Characteristics Associated with the Use of Diagnostic Prostate Biopsy and Biopsy Outcomes in Australian Men

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ABSTRACT

Background: Population characteristics associated with the use of prostate biopsy are poorly understood. We described the use of diagnostic prostate biopsy and subsequent biopsy outcomes in a population-based Australian cohort.

Methods: A total of 91,764 men from the Sax Institute's 45 and Up Study (New South Wales, Australia) recruited during 2006 to 2009 were included. Self-completed baseline questionnaires and linked administrative health data were used. Study period was from the date of recruitment to December 2013. Cox regression and logistic regression identified factors associated with receipt of biopsy and subsequent prostate cancer diagnosis.

Results: During the study period, 5,089 participants had a diagnostic prostate biopsy, and 2,805 men (55.1% of those biopsied) received a cancer diagnosis. Men with a family history of prostate cancer (HR 1.55; 95% confidence interval (CI), 1.43–1.68), severe lower urinary tract symptoms (HR 1.62; 95% CI, 1.41–1.86), or a record of medication for benign prostatic hyperplasia (HR 1.34; 95% CI, 1.23–1.47) had increased risks of receiving a biopsy. Men with a family history of prostate cancer had increased odds of a positive biopsy (OR 1.21; 95% CI, 1.01–1.43). High alcohol consumption (≥21 drinks per week compared with 1–6 drinks per week) was associated with decreased risk of biopsy (HR 0.88; 95% CI, 0.80–0.96) but increased odds of a positive biopsy (OR 1.63; 95% CI, 1.32–2.02).

Conclusions: Certain characteristics are associated with both undertaking diagnostic prostate biopsy and positive biopsy outcomes.

Impact: This highlights the need to improve management of specific groups of men, especially those with clinical symptoms that overlap with prostate cancer, in their investigation for prostate cancer.

Introduction

The population-wide use of prostate-specific antigen (PSA) testing for the early detection of prostate cancer is known to influence disease incidence (1, 2). Although there is no organized program for prostate cancer screening in Australia, almost 37% of men over 45 years old were estimated to receive PSA tests in 2019 (3). Nonsystematic and indiscriminate use of PSA testing has raised concerns about the possible harms of PSA testing, including overdiagnosis and side effects from active treatments for those with low risk or indolent disease (4, 5). There are significant efforts to understand the factors associated with PSA testing (6–8) and evaluation of PSA testing strategies that target men at higher risk of aggressive prostate cancer (9).

Following an abnormal PSA test, a prostate biopsy is required to confirm a prostate cancer diagnosis. Hence, variation in the use of prostate biopsy will influence prostate cancer incidence and the way we interpret studies that depend on prostate biopsy for reporting on outcomes. For instance, the difference in biopsy compliance between ERSPC and PLCO trials was among the key factors suggested to contribute to the differences in the reported impact of PSA testing (10–12). Previous studies have investigated the factors and behaviors of men associated with the use of diagnostic prostate biopsy (13–19). However, they were mostly clinical trials (e.g., of prostate cancer screening or prevention) with specific study and follow-up protocols in selected populations (13–15, 17, 19).

The main study objective was to address the gap in our understanding of the use of diagnostic prostate biopsy at a population level. Using a large prospective Australian cohort study, we examined sociodemographic and health-related characteristics to primarily identify those associated with the use of diagnostic prostate biopsy and secondarily report on the biopsy outcomes for men who had prostate biopsy.

Materials and Methods

Study sample

The Sax Institute's 45 and Up Study is a prospective population-based cohort study of NSW (Australia) residents aged 45 and above at the time of recruitment (20). Participants were randomly selected from the Services Australia (formerly Department of Human Services) Medicare enrolment database. Residents from rural areas and those aged ≥80 years were oversampled. A total of 267,153 participants were recruited between January 2006 and December 2009. All participants self-completed a mailed baseline questionnaire and gave signed consent for follow-up and linkages with selected health databases. Ethics approval for the 45 and Up Study was obtained from the University of

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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NSW Human Research Ethics Committee. Ethics for this study was approved by the NSW Population and Health Services Research Ethics Committee (HREC/14/CIPHS/54).

Only male participants (123,732 men) were included in this study. Department of Veterans' Affairs health card holders were excluded because of incomplete coverage of health services claims in the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS). Men were excluded if they had preexisting prostate cancer (cancer registry record) or a radical prostatectomy [Admitted Patient Data Collection (APDC), Medicare Benefits Schedule claims] before study entry. Study period was defined as the date of recruitment to December 31, 2013.

Record linkage

Probabilistic record linkage with administrative health datasets was conducted by the Centre for Health Record Linkage (CHeReL) (http://www.cherel.org.au). This linkage method is reported to be highly accurate with false positive and false negative rates of <0.5% (21). Linked datasets used in this study were: NSW Cancer Registry (Jan 1994–Dec 2013) for records of primary cancer diagnosis; Registry of Births, Deaths and Marriages (Feb 2006–Jun 2017) for death records; Admitted Patient Data Collection (Admitted Patient Data Collection; Jul 2001–Jun 2017) for hospital admissions and Cause of Death Unit Record File (Feb 2006–Dec 2015) for cause of death records. Linkage with Medicare Benefits Schedule (Jun 2004–Dec 2016) and Pharmaceutical Benefits Scheme (Jun 2004–Dec 2016) for health services and medication claims were conducted by the Sax Institute through deterministic record linkage. Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data were provided by Services Australia.

Characteristics

The following characteristics were derived from self-reported baseline questionnaires: annual household income, in Australian dollars at time of recruitment, body mass index (BMI), erectile dysfunction, lower urinary tract symptoms (LUTS), vasectomy, family history of cancers (for first-degree relatives), smoking status, alcohol consumption, physical activity, and self-rated overall health. The severity of LUTS was derived using the modified IPSS (m-IPSS) scores and classified into the following groups: 0–5 (no or mild), 6–11 (moderate), 12–21 (severe), and no responses.

Medications for benign prostatic hyperplasia (BPH) were determined using pharmaceutical benefits scheme records for finasteride, prazosin, terazosin, doxazosin, dutasteride, and tamsulosin and/or items with ATC code G04C prior to biopsy or censoring for men without a biopsy. Treatment for diabetes was determined using Admitted Patient Data Collection diagnosis codes and Pharmaceutical Benefits Scheme records for metformin, oral hyperglycaemic agents, insulin, and/or ATC code A10 prior to biopsy or censoring for men without a biopsy. Charlson comorbidity index was based on Admitted Patient Data Collection diagnosis codes for a total of 15 comorbid conditions, excluding cancers and metastatic carcinomas prior to biopsy or censoring for those men without a biopsy. History of cancer diagnosis was determined from New South Wales Cancer Registry records of cancer diagnosis other than prostate cancer before study entry. The number of PSA tests was determined using Medicare Benefits Schedule codes (66655, 66656, 66659, 66660) from recruitment to time of first biopsy or censoring for those men without a biopsy.

Outcome measures

Receipt of prostate biopsy was based on Medicare Benefits Schedule items 37218, 37219, and Admitted Patient Data Collection items 37218–00, 37219–00. Associations with receipt of prostate biopsy were assessed using Cox regression with age as the time variable and full adjustment for all other variables in the model (**Tables 1** and **2**). For men with multiple biopsies, the first biopsy was taken as the index biopsy for analysis. Associations with health-related characteristics were adjusted for annual household income, region of birth, marital status, and health insurance cover and all other variables listed in **Table 2**. Men with no record of biopsy receipt were censored at 31 December, 2013, or date of death.

A positive biopsy result was defined as a confirmed prostate cancer diagnosis (NSW Cancer Registry) within 30 days of biopsy. Cases were excluded if the date of biopsy was after the date of confirmed cancer diagnosis. Logistic regression was conducted to identify characteristics associated with a positive biopsy result in men who had prostate biopsies. The fully adjusted regression included age at time of biopsy (or at last biopsy for men with multiple biopsies) and number of biopsies and all other variables listed in **Tables 3** and **4**. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC). Statistical significance was defined as P value <0.05.

Results

The final study sample included 91,764 men (Supplementary Fig. S1). Characteristics of the included men are provided in Supplementary Tables S1 and S2. During the study period, 5,089 men or 5.5% of the study sample had a diagnostic prostate biopsy (**Table 1**).

Sociodemographic characteristics and having a prostate biopsy

The association between increasing age and biopsy use is well-established. In this cohort, the largest percentage of men receiving a biopsy was for those aged 60 to 69 years (**Table 1**). Men in the highest annual household income bracket (HR 1.16; 95% CI, 1.06–1.27; compared with lowest annual income bracket), those who had private health insurance (HR 1.28; 95% CI, 1.18–1.39; compared with no private insurance or concession card health cover), those whose highest level of education was a certificate or diploma (HR 1.12; 95% CI, 1.01–1.25) compared to no school certificate and those who were married or living with a partner (HR 1.15; 95% CI, 1.06–1.24), were more likely to receive a prostate biopsy. Being born in countries other than Australia or New Zealand was associated with a lower risk of receiving a prostate biopsy (HR 0.89; 95% CI, 0.83–0.95).

Health-related characteristics and prostate biopsy

Several characteristics related to male reproductive and urological functions were significantly associated with biopsy use (**Table 2**). Men with self-reported severe LUTS (HR 1.62; 95% CI, 1.41–1.86; compared with no/mild LUTS) and medication for BPH (HR 1.34; 95% CI, 1.23–1.47) had higher risk of prostate biopsy. Interestingly, men with a family history of prostate cancer, but not a family history of other cancers, were more likely to receive a biopsy (HR 1.55; 95% CI, 1.43–1.68; compared with no family history of cancer). 6.8% of the cohort had preexisting cancer (other than prostate cancer), and 1.5% had a history of prostate biopsy (Supplementary Table S2). Both groups of men had increased risks of having a prostate biopsy with HRs of 1.16 (95% CI, 1.05–1.29) and 5.10 (95% CI, 4.59–5.67), respectively. Having a record of a PSA test increased the risk of biopsy with highest odds for men with one test during the study period (HR 2.34; 95% CI, 2.06–2.65).

Several lifestyle and well-being characteristics were associated with a lower risk of receiving a biopsy. These included men who were current or ever smokers (HR 0.90; 95% CI, 0.85–0.96), had high alcohol

Table 1. Associations between sociodemographic characteristics and having a prostate biopsy.

Characteristics	Number of men (row %)		HR (95% CI)[a]
	No biopsy	Biopsy	
Total	86,675 (94.5)	5,089 (5.5)	NA
Age at recruitment, years			
45–49	11,337 (98.1)	215 (1.9)	NA
50–59	29,576 (95.0)	1,557 (5.0)	
60–69	24,637 (91.7)	2,227 (8.3)	
70–79	14,238 (94.1)	890 (5.9)	
≥80	6,887 (97.2)	200 (2.8)	
Area of residence			
Major cities	46,128 (94.6)	2,658 (5.4)	1.00 (Ref)
Inner regional	30,696 (94.3)	1,849 (5.7)	1.05 (0.99–1.11)
Outer regional, remote and very remote	9,851 (94.4)	582 (5.6)	1.03 (0.94–1.13)
Education			
No school certificate or other qualification	8,680 (94.5)	502 (5.5)	1.00 (Ref)
School or intermediate certificate	12,685 (94.2)	787 (5.8)	1.07 (0.95–1.19)
Higher school or leaving certificate	8,597 (95.2)	435 (4.8)	0.94 (0.83–1.07)
Trade or apprenticeship	16,442 (94.4)	967 (5.6)	1.06 (0.95–1.18)
Certificate or diploma	17,076 (94.2)	1,060 (5.8)	1.12 (1.01–1.25)
University degree or higher	23,195 (94.5)	1,338 (5.5)	1.09 (0.98–1.20)
Annual household income			
≤$19,999	15,151 (94.7)	855 (5.3)	1.00 (Ref)
$20,000–$29,999	8,307 (94.2)	514 (5.8)	1.03 (0.92–1.14)
$30,000–$39,999	7,225 (93.7)	483 (6.3)	1.09 (0.98–1.22)
$40,000–$49,999	6,985 (93.7)	470 (6.3)	1.17 (1.04–1.31)
$50,000–$69,999	10,440 (94.1)	653 (5.9)	1.15 (1.03–1.28)
≥$70,000	26,917 (94.8)	1,466 (5.2)	1.16 (1.06–1.27)
No response	11,650 (94.7)	648 (5.3)	1.00 (0.90–1.11)
Region of birth			
Australia, New Zealand	65,128 (94.3)	3,916 (5.7)	1.00 (Ref)
Others	21,547 (94.8)	1,173 (5.2)	0.89 (0.83–0.95)
Health cover			
None of these	14,692 (95.7)	659 (4.3)	1.00 (Ref)
Health care concession card	22,147 (94.4)	1,305 (5.6)	1.11 (1.00–1.22)
Private health insurance	49,836 (94.1)	3,125 (5.9)	1.28 (1.18–1.39)
Married or living with a partner			
No	15,960 (95.4)	776 (4.6)	1.00 (Ref)
Yes	70,715 (94.3)	4,313 (5.7)	1.15 (1.06–1.24)

Abbreviations: CI, confidence interval; NA, not applicable; Ref, reference category.
[a]Cox regression with age as the time variable.

consumption (HR 0.88; 95% CI, 0.80–0.96; 21 drinks vs. 1–6 drinks per week). Men with diabetes (HR 0.87; 95% CI, 0.81–0.94) and higher comorbidity scores (HR 0.45; 95% CI, 0.40–0.51; Charlson comorbidity index ≥1 versus 0) had lower risk of having a biopsy.

Prostate biopsy results

We estimated the proportion of men with a positive biopsy result (confirmed by a prostate cancer diagnosis) following the first, second, third or more biopsy recorded within study period (**Fig. 1**). The percentage of positive biopsy results was highest following the first recorded biopsy (51.8%). The positive biopsy yields decreased with subsequent biopsies (28.8% following the second biopsy, 27.4% for the third or more biopsy recorded). Overall, the odds of receiving a positive result were lower for men with multiple prostate biopsies compared to those who had a single biopsy (unadjusted OR 0.42; 95% CI, 0.34–0.52; **Table 3**).

Increasing age was strongly associated with a positive biopsy result (OR for men aged ≥80, 6.22; 95% CI, 3.24–11.92; compared with men aged 45–49). Among other characteristics associated with increased risk of having a biopsy (**Table 3**), men with a family history of prostate cancer (OR 1.21; 95% CI, 1.01–1.43; compared with no family history of any cancer) had increased odds of being diagnosed with prostate cancer. In contrast, the odds of a positive biopsy result for men with moderate (OR 0.80; 95% CI, 0.44–0.82) or severe LUTS (OR 0.60; 95% CI, 0.44–0.82) were lower than those with no or mild LUTS. Men with medication for BPH (OR 0.24; 95% CI, 0.20–0.29) or history of a previous prostate biopsy (OR 0.38; 95% CI, 0.30–0.48) also had lower odds of a positive biopsy.

Among characteristics associated with decreased risk of having a biopsy (**Table 4**), men born in countries other than Australia or New Zealand (OR 0.77; 95% CI, 0.66–0.89) and those with prescription record for diabetes (OR 0.65; 95% CI, 0.55–0.78) had lower odds of being diagnosed with prostate cancer. Men with two or more comorbidities had higher odds of a positive biopsy (OR 1.46; 95% CI, 1.11–1.90). There was a significant increase in the odds of having a positive biopsy for men with high alcohol consumption. Compared with moderate alcohol consumption (1–6 drinks per week), the ORs for a positive biopsy result were 1.16 (95% CI, 1.00–1.35) and 1.63 (95% CI, 1.32–2.02) for moderately high (7–20 drinks per week) and very high alcohol consumption (≥21 drinks per week), respectively.

Table 2. Associations between health-related characteristics and having a prostate biopsy.

Characteristics	Number of men (row %)		HR (95% CI)[a]			
	No biopsy	Biopsy	Unadjusted	*P* value	HR (95% CI)[a,b] (adjusted)	*P* value
Total	86,675 (94.5)	5,089 (5.5)	NA		NA	
BMI[c]						
Under and normal weight	26,370 (94.4)	1,552 (5.6)	1.00 (Ref)	<0.0001	1.00 (Ref)	0.19
Overweight	40,703 (94.2)	2,514 (5.8)	0.99 (0.93–1.06)		1.00 (0.93–1.06)	
Obese	19,602 (95.0)	1,023 (5.0)	0.83 (0.77–0.90)		0.93 (0.86–1.01)	
Erectile dysfunction[c]						
No	52,117 (94.4)	3,111 (5.6)	1.00 (Ref)	0.001	1.00 (Ref)	0.67
Yes	25,817 (94.4)	1,518 (5.6)	0.91 (0.85–0.97)		0.99 (0.92–1.06)	
No response	8,741 (95.0)	460 (5.0)	0.85 (0.77–0.95)		0.95 (0.86–1.06)	
LUTS[c]						
No or mild (0–5)	61,303 (95.1)	3,173 (4.9)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
Moderate (6–11)	13,015 (92.3)	1,087 (7.7)	1.53 (1.43–1.64)		1.44 (1.34–1.55)	
Severe (12–21)	2,338 (91.1)	229 (8.9)	1.79 (1.56–2.05)		1.62 (1.41–1.86)	
No response	10,019 (94.3)	600 (5.7)	1.17 (1.07–1.28)		1.17 (1.07–1.29)	
Vasectomy[c]						
No	64,051 (94.6)	3,646 (5.4)	1.00 (Ref)	0.0003	1.00 (Ref)	0.11
Yes	22,624 (94.0)	1,443 (6.0)	1.12 (1.05–1.19)		1.05 (0.99–1.12)	
Family history of cancer[c]						
No	50,424 (94.9)	2,706 (5.1)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
Yes- Prostate cancer	8,879 (91.6)	812 (8.4)	1.65 (1.53–1.78)		1.55 (1.43–1.68)	
Yes- Breast and/or ovarian cancer	9,358 (94.5)	546 (5.5)	1.06 (0.96–1.16)		1.04 (0.95–1.14)	
Yes- any other cancers	18,014 (94.6)	1,025 (5.4)	1.05 (0.97–1.12)		1.02 (0.95–1.10)	
Medication for BPH						
No	79,520 (94.7)	4,432 (5.3)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
Yes	7,155 (91.6)	657 (8.4)	1.46 (1.34–1.58)		1.34 (1.23–1.47)	
Treatment for diabetes						
No	67,182 (94.1)	4,191 (5.9)	1.00 (Ref)	<0.0001	1.00 (Ref)	0.0007
Yes	19,493 (95.6)	898 (4.4)	0.66 (0.62–0.71)		0.87 (0.81–0.94)	
History of other cancer diagnosis prior to study entry						
No	80,829 (94.5)	4,712 (5.5)	1.00 (Ref)	0.01	1.00 (Ref)	0.006
Yes	5,846 (93.9)	377 (6.1)	1.14 (1.03–1.27)		1.16 (1.05–1.29)	
History of prostate biopsy prior to study entry						
No	85,745 (94.8)	4,688 (5.2)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
Yes	930 (69.9)	401 (30.1)	5.84 (5.27–6.47)		5.10 (4.59–5.67)	
Number of PSA tests						
0	15,408 (98.0)	321 (2.0)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
1	17,920 (94.5)	1,053 (5.5)	2.43 (2.14–2.75)		2.34 (2.06–2.65)	
2–3	31,746 (93.8)	2,096 (6.2)	2.31 (2.05–2.60)		2.09 (1.86–2.36)	
≥4	21,601 (93.0)	1,619 (7.0)	2.20 (1.95–2.48)		1.71 (1.52–1.94)	
Charlson Comorbidity Index						
0	63,012 (93.7)	4,255 (6.3)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
1	10,313 (95.7)	458 (4.3)	0.61 (0.55–0.67)		0.62 (0.57–0.69)	
≥2	13,350 (97.3)	376 (2.7)	0.41 (0.37–0.46)		0.45 (0.40–0.51)	
Ever smoker[c]						
No	42,439 (94.0)	2,700 (6.0)	1.00 (Ref)	<0.0001	1.00 (Ref)	0.0005
Yes	44,236 (94.9)	2,389 (5.1)	0.81 (0.77–0.85)		0.90 (0.85–0.96)	
Alcohol consumption, drinks per week[c]						
Non-drinkers	19,907 (94.7)	1,120 (5.3)	0.96 (0.88–1.03)	0.0005	1.00 (0.92–1.08)	0.003
1–6	23,676 (94.4)	1,408 (5.6)	1.00 (Ref)		1.00 (Ref)	
7–20	31,184 (94.2)	1,926 (5.8)	1.00 (0.93–1.07)		0.99 (0.92–1.06)	
≥21	11,908 (94.9)	635 (5.1)	0.83 (0.76–0.92)		0.88 (0.80–0.96)	
Physical activity, sessions per week[c]						
0–3	13,134 (95.0)	688 (5.0)	1.00 (Ref)	0.26	1.00 (Ref)	0.39
4–6	13,602 (94.7)	766 (5.3)	1.00 (0.90–1.11)		0.94 (0.85–1.04)	
7–10	20,458 (94.4)	1,212 (5.6)	1.03 (0.94–1.13)		0.95 (0.87–1.05)	
11–17	20,803 (94.0)	1,325 (6.0)	1.09 (0.99–1.19)		0.99 (0.90–1.09)	
≥18	18,678 (94.4)	1,098 (5.6)	1.01 (0.92–1.11)		0.93 (0.84–1.02)	
Self-rated overall health[c]						
Excellent	12,174 (94.3)	730 (5.7)	1.00 (Ref)	<0.0001	1.00 (Ref)	0.01
Very good	32,087 (93.8)	2,133 (6.2)	1.09 (1.00–1.18)		1.09 (1.00–1.19)	
Good	30,251 (94.6)	1,717 (5.4)	0.97 (0.89–1.05)		1.04 (0.95–1.14)	
Fair or poor	12,163 (96.0)	509 (4.0)	0.76 (0.68–0.86)		0.93 (0.82–1.06)	

Abbreviations: BMI, body mass index; BPH, benign prostatic hypertrophy; CI, confidence interval; LUTS, lower urinary tract symptoms; NA, not applicable; Ref, reference category.

[a]Cox regression with age as the time variable.

[b]HR adjusted for annual household income, region of birth, marital status, health cover, and the variables listed in **Table 2**.

[c]LUTS self-reported information from baseline questionnaire.

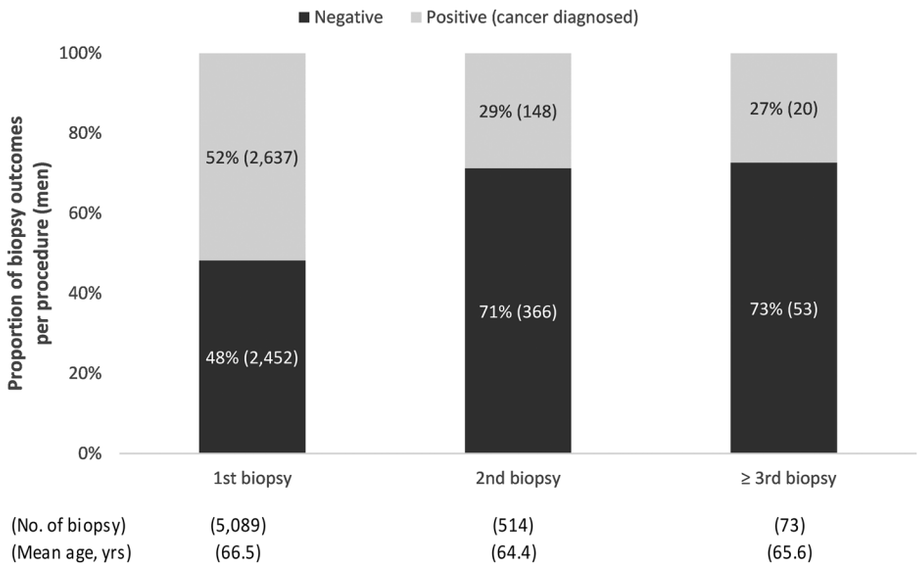

Figure 1.
Biopsy results stratified by the first, second, or third or more biopsy procedure of each man who undertook prostate biopsy within the study period. A positive biopsy result is defined as a record of prostate diagnosis within 30 days of biopsy procedure in the Cancer Registry.

Discussion

In this large Australian cohort, 5.5% of men aged 45 and over underwent diagnostic prostate biopsy (or biopsies) within a period of up to 7 years of follow-up. For those men with a prostate biopsy, just over half (55%) had a positive biopsy for a confirmed prostate cancer diagnosis. We found that men with a family history of prostate cancer and those with male reproductive and urological issues were more likely to have a prostate biopsy. However, only men with family history of prostate cancer had higher odds of a positive biopsy result. Several socio-demographic measures appeared to be associated with both the use and outcomes of prostate biopsy. Men born outside Australia or New Zealand were less likely to have a biopsy but if biopsied, these men were at lower risk of a positive biopsy than Australian or New Zealand born men. Having private health cover or a concession card was associated with increased biopsy use but had inconsistent associations with biopsy outcome. Overall, men with poor lifestyle and health characteristics were less likely to have a biopsy. Notably, men with high alcohol consumption were less likely to have a prostate biopsy but were at increased odds of having a positive biopsy result. To our knowledge, this is the largest population-based cohort study describing characteristics of men associated with the real-world use of diagnostic prostate biopsy and subsequent biopsy outcomes. It indicates that certain sociodemographic and health-related characteristics play a role in who gets a biopsy and their subsequent risk of being diagnosed with prostate cancer.

Previous studies investigating factors and characteristics associated with prostate biopsy use were mostly based on men recruited into clinical trials. Hence, the use of prostate biopsy would likely be influenced by issues such as patient selection and study-specific protocols related to decisions about when to biopsy (e.g., follow-up or mandatory end-of-study biopsy implemented) (13–15, 17, 19). Among these studies, Tangen 2016 was the most representative of a population-wide observational cohort study (15). With 8,228 men enrolled in the placebo arm of the prostate cancer prevention trial (SELECT), the study did not require a mandatory end-of-study prostate biopsy. Associations reported by the SELECT trial were similar to those reported here. After adjusting for age, digital rectal examination outcomes and PSA levels, men with medication for BPH, normal BMI, married men or non-smokers were found to be more likely to receive a biopsy. Notably, both studies reported that men with a family history of prostate cancer had both increased biopsy use and higher risk of a prostate cancer diagnosis. Concern of being at higher risk of prostate cancer among men with family history has been shown to drive higher participation in PSA testing (8, 22, 23). This concern may also result in higher biopsy referral and greater biopsy acceptance, although current evidence at a population level is limited and needs to be further investigated.

Not surprisingly, men with medication for BPH and self-reported urinary symptoms were found to be more likely to have a biopsy as part of their standard clinical investigation and management to monitor their conditions (14, 15). But in fact, these men had lower odds of a positive biopsy compared to those without these conditions. We recognize that other factors could result in the observed lower odds of a positive biopsy result. For instance, men with an enlarged prostate and urinary issues would have prior medical investigations to exclude the likelihood of prostate cancer and include cases with difficult to detect prostate cancer (e.g., small cancer foci and enlarged prostate). Nevertheless, our study highlights a need to improve current management to optimise the selection for biopsy of these men at risk of prostate cancer.

The diagnostic workup and indication for prostate biopsy is driven by clinical suspicion of prostate cancer based on factors such as abnormal PSA levels and the results of a digital rectal examination. Yet, health, lifestyle and behavioral characteristics appeared to influence biopsy receipt and reflected what we know about cancer screening participation (24, 25); men who are "less health conscious" are less likely to participate and comply with testing or follow-up. It is conceivable that some of this association is a result of men with lower life expectancy not being referred to or choosing not to proceed with investigations for prostate cancer. Current Australian guidelines on prostate cancer testing do not recommend screening for men with less than 7 years of life expectancy. Men with a smoking history were found to be less likely to have a biopsy in both our study cohort and the SELECT trial probably because men with a smoking history are less likely to have a PSA test (6, 15). The negative association between high alcohol consumption and

Table 3. ORs for characteristics associated with receiving a positive prostate biopsy in those with an increased risk of having a prostate biopsy.

Variables	Number of biopsied men (row %)		OR (95% CI)		OR (95% CI)[a]	
	No cancer	Cancer	Unadjusted	*P* value	Adjusted	*P* value
Total	2,284 (44.9)	2,805 (55.1)	NA			
Age at biopsy, years						
45–49	35 (63.6)	20 (36.4)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
50–59	625 (55.1)	510 (44.9)	1.43 (0.81–2.50)		1.39 (0.78–2.49)	
60–69	1,117 (48.5)	1,185 (51.5)	1.86 (1.07–3.24)		1.96 (1.10–3.50)	
70–79	434 (34.0)	843 (66.0)	3.40 (1.94–5.96)		3.58 (1.98–6.50)	
≥80	73 (22.8)	247 (77.2)	5.92 (3.22–10.88)		6.22 (3.24–11.92)	
No. of biopsies						
1	1,931 (42.3)	2,636 (57.7)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
≥2	353 (67.6)	169 (32.4)	0.35 (0.29–0.43)		0.42 (0.34–0.52)	
Area of residence						
Major cities	1,196 (45.0)	1,462 (55.0)	1.00 (Ref)	0.98	1.00 (Ref)	0.87
Inner regional	829 (44.8)	1,020 (55.2)	1.01 (0.89–1.13)		1.04 (0.91–1.18)	
Outer regional, remote and very remote	259 (44.5)	323 (55.5)	1.02 (0.85–1.22)		1.00 (0.82–1.22)	
Annual household income						
≤$19,999	322 (37.7)	533 (62.3)	1.00 (Ref)	<0.0001	1.00 (Ref)	0.004
$20,000–$29,999	173 (33.7)	341 (66.3)	1.19 (0.95–1.50)		1.20 (0.93–1.55)	
$30,000–$39,999	214 (44.3)	269 (55.7)	0.76 (0.61–0.95)		0.75 (0.58–0.98)	
$40,000–$49,999	231 (49.1)	239 (50.9)	0.63 (0.50–0.79)		0.80 (0.61–1.04)	
$50,000–$69,999	313 (47.9)	340 (52.1)	0.66 (0.53–0.81)		0.81 (0.63–1.05)	
≥$70,000	747 (51.0)	719 (49.0)	0.58 (0.49–0.69)		0.71 (0.56–0.91)	
No response	284 (43.8)	364 (56.2)	0.77 (0.63–0.95)		0.91 (0.71–1.16)	
Health cover						
None of these	324 (49.2)	335 (50.8)	1.00 (Ref)	<0.0001	1.00 (Ref)	0.06
Health care concession card	485 (37.2)	820 (62.8)	1.64 (1.35–1.98)		1.30 (1.04–1.62)	
Private health insurance	1,475 (47.2)	1,650 (52.8)	1.08 (0.92–1.28)		1.13 (0.94–1.37)	
Number of PSA tests						
0	163 (50.8)	158 (49.2)	1.00 (Ref)	0.13	1.00 (Ref)	0.08
1	458 (43.5)	595 (56.5)	1.34 (1.04–1.72)		1.44 (1.09–1.89)	
2–3	931 (44.4)	1,165 (55.6)	1.29 (1.02–1.63)		1.30 (1.01–1.68)	
≥4	732 (45.2)	887 (54.8)	1.25 (0.98–1.59)		1.27 (0.97–1.65)	
Married or living with a partner						
No	337 (43.4)	439 (56.6)	1.00 (Ref)	0.38	1.00 (Ref)	0.93
Yes	1,947 (45.1)	2,366 (54.9)	0.93 (0.80–1.09)		0.99 (0.83–1.18)	
LUTS[b]						
No or mild (0–5)	1,325 (41.8)	1,848 (58.2)	1.00 (Ref)	<0.0001	1.00 (Ref)	0.0001
Moderate (6–11)	548 (50.4)	539 (49.6)	0.71 (0.61–0.81)		0.80 (0.69–0.94)	
Severe (12–21)	133 (58.1)	96 (41.9)	0.52 (0.39–0.68)		0.60 (0.44–0.82)	
No response	278 (46.3)	322 (53.7)	0.83 (0.70–0.99)	`	0.75 (0.61–0.91)	
Vasectomy[b]						
No	1,613 (44.2)	2,033 (55.8)	1.00 (Ref)	0.14	1.00 (Ref)	0.24
Yes	671 (46.5)	772 (53.5)	0.91 (0.81–1.03)		1.09 (0.95–1.25)	
Family history of cancer[b]						
No	1,197 (44.2)	1,509 (55.8)	1.00 (Ref)	0.02	1.00 (Ref)	0.0007
Yes- Prostate cancer	341 (42.0)	471 (58.0)	1.10 (0.94–1.28)		1.21 (1.01–1.43)	
Yes- Breast and/or ovarian cancer	245 (44.9)	301 (55.1)	0.98 (0.81–1.17)		1.06 (0.87–1.29)	
Yes- any other cancers	501 (48.9)	524 (51.1)	0.83 (0.72–0.96)		0.80 (0.68–0.94)	
Medication for BPH						
No	1,816 (41.0)	2,616 (59.0)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
Yes	468 (71.2)	189 (28.8)	0.28 (0.23–0.34)		0.24 (0.20–0.29)	
History of other cancer diagnosis prior to study entry						
No	2,141 (45.4)	2,571 (54.6)	1.00 (Ref)	0.005	1.00 (Ref)	0.31
Yes	143 (37.9)	234 (62.1)	1.36 (1.10–1.69)		1.13 (0.89–1.43)	
History of prostate biopsy prior to study entry						
No	2,003 (42.7)	2,685 (57.3)	1.00 (Ref)	<0.0001	1.00 (Ref)	<0.0001
Yes	281 (70.1)	120 (29.9)	0.32 (0.26–0.40)		0.38 (0.30–0.48)	
Self-rated overall health[b]						
Excellent	319 (43.7)	411 (56.3)	1.00 (Ref)	0.81	1.00 (Ref)	0.66
Very good	973 (45.6)	1,160 (54.4)	0.93 (0.78–1.10)		0.90 (0.75–1.08)	
Good	764 (44.5)	953 (55.5)	0.97 (0.81–1.15)		0.95 (0.78–1.15)	
Fair or poor	228 (44.8)	281 (55.2)	0.96 (0.76–1.20)		0.95 (0.73–1.25)	

Abbreviations: BMI, body mass index; BPH, benign prostatic hypertrophy; CI, confidence interval; LUTS, lower urinary tract symptoms; NA, not applicable; OR, odds ratio; Ref, reference category.

[a]Logistic regression included all variables listed in **Table 3** and **Table 4**.

[b]LUTS self-reported information from baseline questionnaire.

Table 4. Odds ratios for characteristics associated with receiving a positive prostate biopsy in those with a decreased risk of having a prostate biopsy.

Variables	Number of biopsied men (row %)		OR (95% CI)		OR (95% CI)[a]	
	No cancer	Cancer	Unadjusted	*P* value	Adjusted	*P* value
Total	2,284 (44.9)	2,805 (55.1)	NA			
Education						
No school certificate or other qualification	216 (43.0)	286 (57.0)	1.00 (Ref)	0.09	1.00 (Ref)	0.71
School or intermediate certificate	335 (42.6)	452 (57.4)	1.02 (0.81–1.28)		1.04 (0.81–1.33)	
Higher school or leaving certificate	179 (41.1)	256 (58.9)	1.08 (0.83–1.40)		1.22 (0.92–1.64)	
Trade or apprenticeship	428 (44.3)	539 (55.7)	0.95 (0.77–1.18)		0.99 (0.78–1.26)	
Certificate or diploma	490 (46.2)	570 (53.8)	0.88 (0.71–1.09)		1.02 (0.80–1.31)	
University degree or higher	636 (47.5)	702 (52.5)	0.83 (0.68–1.03)		1.04 (0.81–1.33)	
No school certificate or other qualification	216 (43.0)	286 (57.0)	1.02 (0.81–1.28)		1.04 (0.81–1.33)	
Region of birth						
Australia, New Zealand	1,706 (43.6)	2,210 (56.4)	1.00 (Ref)	0.0006	1.00 (Ref)	0.0004
Others	578 (49.3)	595 (50.7)	0.80 (0.70–0.91)		0.77 (0.66–0.89)	
BMI[b]						
Under and normal weight	689 (44.4)	863 (55.6)	1.00 (Ref)	0.79	1.00 (Ref)	0.41
Overweight	1,127 (44.8)	1,387 (55.2)	0.98 (0.87–1.12)		1.04 (0.90–1.19)	
Obese	468 (45.7)	555 (54.3)	0.95 (0.81–1.11)		1.13 (0.94–1.36)	
Erectile dysfunction[b]						
No	1,491 (47.9)	1,620 (52.1)	1.00 (Ref)	<0.0001	1.00 (Ref)	0.18
Yes	594 (39.1)	924 (60.9)	1.43 (1.26–1.62)		1.13 (0.97–1.31)	
No response	199 (43.3)	261 (56.7)	1.21 (0.99–1.47)		0.94 (0.75–1.18)	
Treatment for diabetes						
No	1,840 (43.9)	2,351 (56.1)	1.00 (Ref)	0.003	1.00 (Ref)	<0.0001
Yes	444 (49.4)	454 (50.6)	0.80 (0.69–0.93)		0.65 (0.55–0.78)	
Charlson comorbidity index						
0	1,947 (45.8)	2,308 (54.2)	1.00 (Ref)	0.005	1.00 (Ref)	0.03
1	197 (43.0)	261 (57.0)	1.12 (0.92–1.36)		1.05 (0.84–1.30)	
≥2	140 (37.2)	236 (62.8)	1.42 (1.14–1.77)		1.46 (1.11–1.90)	
Ever smoker[b]						
No	1,253 (46.4)	1,447 (53.6)	1.00 (Ref)	0.02	1.00 (Ref)	0.40
Yes	1,031 (43.2)	1,358 (56.8)	1.14 (1.02–1.27)		1.06 (0.93–1.20)	
Alcohol consumption, drinks per week[b]						
Non-drinkers	531 (47.4)	589 (52.6)	1.06 (0.91–1.24)	<0.0001	0.99 (0.83–1.18)	<0.0001
1–6	688 (48.9)	720 (51.1)	1.00 (Ref)		1.00 (Ref)	
7–20	841 (43.7)	1,085 (56.3)	1.23 (1.07–1.42)		1.16 (1.00–1.35)	
≥21	224 (35.3)	411 (64.7)	1.75 (1.45–2.13)		1.63 (1.32–2.02)	
Physical activity, sessions per week[b]						
0–3	323 (46.9)	365 (53.1)	1.00 (Ref)	0.50	1.00 (Ref)	0.71
4–6	356 (46.5)	410 (53.5)	1.02 (0.83–1.25)		1.00 (0.80–1.25)	
7–10	536 (44.2)	676 (55.8)	1.12 (0.93–1.35)		1.04 (0.85–1.28)	
11–17	575 (43.4)	750 (56.6)	1.15 (0.96–1.39)		1.12 (0.91–1.37)	
≥18	494 (45.0)	604 (55.0)	1.08 (0.89–1.31)		1.00 (0.81–1.24)	

Abbreviations: BMI, body mass index; CI, confidence interval; NA, not applicable; OR, odds ratio; Ref, reference category.
[a]Logistic regression included all variables listed in **Table 3** and **Table 4**.
[b]Self-reported information from baseline questionnaire.

the likelihood of having a prostate biopsy is an interesting finding. A recent systematic review and meta-analysis demonstrated a positive association between increasing levels of alcohol consumption and the risk of being diagnosed with prostate cancer (26). However, compared with other well-established links between cancer risks and alcohol, the evidence surrounding alcohol and prostate cancer remains unclear. This raised a question as to whether alcohol consumption should be considered as a confounder for biopsy compliance in studies investigating potential risk factors for prostate cancer. As the association between high alcohol consumption (≥21 drinks per week) and biopsy use has not been reported in a population-based study before, further studies are required to establish this first.

We present the associations between the factors of interest and having a positive biopsy as odds ratios. As the outcome was relatively common the odds ratios are not a good estimate of the corresponding relative risks and should not be interpreted as such. Our study is limited by the absence of PSA test results and details of the biopsy procedures, which are important in deciding whether biopsy is required and can influence biopsy yield respectively. PSA levels are not available from the linked study datasets, while the Medicare Benefits Schedule and Admitted Patient Data Collection items used to identify biopsy records do not distinguish between types or technique of biopsy used or number of biopsy cores taken. This information is valuable in interpreting biopsy outcomes for men perceived to be at higher risk of prostate cancer, for instance,

whether a more intense biopsy procedure (hence higher biopsy yield) is given to men with family history of prostate cancer. Cancer diagnoses were only available up to the end of 2013, making it impossible to evaluate recent impacts of multiparametric MRI (mpMRI) in the diagnostic pathway. Hence, further follow-up of the study participants is necessary when more recent data become available. This will enable observations on the changes in population-wide biopsy use and cancer detection rates that are likely to accompany the widespread introduction of mpMRI in the diagnostic pathway.

Loss to follow-up will have occurred for a proportion of this cohort. Deaths were captured by linkage to the Register of Births, Deaths and Marriages but other circumstances, such as emigration will have resulted in an unknown, but likely small proportion of men being lost to follow-up.

Overall, we identified variations in the characteristics of Australian men and their risks of having a diagnostic prostate biopsy and biopsy outcomes. Future studies are required to better understand the justification behind biopsy referral, acceptance and outcomes, especially for men with a family history of prostate cancer, BPH urinary issues and higher alcohol consumption. We also anticipate significant changes in the use of diagnostic prostate biopsy in the population following the more widespread uptake and use of mpMRI.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

K. Chiam: Conceptualization, supervision, methodology, writing–original draft, project administration, writing–review and editing, data interpretation and provision of intellectual content. Final approval of manuscript. **A. Bang:** Formal analysis, methodology, writing–review and editing, data interpretation and provision of intellectual content. Final approval of manuscript. **M.I. Patel:** Methodology, writing–review and editing, data interpretation and provision of intellectual content. Final approval of manuscript. **V. Nair-Shalliker:** Conceptualization, methodology, writing–review and editing, data interpretation and provision of intellectual content. Final approval of manuscript. **D.L. O'Connell:** Conceptualization, methodology, writing–review and editing, data interpretation and provision of intellectual content. Final approval of manuscript. **D.P. Smith:** Conceptualization, supervision, methodology, writing–review and editing, data interpretation and provision of intellectual content. Final approval of manuscript.

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