

ORIGINAL ARTICLE

Reduced prostate cancer risk with green tea and epigallocatechin 3-gallate intake among Hong Kong Chinese men

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BACKGROUND: *In vitro* and *in vivo* studies suggested that polyphenol epigallocatechin 3-gallate (EGCG) in tea may have anti-carcinogenic effect on prostate cells, but this protective effect has less been examined in epidemiology studies. We aimed to investigate the association between prostate cancer (PCA) risk and habitual green tea intake among Chinese men in Hong Kong; meanwhile, the relationship with EGCG was also explored.

METHODS: We consecutively recruited 404 PCA cases and 395 controls from the same hospital who had complete data on habitual tea consumption, including green, oolong, black and pu'er tea. We reconstructed the level of EGCG intake according to a standard questionnaire and the analytic values for EGCG extracted from the literature published by Lin *et al.* in 2003. We calculated odds ratios (ORs) for tea consumption and EGCG intake using unconditional multiple logistic regression, and examined their exposure–response relationships with PCA risk.

RESULTS: A total of 32 cases and 50 controls reported habitual green tea drinking, showing an adjusted OR of 0.60 (95% confidence interval (CI): 0.37, 0.98). A moderate excess risk was observed among the habitual pu'er tea drinkers (OR = 1.44, 95% CI: 1.02, 1.91). A significantly lower intake of EGCG was observed among cases (54.4 mg) than the controls (72.5 mg), which resulted in an inverse gradient of PCA risk with the increasing intake of EGCG (test for trend, $P = 0.015$).

CONCLUSION: PCA risk among Chinese men in Hong Kong was inversely associated with green tea consumption and EGCG intake, but these results need to be replicated in larger studies.

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INTRODUCTION

The incidence rate of prostate cancer (PCA) is on a rising trend in Asian countries with a higher growing rate among Chinese men in Hong Kong.¹ Although PCA has been ranked as the third most common cancer in Hong Kong,² the rate is still much lower than that of the Western countries. This may be the result of a lower exposure to known risk factors (for example, black race, westernized diet) in Asians³ or alternatively, it may also reflect differences in exposures to potential protective factors (for example, green tea intake) that may contribute to the lower incidence rate of PCA among Chinese.^{4,5}

Besides green tea, fermented tea such as oolong tea, black tea and pu'er tea are also popular in Hong Kong. Results from *in vitro* and *in vivo* studies demonstrated that catechins, a type of polyphenols rich in green tea,^{6,7} can inhibit the carcinogenesis and thus restrain the progression of cancer development.^{8,9} Among four major types of catechins derived from the tea (epigallocatechin 3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate and epicatechin),⁶ EGCG is recognized as the most potent catechin that inhibits against carcinogenesis.⁸ *In vitro* studies showed that EGCG can specifically inhibit the growth of LNCaP cells (a cell line of human PCA) and also reduce

androgen actions in the target prostate cell.⁸ Several epidemiological studies investigated the association between tea consumption and PCA risk but the results have been mixed.^{4,5,10–14} A case–control study conducted in Southeast China revealed an inverse dose–response relationship between cups of green tea intake and PCA risk.⁴ An intervention study conducted by Brausi *et al.*¹¹ provided evidence that green tea catechins reduced almost 80% of PCA risk for chemoprevention of PCA patients with high-grade prostatic intraepithelial neoplasia; whereas another intervention study in the United States showed that consumption of green tea catechins reduced the PSA in serum within one year of the intervention, but there was lack of evidence for a beneficial effect on PCA risk,¹² probably because of the too short duration of intervention to manifest an inverse effect of EGCG. There is inconsistent evidence from Japan and Canada in which no significant association between tea consumption and PCA was suggested.^{13,14} A large prospective cohort study in Singapore by following up nearly 28 000 men also revealed that PCA risk was not significantly correlated with daily green tea consumption, but positively associated with black tea consumption.¹⁵ We hypothesized that habitual green tea consumption is negatively associated with PCA and there is an inverse relation between EGCG level and PCA risk. Until now, epidemiological studies on the association

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between habitual green tea consumption and the PCA tended to be inconclusive, while the evidence on the relation with EGCG is even sparse. This study aimed to investigate the association between PCA risk and habitual green tea intake among Chinese men in Hong Kong. In addition, the relationship with the intake of EGCG was also explored.

MATERIALS AND METHODS

Study design and population

This hospital-based case-control study was conducted in a regional hospital of New Territories East Cluster of Hong Kong from August 2011 to June 2016. This regional hospital treated about 6.3% of new PCA incident cases in Hong Kong. The proportions of incident PCA cases in different age groups were similar to those obtained from the Hong Kong Cancer Registry in 2012–2013.¹⁶ Eligible cases were Hong Kong Chinese male residents aged below 85 years who were newly diagnosed primary PCA cases (ICD-10 code C61) confirmed by histology. All the cases were consecutively recruited from the Department of Surgery and the Department of Clinical Oncology, with a response rate of 87.9% and 88.5%, respectively. The cases were interviewed within 3 months after the diagnosis was confirmed. The controls were randomly recruited from the same hospital from different clinics such as urinary stone, hepatobiliary and pancreatic, colorectal, vascular clinic and general medical outpatient clinic. All controls were frequency matched to the cases by 5-year age group and interviewed about 4 weeks after the cases were identified to minimize the potential recall bias regarding the timing of interview (response rate=73.2). Patients who refused to participate in this study were slightly older than the participants (72.5 years vs 69.5 years), and the main reason for refusing interview was lack of interest. We excluded those who had physician-diagnosed cancer in any site or those with difficulties in communication. These exclusion criteria were applied to both cases and controls. We received ethics approval from The Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee and informed consent was obtained from each participant before the fieldwork was started.

Exposure assessment on tea drinking and EGCG estimation

Trained interviewers interviewed the participants using a standardized questionnaire including information on socio-demographic characteristics, habits of tobacco smoking and alcohol consumption, dietary habits (for example, intake of green vegetables, orange vegetables and fruits, deep fried food, tea and coffee consumption), family history of cancer and occupational history.

Each participant was asked to report if he had habitual tea drinking. Habitual tea drinkers were defined as participants who drank tea at least once a week over 5 years preceding diagnosis or recruitment, whereas those who did not have such a habit were defined as non-tea drinkers. Habitual tea drinkers were asked to provide information on types of tea (that is, green tea, oolong tea, black tea, pu'er tea), frequency of tea drinking (cups a day, one cup is equivalent to 250 ml), years of drinking and the concentration of tea drinking expressed by the amount of tea leaves of intake (light: < 2.5 g; moderate: 2.5–5.0 g, heavy: 5.0–7.5 g; very heavy: ≥ 7.5 g) in 250 ml water. The participants were asked to choose the amount of tea leaves displayed in four different bags (that is, 1.25 g, 2.5 g, 5.0 g, 7.5 g, respectively) to best describe the concentration of their tea drinking.

We reconstructed the amount of EGCG consumed from all teas for each participant using a standard questionnaire with the analytic values of EGCG extracted from the literature published by Lin *et al.*⁶ They measured the levels of polyphenols for different types of tea produced in China, Taiwan and Japan that are the major tea exporters to Hong Kong. Lin *et al.*⁶ reported that the mean content of EGCG in one percent infusion (that is, 1 g tea leaves per 100 ml boiling water) for the green, oolong, black and pu'er tea was 19.51 mg, 5.06 mg, 2.42 mg and 2.00 mg, respectively. The mean content of EGCG of these four types of tea (that is, 7.25 mg) was used to estimate the EGCG intake for participants who had no preferable tea type (that is, mixed tea type). In China, tea is traditionally prepared in the proportion of 1 g tea leaves per 100 ml boiling water,⁹ and it has been reported that the catechins contents in tea infusion were positively related to the amount of tea leaves in a linear way.¹⁷ Hence, it is reasonable to estimate the amount of EGCG intake according to their concentration of tea infusion; nevertheless, we did not take into consideration the moisture

and retention factors in the estimation of EGCG. In our study, daily intake of EGCG was estimated by the product of grams of specific tea leaves times cups for tea drinking. Cumulative EGCG consumption for each participant was estimated by the daily intake of EGCG times the years of tea drinking.

Sample size estimation

The sample size was estimated by Kelsey's formula.¹⁸ Based on a case-control study conducted in Southeast China by Jian *et al.*,⁴ at least 72 cases and 72 controls were required to reach a power of 95% and the 5% two-sided significant level, if the OR was 0.27 and the prevalence of green tea consumption was 74.4% among controls.⁴ We recruited 404 cases and 395 controls who had complete information on tea consumption, and the number of participants was much more than what was expected based on the study of Jian *et al.*⁴ As the proportion of green tea consumption of our participants in the control group (12.7%) was lower than that was reported in the study of Jian, statistical power for the relation with green tea intake in our study may be lower than what was expected.

Statistical methods

We used independent *t*-test and Chi-square test to compare the distribution of continuous and categorical variables, respectively. Unconditional multiple logistic regression was performed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) between different exposure characteristics of tea drinking and the PCA risk by adjusting for age at interview, deep fried food consumption, green vegetable consumption, alcohol consumption, coffee consumption, tobacco consumption, education attainment and family prostate cancer history. We also considered adjustment of the variable 'consumption of orange vegetables (for example, tomato, carrot, pumpkin, sweet potato and purple sweet potato) and fruits' (for example, orange, lemon, papaya) but it was not retained in the final model due to lack of statistical significance. We further categorized the amount of EGCG intake by quartile according to the pattern of control subjects to explore the possible dose-response relationship with the PCA risk. We performed statistical analyses using SPSS 20.0 for Windows (SPSS, Chicago, IL, USA). All statistical tests were two-sided and *P*-value less than 0.05 was considered as statistically significant.

RESULTS

Four hundred and four PCA cases and 395 controls who had complete information on tea drinking behaviour were included in this report. As shown in Table 1, PCA cases were slightly older than that of controls (69.5 years vs 68.1 years) and they had a significantly higher proportion of consumption of deep fried food and family history of PCA; nevertheless, the pattern of tobacco smoking, alcohol drinking, orange vegetables and fruits, green vegetables and coffee intake were similar between the cases and controls.

A total of 279 (69.1%) PCA cases and 242 (61.3%) controls had a habitual tea drinking history, showing an adjusted OR of 1.36 (95% CI: 1.00, 1.85; Table 2). Such a moderate hazardous effect was mainly related to a habitual drinking of pu'er tea (adjusted OR=1.44, 95% CI: 1.02, 1.91) and mixed tea type (adjusted OR=2.01, 95% CI: 1.24, 3.26). A significantly inverse relation was linked to a habitual green tea drinking with an OR of 0.59 (95% CI: 0.37, 0.95), and the OR remained almost unchanged (OR=0.60, 95% CI: 0.37, 0.98) after the adjustment of age at interview, deep fried food consumption, green vegetable consumption, alcohol consumption, coffee consumption, tobacco consumption, education attainment and family prostate cancer history (OR=0.60, 95% CI: 0.37, 0.98). Results from stratified analyses according to the concentration of different types of tea consumption indicated a likely inverse exposure-response relationship with green tea but a positive gradient with oolong and pu'er tea intake; however, the results of oolong and black tea intake were not statistically significant due to insufficient power for an intensive analysis. The most popular tea type in our study population was pu'er tea, followed by oolong and green tea, whereas black tea was the least popular one.

Table 1. Selected characteristics of prostate cancer cases and controls among Hong Kong Chinese men

Characteristic	Cases (N = 404)	Controls (N = 395)	P-value
Age, mean (s.d.)	69.5 (7.1)	68.1 (8.2)	0.011
<i>Tobacco smoking, n (%)</i>			
Never	209 (51.7)	189 (47.9)	0.173
Former	137 (33.9)	130 (32.9)	
Current	58 (14.4)	76 (19.2)	
<i>Alcohol consumption, n (%)</i>			
Non-users	312 (77.2)	304 (77.0)	0.933
Users	92 (22.8)	91 (23.0)	
<i>Educational attainment, n (%)</i>			
Primary or below	172 (42.6)	150 (38.0)	0.204
Secondary	177 (43.8)	198 (50.1)	
Tertiary	55 (13.6)	47 (11.9)	
<i>Family prostate cancer history, n (%)</i>			
No	374 (92.6)	383 (97.0)	0.007
Yes	30 (7.4)	12 (3.0)	
<i>Deep fried food consumption, n (%)</i>			
< 1 time per month	198 (49.0)	207 (52.4)	< 0.001
1–3 times per month	123 (30.5)	149 (37.7)	
≥ 1 time per week	83 (20.5)	39 (9.9)	
<i>Green vegetable consumption, n (%)</i>			
< 1 time per week	4 (1.0)	9 (2.3)	0.246
1–3 times per week	39 (9.7)	31 (7.8)	
≥ 4 times per week	361 (89.3)	355 (89.9)	
<i>Orange fruits, n (%)</i>			
< 1 time per week	50 (12.4)	38 (9.6)	0.283
1–3 times per week	39 (9.7)	48 (12.2)	
≥ 4 times per week	315 (77.9)	309 (78.2)	
<i>Orange vegetable consumption, n (%)</i>			
< 1 time per week	29 (7.2)	23 (5.8)	0.485
1–3 times per week	101 (25.0)	111 (28.1)	
≥ 4 times per week	274 (67.8)	261 (65.1)	
<i>Coffee consumption, n (%)</i>			
Non-users	304 (75.2)	312 (79.0)	0.238
Users	100 (24.7)	83 (21.0)	

Table 3 shows a collective index of tea drinking expressed as an intake of EGCG derived from each type of tea. Overall, EGCG intake ranged from 1.29 mg to 489.4 mg (median = 54.4 mg) for cases and from 1.94 mg to 815.6 mg (median = 72.5 mg) for controls. Compared with the low intake of EGCG, those consumed middle or high level of EGCG demonstrated a significantly reduced risk of PCA by 44%, respectively. Further analysis according to levels of cumulative EGCG consumption revealed a clear inverse exposure–response relationship with PCA risk (test for trend, $P = 0.015$).

DISCUSSION

In this study, we demonstrated a significantly inverse association between habitual green tea consumption and PCA risk that is consistent with findings from some other studies in different populations.⁴ Catechins have been recognized as a major protective compound in tea leaves against cancer through reducing androgen's action on the target prostate cell and thereafter inhibit the carcinogenesis progress.⁸ Green tea has a higher concentration of catechins than other types of tea,^{5,6,19} which explains the inverse relation between green tea consumption and the risk of PCA.

We observed that habitual consumption of pu'er tea was significantly associated with an increased PCA risk among our participants. Pu'er tea has long been one of the most popular teas in Hong Kong. The prevalence of weekly green tea intake of our controls was relatively lower (12.7%), but this was similar to a case–control study on male lung cancer in which controls were randomly selected from the Hong Kong general population (11.2%, 35–79 years old). Compared with the green tea, pu'er tea contains less catechins and thus its negative association with PCA may not be observed. Traditionally, making pu'er tea requires a process of fermentation, which involves microbial fermentation and oxidation of tea leaves after they have been dried and rolled. In the Chinese context, pu'er tea product is commonly being stored for many years and needs to be processed in a moisture and dry circumstance respectively to enhance its flavour and fragrance.²⁰ However, such a special storage method of pu'er tea particularly in a moist environment²¹ or in a household of Hong Kong with relatively high humidity (for example, 80% in summer season)²² might increase microbial activities, causing the fermented tea to mould, and/or become contaminated by some known or suspected carcinogens (such as aflatoxins²⁰) or pesticide; however, this is just an interesting speculation, which is worthy of further investigation. Similar associations were also observed to the oolong tea, however, the associations were not statistically significant and chance is likely. We found an excess risk of PCA among the mixed tea drinkers but the reasons remain unclear; it is possible that a high percentage of mixed tea drinkers were the habitual pu'er tea drinkers. This study thus provides justifications for further research to disentangle the effects of pu'er tea and EGCG from a possible carcinogen contamination and discover the biological mechanisms behind.

Interestingly, a medium and high level of daily EGCG consumption was associated with a decreased risk of PCA (test for trend, $P = 0.015$) among our participants, which supports a hypothesis raised by previous experimental studies on a role of cancer protection from tea polyphenols.^{9,9} EGCG is the main indicator of catechins, which was derived from all teas consumed based on a semi-quantitative approach by using analytic values documented in the literature.⁶ Green tea leaves contain a higher amount of EGCG than pu'er and other teas. The negative association between green tea and PCA is likely due to the potent EGCG, which inhibits the growth of PCA cell and expression of PSA and thus exerts the activities of anti-carcinogenesis.⁸

To the best of our knowledge, our study is the first to examine the association between collective EGCG intake from habitual tea intakes and the PCA risk. However, misclassification on EGCG estimation may be a concern as we assessed EGCG intake based on self-report standard questionnaire with analytic values of EGCG derived from the published literature.²³ Tea catechins are water-soluble compounds²⁴ and most of the catechin components are excreted within the first 9 h after intake,²⁵ while the half-life of EGCG was even shorter (around 5 to 5.5 h).¹⁷ There are technical difficulties in a direct measurement on EGCG from biological samples, especially conducting an exposure assessment on a lifetime cumulative EGCG exposure. Results from test–retest reliability analysis showed a good agreement ($R = 0.87$) between the initial interview and the second interview from the same 20 respondents, which indicates our findings on exposure assessment on tea consumption and EGCG are reliable. We regarded the EGCG content reported by the study of Lin *et al.*⁶ as the most relevant because they tested the levels of different tea polyphenols from different types of tea produced in China, Taiwan and Japan, which are the major tea exporters to Hong Kong.

A similar proportion of incident PCA in different age groups to those obtained from the Hong Kong Cancer Registry¹⁶ indicate a good comparability of our cases with the general population. Selection of controls from the same hospital may be a concern of

Table 2. Distribution of specific tea types among habitual tea consumption and its association with prostate cancer risk

Variables	Cases (N = 404)	Controls (N = 395)	Crude OR (95% CI)	Adjusted OR (95%CI) ^a	P for trend
<i>Tea drinking, n (%)^b</i>	279 (69.1)	242 (61.3)	1.41 (1.05, 1.89)	1.36 (1.00, 1.85)	0.050
Green tea	32 (7.9)	50 (12.7)	0.59 (0.37, 0.95)	0.60 (0.37, 0.98)	0.048
Oolong tea	78 (19.3)	65 (16.5)	1.22 (0.85, 1.75)	1.34 (0.92, 1.96)	0.159
Black tea	5 (1.2)	6 (1.5)	0.81 (0.25, 2.68)	0.74 (0.21, 2.55)	0.680
Pu'er tea	151 (37.4)	115 (29.1)	1.45 (1.08, 1.95)	1.44 (1.02, 1.91)	0.046
Mixed tea ^c	58 (14.4)	29 (7.3)	2.12 (1.32, 3.38)	2.01 (1.24, 3.26)	0.005
<i>Concentration, n (%)</i>					
Green tea					
Low	9 (2.2)	11 (2.8)	1.00	1.00	
Medium	21 (5.2)	28 (6.8)	0.95 (0.33, 2.72)	1.53 (0.39, 5.93)	
High	1 (0.2)	8 (2.0)	0.15 (0.02, 1.46)	0.16 (0.01, 2.22)	
Very high	1 (0.2)	3 (0.8)	0.41 (0.04, 4.62)	0.34 (0.02, 6.05)	0.664
Oolong tea					
Low	13 (3.2)	11 (2.8)	1.00	1.00	
Medium	41 (9.9)	38 (9.6)	0.89 (0.36, 2.23)	0.81 (0.28, 2.33)	
High	19 (4.7)	13 (3.3)	1.24 (0.43, 3.60)	1.24 (0.38, 4.05)	
Very high	5 (1.2)	3 (0.8)	1.41 (0.27, 7.28)	2.08 (0.29, 14.62)	0.446
Black tea					
Low	0 (0.0)	2 (0.5)	—	—	
Medium	5 (1.2)	2 (0.5)	—	—	
High	0 (0.0)	2 (0.5)	—	—	
Very high	0 (0.0)	0 (0.0)	—	—	
Pu'er tea					
Low	27 (6.7)	19 (4.8)	1.00	1.00	
Medium	70 (17.1)	57 (14.4)	0.85 (0.43, 1.69)	0.97 (0.47, 2.02)	
High	39 (9.7)	35 (8.9)	0.78 (0.37, 1.65)	0.82 (0.37, 1.82)	
Very high	15 (3.7)	4 (1.0)	2.64 (0.76, 9.21)	3.47 (0.92, 13.06)	0.416

Abbreviations: CI, confidence interval; OR, odds ratio. ^aAdjusted for age at interview, deep fried food consumption, green vegetable consumption, alcohol consumption, coffee consumption, tobacco consumption, education attainment, family prostate cancer history. ^bThe reference group was defined as the participants who did not have a habitual tea consumption on specific type of tea (that is, tea drinking vs non-tea drinking; green tea drinking vs non-green tea drinking). ^cMixed tea drinking referred to those who had no preferable type of tea.

Table 3. Associations between EGCG intake from teas and prostate cancer risk among Hong Kong Chinese men

Variables	Cases N(%)	Controls N(%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^a	P for trend
<i>Habitual EGCG consumption (mg per day)^b</i>					
Low	101 (36.2)	58 (24.0)	1.00	1.00	
Middle	117 (41.9)	120 (49.6)	0.56 (0.37, 0.85)	0.56 (0.36, 0.86)	
High	58 (20.8)	63 (26.0)	0.53 (0.33, 0.86)	0.56 (0.33, 0.94)	0.015
<i>Cumulative consumption of EGCG from tea (mg × years)^b</i>					
Low	100 (35.8)	61 (25.2)	1.00	1.00	
Middle	127 (45.5)	113 (46.7)	0.69 (0.46, 1.03)	0.65 (0.42, 1.01)	
High	49 (17.6)	67 (27.7)	0.45 (0.27, 0.73)	0.46 (0.27, 0.79)	0.003

Abbreviations: CI, confidence interval; EGCG, epigallocatechin 3-gallate; OR, odds ratio. ^aAdjusted for age at interview, deep fried food consumption, green vegetable consumption, alcohol consumption, coffee consumption, tobacco smoking, education attainment, family prostate cancer history. ^bDaily intake of EGCG intake was categorized into three levels by interquartile according to the exposure distribution of control (low: < 36 mg; middle: 36–145 mg; high: > 145 mg). ^cCumulative EGCG intake was categorized into three levels by interquartile according to the exposure distribution of control (low: < 248 086 mg; middle: 248 086–1 587 750 mg; high: > 1 587 750 mg).

external generalization of the results but this increases the comparability between the cases and controls. We randomly recruited controls with a variety of disease types to minimize the potential selection bias. We carried out sensitivity analysis by classifying the controls into five subgroups according to their diagnoses and/or diseases, and the results revealed a consistent negative association between green tea consumption and PCA risk, which indicates that the potential selection bias by using hospital controls should not be a major concern (Supplementary

Table 1). Recall bias and/or interviewer bias may be a concern to all case–control studies but it has been carefully considered in our study. We used a standardized approach to interview all the participants and we interviewed the controls in about 4 weeks after the PCA cases were recruited. We compared the habitual tea drinking profile between a subgroup of 45 participants (who were initially suspected to have PCA but eventually were confirmed histologically as non-cancer cases) with the true cancer cases and showed that there was no significant difference in reporting the

history of habitual tea drinking. Recall or interview bias, if it is present in our study, should not be a major issue. Green tea intake is less likely to be a surrogate for adherence to a more traditional Asian lifestyle. We carried out an in-depth analysis on the correlation of habitual green tea drinking with variables that might reflect the adoption of a western lifestyle, including obesity, education attainment, deep fried food consumption and low green vegetable intake. As shown in Supplementary Table 2, the correlation coefficients were low (that is, -0.07 , 0.10 , -0.03 and 0.09 , respectively) between habitual green tea consumption and these western lifestyle factors.

In conclusion, our findings are consistent with previous studies showing a significantly inverse association between green tea intake and PCA risk, whereas a positive association with the consumption of pu'er tea was indicated. An inverse relationship with a collective intake of EGCG supports the findings from previous studies that the consumption of EGCG may be protective to PCA. As only 32 cases and 50 controls who were habitual green tea drinkers were included, results from this report need to be replicated in larger cohort studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Prostate Cancer and Prostatic Diseases website (<http://www.nature.com/pcan>)