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ORIGINAL ARTICLE

# Effects of diabetes mellitus and Metformin administration on prostate cancer detection at biopsy among Chinese men: a case-control study

Meng-Bo Hu[1]*, Pei-De Bai[2]*, Yi-Shuo Wu[1], Li-Min Zhang[1], Wen-Hui Zhu[1], Ji-Meng Hu[1], Tian Yang[1], Hao-Wen Jiang[1], Qiang Ding[1]

[1]Department of Urology, Huashan Hospital, Fudan University, Shanghai 200040, China; [2]Department of Urology, The First Affiliated Hospital, Xiamen University, Xiamen 361003, Fujian Province, China.

* These two authors contributed equally to this work.

## Summary

***Purpose:*** *To determine the associations among diabetes status, Metformin administration and prostate cancer (PCa) detection at biopsy in Chinese population.*

***Methods:*** *A case-control study was conducted among a prospectively enrolled prostate biopsy cohort of 518 patients from Jan 2013 to Dec 2014 at our institute. Diabetes status and Metformin administration were determined through medical records and self-report. Different clinical characteristics were registered and compared among different groups. Univariate and multivariate logistic regression analyses were performed to evaluate the effects of diabetes status and Metformin administration on the detection of overall as well as high-grade PCa at biopsy.*

***Results:*** *PCa was detected in 229 (44.2%) men, and high-grade PCa (Gleason score ≥8) was detected in 65 (12.5%) men. Diabetes was observed in 96 men, and 28 of them were administered with Metformin. Both overall and high-grade cancer detection rates were significantly higher in diabetic patients (p<0.001). In multivariate analysis, diabetes status was a risk factor for high-grade cancer detection (OR 7.699, 95%CI 3.483-17.020, p<0.001), but not for total PCa detection (OR 1.774, 95%CI 0.831-3.787, p=0.138). Meanwhile, Metformin administration was proved to be a protective factor for high-grade disease (OR 0.420, 95%CI 0.201-0.879, p=0.021) in multivariate analysis, while no correlation was detected with overall cancer detection (OR 0.786, 95%CI 0.172-3.593, p=0.756).*

***Conclusions:*** *Diabetes status was positively associated with biopsy-mediated high-grade PCa detection in Chinese population, while the positive association would be partly compromised by Metformin administration.*

***Key words:*** *biopsy, diabetes mellitus, metformin, prostate cancer*

## Introduction

Prostate cancer (PCa) is a global health concern among elderly male [1-4]. The morbidity and mortality rate of PCa in Asian population, rising rapidly in the past few decades, was still relatively low as compared with Western populations [5,6]. westernised life style was gradually considered as a risk factor for Asian PCa patients. The westernised life style might cause a couple of metabolic abnormalities such as obesity, diabetes mellitus (DM) and hypertension [3], which were proved to be associated with the development and progression of PCa.

DM is one of the most common chronic diseases around the world. The global prevalence of DM has increased substantially in recent years [7]. DM is proved to be an independent risk factor

*Correspondence to:* Hao-Wen Jiang, MD. Department of Urology, Huashan Hospital, Fudan University, No. 12 Middle Wulumuqi Rd, Shanghai 200040, China.
Tel: + 86 21 52889999, E-mail: oncouro_jhw@126.com
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for development and progression of various cancers such as breast, colorectal and liver cancer [8]. However, the association between PCa and DM is quite conflicting and inconclusive. Some previous studies reported a positive association between DM and higher incidence of PCa [9-11]. On the contrary, others revealed none [12-14] or inverse correlation between DM and the risk of PCa [6,14-18]. Metformin is a widely-used drug for DM treatment [19-21]. Several observational studies revealed that Metformin administration could decrease the morbidity and mortality of PCa [19,22-25], while other studies failed to detect such an association [15].

Since the associations among DM, Metformin administration and PCa has not been fully addressed in Asian populations, we conducted the present case-control study, based on a prospectively enrolled biopsy cohort at our hospital, to discuss the effects of DM and Metformin administration on the risk of biopsy-mediated overall and high-grade PCa (HGPCa, Gleason score ≥8) detection in Chinese men. The research outcomes might help better understand the complex interactions, as well as optimizing current PCa screening strategies in Chinese men.

## Methods

*Study population and study variables*

After obtaining Huashan Institutional Review Board approval, we prospectively enrolled a cohort of 559 consecutive patients who underwent initial multicore (≥10) prostate biopsy with transrectal ultrasound (TRUS) guidance from Jan 2013 to Dec 2014 at our institute. The research was carried out strictly in accordance with the Helsinki Declaration of 1975, as revised in 2000. Patient records were anonymized and de-identified prior to analysis. Written informed consents were obtained from all patients for including their clinical records in the study before biopsy. The indications for patients undergoing prostate biopsy were: (1) prostate specific antigen (PSA) level >4 ng/ml; (2) free to total PSA ratio (f/t PSA) <0.16 or PSA density (PSAD) >0.15; (3) abnormal results from digital rectal examination (DRE), TRUS or magnetic resonance imaging (MRI). The biopsy tissues were processed and evaluated by the same pathologist at our institute. The bioptic Gleason score of adenocarcinoma was determined according to the 2005 International Society of Urological Pathology consensus. HGPCa was defined as the presence of a Gleason score ≥8. A total of 34 patients were excluded due to unavailable DM data, and 7 patients were excluded for non-Chinese racial background, resulting in a final population of 518 patients for analysis.

*Data collection*

Age, pre-treatment PSA, prostate volume (PV), DRE findings, diagnostic imaging findings, DM status and treatments, the history of hypertension, smoking and drinking, the family history of PCa and pathological outcomes of prostate biopsy were collected by reviewing patients' medical charts. The DM status, based on patients' annual medical examinations and medical histories, was diagnosed by WHO 1999 criteria, which was "1: Classic symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥11.1 mmol/L; or 2: Fasting (≥8-hour) plasma glucose concentration ≥7.0 mmol/L; or 3: A 2-hr postload plasma glucose concentration ≥11.1 mmol/L during a 75-g oral glucose tolerance test." The height and weight of patients were examined on the day of biopsy. Body mass index (BMI, kg/m$^2$) was calculated as weight (kg) divided by the squared height (m). PV was calculated from TRUS measurement at the procedure.

*Statistics*

All men were classified into two groups according to their DM status: DM and non-DM. Based on their treating methods, DM patients were further categorized into Metformin group and non-Metformin group. Baseline characteristics (age, BMI, PSA, PV, DRE findings, family history of PCa, history of smoking, drinking and hypertension) and PCa/HGPCa detection rates across different categories were compared using chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. Univariate and multivariate logistic regression analyses were performed to evaluate the effects of different DM status, Metformin administration on PCa/HGPCa detection at biopsy. All statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL, USA). Statistical significance was defined as two-tailed p-value <0.05.

## Results

*Study population and baseline characteristics*

A total of 518 men were included in the present study. The baseline characteristics of the biopsy patients are presented in Table 1. The median age at biopsy was 71 years. The median BMI was 23.6 kg/m$^2$. The median PSA level was 12.4 ng/ml. The median PV was 51 ml. A total of 30.1% of the biopsied patients had positive DRE findings. A total of 52.1, 50 and 51.9% of these patients had a history of smoking, drinking and hypertension, respectively. In total, PCa was detected via biopsy in 229 (44.2%) men, and HGPCa was detected in 65 (12.5%) men.

*Diabetes mellitus and prostate cancer detection*

DM was observed in 96 patients. At biopsy, DM status was significantly associated with a higher PSA levels (16.1 vs. 12.1 ng/ml, p=0.014, Table 1), a greater percentage of positive DRE findings (46.9 vs 26.3%, p<0.001, Table 1) and hypertension (64.6

vs 49.1%, p=0.006, Table 1). However, no statistically significant differences were found in age, BMI, PV, history of smoking/drinking or family history of PCa between two groups. Both PCa detection rate (62.5 vs 40.0%, p<0.001, Table 1) and HGPCa detection rate (35.4 vs 7.3%, p<0.001, Table 1) were significantly higher in the DM group compared with the non-DM group.

In crude logistic regression analysis, there was an increased risk of PCa detection at biopsy in the DM group compared with the non-DM group (OR 2.495, 95%CI 1.580-3.940, p<0.001, Table 2), which was also confirmed after adjusting for age (OR 2.407, 95%CI 1.507-3.844, p<0.001, Table 2). After adjusting for multiple confounders (age, PSA, PV, DRE, and the history of hypertension), the positive correlation became unclear (OR 1.774, 95%CI 0.831-3.787, p=0.138, Table 2). However, HGPCa detection proved to be positively correlated with DM status in all three different models (crude:OR 5.821, p<0.001; age-adjusted: OR 5.988, p<0.001; multivariate-adjusted: OR 7.899, p<0.001; Table 2).

*Metformin administration and prostate cancer detection*

A total of 96 DM patients were stratified by the administration of Metformin, where 28 (29.2%) patients were in the Metformin group. HGPCa detection rate (14.3 vs 44.1%, p=0.005, Table 3) was significantly lower in the Metformin group as compared with the non-Metformin group, while no correlation was determined in PCa detection (57.1 vs 64.7%, p=0.492, Table 3).

In logistic regression analysis, Metformin administration was associated with a lower risk of HGPCa detection (crude:OR 0.390, p=0.006; age-adjusted: OR 0.392, p=0.008; multivariate-adjusted:

**Table 1.** Clinical characteristics of 518 men undergoing prostate biopsy stratified by diabetes status

| *Characteristics* | *Total* | *DM* | *Non-DM* | *p value* |
|---|---|---|---|---|
| Total patients, n | 518 | 96 | 422 | - |
| Age, years, median (IQR) | 71(13) | 72(13) | 70(13) | 0.126† |
| BMI, kg/m², median (IQR) | 23.6(3.8) | 24.2(3.4) | 23.4(3.7) | 0.155† |
| PSA, ng/ml, median (IQR) | 12.4(18.0) | 16.1(45.4) | 12.1(14.8) | 0.014† |
| PV, ml, median (IQR) | 51.0(31.1) | 44.0(29.0) | 52.2(29.0) | 0.274† |
| Abnormal DRE findings, n (%)* | 156(30.1) | 45(46.9) | 111(26.3) | <0.001‡ |
| History of smoking, n (%)* | 270(52.1) | 52(54.2) | 218(51.7) | 0.658‡ |
| History of drinking, n (%)* | 259(50.0) | 45(46.9) | 214(50.7) | 0.498‡ |
| History of hypertension, n (%)* | 269(51.9) | 62(64.6) | 207(49.1) | 0.006‡ |
| Family history of PCa, n (%)* | 177(34.2) | 28(29.2) | 149(35.3) | 0.253‡ |
| PCa detected at biopsy, n (%)* | 229(44.2) | 60(62.5) | 169(40.0) | <0.001‡ |
| HGPCa detected at biopsy, n (%)* | 65(12.5) | 34(35.4) | 31(7.3) | <0.001‡ |

BMI: body mass index, DM: diabetes mellitus, DRE: digital rectal examination, HGPCa: high-grade prostate cancer, IQR: interquartile range, PCa: prostate cancer, PSA: prostate specific antigen, PV: prostate volume *The exact number and percent of patients in total, DM or non-DM groups, respectively. †Using the Kruskal-Wallis test in comparison between DM and non-DM groups. ‡Using the chi-square test in comparison between DM and non-DM groups.

**Table 2.** Effects of diabetes status on overall and high-grade prostate cancer detection at biopsy

| | *OR (DM vs non-DM)* | *95% CI* | *p value* |
|---|---|---|---|
| PCa detection | | | |
| Crude | 2.495 | 1.580-3.940 | <0.001 |
| Age-adjusted | 2.407 | 1.507-3.844 | <0.001 |
| Multivariate-adjusted† | 1.774 | 0.831-3.787 | 0.138 |
| HGPCa detection | | | |
| Crude | 5.821 | 3.063-11.065 | <0.001 |
| Age-adjusted | 5.988 | 3.131-11.449 | <0.001 |
| Multivariate-adjusted† | 7.699 | 3.483-17.020 | <0.001 |

DM: diabetes mellitus, OR: odds ratio, CI: confidence interval, PCa: prostate cancer, HGPCa: high-grade prostate cancer, PSA: prostate specific antigen, PV: prostate volume, DRE: digital rectal examination. †Adjusted for age, PSA, PV, DRE, and history of hypertension (PSA and PV were logarithmically transformed).

**Table 3.** Clinical characteristics of 96 diabetic patients stratified by Metformin administration

| *Characteristics** | *Total* | *Metformin* | *Non-Metformin* | *p value* |
|---|---|---|---|---|
| Total patients, n(%) | 96(100%) | 28(29.2%) | 68(70.8%) | - |
| Age, years | 72(13) | 70(15.8) | 73.5(13.7) | 0.132† |
| BMI, kg/m² | 24.2(3.4) | 24.2(13) | 23.8(3.5) | 0.672† |
| PSA, ng/ml | 16.1(45.6) | 12.0(28.5) | 17.0(50.9) | 0.403† |
| PV, ml | 44(29.0) | 38(26) | 45.5(35) | 0.106† |
| Abnormal DRE findings, n(%) | 45(46.9) | 10(35.7) | 35(51.5) | 0.163‡ |
| History of smoking, n(%) | 52(54.2) | 14(50) | 38(55.9) | 0.604‡ |
| History of drinking, n(%) | 45(46.9) | 14(50) | 31(45.6) | 0.697‡ |
| History of hypertension, n(%) | 62(64.6) | 16(57.1) | 46(67.6) | 0.333‡ |
| Family history of PCa, n(%) | 28(29.2) | 12(42.9) | 16(23.5) | 0.059‡ |
| PCa detected at biopsy, n(%) | 60(62.5) | 16(57.1) | 44(64.7) | 0.492‡ |
| HGPCa detected at biopsy, n(%) | 34(35.4) | 4(14.3) | 30(44.1) | 0.005‡ |

BMI: body mass index, PSA: prostate specific antigen, PV: prostate volume, DRE: digital rectal examination, PCa: prostate cancer, HGPCa: high-grade prostate cancer, DM: diabetes mellitus *Continuous variables are shown as the median value with interquartile range. †Using the Kruskal-Wallis test. ‡Using the chi-square test.

**Table 4.** Effects of Metformin administrations on overall and high-grade prostate cancer detection at biopsy

| | *OR (Metformin vs non-Metformin)* | *95% CI* | *p value* |
|---|---|---|---|
| PCa detection | | | |
| Crude | 0.727 | 0.296-1.786 | 0.487 |
| Age-adjusted | 0.748 | 0.301-1.858 | 0.531 |
| Multivariate-adjusted† | 0.786 | 0.172-3.593 | 0.756 |
| HGPCa detection | | | |
| Crude | 0.390 | 0.199-0.763 | 0.006 |
| Age-adjusted | 0.392 | 0.196-0.783 | 0.008 |
| Multivariate-adjusted† | 0.420 | 0.201-0.879 | 0.021 |

OR: odds ratio, CI: confidence interval, PCa: prostate cancer, HGPCa: high-grade prostate cancer, PSA: prostate specific antigen, PV: prostate volume, DRE: digital rectal examination. †Adjusted for age, PSA, PV and DRE (PSA and PV were logarithmically transformed).

OR 0.420, p=0.021; Table 4). Meanwhile, we failed to detect any correlation between Metformin administration and risk of PCa detection (Table 4).

## Discussion

DM and PCa are among the most critical global health concerns. DM is generally recognized as a risk factor for many types of cancer such as bladder, liver, kidney, breast, pancreas and colorectal cancer [26]. However, there were inconsistent reports about the association between DM and PCa. Waters et al. [14] analysed 5,941 PCa cases among 86,303 populations including European-American, African-American, Latino, Japanese-American, and native Hawaiian men in a multi-ethnic cohort. The analysis indicated that DM patients had a lower risk of developing PCa than non-DM patients (RR 0.81, 95%CI 0.74-0.87, p<0.001). On the contrary, several studies in Asian populations showed opposite conclusions. Tseng et al. [10] analysed 494,630 men for all ages and 204,741 men ≥40 years old without PCa from Taiwan general population, and confirmed that DM was a risk factor of PCa prevalence, where the risk was most remarkable in the youngest age level (40-64 years). Li et al. [11] analysed 230 PCa patients among 22,458 Japanese men from 1995 to 2003 in Ohsaki cohort, where DM patients suffered a higher risk of developing PCa than non-DM patients (RR 1.89, 95%CI 1.02-3.50, p<0.05). The differences in diet, lifestyle, duration and severity of DM, complications of the disease, application of drug control or screening program might potentially lead to contradictory outcomes.

To our knowledge, the current study is the first to report the association between DM and PCa/HGPCa detection at biopsy in a Chinese population. We identified that DM status was significantly correlated with higher PSA level, greater percentage of positive DRE findings, higher possibility of hypertension, higher PCa and HGPCa detection rate. A

higher risk of HGPCa detection at biopsy was identified in the DM group after adjusting for multiple variables (OR 7.699, p<0.001) as compared with non-DM patients. Therefore, we considered DM as a risk factor for HGPCa in Chinese population.

Metformin is one of most extensively used oral hypoglycaemic agents in type 2 DM. Metformin could decrease the level of glucose mainly by reducing hepatic gluconeogenesis, causing a secondary decreased insulin levels, and promoting glucose uptake in muscle [19,22,27]. Besides decreasing glucose levels, Metformin could also decrease body weight [28,29]. Some studies demonstrated that Metformin could reduce the risk of cancers, including breast cancer, renal cancer and prostate cancer, etc. [30-32]. Others indicated that Metformin could reduce the incidence and mortality rate of prostate cancer [22,27,33]. Loubiere et al. [34] found that Metformin could decrease adenosine triphosphate in a dose-dependent manner, and this decrease was significantly associated with the inhibition of lipogenesis in LNCaP and DU145 cells. In the present study, DM patients with Metformin administration had a lower risk of HGPCa development as compared with DM patients with other treatments in multivariate regression analysis (OR 0.42, p=0.021). Therefore, we deduced that the increased risk of HGPCa in DM patients might be partly compromised by administration of Metformin in Chinese men.

The present study revealed that DM was a risk factor while Metformin administration was a protective factor for HGPCa onset. Since HGPCa was the real life-threatening disease for elderly males, the outcomes indicated that more aggressive biopsy strategy should be applied in DM patients, while the compromised strategy might be taken in those administered Metformin. The results require further validation and the proposed strategy appeals for future randomized controlled trial to practice and confirm.

There were several limitations in the present study. First, the DM status was determined based on medical records and self-report, which might ignore some early-phase DM patients. Second, type 2 DM and type 1 DM could not be differentiated in the study, which might be a potential confounder. Besides, since the sample capacity was quite limited, we failed to conduct more sub-group analyses. Additional multicentre clinical investigations should be conducted to help better demonstration of these associations.

## Conclusion

The present study indicated a higher risk of biopsy-mediated HGPCa detection in DM patients among Chinese men. Meanwhile, the increased risk might be partly compromised by the administration of Metformin. The underlying mechanism requires further investigation.

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## Conflict of interests

The authors declare no conflict of interests.

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