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Is it time to abandon the digital rectal examination? Lessons from the PLCO Cancer Screening Trial and peer-reviewed literature.

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Key words: Digital rectal examination, prostate cancer, prostate cancer screening, Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial

[Short Title: Time to abandon the DRE]
Abstract:

Objective: In 2012 the US Preventive Services Task Force released recommendations against prostate specific antigen (PSA) based screening for prostate cancer, but did not fully address screening via digital rectal exam (DRE). As such, many practitioners continue to perform DRE in attempts to identify men with clinically significant prostate cancer (CSPC). This study seeks to determine the value of DRE in detecting CSPC in the era of PSA-based screening.

Methods: Data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial, a nationwide population-based study evaluating cancer screening programs and their impact on cancer mortality, was analyzed for PSA, DRE, and cancer status. In the screening arm of the PLCO, 38,340 men received annual PSA and DRE examinations for the first three years. Those with an abnormal test result were referred to their individual care provider for biopsy. The ability of DRE to detect CSPC, defined as intermediate risk or higher based on National Comprehensive Cancer Network guidelines and age ≤ 75, was evaluated in the context of both normal and abnormal PSA.

Results: 5,064 men had abnormal DRE in the setting of normal PSA, of which 99 (2%) were diagnosed with CSPC. When both PSA and DRE were abnormal, 218 (20%) participants were diagnosed with CSPC (RR = 2.06 [1.78-2.39] versus abnormal PSA alone).

Conclusions: DRE screening in the setting of normal PSA captured an additional 2% of men with CSPC. This incremental gain suggests that routine DRE screening subjects a large number of men to invasive, potentially uncomfortable examinations for relatively minimal gain.

Key Limitations: Our conclusions are based on data derived from the PLCO study which has been criticized on the basis of inconsistent biopsies following positive screening tests, lack of end of study biopsies to determine population disease burden, and low numbers of black men.
Introduction:

The United States Preventive Services Task Force (USPSTF) recommendation against routine prostate specific antigen (PSA) based prostate cancer (PCa) screening prompted controversy. Providers have since reduced PSA screening, however, there has been less focus on digital rectal examination (DRE). Prior to PSA screening, DRE was the primary clinical instrument. PSA outperforms DRE in detection of PCa and clinically significant PCa (CSPC). If PSA is used with a threshold of 4.0 ng/mL to prompt biopsy consideration, it is unclear if adding DRE improves CSPC detection.

Others highlight the problematic nature of this “clinical relic”, with thought leaders who supported continued use of DRE stating judgment should be delayed until completion of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). Now completed, the PLCO warrants analysis to determine the utility of DRE for identifying CSPC.

Methods

The PLCO randomized men to the control arm, consisting of usual care, or intervention arm, consisting of initial PSA and DRE during enrollment and annual screening for five years for PSA and three years for DRE. PSA was considered normal (≤4ng/ml) or abnormal (>4ng/ml). DRE was considered normal, abnormal – non-suspicious, or abnormal – suspicious. Participants were followed for up to 13 years.

We identified participants randomized to intervention receiving PSA or DRE in the first three years, the only period when both were performed concurrently. Patients with abnormal PSA or DRE and all men receiving PCa diagnosis following abnormal screen were identified.

Using NCCN PCa guidelines and age at diagnosis, we defined CSPC as a tumor associated with PSA >10ng/ml, Gleason ≥7, or clinical stage ≥T2b in individuals ≤75 years of age.
We analyzed CSPC diagnosis rate following abnormal PSA or DRE in each study year as well as overall, using chi-square. We did not analyze data from years 4 and 5, as there were no DREs for comparison. Analysis of association between Gleason score and PSA or DRE status was via chi-square and ordinal logistic regression.

**Results:**

35,873 men received 129,028 PSAs and 124,694 DREs over the first three years following randomization.

To facilitate discussion, the terms isolated, concordant and discordant are used to define the relationship between PSA and DRE status. For example, an **isolated** abnormal DRE indicates abnormal DRE without considering PSA status. A **concordant** abnormal DRE indicates abnormal DRE and abnormal PSA within one calendar year. A **discordant** abnormal DRE indicates abnormal DRE with normal PSA.

**Isolated PSA**

Of PSA tests, 10,490 (8.1%) were abnormal (>4.0ng/dl) and resulted in 3,422 (32.6% of abnormal screens) biopsies. Biopsies triggered by isolated abnormal PSA identified 1,317 men (38.5% of those biopsied) with PCa, with 680 (19.9% biopsied) considered CSPC. Significantly more CSPC was detected on initial PSA than in any study year (p<.001). Detection rates in subsequent years were not significantly different (Table 1).

**Isolated DRE**

Of DRE tests, 9,362 (7.5%) were abnormal and suspicious for PCa and were associated with 2,024 (21.6% abnormal screens) biopsies. Participants with isolated abnormal DRE were significantly (P<0.05) less likely to receive biopsy than those with isolated abnormal PSA in each study year. Biopsies triggered by isolated abnormal DRE identified 616 men (30.4%
biopsied) with PCa, with 317 (15.6% biopsied) considered CSPC. The rate of PCa detection prompted by DRE did not differ significantly based on study year. However, the rate was significantly lower than that associated with isolated abnormal PSA for each year and overall (p<.01) except for year 2 (p=.12; Table 2).

**PSA vs DRE**

Our analysis reemphasizes superiority of PSA as an independent screen for CSPC compared to DRE. Abnormal PSA led to detection of 680 cases of CSPC vs 317 from abnormal DRE, with most (218/317, 69%) of those also having abnormal PSA. Additionally, isolated abnormal PSA prompted diagnosis of 1 case of CSPC for every 4.4 biopsies while isolated abnormal DRE prompted diagnosis of 1 case of CSPC for every 6 biopsies. However, due to disproportionately smaller percentage of participants receiving biopsies following isolated abnormal DRE vs isolated abnormal PSA, this detection difference meant that 104 men would have to be screened by DRE to detect 1 case of CSPC vs 50 men for PSA.

**Discordant abnormal DRE:**

We examined utility of DRE to detect CSPC missed by PSA. For each study year, roughly 85% of abnormal DRE were associated with normal PSA. A small percentage of these participants were shown to have CSPC on biopsy. The initial year of the study is arguably the best representation of an unscreened population. In this subset, 32,936 men received DRE, to detect 24 cases of CSPC in the setting of normal PSA. This suggests that in normal clinical practice, 1,372 men would require DRE to detect a single case of CSPC missed by PSA. Furthermore, CSPC detection rate in these participants was significantly lower than all other groups (p<0.05, Table 2b).

**Concordant abnormal DRE/PSA:**
There were 1,074 participants with both abnormal PSA and DRE within any given study year. Participants with concordant abnormal DRE were significantly more likely to receive biopsy (p<0.05). In addition, biopsies triggered by concordant abnormal DRE identified 357 men (53.0% of biopsies) with PCa, of which 218 (32.3%) were clinically significant. Biopsies triggered by concordant abnormal DRE and PSA were significantly more likely to detect overall PCa and CSPC than biopsies triggered by either isolated abnormal DRE or isolated abnormal PSA (p<0.05; Table 3).

CSPC

The percentage of high grade CSPC increased in stepwise manner when comparing among discordant abnormal DRE, discordant abnormal PSA, and concordant abnormal DRE/PSA, however this did not reach statistical significance on chi-square analysis (p=.31). Likewise, CSPC identified by discordant abnormal PSA was associated with higher Gleason scores than those identified by discordant abnormal DRE (odds ratio – 1.15 [0.76-1.74]) and CSPC identified by concordant DRE/PSA was associated with higher Gleason score than those identified by discordant abnormal DRE (odds ration – 1.55 (0.98-2.45). However, neither association reached statistical significance by ordinal logistic regression analysis.

Discussion:

This analysis of the PLCO data demonstrates, with normal PSA, the DRE rarely assists diagnosing CSPC. If both are abnormal, chances of biopsy positivity increase, and dual positivity could potentially assist counseling toward biopsy. However, if patients elect screening after ‘shared decision-making’ and PSA was used as intended, biopsy would be recommended regardless of DRE. No data suggests providers grade the strength of their positive recommendations on a scale, although this may be possible.
Andriole et al characterized the baseline round of screening in the PLCO\(^6\). They noted 66 cancers in those with abnormal DRE and PSA <4. \(28/66\) (42\%) were high grade (authors mistakenly say 47\% later in manuscript). DRE positivity at this point was 7.5\%. This was below the 11.6\% DRE positivity Crawford et al.\(^7\) noted in 31,953 men screened in 1993, and below the 9.4\% DRE positivity Smith et al.\(^8\) noted among 19,476 men in the PSA-2 study.

Biopsy positivity from PLCO was 16.6\% for men with suspicious DRE and normal PSA. In Crawford et al, the rate was 14.6\% for abnormal DRE and PSA ≤4. These numbers differ from earlier publications suggesting high-grade cancer in 34\% of Caucasians with abnormal DRE and PSA ≤4 (higher in African Americans)\(^9\).

An analysis similar to ours was performed with ERSPC data, reported by Gosselaar et al\(^{10}\). They reviewed the data recognizing prior reports suggesting abnormal DRE as a risk factor for high grade disease\(^{11,12}\). They reviewed men with an initially suspicious DRE, a PSA ≥ 3, and benign biopsy to determine risk for significant cancer at rescreening than men with initially normal DRE. At 8 years after initial negative biopsy, initially suspicious DRE did not influence the chance for subsequent PCa detection, CSPC or overall.

The ERSPC omitted DRE halfway through the screening phase because sensitivity and PPV of DRE was low at a PSA <4. The authors felt DRE was “controversial” for screening\(^{10}\), and found only a small proportion of men with suspicious DRE were eventually diagnosed with high grade disease. Coincidence may have been an important factor since a substantial proportion had tumor volumes <0.5 mL, making it highly unlikely they were palpable and their exams could be considered false positives. They concluded it unnecessary to rescreen men with initially suspicious DRE earlier or more frequently than men with normal DRE. The data we present seems highly relevant domestically, since PLCO is felt to more closely approximate practice
patterns in the US than ERSPC\textsuperscript{1}. This is important to consider for critics highlighting the low biopsy rate among men with abnormal DRE as a potential confounder.

Our project was not designed nor intended to challenge PCa screening. However, after 13 years, no mortality benefit was seen from screening in PLCO compared with opportunistic screening\textsuperscript{13}. For champions of screening, this may be a welcomed addition to the literature since DRE was already shown to be a barrier to such efforts. Based on surveying 13,580 men, DRE was found to be a significant barrier to participation in screening\textsuperscript{14}. PSA plus DRE-based programs resulted in lower PCa detection, with significant increase in negative biopsies. The authors concluded DRE is nonspecific, has low sensitivity, and has no predictive potential in PCa screening. They suggested future mass screening efforts include only PSA. Philip et al agreed, noting significant disagreement between DRE staging and biopsy, as well as poor correlation between DRE and pathologic stage in men undergoing radical prostatectomy\textsuperscript{15, 16}. In another study, 41\% of African Americans, a group considered at higher risk for CSPC, reported fears of screening-related physical discomfort and embarrassment, which seem justified by other reports\textsuperscript{17-19}.

The DRE is recognized as an imperfect clinical tool within urology. It has poor interobserver reliability, irrespective of experience\textsuperscript{20, 21}. Even when nodules are reportedly detected manually, they correlate poorly with tumor location in biopsy or prostatectomy specimens\textsuperscript{22}.

Screening examinations are supposed to have high sensitivity and PPV. In an earlier meta-analysis, PPV of abnormal DRE was 28\%\textsuperscript{23}. Candas et al looked at 11,811 initial visits and 46,571 annual follow-up visits of Canadians and found if PSA was normal and DRE abnormal at initial visit, subsequent cancer detection rate was only 0.46\%\textsuperscript{24}.

Issa et al previously reported on 628 patients undergoing biopsy for suspected malignancy\textsuperscript{25}. Among men with normal PSA, the adjusted odds ratio between abnormal DRE and positive
biopsy was 0.53 with a 95% confidence interval of 0.27 to 1.06. It wasn’t until PSA exceeded 10 that the CI did not include 1. In this study, the proportion of abnormal DRE results was similar among patients with negative (44%) and positive biopsy (46%). The authors noted the possibility that knowledge of PSA value may bias interpretation of DRE to justify clinical decision making on whether to perform biopsy.

In reviewing ERSPC, Schroder et al noted DRE has “poor performance” in the setting of low PSA. They stated cancers found by DRE in the setting of PSA considered normal by current standards (<4), were often nonaggressive and not likely to be life-threatening. They agreed “the procedure is bothersome and not without danger for participants” and asserted DRE should be replaced with a more sensitive test and should no longer be recommended for routine screening.

In a response, Basler and Thompson were not ready to dismiss DRE, but felt questioning its value was “critical” since it “is certainly not a high-performance screening test”. They further stated “the proof of the relevance of this issue will eventually be established upon the completion of the PLCO”. Interestingly, in a counter-response, Schroder noted the fact that PPV of DRE increased with rising PSA in a blind fashion showed the value of DRE is PSA dependent. This is what we have found in PLCO data as well.

Okotie et al reviewed 303 prostatectomy specimens subsequent to positive biopsies prompted by abnormal DRE alone. Patients were generated from 36,000 men in a screening study from 1989-2001. In this group of DRE-alone positives, 80% were organ confined and 80% were Gleason 2-6, which is problematic since it includes scores no longer considered by many to truly reflect malignancy.

While some may accept the evidence and the argument that DRE should disappear from screening protocols, we suspect many will assert it still has a role in follow-up of patients with
prior PCa diagnosis. DRE is often performed after therapy to evaluate for palpable abnormalities in the gland or fossa to suggest local recurrence or disease progression, but studies show progression does not occur in absence of increasing PSA. Granted, some high-grade cancers may produce little PSA, but the reported discovery of recurrence detected by DRE with undetectable PSA is extremely rare. Some have boldly suggested DRE may be used to justify return clinic visits for financial gain, as omitting this exam may allow for remote follow-up among PCa patients.

Lightner et al evaluated 63 patients with biochemical failure after prostatectomy, 90% of which did not have metastatic disease. Of 30 patients with undetectable PSA after surgery, 18 had a suspicious DRE and underwent biopsy, all of which were negative. This highlights that DRE interpretation is very difficult postoperatively.

No literature supports repeat DRE after radical radiotherapy. Johnstone et al reported on 235 patients after definitive radiotherapy. Of 1,544 DREs performed, 81% were normal. It was determined 200 DREs were needed to find a single recurrent nodule, and all were in context of increasing PSA. Thus, the yield of DRE after radiotherapy was negligible for recurrence.

Likewise, Doneux et al described 899 patients receiving radiation and neoadjuvant ADT for localized disease followed with PSA and DRE for recurrence. Recurrence occurred in 39 patients (4%), none detected by DRE alone.

Another reason often used to justify DRE is predicting gland volume in men with symptoms of benign prostatic hyperplasia (BPH). However, DRE underestimates volume, particularly when >30 grams. Additionally, careful history including a validated questionnaire (e.g., International Prostate Symptom Score) can initiate management. Interestingly, Bosch et al
evaluated 1688 men and found PSA outperforms DRE in estimating if volume is > or < 30, 40, or 50 cc\textsuperscript{37}.

DRE entered into ATLS in 1976 to aid identification of spinal cord injury (SCI), intestinal injury, and urethral disruption. By the 8\textsuperscript{th} version of ATLS, DRE went from an absolute requirement to being “selectively” employed prior to urethral catheterization\textsuperscript{38}. Even among high volume trauma centers, urethral disruption is rare, and, therefore, so is physician exposure. Many experienced clinicians have never felt a ‘high-riding’ prostate, which can be especially difficult to palpate in the setting of a pelvic hematoma\textsuperscript{39, 40}. Sensitivity of DRE for identifying urethral disruption is reported as 2\%\textsuperscript{41}.

Numerous publications suggest omitting DRE from trauma evaluations, adult and pediatric\textsuperscript{42-44}. Porter and Ursic (2001) reported a prospective study of 423 patients visiting a Level 2 trauma center and DRE influenced decision making in only 1.2\%\textsuperscript{45}. Esposito et al (2005) prospectively studied >400 patients at a Level 1 trauma center\textsuperscript{42}. They demonstrated DRE is at best equivalent, and in most cases inferior to other clinical indicators of injury and concluded omission in all trauma patients seems permissible, safe, and advantageous. No index injury would’ve been missed by omitting DRE, and doing so would’ve avoided more false negatives and false positives. They asserted that eliminating routine DRE from secondary survey could conserve time and resources, decrease unpleasant encounters, and protect patients and providers from the potential for further harm.

Similarly, evaluating >1400 patients, Shlamovitz et al found DRE sensitivity for trauma was 23\%\textsuperscript{44}. They concluded an exam missing 77\% of index injuries cannot be supported, noting poor sensitivity for injuries of the spinal cord, bowel, rectum, bony pelvis, and urethra. This group and others report similar conclusions for children\textsuperscript{43, 46}.
Previously, DRE was part of colon cancer screening. As of 2002, the USPSTF no longer advocates this practice\(^47\). They advised home use of guaiac-based cards, and neither DRE nor testing stool obtained during DRE were recommended.

Our findings may be welcomed by patients and providers. An Irish study evaluated frequency of DRE and found reluctance of providers to perform the exam for prostate assessment\(^48\). The National Ambulatory Medical Survey and Veterans Administration data suggests physicians perform significantly less DREs than physician assistants or nurse practitioners\(^49, 50\). PSA was drawn significantly more than DRE was performed (33.1\% vs. 23\%; \(P<0.001\)), and, among veterans, the majority undergoing PSA screening (52.9\%) did not have DRE\(^49,50\). It appears fear predicts frequency of DRE, which is felt to create an atmosphere of vulnerability and humiliation\(^51, 52\). In regard to PCa screening among veterans, DRE is significantly less likely to be performed by residents and in patients with body mass index \(> 40 \text{ kg/m}^2\)\(^53\).

The American Cancer Society continues to recommend PSA (“should be”), but does not require DRE (“may also be”)\(^54, 55\). The American Urological Association states there is no evidence DRE is beneficial and it should not be used as in primary screening, but may potentially be useful as a secondary test in men referred for elevated PSA\(^56\). This varies from the 2009 position, which is cited by the American College of Physicians’ guideline, suggesting revision\(^57\).

Criticisms of PLCO limitations are described elsewhere. Pinsky et al evaluated factors related to biopsy during the first 3 years, based on concern of what appears to be a low biopsy rate\(^58\). They found providers likely adjusted strategy based on age-adjusted PSA. Nonetheless, this study is felt to reflect US practice. Data from PLCO shows men with abnormalities of both PSA and DRE were twice as likely to be diagnosed with CSPC. This seemingly supports the potential role of DRE for secondary evaluation. However, if biopsy is considered based on abnormal
PSA, DRE seems moot. If patients or providers debate on undergoing biopsy and decision-making would be influenced, that would open the door to utility of DRE. This, however, has not been specifically studied.

Conclusions:

DRE is not useful in detecting CSPC in men undergoing PSA screening. It is unreliable, with poor sensitivity and PPV, and a barrier to screening. It fails to provide useful information among men with suspected BPH, trauma patients, and is unnecessary for colon cancer screening. Changes in guidelines reflect data presented. DRE should be abandoned in common clinical practice. We recognize that some providers may still find value of the DRE in select patient populations as it may facilitate an important dialogue about prostate cancer screening. For such situations, we agree that clinical judgment is critical.

Transparency:

Declaration of funding:

No funding was used or necessary for this study.

Declaration of financial/other relationships:

No significant/relevant relationships, financial, employment, or otherwise, exists for any of the authors. CMRO Peer Reviewers on this manuscript have no relevant financial or other relationships to disclose.
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Prior presentation:

References:

9. Fowler JE, Bigler SA, Farabaugh PB. Prospective study of cancer detection in black and white men with normal digital rectal examination but prostate specific antigen equal or greater than 4.0 ng/mL. Cancer 2002 Mar;94(6):1661-7.
52. Consedine NS, Horton D, Ungar T, Joe AK, Ramirez P, Borrell L. Fear, knowledge, and efficacy beliefs differentially predict the frequency of digital rectal examination versus prostate...
Table Legends:

**Table 1:** We analyzed the ability of PSA to detect CSPC with (1a) and without (1b) abnormal DRE data.

**Table 2:** We analyzed the ability of DRE to detect CSPC with (2a) and without (2b) abnormal PSA data. When compared to PSA, DRE diagnosed significantly fewer cases of CSPC initially (p<.0001), at Year 1 (p=.0008), Year 3 (p=.0027), and overall (p<.0001). There was no significant difference for Year 2 (p=.12).

**Table 3:** We analyzed the detection rate for PCa and CSPC in participants with concomitant abnormalities of both DRE and PSA. The detection rate for CSPC in this setting was higher than that prompted by individual abnormalities of either DRE or PSA for each study year (p<.05).

**Table 4:** The distribution of histologic grade differed across screening modalities. An isolated abnormal DRE had the highest rate of detecting PCA with Gleason score ≤6 and the lowest rate of detection PCA with Gleason score ≥9. Percentages presented are out of total CSPC detected by each modality.
Table 1: We analyzed the ability of PSA to detect CSPC with (1a) and without (1b) abnormal DRE data. Significantly more CSPC was detected on initial PSA than in any study year (p<.001).

**Table 1a: Isolated abnormal PSA**

<table>
<thead>
<tr>
<th></th>
<th>Participants receiving PSA</th>
<th>Isolated Abnormal PSA</th>
<th>Number Biopsied</th>
<th>PCa Detected (%)</th>
<th>CSPC Detected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>34,224</td>
<td>2,718</td>
<td>1,106</td>
<td>488 (44)</td>
<td>297 (27)</td>
</tr>
<tr>
<td>Year 1</td>
<td>32,660</td>
<td>2,502</td>
<td>818</td>
<td>297 (36)</td>
<td>143 (17)</td>
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<tr>
<td>Year 2</td>
<td>31,655</td>
<td>2,593</td>
<td>797</td>
<td>267 (34)</td>
<td>117 (14)</td>
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<tr>
<td>Year 3</td>
<td>30,489</td>
<td>2,677</td>
<td>789</td>
<td>265 (34)</td>
<td>123 (16)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>5,768</strong></td>
<td><strong>2,997</strong></td>
<td><strong>1,317 (44)</strong></td>
<td><strong>680 (23)</strong></td>
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**Table 1b: Discordant abnormal PSA**

<table>
<thead>
<tr>
<th></th>
<th>Participants receiving PSA</th>
<th>Discordant Abnormal PSA</th>
<th>Number Biopsied</th>
<th>PCa Detected (%)</th>
<th>CSPC Detected (%)</th>
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<tbody>
<tr>
<td>Initial</td>
<td>34,224</td>
<td>2,320</td>
<td>868</td>
<td>338 (39)</td>
<td>193 (22)</td>
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<tr>
<td>Year 1</td>
<td>32,660</td>
<td>2,188</td>
<td>686</td>
<td>231 (34)</td>
<td>102 (15)</td>
</tr>
<tr>
<td>Year 2</td>
<td>31,655</td>
<td>2,239</td>
<td>649</td>
<td>188 (29)</td>
<td>79 (12)</td>
</tr>
<tr>
<td>Year 3</td>
<td>30,489</td>
<td>2,302</td>
<td>633</td>
<td>202 (32)</td>
<td>88 (14)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>4,694</strong></td>
<td><strong>2,367</strong></td>
<td><strong>960 (41)</strong></td>
<td><strong>462 (20)</strong></td>
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</table>
Table 2a: Isolated abnormal DRE

<table>
<thead>
<tr>
<th></th>
<th>Participants receiving DRE</th>
<th>Abnormal DRE</th>
<th>Number Biopsied</th>
<th>PCa Detected (%)</th>
<th>CSPC Detected (%)</th>
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<tbody>
<tr>
<td>Initial</td>
<td>32,936</td>
<td>2480</td>
<td>630</td>
<td>211 (33)</td>
<td>128 (20)</td>
</tr>
<tr>
<td>Year 1</td>
<td>31,547</td>
<td>2237</td>
<td>495</td>
<td>133 (27)</td>
<td>69 (14)</td>
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<tr>
<td>Year 2</td>
<td>30,716</td>
<td>2327</td>
<td>460</td>
<td>153 (33)</td>
<td>65 (14)</td>
</tr>
<tr>
<td>Year 3</td>
<td>29,495</td>
<td>2318</td>
<td>439</td>
<td>120 (27)</td>
<td>55 (13)</td>
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<tr>
<td>Overall</td>
<td>6138</td>
<td>1911</td>
<td>616 (32)</td>
<td>317 (17)</td>
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Table 2b: Discordant Abnormal DRE

<table>
<thead>
<tr>
<th></th>
<th>Participants receiving DRE</th>
<th>Discordant Abnormal DRE</th>
<th>Number Biopsied</th>
<th>PCa Detected (%)</th>
<th>CSPC Detected (%)</th>
</tr>
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<tbody>
<tr>
<td>Initial</td>
<td>32,936</td>
<td>2,082</td>
<td>392</td>
<td>61 (16)</td>
<td>24 (6)</td>
</tr>
<tr>
<td>Year 1</td>
<td>31,547</td>
<td>1,923</td>
<td>363</td>
<td>67 (18)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Year 2</td>
<td>30,716</td>
<td>1,973</td>
<td>312</td>
<td>74 (23)</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Year 3</td>
<td>29,495</td>
<td>1,943</td>
<td>283</td>
<td>57 (20)</td>
<td>20 (7)</td>
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<tr>
<td>Overall</td>
<td>5,064</td>
<td>1,281</td>
<td>259 (20)</td>
<td>99 (8)</td>
<td></td>
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</table>

Table 2: We analyzed the ability of DRE to detect CSPC with (2a) and without (2b) abnormal PSA data. When compared to PSA, DRE diagnosed significantly fewer cases of CSPC initially (p<.0001), at Year 1 (p=.0008), Year 3 (p=.0027), and overall (p<.0001). There was no significant difference for Year 2 (p=.12).

Table 3: Concordant Abnormal DRE and PSA

<table>
<thead>
<tr>
<th></th>
<th>Participants receiving DRE</th>
<th>Abnormal DRE and PSA</th>
<th>Number Biopsied</th>
<th>PCa Detected (%)</th>
<th>CSPC Detected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>32,907</td>
<td>398</td>
<td>238</td>
<td>150 (63)</td>
<td>104 (44)</td>
</tr>
<tr>
<td>Year 1</td>
<td>31,520</td>
<td>314</td>
<td>132</td>
<td>66 (50)</td>
<td>41 (31)</td>
</tr>
<tr>
<td>Year 2</td>
<td>30,686</td>
<td>354</td>
<td>148</td>
<td>79 (53)</td>
<td>38 (26)</td>
</tr>
<tr>
<td>Year 3</td>
<td>29,449</td>
<td>375</td>
<td>156</td>
<td>63 (40)</td>
<td>35 (22)</td>
</tr>
<tr>
<td>Overall</td>
<td>1,074</td>
<td>630</td>
<td>357 (57)</td>
<td>218 (35)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: We analyzed the detection rate for PCa and CSPC in participants with concomitant abnormalities of both DRE and PSA. The detection rate for CSPC in this setting was higher than that prompted by individual abnormalities of either DRE or PSA for each study year (p<.05).
<table>
<thead>
<tr>
<th></th>
<th>≤6</th>
<th>7</th>
<th>8</th>
<th>≥9</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discordant Abnormal DRE</td>
<td>30  (30%)</td>
<td>57  (58%)</td>
<td>8  (8%)</td>
<td>4  (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Discordant Abnormal PSA</td>
<td>131 (28%)</td>
<td>254 (55%)</td>
<td>50 (11%)</td>
<td>22 (5%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Concordant Abnormal DRE and PSA</td>
<td>53 (24%)</td>
<td>118 (54%)</td>
<td>27 (12%)</td>
<td>19 (9%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Table 4: The distribution of histologic grade differed across screening modalities. An isolated abnormal DRE had the highest rate of detecting PCA with Gleason score ≤6 and the lowest rate of detection PCA with Gleason score ≥9. Percentages presented are out of total CSPCA detected by each modality.