). Susceptibility to prostate cancer: studies on interactions between UVR exposure and skin type. *Carcinogenesis*, **24**, 711-7.

Egan KM (2006). Commentary: sunlight, vitamin D, and the cancer connection revisited. *Int J Epidemiol*, **35**, 227-30.

Gilbert R, Metcalfe C, Oliver SE, et al (2009). Life course sun exposure and risk of prostate cancer: population-based nested case-control study and meta-analysis. *Int J Cancer*, **125**, 1414-23.

Grant WB (2010). A multicountry ecological study of risk-modifying factors for prostate cancer: apolipoprotein E epsilon4 as a risk factor and cereals as a risk reduction factor. *Anticancer Res*, **30**, 189-99.

Gupta D, Lammersfeld CA, Trukova K, Lis CG (2009). Vitamin D and prostate cancer risk: a review of the epidemiological literature. *Prostate Cancer Prostatic Dis*, **12**, 215-26.

Hanchette CL, Schwartz GG (1992). Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. *Cancer*, **70**, 2861-9.

Institute NC (2004). Cancer Mortality Map. *US National Institute of Health*.

John EM, Schwartz GG, Koo J, et al (2005). Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Res*, **65**, 5470-9.

Lin SW, Wheeler DC, Park Y, et al (2012). Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. *Int J Cancer*, **131**, 1015-23.

Moon SJ, Fryer AA, Strange RC (2005). Ultraviolet radiation, vitamin D and risk of prostate cancer and other diseases. *Photochem Photobiol*, **81**, 1252-60.

Nair-Shalliker V, Smith DP, Egger S, et al (2011). Sun exposure may increase risk of prostate cancer in the high UV environment of New South Wales, Australia: A case-control study. *Int J Cancer*, **131**, E726-32.

Patel AR, Klein EA (2009). Risk factors for prostate cancer. *Nat Clin Pract Urol*, **6**, 87-95.

Polek TC, Weigel NL (2002). Vitamin D and prostate cancer. *J Androl*, **23**, 9-17.

Tuohimaa P, Pukkala E, Scelo G, et al (2007). Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: vitamin D as a possible explanation. *Eur J Cancer*, **43**, 1701-12.

Tuohimaa P, Tenkanen L, Ahonen M, et al (2004). Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int J Cancer*, **108**, 104-8.