Prostate cancer detection upon transrectal ultrasound-guided biopsy in relation to digital rectal examination and prostate-specific antigen level: what to expect in the Chinese population?

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We investigated the prostate cancer detection rates upon transrectal ultrasound (TRUS)-guided biopsy in relation to digital rectal examination (DRE) and prostate-specific antigen (PSA), and risk factors of prostate cancer detection in the Chinese population. Data from all consecutive Chinese men who underwent first TRUS-guided prostate biopsy from year 2000 to 2013 was retrieved from our database. The prostate cancer detection rates with reference to DRE finding and PSA level of < 4, 4–10, 10.1–20, 20.1–50 and > 50 ng ml\(^{-1}\) were investigated. Multivariate logistic regression analyses were performed to investigate for potential risk factors of prostate cancer detection. A total of 2606 Chinese men were included. In patients with normal DRE, the cancer detection rates were 8.6%, 13.4%, 21.8%, 41.7% and 85.2% in patients with PSA < 4, 4–10, 10.1–20, 20.1–50 and > 50 ng ml\(^{-1}\) respectively. In patients with abnormal DRE, the cancer detection rates were 12.4%, 30.2%, 52.7%, 80.6% and 96.4% in patients with PSA < 4, 4–10, 10.1–20, 20.1–50 and > 50 ng ml\(^{-1}\) respectively. Older age, smaller prostate volume, larger number of biopsy cores, presence of abnormal DRE finding and higher PSA level were associated with increased risk of prostate cancer detection upon multivariate logistic regression analyses (\(P < 0.001\)). Chinese men appeared to have lower prostate cancer detection rates when compared to the Western population. Taking the different risk factors into account, an individualized approach to the decision of TRUS-guided biopsy can be adopted.

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cancer detection in patients with abnormal DRE versus patients with normal DRE was calculated. The Gleason score pattern was further stratified with reference to DRE finding and the aforementioned PSA ranges. Univariate and multivariate logistic regression analyses including the above-mentioned clinical variables were performed to investigate for potential risk factors of prostate cancer detection upon TRUS-guided biopsy.

Continuous variables were expressed as mean values with standard deviations, and categorical variables were expressed as percentages of the cohort. The cancer detection rate and the Gleason score pattern being detected were expressed as a percentage of the patients with the corresponding DRE finding and PSA range. In the logistic regression analyses, $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

According to our TRUS-guided prostate biopsy database, a total of 2606 Chinese patients underwent first TRUS-guided prostate biopsy from year 2000 to 2013. It consisted of 155 patients (5.9%) with PSA < 4 ng ml$^{-1}$, 1548 patients (59.4%) with PSA 4–10 ng ml$^{-1}$, 468 patients (18.0%) with PSA 10.1–20 ng ml$^{-1}$, 213 patients (8.2%) with PSA 20.1–50 ng ml$^{-1}$ and 222 patients (8.5%) with PSA >50 ng ml$^{-1}$. The mean age was 68.4 ± 8.0 years. The mean TRUS estimated prostate volume was 44.8 ± 23.7 ml. In our cohort, 69.8% had 10-core biopsies (i.e., standard sextant biopsies plus four lateral biopsies of peripheral zones), and 21.5% had 12-core biopsies (i.e., standard sextant biopsies plus a laterally directed sextant biopsies). The mean number of cores taken during the biopsy was 10.1 ± 1.6. Abnormal DRE was noted in 23.9% of the cohort. The overall cancer detection rate was 27.6% (Table 1). For patients who had prostate cancer upon TRUS-guided prostate biopsy, the commonest Gleason score was 6 (35.3%), followed by Gleason score of 7 in 21.2% and Gleason score of 9 in 16.6% of the patients (Figure 1).

Table 1: Baseline characteristics of the cohort

| Value                  | Percentage of patients |
|------------------------|------------------------|
| Total number of patients | 2606                   |
| Number and percentage of patients with reference to PSA level (ng ml$^{-1}$) |
| <4                     | 5.9                    |
| 4–10                   | 59.4                   |
| 10.1–20                | 18.0                   |
| 20.1–50                | 8.2                    |
| >50                    | 8.5                    |
| Age (year, mean±s.d.)  | 68.4±8.0               |
| Estimated prostate volume on TRUS (ml, mean±s.d.) | 44.8±23.7 |
| Biopsy scheme (number of patients) |
| 10-core biopsies       | 69.8                   |
| 12-core biopsies       | 21.5                   |
| Others                 | 8.7                    |
| Number of cores taken (mean±s.d.) | 10.1±1.6 |
| PSA level (ng ml$^{-1}$, mean±s.d.) | 71.0±462.1 |
| DRE (number of patients) |
| Normal                 | 76.1                   |
| Abnormal               | 23.9                   |
| Overall cancer detection rate | 27.6               |

s.d.: standard deviation; PSA: prostate-specific antigen; TRUS: transrectal ultrasound; DRE: digital rectal examination.

Figure 1: Gleason score pattern distribution in the cohort.

Table 2: Cancer detection rate and Gleason score pattern with reference to DRE finding and PSA level

| Cancer detection rate stratified according to Gleason score patterns (%) | Overall cancer detection rate (%) |
|-----------------------------|-----------------------------|
| <4.0                       | 8.6  | 0  | 0  | 8.6                     |
| 4–10                       | 9.6  | 2.3| 1.5| 13.4                    |
| 10.1–20                    | 11.7 | 4.4| 5.7| 21.8                    |
| 20.1–50                    | 14.2 | 11.5|16.0| 41.7                    |
| >50                        | 7.4  | 18.5|59.3| 85.2                    |

Normal DRE

| PSA level (ng ml$^{-1}$) | 2–6 | 7  | 8–10 | Cancer detection rate (%) |
|--------------------------|-----|----|------|---------------------------|
| <4.0                     | 5.6 | 4.5| 2.3  | 12.4                      |
| 4–10                     | 12.4| 7.7|10.1  | 30.2                      |
| 10.1–20                  | 17.6| 16.5|18.7 | 52.7                      |
| 20.1–50                  | 15.5| 17.6|47.5 | 80.6                      |
| >50                      | 6.0 | 19.3|71.1 | 96.4                      |

Abnormal DRE

| PSA level (ng ml$^{-1}$) | 2–6 | 7  | 8–10 | Cancer detection rate (%) |
|--------------------------|-----|----|------|---------------------------|
| <4.0                     | 5.6 | 4.5| 2.3  | 12.4                      |
| 4–10                     | 12.4| 7.7|10.1  | 30.2                      |
| 10.1–20                  | 17.6| 16.5|18.7 | 52.7                      |
| 20.1–50                  | 15.5| 17.6|47.5 | 80.6                      |
| >50                      | 6.0 | 19.3|71.1 | 96.4                      |

PSA: prostate-specific antigen; DRE: digital rectal examination.
0% in patients with PSA <4 ng ml\(^{-1}\), which increased to 5.7% in patients with PSA 10.1–20 ng ml\(^{-1}\), and then increased significantly to 16.0% and 59.3% in patients with PSA 20.1–50 and >50 ng ml\(^{-1}\) (Table 2 and Figure 2).

In patients with abnormal DRE, even at PSA <4 ng ml\(^{-1}\), 4.5% and 2.3% of the patients had Gleason score of 7 and 8–10 respectively. The percentage of patients having Gleason score of 7 increased with PSA to up to 19.3% at PSA >50 ng ml\(^{-1}\). Similarly, the percentage of patients having Gleason score of 8–10 increased with PSA, and 47.5% and 71.1% of patients with PSA 20.1–50 and >50 ng ml\(^{-1}\) had Gleason score of 8–10 (Table 2 and Figure 3).

Upon both univariate and multivariate logistic regression analyses (Table 3), older age, smaller prostate volume, presence of abnormal DRE finding and higher PSA level were associated with increased risk of prostate cancer detection. Larger number of biopsy cores was associated with reduced risk of prostate cancer detection upon univariate logistic regression analysis (odds ratio [OR]: 0.92, 95% confidence interval [CI]: 0.88–0.97, \(P = 0.003\)), but became a risk factor for prostate cancer detection upon multivariate logistic regression analysis (OR: 1.16, 95% CI: 1.06–1.26, \(P < 0.001\)).

DISCUSSION
Since the first investigation on tissue-specific antibodies in the human prostate in 1969,\(^2\) the role of PSA in prostate cancer diagnosis has been extensively investigated. Most notably, Catalona et al. conducted many important hallmark studies on the clinical application of PSA in deciding when to perform TRUS-guided prostate biopsy.\(^6\,\,7\) However, due to the significant differences between ethnicities, it would be inappropriate to counsel Chinese men on the implication of elevated PSA level and the probability of having prostate cancer using results that were largely based on Western population. There is a need for Chinese-specific data to provide some basic but important information concerning prostate cancer detection. Hence, we conducted this study to look into prostate cancer detection upon TRUS-guided biopsy in relation to DRE and PSA level, and to investigate for risk factors of prostate cancer detection in the Chinese population.

Our TRUS-guided prostate biopsy database was based on all consecutive Chinese men who underwent first TRUS-guided prostate biopsy at our unit from year 2000 to 2013. The decision to undergo biopsy was often a clinical decision made in an individualized approach. In our study, we took reference from several landmark papers published previously,\(^5,\,12,\,13\) and decided to use 4 ng ml\(^{-1}\), 10.0 ng ml\(^{-1}\), 20 ng ml\(^{-1}\) and 50 ng ml\(^{-1}\) as the PSA cut-off values to categorize the patients, so as to facilitate the comparison of our prostate cancer detection results with those available in the literature. Our results showed that the cancer detection rates with reference to PSA in Chinese men were much lower than that reported in the Western population. In the Prostate Cancer Prevention Trial,\(^12\) the cancer detection rate was 15.2% in patients who had normal DRE and PSA <4.0 ng ml\(^{-1}\), compared to 8.6% in our study with a percentage difference of −43.4%. In the study by Catalona et al.,\(^3\) for patients with normal DRE, the cancer detection rate was 20.7% for PSA 4.1–9.9 ng ml\(^{-1}\), compared to 13.4% in our study for PSA 4–10 ng ml\(^{-1}\) with a percentage difference of −35.3%; for patients with abnormal DRE, the cancer detection rate was 40.8% for PSA 4.1–9.9 ng ml\(^{-1}\), compared to 30.2% in our study for PSA 4–10 ng ml\(^{-1}\) with a percentage difference of −26.0%. In the study by Gerstenbluth et al.,\(^13\) the cancer detection rates were 73.6%, 90.3% and 93.8% for patients with PSA 20–29.9, 30–39.9 and 40–49.9 ng ml\(^{-1}\) respectively, which were much higher than our results of 59.6% in patients with PSA 20.1–50 ng ml\(^{-1}\).

The prostate cancer detection rates in our study appeared to be lower than that in the Western population, unfortunately, we were unable to compare the other potential confounding factors based on...
the published data. Nevertheless, our results implied that we might be over-diagnosing a lot more patients with prostate cancer, which in turn may result in over-treatment of a disease that may well be managed conservatively. The optimal PSA cut-off value for consideration of TRUS-guided prostate biopsy in the Chinese population is yet to be determined. Our study also illustrated the importance of a proper DRE. Patients with abnormal DRE had much higher cancer detection rates of up to +141.7% when compared to patients with normal DRE at the PSA range of 10.1–20 ng ml$^{-1}$. Moreover, in patients with abnormal DRE, 4.5% of them had Gleason score of 7 and 2.3% of them had Gleason score of 8–10 even at PSA <4 ng ml$^{-1}$, compared with 0% in patients with normal DRE.

Interestingly, larger number of biopsy cores was associated with reduced risk of prostate cancer detection upon univariate logistic regression analysis (OR: 0.92, 95% CI: 0.88–0.97, P = 0.003), but became a risk factor for prostate cancer detection upon multivariate logistic regression analysis (OR: 1.16, 95% CI: 1.06–1.26, P < 0.001). Theoretically, a larger number of biopsy cores should detect more prostate cancers. We performed post hoc subgroup analyses to look into the baseline characteristics based on the number of biopsy cores taken (<10 biopsy cores group vs ≥10 biopsy cores group). The mean PSA level in the <10 biopsy cores group was 191.81 ± 631.61 ng ml$^{-1}$, and the mean PSA level in the ≥10 biopsy cores group was 59.63 ± 441.58 (P < 0.001). 42.9% of the patients in the <10 biopsy cores group and 22.1% of the patients in the ≥10 biopsy cores group had abnormal DRE finding (P < 0.001). We postulated that patients who were highly suspected to have advanced or metastatic disease based on the PSA level and DRE finding were more likely to have less biopsy cores taken; there is no standardized biopsy scheme in our cohort and the number of biopsy cores to be taken was subjected to the clinician’s decision during the procedure. Hence, larger number of biopsy cores was associated with reduced risk of prostate cancer detection upon univariate logistic regression analysis, but became a risk factor for prostate cancer detection upon multivariate logistic regression after adjusting for other potential confounding factors. Moreover, older age, smaller prostate volume, presence of abnormal DRE finding and higher PSA level were associated with increased risk of prostate cancer detection upon both univariate and multivariate logistic regression analyses. The multivariate logistic regression analyses were performed via a predictive approach. There were neither confounders nor effect modifiers affecting the association between PSA and prostate cancer detection upon TRUS-guided prostate biopsy. All the above factors should be considered while deciding on TRUS-guided prostate biopsy, and a more individualized approach can thus be adopted.

The main limitation in our study is the lack of a standardized biopsy scheme, which may in turn affect the prostate cancer detection rates in relation to DRE and PSA level. Moreover, the nature of TRUS-guided random prostate biopsy is prone to sampling error and may interfere with the results. Unfortunately, despite the intrinsic problem of this reference test, it is still the conventional method for prostate cancer diagnosis in our locality. The utility of magnetic resonance imaging-guided targeted prostate biopsy might be a better method for diagnosing prostate cancer, and this issue should be explored in future studies.

There are limited data on the prostate cancer detection rates upon TRUS-guided prostate biopsies in the Asian population. In Japanese men, the reported cancer detection rates upon TRUS-guided prostate biopsies ranged from 13% in men with normal DRE and PSA 4.1–10 ng ml$^{-1}$ to up to 36.2% in men with PSA 4.01–10 ng ml$^{-1}$. In a Korean study including 508 patients with normal DRE, the cancer detection rate was 19.5% in patients with PSA 4.1–10 ng ml$^{-1}$. There was a high variability in cancer detection rates even among the Asian population, and ethnic-specific data is necessary to provide comprehensive information for patients who would consider TRUS-guided prostate biopsy. In the study by Gao et al. including 158 biopsies in Chinese men, the cancer detection rates were 9.5%, 14.8%, 25.8% and 79.2% for men with PSA <4, 4.1–10, 10.1–20 and >20 ng ml$^{-1}$ respectively. The reported cancer detection rates were not further stratified with the DRE finding, but were comparable to the results of our study. In another study by Zheng et al. on 237 Chinese men with PSA 4–10 ng ml$^{-1}$, prostate cancer was diagnosed in 18.6% of the patients. The DRE finding was not reported, but the cancer detection was slightly higher than that in our study.

To the best of our knowledge, this is the largest study on prostate cancer detection upon TRUS-guided prostate biopsy in the Chinese population. We believe our results provide important information for Chinese men who would consider TRUS-guided prostate biopsy for suspected prostate cancer. The huge differences in prostate cancer detection with reference to PSA in Chinese men raised significant concerns on the clinical applicability of the previously established results, which were largely based on the Western population. We believe that a much lower prostate cancer detection rate in Chinese men should be an important factor to consider before deciding on TRUS-guided prostate biopsy. Why the cancer detection rate was lower in the Chinese population within the same range of PSA may not be simply explained by a lower incidence of prostate cancer in Chinese men, and further basic science research would be necessary to look into the reasons behind. More importantly, apart from prostate cancer diagnosis, PSA also plays an important role in risk stratification of the disease. Further studies are warranted to investigate its prognostic role in the Chinese population.

AUTHOR CONTRIBUTIONS
JYCT and MKY carried out the study. SKKY, JHLT, WKM, KLH and MKT participated in the study design. JYCT, SKKY, CKWW, BSHH and ATLN collected the data. JYCT, JHLT, CKWW, BSHH, ATLN, WKM and KLH coordinated the study. JYCT, SKKY and CKWW performed statistical analyses. JYCT and MKY drafted the manuscript. JHLT, WKM, KLH and MKY supervised the study.

COMPETING INTEREST
All authors declare no competing interests.

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