Environmental risk factors of prostate cancer: a case-control study

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KEY MESSAGES

1. This study provides the first epidemiological evidence on the link between chronic bisphenol A (BPA) exposure and prostate cancer risk.
2. Policies to remove toxicant BPA at source should be implemented to ameliorate prostate cancer risk. Personalised education programmes should be implemented to modify unhealthy dietary habits and avoid hazardous working schedules that disrupt the circadian rhythm.
3. The validated assessment tool can be used as a reasonable reference in the Hong Kong population to identify potential sources of BPA exposure via the route of ingestion and evaluate the exposure level in daily living.

Hong Kong Med J 2018;24(Suppl 4):S30-3
HMRF project number: 11121091

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Introduction

Advancing age, race, and family history of prostate cancer are established risk factors of prostate cancer.[1] The influence of environmental factors on prostate cancer aetiology remains unclear. Geographic variations in age-standardised incidence of prostate cancer have been positively correlated to detection rates of urinary bisphenol A (BPA). Oestrogen-like BPA has been linked to prostate cancer risk in animals, but evidence for this link in humans is scarce. There is no information on environmental exposure and prostate cancer aetiology in a Hong Kong population. The aim of the present study was to document the association between environmental exposure to BPA and the risk of prostate cancer among Hong Kong Chinese men, and to examine the exposure-response relationship between cumulative BPA exposure index and prostate cancer risk.

Methods

This case-control study was conducted between August 2011 and November 2016. Consecutive Chinese men aged 35 to 84 years who were diagnosed with primary prostate cancer (ICD-10 code C61) by histology were recruited from the Department of Surgery and Clinical Oncology of a regional hospital. Controls were selected at random from patients being treated at the same hospital for diseases other than prostate cancer or benign prostate hyperplasia (BPH). We also recruited a total of 855 patients with biopsy-confirmed BPH; they were likely biased controls, as they may share some common exposure with the cases. Therefore, comparisons were based mainly on cases with prostate cancer and controls without BPH; patients with BPH were used only as supporting data.

Participants were interviewed by trained staff using a standardised questionnaire that covered information on education level, smoking habit, alcohol drinking, dietary habit, supplement intake, physical activity, history of benign disease in genitourinary system, family cancer history of first-degree relatives, occupation, shift work, and environmental exposure to BPA. Diagnostic and histological data were extracted from hospital records.

A new tool to assess environmental BPA exposure was developed, based on a literature review, to reconstruct each participant's past exposure to BPA according to a master list of food or beverage containers under different handling processes. The assessment tool was further validated by two experts in environmental hygiene and food safety who blindly rated the exposure intensity of BPA based on the same master list and same rating scale. High inter-rater and inter-method agreement on interclass correlation coefficient was achieved, indicating good replication and validation of the new assessment tool for evaluation of BPA exposure (Table 1). A novel cumulative BPA exposure index was constructed based on a standard approach commonly used in assessing hazardous substances in workplace environment: multiplying the square of exposure score by the frequency (per week) and years of use for each type of container under a specific handling practice, and then summed over all types of containers in a lifetime.

Risk factors between cases and controls were compared using Chi square or Student's *t* tests. Multiple logistic regression analysis was performed to determine odds ratio (OR) and 95% confidence interval (CI). An exposure-response relationship was considered significant when a P value for trend was <0.05.

Results

Cases (n=431) and controls (n=402) were comparable in terms of age at diagnosis (69.4 vs 68.2 years). More cases than controls were married (P=0.039) or retired (P=0.046) [Table 2]. Among potential risk factors of prostate cancer in Hong Kong Chinese men, family history of prostate cancer was more common in cases than controls (9.5% vs 3.0%, P<0.001, Table 3), with an adjusted OR of 3.68 (95% CI=1.85-7.34). Weekly consumption of deep-fried food and pickled vegetables was associated with an increased risk of prostate cancer by 85% (95% CI=15%-195%) and 87% (95% CI=7%-228%), respectively. Night shift work was hazardous (OR=1.76, 95% CI=1.07-2.89), but habitual green tea drinking was protective (OR=0.56, 95% CI=0.34-0.91). A positive exposure-response relationship between cumulative BPA exposure index and prostate cancer was observed, with a more prominent gradient in men under the age of 70 years. The use of commercial food containers was positively related to prostate cancer risk, but only habitual drinking of chilled water in a plastic container showed a significant association.

TABLE 1. Intraclass correlation coefficient for the inter-method and inter-rater agreement on bisphenol A exposure

Master list of environmental bisphenol A exposure	Literature review	Intraclass correlation coefficient (95% confidence interval)*	
		Expert 1	Expert 2
Including all items			
Literature review	1.00	0.90 (0.81-0.95)	0.86 (0.73-0.93)
Expert 1		1.00	0.94 (0.88-0.97)
Expert 2			1.00
Excluding items of glass or metal			
Literature review	1.00	0.87 (0.71-0.85)	0.82 (0.58-0.92)
Expert 1		1.00	0.92 (0.82-0.97)
Expert 2			1.00

* Coefficient of <0.40, 0.40-0.75, and >0.75 is interpreted as poor, moderate-to-good, and excellent agreement, respectively

TABLE 2. Sociodemographic variables of prostate cancer cases and hospital controls

Variable	Cases (n=431)*	Controls (n=402)*	P value
Age, y	69.4±7.3	68.2±8.2	0.027
Education			0.562
Primary or below	177 (41.1)	157 (39.1)	
Secondary school	197 (45.7)	198 (49.2)	
College or above	57 (13.2)	47 (11.7)	
Place of birth			0.481
Hong Kong	161 (37.3)	167 (41.6)	
Mainland China	249 (57.8)	216 (53.7)	
Southeast Asia	21 (4.9)	19 (4.7)	
Marital status			0.039
Married	400 (92.8)	352 (87.5)	
Widower	14 (3.3)	24 (6.0)	
Single or divorced	17 (3.9)	26 (6.5)	
Retirement status			0.046
Retired	329 (76.3)	286 (71.1)	
Employed	102 (23.7)	116 (28.9)	

* Data are presented as mean ± standard deviation or No. (%) of patients

Discussion

Our study found that some dietary habits, night shift work, and environmental BPA exposure are risk factors of prostate cancer among Hong Kong Chinese men. Prostate cancer was positively associated with consumption of deep-fried food and pickled vegetables, independent of other risk factors or confounders. Deep-fried food has high levels of heterocyclic amines and other mutagens/carcinogens. The carcinogenic effect of preserved food on prostate cells may be related to some mutagenic activities in pickled vegetables (mustard greens). An inverse association of prostate cancer with habitual green tea intake may be related to epigallocatechin 3-gallate, which is a potent catechin that specifically inhibits carcinogenesis of prostate cells.

According to the International Agency for Research on Cancer in 2007, shift work that disrupts the circadian rhythm is probably carcinogenic to humans (Group 2A).[2] Night shift work may lead to sustained low levels of melatonin, increasing prostate cancer risk. Sleep deprivation secondary to night shift work increases the pro-inflammatory response process but decreases the immune defence against free radicals, thus increasing the carcinogenesis process.[3]

In 2014, evidence of a direct link between BPA exposure and human prostate cancer was first reported.[4,5] Abnormalities of centrosome (a hallmark of malignant transformation) induced by low levels of BPA were highlighted as the potential mechanism in promoting the formation of prostate cancer.[5] Our study provides the first epidemiological evidence that cumulative exposure to BPA is associated with an increased risk of prostate cancer in a Chinese population. In addition, an exposure-response relationship was observed among Chinese men aged

TABLE 3. Potential risk factors of prostate cancer in Hong Kong Chinese men

Variables	Prevalence*		P value	Main effect model	Full model
	Cases (n=431)	Controls (n=402)		Adjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Family prostate cancer history			<0.001		
Negative	390 (90.5)	390 (97.0)		1.00	1.00
Positive	41 (9.5)	12 (3.0)		3.54 (1.81-6.95)	3.68 (1.85-7.34)
Deep-fried food consumption			<0.001		
<1 time per month	208 (48.3)	210 (52.2)		1.00	1.00
1-3 times per month	137 (31.8)	152 (37.8)		1.03 (0.75-1.41)	0.91 (0.65-1.27)
≥1 time per week	86 (20.0)	40 (10.0)		2.36 (1.51-3.68)	1.85 (1.15-2.95)
Pickled vegetables consumption			0.006		
<1 time per month	204 (47.3)	199 (49.5)		1.00	1.00
1-3 times per month	175 (40.6)	180 (44.8)		0.95 (0.74-1.28)	0.90 (0.66-1.23)
≥1 time per week	52 (12.1)	23 (5.7)		2.24 (1.31-3.84)	1.87 (1.07-3.28)
Green Tea drinking habit			0.040		
Non-habitual	396 (91.9)	351 (87.3)		1.00	1.00
Habitual	35 (8.1)	51 (12.7)		0.60 (0.387-0.96)	0.56 (0.34-0.91)
Nightshift work			0.005		
Never	366 (84.9)	372 (92.5)		1.00	1.00
Ever	58 (13.5)	30 (7.5)		1.87 (1.16-3.01)	1.76 (1.07-2.89)
Cumulative bisphenol A index					
All participants			0.018		
Low	75 (17.4)	101 (25.1)		1.00	1.00
Middle	232 (53.8)	201 (50.0)		1.66 (1.15-2.40)	1.54 (1.05-2.26)
High	124 (28.8)	100 (24.9)		1.88 (1.24-2.86)	1.57 (1.01-2.44)
P value for trend				0.014	0.057
Participants aged <70 years			0.048		
Low	40 (16.7)	61 (24.8)		1.00	1.00
Middle	123 (51.5)	124 (50.4)		1.62 (0.99-2.64)	1.56 (0.94-2.59)
High	76 (31.8)	61 (24.8)		2.10 (1.22-3.64)	1.79 (1.01-3.18)
P value for trend				0.017	0.056

* Data are presented as No. (%) of patients

>70 years who were born around or prior to the time BPA was introduced in the industrialised world. This correlation suggests a potential influence of early exposure in the development of prostate cancer. Although only habitually drinking chilled water in a plastic container was identified as a significant risk factor, there is a positive association between other types of commercial food or beverage containers and prostate cancer risk.

There are limitations to the study. Several factors might generate biases. Selection bias is a concern as all cases were recruited from a single centre. Nonetheless, the age distribution of our cases was similar to that from the Hong Kong Cancer Registry. Using hospital patients as controls may be a concern, as their lifestyle habits may differ from those of the general population. However, hospital controls with diverse diagnoses may reduce the potential selection bias, but the response rate of hospital controls was higher than that of healthy controls from the general population. Cumulative BPA exposure index is regarded as the best available indicator for chronic BPA exposure by ingestion because it is generally infeasible for case-control studies to have bio-monitoring data. Hence, capture of reliable chronic exposure to BPA has to rely on a well-designed questionnaire covering long-term exposure. We developed and validated a new assessment tool to evaluate chronic BPA exposure, with the collective index representing the chronic

exposure to environmental BPA via ingestion. Although BPA may also enter into human body via direct contact or inhalation, routes other than ingestion cannot be totally ignored. Misclassification of BPA exposure is a concern, as we did not consider exposure variations over time. This possible recall bias may be non-differential misclassification, which in turn lead to a potential underestimation of the association between cumulative BPA exposure index and prostate cancer, partly because the use of BPA in food and water containers has recently declined. Our sample is relatively small and has limited power to determine in-depth associations of specific type of food container under different handling process. Only 855 biopsy-negative controls (rather than the estimated 1200) were eventually obtained when we recruited 431 'true cases'. Further evidence from multiple logistic regression analysis for the 855 patients with BPH and 401 controls without BPH showed a greater gradient between cumulative BPA exposure index and BPH (adjusted ORs for the low, middle, and high cumulative BPA exposure index were 1.00, 2.08, and 2.55, respectively) than that was observed between cumulative BPA exposure index and prostate cancer. As BPH and prostate cancer may share some risk factors, any association between BPA and prostate cancer is likely to be biased if the patients with BPH were used as the controls.

Conclusions

Among Hong Kong Chinese men, risk factors of prostate cancer are family history of prostate cancer, night shift work, and frequent consumption of deep-fried food and pickled vegetables, whereas habitual green tea drinking has a moderately beneficial effect. Chronic exposure to environmental BPA is associated with an elevated prostate cancer risk, in particular for those with prostate cancer occurred below the age of 70 years. Frequent drinking of chilled water from a plastic container is the most significant source of environmental BPA by ingestion. Policies to remove the toxicant BPA at source should be implemented to ameliorate the prostate cancer risk. Personalised education programmes are recommended to promote healthy dietary habits and avoid hazardous working schedules. The newly developed assessment tool can be used as a reference in Hong Kong populations to help understand potential sources and exposure levels of environmental BPA by ingestion.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11121091). The authors thank the following for their helpful advice and support: Dr Lam Tsan Augustine, Dr Lee Man Kei, Ms Law Ka Wai, Ms Lau Fung Ching Elsa, Ms Chan Wah Mui Virene, Mr Steven Leung, Ms Wong Lai Hung, Family Medicine Training Centre, Prince of Wales Hospital; Prof Ng Siu Man Simon, Department of Surgery, Prince of Wales Hospital; Miss Yip Siu Ying Jenny and Miss Lau Sui Yan Becky, Division of Urology, The Chinese University of Hong Kong; Miss Lee Ming Yi Priscilla, Miss Tsoi Hiu Man Tess, and Miss Kwok Ho Ling Bonnie, JC School of Public Health and Primary Care, The Chinese University of Hong Kong; Prof Jenifer C Hartle, Department of Health Science and Recreation, San Jose State University; and Prof Leung Ka-sing, Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University. The authors also thank the patients and staff of the departments of oncology and surgery for their support.

Results of this study have been published in: Tse LA, Lee PM, Ho WM, et al. Bisphenol A and other environmental risk factors for prostate cancer in Hong Kong. Environ Int 2017;107:1-7.

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