Research

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Digital rectal examination in primary care is important for early detection of prostate cancer:

a retrospective cohort analysis study

Abstract

Background
Currently, there is no standardised screening for prostate cancer in Europe. Assessment of risk is opportunistically undertaken in consultation with the GP or urologist. Evaluation of the prostate gland consists of a prostate-specific antigen (PSA) serum level and a digital rectal examination (DRE) of the gland. DRE is an essential part of the assessment that can independently predict prostate cancer in the setting of a normal PSA level.

Aim
To evaluate the clinical usefulness of the DRE in general practice and urology clinics, and to ascertain its positive predictive value and sensitivity.

Design and setting
A retrospective analysis study of a cohort of Irish men who underwent TRUS guided biopsy of the prostate in a single Irish tertiary referral centre, despite a normal PSA level. Patients were identified from a Rapid Access Prostate Clinic patient database. Pathological biopsy results were correlated with clinical DRE findings.

Method
Patient demographics, PSA levels, and DRE findings from a prospectively established database and hospital data systems from May 2009 to October 2013 were analysed.

Results
Of 103 men referred over a 53-month period with a normal age-adjusted PSA level, 67% were referred on the basis of an abnormal DRE alone. Thirty-five per cent of males with a normal PSA had prostate cancer. DRE alone had a sensitivity and specificity of 81% and 40% respectively in diagnosing prostate cancer, with a positive predictive value of 42%. Seventy-six per cent of these men had high-grade disease.

Conclusion
DRE is a key part of the assessment for prostate cancer. It can independently identify patients at risk of prostate cancer, with a substantial proportion of these having clinically significant disease requiring treatment. This study reinforces the importance of DRE in the primary care setting in the assessment for prostate cancer. An abnormal DRE, even in the setting of a normal PSA level, necessitates referral.

Keywords
digital rectal examination; opportunistic screening; primary care; prostate cancer.

INTRODUCTION

Since the introduction of the Rapid Access Prostate Clinic (RAPC) in May 2009, 1451 men have been assessed and biopsied. The RAPC was established by the National Cancer Control Programme (NCCP) as part of its strategy for cancer control in Ireland, published in 2006.[1] Its intention is to provide GPs with a direct pathway for evaluation of men in whom there is a high risk of prostate cancer.

Prostate cancer is the most common non-cutaneous malignancy in men and the second leading cause of cancer-related death in Ireland.[2] Its incidence has risen in Ireland from 11.6% in 1994 to 19.4% in 2010, with the highest increase being in the 55–64-year age group.[3]

While the incidence of prostate cancer is rising, the rate of prostate cancer-specific mortality in patients with high-risk disease has remained relatively unchanged.[4] This is partly due to the early diagnosis and treatment of prostate cancer through implementation of the RAPC and partly due to broader awareness of the disease by the general public, with international campaigns such as *Movember* (ie.movember.com). The early detection of cancer is a key aim of the NCCP's national cancer strategy, with the goal of reducing cancer incidence, morbidity, and mortality in line with other EU countries by the year 2015.

Both digital rectal examination (DRE) and prostate-specific antigen (PSA) testing form two of the key components of the assessment of the prostate gland. The limitations of PSA as a biomarker for prostate cancer are well known. In 2004 Thompson *et al* showed that there was no absolute lower value of PSA below which there is a negligible risk of prostate cancer. It was shown too that PSA is not a dichotomous marker, but one whose values reflect a continuum of risk for prostate cancer.[5] The Prostate Cancer Prevention Trial (PCPT) revealed that 15% of men with a PSA <4.0 g/L will have prostate cancer, with 15% of these having high-grade disease. PSA is not specific for malignancy and is elevated in many other conditions including benign prostatic hyperplasia (BPH), urinary retention, prostatitis, trauma, and physical manipulation.[6] A PSA cut-off of 4.0 g/L yields a sensitivity and specificity of 20.5% and 94% for the presence of prostate cancer respectively, with slight improvement seen with age stratification.[7]

The recent 'Melbourne Consensus Statement on the early detection of prostate cancer'[8] advises that PSA testing should not be considered on its own, but rather in conjunction with other variables. PSA in itself is a poor predictor of current prostate cancer risk and addition of parameters such as the DRE, ethnicity, family history, and risk prediction models help to better risk-stratify men. DRE is found to add significantly to information on prostate cancer risk when evaluated in conjunction with other parameters such as PSA.[9] A case–control study comparing men who

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How this fits in

Digital rectal examination (DRE) is an integral component of the assessment of the prostate gland that is often overlooked or undervalued. A normal prostate-specific antigen (PSA) level does not preclude a diagnosis of prostate cancer. This study shows that a number of men with a normal PSA and an abnormal DRE were diagnosed with moderate- to high-risk prostate cancer. DRE has the ability to aid in the diagnosis of prostate cancer in men who wish to undergo assessment, and should be a mandatory component of that process.

died from prostate cancer with a control group found that those who had undergone DRE within 10 years of diagnosis had a significant (50–70%) reduced risk of prostate cancer-specific mortality.[10]

The RAPC, with the above in mind, has clear guidelines for patient referral. Referrals of patients aged 50–70 years (40–70 years if first-degree relative affected or of African ethnicity) with two abnormal PSA readings at least 6 weeks apart can be submitted online via the 'Healthlink' system, via fax, or via post from GPs within the relevant catchment area.[11] A single PSA cut-off level is not used, but rather an age-specific PSA range (Table 1).[12] Previously the European Randomized Study of Screening for Prostate Cancer (ERSPC) guidelines, which indicated a biopsy at a PSA level >4.0 g/L, were generally used as the standard cut-off level in opportunistic screening.[13] Despite availability of other diagnostic approaches and increasing reliance on PSA as the main predictor of prostate cancer, an abnormal DRE alone is still considered an indication for prostate biopsy at the clinic, where patients are assessed by a specialist urology nurse and a consultant urologist. A full history and physical examination is performed, including a DRE, which again forms a key

Table 1. Age-specific PSA range

Age, years	Upper limit of normal PSA, ng/mL
<50	2.5
50–59	3.5
60–69	4.5
70–79	6.5

part of the patient assessment. Patients then proceed to trans-rectal ultrasound (TRUS) biopsy at the same visit if warranted.

The aim of this study was to evaluate the role of DRE in the detection of prostate cancer in men with PSA levels within the normal age-specific range.

METHOD

Between May 2009 and October 2013, 1451 men attended the RAPC and underwent TRUS biopsy. Men were aged 45–80 years. Data including patient demographics, reason for referral, PSA, GP assessment of the DRE, and urologist assessment of the DRE were collected prospectively on all patients and stored in a coded database. Men were assessed in an outpatient setting initially, where a decision was made by a consultant urologist as to whether progression to TRUS biopsy was required. Biopsy occurred on the same day as the consultation in the endoscopy suite. All biopsies were reported by two consultant pathologists at the institution. Histological findings of TRUS biopsy were correlated with DRE findings in all patients with a normal age-specific PSA. Inclusion criteria for the study consisted of all patients who had a normal age-specific PSA at time of referral. All data were then collated in a coded database to ensure patient anonymity.

The diagnostic accuracy of DRE as a predictor of positive prostate biopsy was assessed using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) analyses. Sensitivity was defined as the percentage of biopsy-positive patients referred with an abnormal DRE among all biopsy-positive patients. Specificity was defined as the percentage of biopsy-negative patients whose DRE was not definitely abnormal among all biopsy-negative patients.

Sensitivity = a/(a+c)
Specificity = d/(b+d)

- (a = biopsy-positive patients with an abnormal DRE [$n = 29$].
- b = biopsy negative patient with an abnormal DRE [$n = 40$].
- c = biopsy-positive patients with a normal DRE [$n = 7$].
- d = biopsy-negative patients with a normal DRE [$n = 27$].)

PPV was calculated as a/(a+b) and NPV as d/(c+d) where PPV was taken as the proportion of patients with prostate cancer among all those with an abnormal DRE, and NPV as the proportion of cancer-free

patients among all those with a normal DRE.

RESULTS

Seven per cent of total referrals to the RAPC over the 53 months (103 out of 1451) had a normal age-specific PSA (age range 45–80 years, mean 63.3 years). Of these 103, 67% (n = 69) were referred based solely on an abnormal DRE in the presence of a normal PSA level for their age. The remaining 33% (34 out of 103) were referred by their GP's with a PSA level perceived as raised, with an absolute PSA threshold of >4.0 g/L rather than age-specific PSA cut-offs. Five of these men were referred on the basis of their PSA readings being perceived as raised; they were also found to have an abnormal DRE.

Abnormalities on DRE were recorded by GPs in 72% (74 out of 103) of patients, with urologists reporting an abnormal examination in 58% (60 out of 103). This yields a concordance rate of 76% in DRE findings. Thirty-five per cent (36 out of 103) of men referred with a normal age-matched PSA were diagnosed with prostate cancer. Eighty-one per cent of these men (29 out of 36) were biopsied solely on the basis of an abnormal DRE (final histopathology is shown in Table 2). The remaining seven patients referred by their GP on the basis of a PSA level interpreted to be elevated, with a normal DRE examination by both the GP and consultant urologist, were diagnosed with prostate cancer. The reasons for proceeding with prostate biopsies in these cases included a positive family history and abnormal PSA kinetics. The sensitivity and specificity of DRE alone was 81% and 40% respectively, with a PPV of 42% and a NPV of 79%.

All 103 patients in the cohort had a normal age-matched PSA level, although 33% (34/103) were referred with a PSA level interpreted to be elevated by their GP (for example, on the basis of abnormal PSA kinetics, or above a PSA cut-off >4.0 g/L).13

Table 2. Pathological Gleason Grade and age distribution

Gleason grade of prostate cancer in DRE-positive patients	Cases, n (%)	Mean age, years (range)
Gleason 3+3	7 (24.1)	58.14 (53–73)
Gleason 3+4	12 (41.4)	67.50 (60–73)
Gleason 4+3	5 (17.2)	65.20 (52–72)
Gleason 4+4	3 (10.3)	69.00 (65–74)
Gleason 4+5	2 (7)	62.50 (61–64)
Total	29 (100)	

DISCUSSION

Summary

In the study, 103 men were referred to the RAPC with an age-matched PSA level within normal limits. Of these, 67% were referred on the basis of an abnormal DRE, with a further 5% having both an increased PSA velocity/PSA >4.0 g/L and an abnormal DRE. Thirty-nine per cent of the 74 men found by their GP to have an abnormal DRE (29/74) went on to be diagnosed with prostate cancer. Of these men diagnosed with prostate cancer who were found to have an abnormal DRE, 76% had clinically significant disease (Gleason ≥7).

Strengths and limitations

The institution is a large tertiary referral centre with a large volume of RAPC referrals from GPs in the catchment area, creating a large patient cohort for analysis. All data on patients referred via the RAPC are stored prospectively in a database.

The study relies on adequate documentation of DRE findings by both the GP in the initial referral, and the consultant urologist at the time of assessment or TRUS biopsy. To the best of the authors' knowledge these were documented in all cases examined. As with most clinical examinations, there is a degree of inter-examiner variability in the assessment of the prostate on DRE. This may be accentuated between GPs and urologists based on the number of examinations they themselves perform and therefore their experience at interpreting DRE. However, the high concordance of examination findings demonstrated in the data is reassuring and in line with those previously reported.[14]

Comparison with existing literature

Screening for prostate cancer is a contentious issue surrounded by much confusion and controversy. It can lead to overdiagnosis and exposure of patients to unnecessary investigations such as TRUS biopsy, as well as over-treatment of indolent disease. Currently in Europe there is no formalised screening programme for prostate cancer. In Ireland opportunistic screening for prostate cancer is undertaken, largely by primary care physicians. Most guideline statements have promoted the role of shared decision-making for men regarding PSA testing, and for it to be evaluated in conjunction with other parameters such as DRE, risk prediction models, age, ethnicity, and family history.[15-17] Adams *et al* presented on the fate of men presenting with a PSA >100 g/L at the American Urological Association in

2013 and in their study cohort found a 9.7% 3-year survival rate, with a 19.7% rate of cord compression and hospitalisation rate of 64%.[18]

The ERSPC trial follow-up to date has shown a 30% reduction in metastatic prostate cancer and a 21% reduction in prostate cancer-specific mortality in the screened arm with intention to treat analysis.[19,20] Recently published data from the Rotterdam arm of the trial found a 32% reduction in prostate cancer specific mortality in the 55–69-year age group.[21] While the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial found no long-term benefit in PSA and DRE testing, with no subsequent gain from treatment over observation, this trial has a 52% PSA contamination in its control arm.[22] Sun *et al* recently found that, in men with a ≥10-year life expectancy and localised prostate cancer, radical prostatectomy was associated with a greater overall survival than observation alone and radiotherapy.[23]

The ERSPC screening guidelines indicated biopsy at a PSA ≥4.0 g/L, a positive DRE, or a previous positive TRUS biopsy on active surveillance. Schroder *et al* found that DRE alone detected 55.8% of prostate cancer in the Rotterdam arm of the ERSPC,[24] with a 17.3% detection rate in the PSA<4.0 g/L group who would otherwise have gone without being biopsied. Roberts *et al* similarly estimated that the positive predictive value of DRE alone stood at 18%.[25]

There is undoubtedly an element of inter-examiner variability in the clinical examination of the prostate. There are few studies assessing this degree of variability. Smith and Catalona established that among urologists the reproducibility of DRE findings was high. This current study found a 76% concordance rate between the GP and urologists assessment of the prostate, which is similar to their finding of 84%.[14]

There is no absolute cut off value for PSA at which the risk of prostate cancer is negligible. But there is obvious risk associated with lowering the PSA threshold to reduce the specificity of the test and exposing an increased number of men to the risk associated with TRUS biopsy. Prior to PSA testing DRE was the only screening tool available for the assessment of the prostate gland. There is substantial evidence to indicate that an abnormal DRE is a good predictor for the presence of prostate cancer,[26] and Borden *et al* showed that an abnormal DRE was an independent predictor for high-risk disease. While prediction of risk in patients with a normal PSA level and a normal DRE is outside of the scope of the data, Thompson *et al* assessed risk of high-grade prostate cancer based on PSA level, DRE, and patient age in the placebo arm of the PCPT. They found the risk of prostate cancer to be <10% in men aged 65 years with a normal DRE and PSA <4.0 g/L, with only a marginal increase in men aged 75 years.[27] This risk decreased with lower values of PSA. Similarly, using the same model, if both PSA and DRE are abnormal the risk of high-grade prostate cancer increases with both PSA level and age.

Given the relatively low sensitivity and specificity of PSA and DRE in an unbiased population, a combination of both PSA levels and DRE in men who decide to undergo analysis of their prostate gland following consultation with their GP would increase the PPV, sensitivity, and specificity of either test in isolation. The diagnosis of non-life-threatening prostate cancer has been estimated at approximately 50% in the latest data from the ERSPC,[19] resulting in significant distress, and risk of over-treatment and unnecessary treatment-related morbidity to the patient. However, active surveillance is a validated option of management of patients who fit 'low grade' disease profile to avoid side effects and expenses of treatment. Given the Rotterdam arm of the ERSPC showed a reduction in prostate cancer-specific mortality of 32% in the age range of 55–69 years,[20] many men in this age group may choose to have an assessment of their prostate cancer risk. Given the clinically significant disease that is detected by a positive DRE, the authors recommend its use in conjunction with PSA in those men who are appropriately counselled on the risks associated with over-detection of prostate cancer.

Implications for research and practice
DRE is an inexpensive examination and is easy to perform in a clinical setting. This study has demonstrated that a substantial number of patients ultimately diagnosed with high-grade prostate cancer would not have been referred to the RAPC based on their PSA levels alone. DRE adds to the sensitivity and specificity of the PSA and is an integral part of the assessment for the early detection of prostate cancer. The detection of prostate cancer on the basis of DRE alone, coupled with the high concordance of DRE findings between GPs and urologists, supports our message that GPs should always perform DREs as part of their assessment for the early detection of prostate cancer.

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