Systematic review of clinical features of suspected prostate cancer in primary care

Sheila-Mae Young MD   Praveen Bansal MD CCFP FCFP   Emily T. Vella PhD   Antonio Finelli MD
Cheryl Levitt MB BCh CCFP FCFP   Andrew Loblaw MD MSc FRCPC

Abstract

Objective To systematically review the literature and provide an update and integration of existing peer-reviewed guidelines with recent systematic reviews and with primary studies related to the early recognition and management of prostate cancer in primary care.

Data sources We searched MEDLINE and EMBASE for relevant articles. The quality of the evidence to support existing guideline recommendations and the consistency of recommendations with updated evidence were assessed. Applicability in a Canadian primary care setting was also evaluated.

Study selection All studies conducted in the primary care setting that provided information on clinical features predictive of prostate cancer were included. Also, studies that assessed the accuracy of nomograms to predict prostate cancer were reviewed.

Synthesis The findings suggest that lower urinary tract symptoms are not highly predictive of prostate cancer. However, evidence suggests that FPs might be good at discriminating between patients with and without prostate cancer using digital rectal examination and prostate-specific antigen testing. Nomograms might also be useful in assessing patients for aggressive prostate cancers.

Conclusion The results of this review can be used to inform recommendations for referral for suspected prostate cancer in the primary care setting. They could also inform development of prostate cancer diagnostic assessment programs.

EDITOR'S KEY POINTS
- Prostate cancer is the most common cancer diagnosed in men. For FPs and other primary care providers, it is often difficult to distinguish the early presentation of prostate cancer from other benign ailments and thus justify referral for investigations and specialist consultation. This systematic review provides an update of existing peer-reviewed guidelines related to the early recognition and management of prostate cancer in primary care.

- The findings from this review suggest that there are no signs or symptoms that are good predictors of prostate cancer. In the reviewed studies, lower urinary tract symptoms were not highly predictive of prostate cancer. However, it seems FPs are good at discriminating between patients with and without prostate cancer, and digital rectal examinations performed by FPs are useful tools in evaluating suspected prostate cancer. Prostate-specific antigen testing showed the highest predictive value for detecting prostate cancer.

- Unfortunately, only 2 of the reviewed studies were conducted in primary care settings; other studies were included if they examined patients referred from primary care. More studies in the primary care setting are required to specifically investigate which signs, symptoms, or test results are predictive of prostate cancer.

Revue systématique des caractéristiques cliniques suggestives d'un cancer de la prostate en contexte de soins primaires

Sheila-Mae Young MD   **Praveen Bansal** MD CCFP FCFP   **Emily T. Vella** PhD   **Antonio Finelli** MD
Cheryl Levitt MB BCh CCFP FCFP   **Andrew Loblaw** MD MSc FRCPC

Résumé

Objectif Faire une revue systématique de la littérature à propos des plus récentes directives vérifiées par des pairs et de leur application, et ce, à l'aide de revues systématiques récentes et d'études portant sur la détection précoce et sur le traitement du cancer de la prostate en contexte de soins primaires.

Sources des données On a consulté MEDLINE et EMBASE à la recherche d'articles pertinents. La qualité des preuves à l'appui des directives existantes et leur cohérence avec les données les plus récentes ont été évaluées. On a également vérifié leur applicabilité dans un milieu de soins primaires au Canada.

Choix des études On a retenu toutes les études effectuées en contexte de soins primaires qui contenaient des informations sur les caractéristiques cliniques prédictives de cancer prostatique. Ont aussi été examinées les études qui évaluaient la précision des nomogrammes comme facteur prédictif d'un cancer prostatique.

Synthèse Ces résultats suggèrent que les symptômes du tractus urinaire distal ne constituent pas de très bons prédicteurs du cancer de la prostate. Les données suggèrent toutefois que les MF pourraient être habiles pour distinguer les patients souffrant ou non de cancer grâce au toucher rectal et au dosage de l'antigène prostatique spécifique. Des nomogrammes pourraient également être utiles pour évaluer les patients qui ont un cancer prostatique agressif.

Conclusion Les résultats de cette revue peuvent servir à indiquer aux soignants de première ligne les cas où un patient qu'on suspecte d'avoir un cancer prostatique doit être dirigé en spécialité. Ils pourraient aussi susciter le développement de programmes d'évaluation du diagnostic du cancer de la prostate.

POINTS DE REPÈRE DU RÉDACTEUR

• Le cancer de la prostate est le cancer le plus souvent diagnostiqué chez l'homme. Pour le MF et pour les autres soignants de première ligne, il est souvent difficile de distinguer les signes précoces de ce cancer de ceux d'autres affections bénignes et ainsi de choisir les cas nécessitant une consultation en spécialité. Cette revue systématique rappelle les plus récentes directives vérifiées par des pairs à propos du diagnostic précoce et du traitement du cancer prostatique en contexte de soins primaires.

• Selon les données recueillies dans cette revue, il n'existe pas de signes ni de symptômes qui soient de bons prédicteurs d'un cancer de la prostate. D'après les études consultées, les symptômes du tractus urinaire distal ne constituent pas des facteurs hautement prédictifs de ce cancer. Il semble toutefois que les MF soient très habiles à distinguer les patients qui présentent un cancer de la prostate de ceux qui n'en ont pas; ainsi, le toucher rectal effectué par le MF est un examen utile pour évaluer la possibilité d'un tel cancer. C'est toutefois le dosage de l'antigène spécifique de la prostate qui demeure le meilleur moyen pour détecter un cancer prostatique.

• Malheureusement, seulement 2 des études examinées avaient été effectuées en contexte de soins primaires; on a quand même accepté d'autres études, mais seulement celles qui concernaient des patients dirigés en consultation à partir d'un milieu de soins primaires. Dans la plupart des études effectuées en contexte de soins primaires, on devait avoir vérifié spécifiquement les signes, les symptômes et les résultats d'examens qui ont une valeur prédictive pour un cancer de la prostate.

Prostate cancer is the most commonly diagnosed cancer among men and the third leading cause of cancer-related death among men in Canada.[1] However, prostate cancer is a slow-progressing disease, and the 5-year relative survival ratio is 96%.[1] Screening has not been recommended in Canada, and therefore FPs and other primary care providers (PCPs) are faced with determining when to suspect prostate cancer and when to refer patients for further testing, given that some men diagnosed with prostate cancer might survive unaffected.

Cancer Care Ontario's Provincial Primary Care and Cancer Network collaborated with the Program in Evidence-based Care to develop this updated systematic review, which will inform primary care referral guidelines for patients who present with signs and symptoms that might raise suspicion of prostate cancer. This review does not address screening asymptomatic men for prostate cancer. Before this review, there were no Canadian or provincial guidelines that addressed referral of symptomatic patients for prostate cancer.

The following questions were evaluated in completing this overall objective.
• What signs, symptoms, and other clinical features are predictive of prostate cancer?
• What is the diagnostic accuracy of investigations for prostate cancer?

DATA SOURCES

As a foundation, we chose a priori to update the literature review used to support the 2009 guidelines from the New Zealand Guidelines Group (NZGG) and the 2005 guidelines from the National Institute for Health and Care Excellence (NICE).[2,3] These guidelines were considered to be of high quality, comprehensive, recent in publication, and relevant to this topic.

Literature review and analysis
The search strategies from the 2009 NZGG and 2005 NICE guidelines were kindly provided.[2,3] MEDLINE and EMBASE were searched for additional English-language papers published from 2005 to April 2012. Reference lists of papers and review articles were scanned for further citations.

Study selection
Systematic reviews or primary studies that provided possible clinical features predictive of prostate cancer were included. An attempt was made to include only studies conducted in primary care. The working group believed that nomograms might be useful in the primary care setting to assist FPs and other PCPs in managing their patients and chose to include studies assessing the

accuracy of nomograms for predicting prostate cancer. Case reports and prostate cancer screening studies were excluded.

Articles were selected by title and abstract by 1 methodologist (E.T.V.), and full articles were reviewed by the other authors. Systematic reviews and meta-analyses were assessed for quality using the AMSTAR (Assessment of Multiple Systematic Reviews) tool.[4] The quality of primary studies was assessed using a modified QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool, which is based on the Cochrane Collaboration method for assessing the methodologic quality of diagnostic studies.[5] Data were not pooled owing to considerable heterogeneity among studies.

SYNTHESIS

Literature search results
Of 16 596 articles identified in the updated literature search since the NICE and the NZGG guideline searches, based on the title and abstract 257 were deemed relevant for a full-article review.[2,3] Of these, 1 systematic review and 10 primary studies that met the study selection criteria were included.[6-15] Three additional studies were found from the reference lists.[16-18] From the NICE systematic review, 4 primary studies were included in this review.[20-23] One primary study was included from the NZGG review.[24] No additional practice guidelines were identified other than the NICE and NZGG guidelines that were identified a priori (**Figure 1**).

Study design and quality
Reviews. Only 1 systematic review of nomograms for prostate cancer was included.[16] This 2009 review by Shariat et al scored low on the AMSTAR rating for several reasons: the types of studies searched and how they were selected and extracted were not described in detail, only 1 electronic database was searched (AMSTAR suggests at least 2 should be searched), no meta-analyses were performed, and a list of excluded studies was not provided (**Table 1**).[4,16] However, the review by Shariat et al does provide a comprehensive list of available nomograms and whether they have been internally or externally validated.

Primary studies. Seven prospective cohort studies,[6,12,13,15,20,21,23] 7 retrospective cohort studies,[9-11,14,17-19] 2 retrospective case series studies,[7,22] and 2 case-control studies[8,24] were included. The details and factors that might have affected the quality of each of these studies are highlighted in **Table 2**.[6-15,17-24] Because of the lack of studies performed in the primary care setting, a post hoc decision was made to include studies conducted in secondary and tertiary care settings if they included

Figure 1. Results of literature search strategies
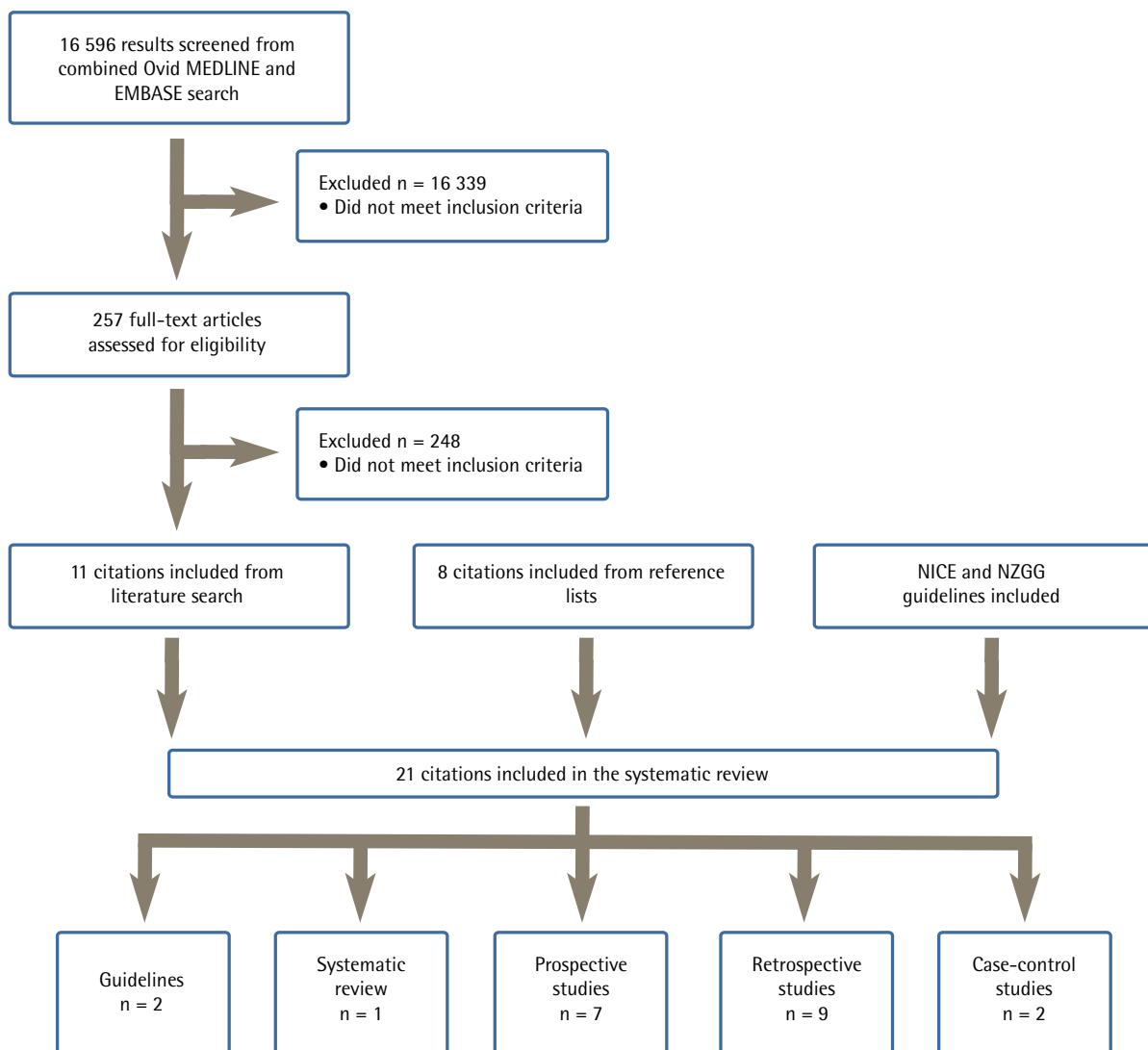
NICE—National Institute for Health and Care Excellence, NZGG—New Zealand Guidelines Group.

patients who were referred from the primary care setting. For studies assessing nomograms, only those studies that included patients from a referred population and that included variables that were available to FPs before referral to a specialist were included. Other methodologic concerns were that some studies did not recruit consecutive patients or were not blinded to the patients' signs, symptoms, or diagnoses.

Outcomes

What signs, symptoms, and other clinical features are predictive of prostate cancer?

Summary of NICE 2005 systematic review: Although none of the review articles included in the NICE review was conducted in primary care, 1 study in a 1997 review by Selley et al[25] included patients referred from primary care with bladder outflow obstruction.[23] Prostate cancer was positively suggested in 8 of 287 patients' primary care referral letters, and 4 of these had histologically confirmed prostate cancer.

A 2004 study by Gjengstø et al included in the NICE review examined patients' reasons for consulting their FPs.[21] A total of 360 of 872 (41.3%) patients were diagnosed with prostate cancer. Among the 373 patients

Table 1. Evaluation of included systematic review of nomograms using AMSTAR

ITEM	SHARIAT ET AL,[16] 2009
AMSTAR items[4]	
• Was an a priori design provided?	Yes
• Was there duplicate study selection and data extraction?	Unclear
• Was a comprehensive literature search performed?	No
• Was the status of publication (eg, gray literature) used as an inclusion criterion?	Unclear
• Was a list of studies (included and excluded) provided?	No
• Were the characteristics of the included studies provided?	Yes
• Was the scientific quality of the included studies assessed and documented?	Yes
• Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
• Were the methods used to combine the findings of the studies appropriate?	NA
• Was the likelihood of publication bias assessed?	No
• Was the conflict of interest stated?	Yes
Total AMSTAR points*	5

AMSTAR—Assessment of Multiple Systematic Reviews, NA—not applicable.
*Out of a possible total of 11.

who consulted their FPs because of lower urinary tract symptoms (LUTS), 34% were diagnosed with prostate cancer, whereas of the 462 patients without urologic symptoms who consulted their FPs (those attending for a health check, nonurologic disease, or concerns about having cancer), 47% were diagnosed with prostate cancer.

The NICE 2005 review also included a retrospective study by Månsson et al from 1999.[22] Using a Swedish database of patients with prostate cancer, they reported the sensitivity of symptoms presented to FPs at first consultation. Skeletal or abdominal pain was reported in 22% of patients with prostate cancer, followed by the general symptoms of weight loss, dyspnea, tiredness, vertigo, and fever in 11% of patients, urinary urgency in 8% of patients, nocturia in 8% of patients, and urinary tract infection in 6% of patients.

Based on the systematic review, NICE concluded that prostate cancer often presents with symptoms of urinary outflow obstruction.[2] Other presenting symptoms include urinary tract infection and features of metastasis such as bone pain. An additional conclusion was that most prostate cancers can be palpated by the GP through digital rectal examination (DRE); however, an abnormal finding might be the result of conditions other than cancer.

Summary of NZGG 2009 systematic review: The NZGG 2009 review included 1 primary case-control study by Hamilton et al conducted in the primary care setting (217 cases, 1080 controls).[24] Using multivariable analysis, 8 features were associated with prostate cancer. The positive predictive values (PPVs) against a background risk of 0.35% were 3.1% for urinary retention; 3.0% for impotence; 2.2% for frequency; 3.0% for hesitancy; 2.2% for nocturia; 1.0% for hematuria; 0.75% for weight loss; 2.8% for abnormal rectal examination findings deemed benign; and 12% for abnormal rectal examination findings deemed malignant. The authors suggested that LUTS, especially urinary retention, frequency, hesitancy, and nocturia, as well as impotence, should prompt prostate-specific antigen (PSA) testing.

Summary of nomograms in the literature: The 2009 review by Shariat et al described studies of nomograms for the prediction of prostate cancer at initial biopsy.[16] Only 1 study, by Karakiewicz et al, included an internally and externally validated nomogram that contained variables available to an FP or other PCP before referral.[18] These variables included age, DRE findings, PSA level, and percent free PSA. The cancer detection rate for this model was 35% to 42%, and the discrimination rate was 77%. However, Kawakami et al found that their nomogram, which also included age, DRE findings, PSA level, and percent free PSA, had a significantly more accurate area under the curve (AUC=0.73) compared with Karakiewicz and colleagues' (AUC=0.71) nomogram (*P*<.01).[11] Further, Kawakami et al went on to develop a nomogram in a Japanese population using age, PSA level, DRE findings, family history of prostate cancer, and number of previous malignancies other than in the prostate as variables.[10] Using data from Japanese patients with PSA levels less than 10 μg/L derived from the same retrospective cohort in the other study by Kawakami et al, they externally validated this nomogram and calculated the AUC to be 0.67.[10,11]

A 2011 Canadian prospective, multi-institutional study by Nam et al evaluated 2 nomograms for prostate cancer, one from the Prostate Cancer Prevention Trial (PCPT) and another from Sunnybrook Hospital (the prostate risk calculator) in Toronto, Ont.[12] Patients were included if they had abnormal PSA levels (>2.6 μg/L) or abnormal DRE findings, but it was unclear if all patients were from primary care settings. They found the AUC for the Sunnybrook nomogram was significantly higher than for the PCPT nomogram for predicting prostate cancer, as well as for aggressive prostate cancer with a Gleason score of 7 or higher (*P*=.001). In addition, if patients chose a risk of 30% for prostate cancer as a threshold to agree to a biopsy, then the net benefit (the relative value of false-positive vs false-negative

Table 2. Study characteristics for clinical questions about signs, symptoms, investigations, or risk factors for prostate cancer

AUTHOR	STUDY TYPE, COUNTRY, SETTING	NO. OF PATIENTS	NO. OF PATIENTS WITH PROSTATE CANCER (%)	INVESTIGATIONS USED	CONSECUTIVE PATIENTS	BLINDED TO INDEX	MISSING OR UNINTERPRETABLE DATA EXPLAINED	WITHDRAWALS EXPLAINED
Prospective								
• Baughan et al,[6] 2011	Prospective over 6 mo, Scotland, PC	582 referred with suspected prostate cancer	306 (53)	Not given	No	No	Yes	No
• Fowler et al,[20] 2000	Prospective over 8 y, US, tertiary care referred mainly from PC	536 with abnormal DRE findings and PSA level ≥ 4 µg/L (179 black and 357 white men)	103 (19)	Various biopsy techniques	Yes	Yes	Yes	Yes
• Gjengstø et al,[21] 2004	Prospective over 4 y, Norway, secondary care referred from PC	872 mostly aged < 70 y without serious comorbidity, PSA level < 20 µg/L, and no locally advanced disease on DRE	360 (41)	2-dimensional TRUS-guided modified sextant biopsy	No	No	Yes	Yes
• Nam et al,[13] 2007	Prospective over 6 y, Canada, mainly a referred population	3108 with abnormal DRE findings and PSA level ≥ 4 µg/L	1304 (42)	6 to 15 ultrasound-guided needle core biopsies	Yes	No	Yes	Yes
• Nam et al,[12] 2011	Prospective over 2 y, Canada, referred population	2130 with abnormal DRE findings and PSA level > 2.6 µg/L	867 (41)	TRUS-guided needle core biopsy	No	Yes	Yes	Yes
• Powell et al,[23] 1989	Prospective, UK, secondary care referred from PC	287 with symptoms of bladder outflow obstruction	19 (6.6)	All patients with elevated PSA levels had cystoscopy and TRUS or Tru-Cut biopsy; 30% with normal PSA levels had TRUS	Yes	No	Yes	Yes
• Serag et al,[15] 2012	Prospective, UK, tertiary care referred from PC	397 referred with suspected prostate cancer based on UK guideline	169 (43)	Biopsy or high index of suspicion warranting androgen deprivation therapy, follow-up 12 mo	Yes	Yes	No	No
Retrospective								
• Allen et al,[17] 2004	Retrospective over 1 y, UK, 2-wk-wait referral	35 referred for elevated PSA levels	11 (31)	Various	Yes	No	No	No
• Borre,[7] 2009	Retrospective, Denmark, secondary care referred from PC	538 with prostate cancer treated with radical prostatectomy	538 (100); 350 with LUTS, 188 no LUTS	Not given	Yes	No	Yes	Yes

Table 2 continued from **page e31**

AUTHOR	STUDY TYPE, COUNTRY, SETTING	NO. OF PATIENTS	NO. OF PATIENTS WITH PROSTATE CANCER (%)	INVESTIGATIONS USED	CONSECUTIVE PATIENTS	BLINDED TO INDEX	MISSING OR UNINTERPRETABLE DATA EXPLAINED	WITHDRAWALS EXPLAINED
• Hawary et al,[9] 2008	Retrospective over 6 mo, UK, secondary care referred from PC	41 with elevated age-specific PSA levels	18 (44)	Not given	Yes	No	Yes	Yes
• Karakiewicz et al,[18] 2005	Retrospective, Canada and Germany, mainly a referred population	For nomogram 2: internal validation 1762, external validation 514, ≤50 µg/L with abnormal DRE findings or abnormal PSA or free PSA levels	For nomogram 2: internal validation 739 (42), external validation 189 (37)	Sextant biopsy	Unclear	No	No	No
• Kawakami et al,[11] 2008	Retrospective, Japan, referred population	For nomogram 1: 1083, PSA level <20 µg/L; for Karakiewicz nomogram: 1762	For nomogram 1: 37%; for Karakiewicz nomogram: 42%	Extended biopsy	Unclear	No	No	No
• Kawakami et al,[10] 2008	Retrospective, Japan, referred population	External validation: 544 PSA level < 10 µg/L	External validation: 221 (41)	Mostly extended biopsy	Yes	No	No	No
• Månsson et al,[22] 1999	Retrospective over 5 y, Sweden, PC	63 with prostate cancer	63 (100)	Swedish Cancer Registry	Yes	No	Yes	Yes
• Mathew and Desai,[19] 2009	Retrospective over 6 mo, UK, secondary care referred from PC	115 referred for elevated PSA levels, 3 referred for elevated PSA levels and abnormal DRE findings, 4 referred for elevated PSA levels and LUTS	45 (39) with elevated PSA level, 3 (100) with elevated PSA level and abnormal DRE findings, 2 (50) with elevated PSA level and LUTS	Imaging and pathology reports	Yes	No	No	No
• Quinlan et al,[14] 2009	Retrospective, Ireland, tertiary care, some referred from PC	200 with LUTS, 148 referred from PC	3 (2)	Not given	Yes	No	Yes	Yes
Case-control								
• Buckley et al,[8] 2011	Case-control over 5 y, Scotland, PC linked with secondary care records	984 cases, 1968 controls	984	Not given	Yes	No	Yes	Yes
• Hamilton et al,[24] 2006	Case-control, UK, PC records	217 cases, 1080 controls	217	Electronic records	No	Yes	Yes	Yes

DRE—digital rectal examination, LUTS—lower urinary tract symptoms, PC—primary care, PSA—prostate-specific antigen, TRUS—transrectal ultrasound, UK—United Kingdom, US—United States.

results) was better for the Sunnybrook model compared with the PCPT nomogram. The Sunnybrook nomogram also provided better net benefit at a risk threshold of 15% for aggressive prostate cancer. The variables for the Sunnybrook nomogram included age, urinary prostate symptom score, PSA level, ratio of free to total PSA, ethnic background (Asian, Caucasian, African descent, other), family history of prostate cancer, and DRE findings. All of these factors were found to be significantly (*P* < .01) associated with prostate cancer using multivariable analysis when this nomogram was developed in 2007 with patients referred with abnormal PSA values or DRE findings; however, it was unclear whether patients were referred from primary care.[13]

Summary of literature since the 2009 NZGG guidelines: Borre investigated the difference in tumour characteristics and treatment outcomes in men undergoing radical prostatectomy for prostate cancer who had either LUTS (n = 350) or were asymptomatic (n = 188) (incidental PSA screening).[7] Men with a familial predisposition for prostate cancer were excluded. Patients were categorized as asymptomatic or symptomatic by asking them their reasons for consulting their FPs. No differences were found in tumour characteristics or treatment outcome except for a higher Gleason score for the radical prostatectomy specimen among asymptomatic patients compared with symptomatic patients. This suggests a poorer prognosis for asymptomatic compared with symptomatic patients undergoing radical prostatectomy. The median PSA value before radical prostatectomy was identical in both groups. The authors questioned the recommendation by the Danish Urological Society to perform PSA testing in men with LUTS.

An audit of urgent referrals by GPs in Scotland found that 53% (306 of 582) of patients who were urgently referred were diagnosed with prostate cancer.[6] Likewise, a prospective study in the United Kingdom (UK) found that the overall prostate cancer detection rate for men referred by their GPs based on the NICE guideline was 43%, with 80% being assessed with intermediate- or high-risk prostate cancer and 15% with metastatic presentation.[15] These rates were not significantly different compared with rates in a historical cohort of men referred before the NICE guideline. However, more low-risk and fewer high-risk prostate cancers were found among younger men (aged 50 to 69 years) in the cohort after the implementation of the NICE guideline compared with the historical cohort.

What is the diagnostic accuracy of investigations for prostate cancer?

Summary of NICE 2005 systematic review: The 1997 systematic review by Selley et al, mentioned in the NICE 2005 review, included a 1989 study by Powell et al that selected patients referred from primary care with bladder outflow obstruction.[23,25] In 23% of 287 patients, a DRE of the prostate was not performed or not recorded in primary care referral letters. Of the 211 patients who had their PSA levels measured, 36 had elevated PSA levels (>10 µg/L) and underwent further urologic assessment. Seventeen patients with elevated PSA levels had histologically confirmed prostate cancer (PPV = 47%). Only 30% of patients with normal PSA levels had further assessment, and 2 of these patients had prostate cancer (sensitivity was 17 of 19 or 89.5%). Although the authors reported a specificity of 90% for PSA testing, exclusion of the 70% of patients with normal PSA levels who were not further evaluated would result in a specificity of 72% or 73%.

In addition, Gjengstø et al examined FPs' reasons for referral.[21] An elevated PSA level was the most common reason for FPs to refer patients. Of the 647 patients with elevated PSA levels, 222 (34.3%) were diagnosed with prostate cancer. The PPV for detecting prostate cancer was highest when the reason for referral was both an elevated PSA level and a suspicious DRE finding (125 of 185 [67.6%]). The PPV was lower (7 of 24 [29.2%]) when the reason for referral was suspicious DRE findings alone.

Summary of NZGG 2009 systematic review: The NZGG review found no additional articles since the publication of the NICE 2005 guideline for this research question.[3] However, in 2006 Hamilton et al also addressed this question.[24] The PPV for an abnormal rectal examination finding assessed as benign by a GP was 2.8%, whereas the PPV was 12% for those assessed as malignant. As well, for PSA testing, this study found that once the PSA result was added to the multivariable analysis, a PSA level greater than 4 µg/L was the only variable significantly associated with prostate cancer (*P* = .001). The authors suggest this finding can provide useful information for the sequential diagnostic assessment of patients with symptoms of prostate cancer. If LUTS are identified, the authors suggest a PSA test be performed, as the PSA result would be the best predictor of prostate cancer; the symptoms would no longer be relevant.

Summary of literature since the 2009 NZGG guidelines: Hawary et al reviewed 41 men referred with an elevated age-specific PSA level from a 2-week-wait referral clinic in the UK.[9] Eighteen (43.9%) cases of prostate cancer were diagnosed in this group, and 2 (4.9%) cases were suitable for radical prostatectomy. *Suitability* was defined as those patients with localized and locally advanced prostate cancer (with respect to age or PSA level only) with a possible life expectancy of greater than 10 years. In addition, all patients diagnosed with prostate cancer were older than 50 years of age.

A retrospective study reviewed all patients referred under the 2-week-wait initiative in the UK to a single urologic clinic.[17] Eleven of 35 (31%) patients referred

with raised PSA levels (ranging from 3.4 to 480 µg/L, median 13.9 µg/L) were diagnosed with prostate cancer. Five of these patients had metastases at presentation.

Similarly another retrospective audit of all 2-week-wait referrals to a single urologic department in the UK found that 39% (45 of 115) of the men referred for elevated PSA levels were diagnosed with prostate cancer.[19] As well, 2 out of 4 men with elevated PSA levels and LUTS were diagnosed with prostate cancer, and all 3 men with elevated PSA levels and abnormal DRE findings were found to have prostate cancer.

In 2009, Quinlan et al reviewed patients referred with LUTS in their tertiary referral centre in Ireland.[14] Of 148 men referred by their GPs, 48 (32%) received DRE and 3 (6%) of them had prostate cancer. Findings of DRE for 2 of those 3 were reported as benign, and for the third the prostate was reported to be hard. However, 39 of 41 (95%) patients whose GPs reported DRE findings as benign, enlarged, or normal were eventually diagnosed with benign prostatic hyperplasia. Seven of these patients had PSA levels greater than 4 µg/L, and 4 had no PSA level measured. The authors suggested that DREs be performed so that abnormal DRE findings result in expedited referral.

DISCUSSION

Two studies showed that LUTS were poor predictors of prostate cancer and its prognosis.[7,21] In addition, using multivariable analysis, Hamilton and colleagues found that PSA test results were the only variable significantly associated with prostate cancer, whereas other urologic symptoms were not predictive.[24] This finding suggests that LUTS are not highly predictive of prostate cancer. However, 3 studies suggest that FPs are good at discriminating between patients with and without prostate cancer.[14,23,24] Four of 8 patients for whom referral letters suggested possible prostate cancer were later diagnosed with prostate cancer.[23] As well, the studies by Quinlan et al and Hamilton et al suggest that DREs performed by FPs are useful tools in evaluating suspected prostate cancer.[14,24] Four published audits of compliance with the NICE guideline found that a high proportion of men referred for suspected prostate cancer were diagnosed with the disease.[6,15,17,19] Furthermore, compared with LUTS and DRE findings, PSA testing showed the highest predictive value for detecting prostate cancer, with PPVs ranging from 34% to 47%.[9,21,23] Therefore, although LUTS might not be good predictors of prostate cancer within the primary care population, PSA testing and DREs appear to be valuable tests for determining the possibility of prostate cancer. Nam and colleagues[12] included urologic symptoms in the Sunnybrook nomogram and found that a composite score for LUTS, rather than individual symptoms as suggested by Hamilton et al,[24] was a significant predictor of prostate cancer, using multivariable analysis with PSA results in the model. Although it was unclear whether the patients in Nam and colleagues' study were referred from primary care, the nomogram includes information that is easily available to FPs and other PCPs.[12] Furthermore, their nomogram was predictive of aggressive prostate cancers with a Gleason score of 7 or higher. Hawary et al explain that, while it is necessary to reveal the signs and symptoms that are predictive of prostate cancer, it is also important to differentiate which prostate cancers are potential candidates for curative treatment.[9]

Limitations

Through our own search and by searching the reference lists of several systematic reviews, attempts were made to be thorough. However, because our literature search was an update of the searches completed for the NICE and NZGG guidelines, we trusted that the original searches were equally as rigorous and that relevant articles were not missed. We also limited our review to only those studies published in English and we did not include unpublished literature.

Because of the nature of the question, we were limited to observational studies, and no randomized trials were available in this setting. The main concern with these studies in addressing our research questions is that all but 2 of the studies[6,24] were not conducted in the primary care setting. Although other studies were included if they selected patients who were referred from primary care, it was difficult to draw strong conclusions for the primary care population.

Conclusion

The findings from this review suggest that there are no signs or symptoms that are good predictors of prostate cancer. Lower urinary tract symptoms have been examined in a few studies, but it appears that patients with LUTS are not at any greater risk of developing prostate cancer or having a poorer prognosis with prostate cancer than asymptomatic patients are. However, as suggested in a systematic review by Hamilton and Sharp, patients with LUTS might be seeking reassurance that they do not have prostate cancer.[26] Further, the treatment of an enlarged prostate is very different from that for prostate cancer. Therefore, FPs and other PCPs might consider DREs and PSA testing in patients with LUTS, as recommended in the benign prostatic hyperplasia guidelines by the Canadian Urological Association, and refer those with suspicious findings to a urologist for investigation.[27] There is some evidence to suggest that FPs can use DRE and PSA testing to distinguish prostate cancer from benign

disease, but there is little evidence to suggest that DRE or PSA testing could predict aggressive prostate cancer in the primary care setting.[14,23,24] The Sunnybrook nomogram by Nam et al might be an appropriate model for FPs to use to assess the risk of aggressive prostate cancer.[12] The findings of this systematic review have been used to inform guidelines for referral of patients with suspected prostate cancer by FPs and other PCPs.[28] However, further studies in the primary care setting are required to specifically investigate which signs, symptoms, or test results are predictive of prostate cancer.

Dr Young is Regional Primary Care Lead with Cancer Care Ontario (CCO) for Central East Ontario. **Dr Bansal** is Regional Primary Care Lead for CCO for Central West Ontario. **Dr Vella** is Health Research Methodologist in the Department of Oncology at McMaster University in Hamilton, Ont, and for CCO's Program in Evidence-based Care. **Dr Finelli** is a urologist in Toronto, Ont. **Dr Levitt** is Professor in the Department of Family Medicine at McMaster University and the Past Provincial Primary Care Cancer Lead with CCO. **Dr Loblaw** is a radiation oncologist in Toronto.

Correspondence
Dr Emily T. Vella, McMaster University, Oncology, 711 Concession St, Hamilton, ON L8V 1C3; e-mail **ccopgi@mcmaster.ca**

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