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Utility of Digital Rectal Examination (DRE) as an Adjunct to Prostate Specific Antigen (PSA) in the Detection of Clinically Significant Prostate Cancer

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Abstract

Purpose—Guidelines from the National Cancer Care Network (NCCN) advocate digital rectal examination (DRE) screening only in men with elevated prostate specific antigen (PSA). We sought to investigate the effect of PSA on the association between DRE and clinically significant prostate cancer (CSPC) in a large, US cohort.

Materials and Methods: Men who underwent DRE (n=35,350) within the screening arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial were evaluated for development of CSPC (Gleason ≥ 7) with follow-up of 343,273 person-years. The primary outcome was rate of CSPC among men with and without suspicious DRE. We performed competing-risks regression to evaluate the interaction between time-varying suspicious DRE and PSA.

Results: 1,713 CSPCs were detected with 10-year cumulative incidence of 5.9% (95% confidence interval [CI] 5.6%, 6.2%). Higher risk was seen among suspicious vs. non-suspicious DRE. Increases in absolute risk were small and clinically irrelevant for normal (<2 ng/mL) PSA (1.5% vs 0.7% risk of CSPC at 10 years), clinically relevant for elevated (≥3 ng/mL) PSA (23.0% vs 13.7%), and of modest clinical relevance for equivocal (2–3 ng/mL) PSA (6.5% vs 3.5%).

Conclusions: DRE demonstrated prognostic utility when PSA >3, limited utility when PSA <2, and marginal utility for PSA 2–3. These findings support restriction of DRE to men with higher PSA as a reflex test to improve specificity. It should not be used as a primary screening modality to improve sensitivity.

Keywords

digital rectal examination; early detection of cancer; prostate cancer; prostate-specific antigen

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Introduction

The landscape of prostate cancer screening and diagnosis in the United States has evolved dramatically over the past decade. These changes have led to reverse stage migration in prostate cancer as patients now present with higher grade and stage disease.(1, 2) In this setting, researchers and policy makers have reevaluated the role of screening and methods of implementation in order to alter the epidemiological trends toward higher-risk disease.

One aspect of prostate cancer screening that remains unsettled is the role of digital rectal examination (DRE). DRE was the fundamental component of prostate cancer screening regimens prior to widespread dissemination of prostate specific antigen (PSA).(3) By the 1990s, regimens consisting of both DRE and PSA were often used, with prostate biopsy recommended if either was abnormal.(4) However, concerns regarding insensitivity of DRE for screening were ultimately recognized in the European Randomized Study of Screening for Prostate Cancer (ERSPC), which abandoned DRE as a primary screening tool due to inefficiency of DRE for cancer detection during initial stages of the trial.(5, 6) Subsequent ERSPC data revealed that abnormal DRE was associated with prostate cancer in the setting of elevated PSA, yet the role of DRE in the setting of normal PSA remained understudied.(7, 8) This is reflected in the conflicting guidelines regarding use of DRE – the American Urological Association (AUA) found no evidence in support of DRE whereas the National Cancer Care Network (NCCN) advocated DRE screening only in those men with elevated PSA.(9, 10)

We recently reported that DRE was associated with the detection of CSPC, independent of PSA levels.(11) Given this finding, two distinct roles for DRE within prostate cancer screening protocols are possible: 1. a primary screening test to improve the sensitivity of PSA, or 2. a reflex test to improve its specificity. To determine whether either, both or neither of these approaches are clinically useful, we investigated the effect of serum PSA levels on the association between DRE and subsequent detection of clinically significant prostate cancer (CSPC) in a large, nationally representative cohort.

Methods

Data Source and Study Population

We analyzed all men who underwent DRE (n=35,350) as part of the screening protocol of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial. The PLCO trial is a multi-institutional, randomized controlled trial of prostate cancer screening that has been described previously.(12) Briefly, from 1993 through 2001, men aged 55 to 74 years old were randomized to routine prostate cancer screening with DRE and PSA or usual care. Men in the screening arm underwent annual DRE and PSA for the first four and six years of the trial, respectively. As information on DRE in men in the usual care arm was not recorded as part of the trial, these men were excluded from the current analysis. Following a positive screening test (elevated PSA or positive DRE), the subsequent diagnostic and therapeutic course of each man was determined by his individual physician. Follow-up was available for thirteen years after trial initiation, throughout which study coordinators actively tracked trial

participants' screening test results, medical records, diagnostic evaluations, treatments, and oncologic endpoints.

Study Variables

The primary independent variable was the presence or absence of suspicious abnormality on DRE by the screening clinician (physician, physician assistant, or nurse).(13) DRE was considered positive or "suspicious" in the presence of induration, nodularity, significant asymmetry or loss of anatomic landmarks as determined by the examiner.(12) Quality assurance protocols selected certain men for repeat DRE at the same screening encounter by an independent examiner. In the event of discordant results, an individualized screening outcome and diagnostic course was determined for each patient. Examiners were blinded to PSA results, as blood draws were typically performed prior to and within a two-hour window of examination.(12)

Our primary endpoint was detection of CSPC (Gleason score ≥ 7, Gleason grade group ≥2). Gleason score was determined using the highest pathological grade among all tissue samples for each subject, with 54% and 46% of Gleason scores resulting from biopsy and radical prostatectomy, respectively.

DRE is an indication for biopsy, raising the possibility of verification bias. Two factors mitigate this being a strong effect in the current study. First, men with positive DRE and negative PSA had a biopsy rate of just 27% within 3 years of the examination, suggesting that DRE was not a strong indication for biopsy.(13) Second, our endpoint of CSPC is less subject to verification bias because it is less prone to overdiagnosis.

Statistical Analysis

We performed age-adjusted competing-risks regression analysis to evaluate the relationship between DRE and PSA and detection of CSPC using Fine and Gray models.(14) Both ever suspicious DRE and highest PSA to date were considered time-varying variables across all four screening encounters for each patient.

Patients were categorized throughout follow-up according to their latest DRE and PSA status. At the time of first screening, patients were categorized by the result of the DRE screening, and those with a suspicious DRE remained in this category for the duration of follow up. If and when a patient with an initial non-suspicious DRE had a suspicious finding, they were transferred to the suspicious group for the remainder of the study. If a patient who had not had a suspicious DRE missed a screening, they were removed from the analysis until the following screening. Similarly, for PSA, patients were categorized by their initial PSA level, and if a subsequent PSA was higher they were moved to a new category. After the fourth screening, patients remained in the same category throughout follow-up.

Cumulative incidence of CSPC was characterized for patients according to DRE status and stratified by PSA level into three groups: normal (< 2 ng/ml), equivocal (≥ 2 and < 3 ng/ml), and elevated (≥ 3 ng/ml). Using these models stratified by PSA levels, cumulative incidence curves were constructed and 10-year relative risks of CSPC for suspicious DRE were determined.

Statistical analyses were performed using the R statistical package (v.3.2.3), and were two-sided with a significance level set at 0.05 and confidence intervals presented at a 95% level. Bootstrapping methods were used to determine confidence intervals for model-based estimates.

Results

With follow-up of 343,273 person-years, 1,713 CSPCs were detected in 35,350 men (Table 1). Overall 10-year cumulative incidence of CSPC was 5.9% (95% confidence interval [CI]. 5.6% to 6.2%). As previously reported, suspicious DRE and higher PSA were both associated with higher risk of CSPC.(11) There was a statistically significant interaction between PSA and DRE, as suspicious DRE was associated with a smaller increase in the relative risk of CSPC in men with higher PSA compared to those with lower PSA ($p<0.001$).

Ten year cumulative incidence of CSPC was higher among those with suspicious vs non-suspicious DRE across all PSA level categories (Figure 1). When stratifying according to PSA grouping, cumulative incidence of CSPC remained higher among those with suspicious vs non-suspicious DRE across all PSA groups ($p<0.001$ for all analyses Table 2, Figure 2): normal (1.5% vs 0.73), equivocal (6.5% vs 3.5), and elevated (23% vs 14%). In relative terms, there was a 2.1 (95% CI 1.6–2.6), 1.9 (1.5–2.9), and 1.7 (1.6–2.0) fold increase in cumulative incidence of CSPC comparing those with suspicious to those with non-suspicious DRE across the three PSA groups, respectively. In absolute terms, suspicious DRE was associated with 0.8% (bootstrap 95% CI 0.4%−1.0%), 3.0% (1.9%−4.0%), and 9.3% (7.8%−10.6%) absolute increases in the cumulative incidence of CSPC across the three PSA groups, respectively. Subgroup analysis stratified by pathology source (biopsy only or prostatectomy), and in African Americans showed similar trends (Supplemental Tables 1–3).

Discussion

DRE was the fundamental component of prostate cancer screening regimens during the initial wave of population-based screening in the 1980s.(3) With widespread dissemination of PSA testing in subsequent decades, the national discourse regarding prostate cancer screening has been dominated by PSA, culminating with the results and controversy surrounding the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.(15, 16) As researchers and policy makers have focused on optimizing PSA for screening, the role of DRE has remained largely understudied. As mentioned above, the 2013 AUA guideline on the early detection of prostate cancer suggested that DRE may be useful as an adjunct to PSA in determining need for prostate biopsy but that sufficient evidence was lacking.(9) In contrast, the 2016 NCCN guideline recommended DRE use but only in those men with elevated PSA, while also noting that DRE may be considered as a baseline test in all patients due to its ability to detect high-grade cancer in the absence of PSA elevation.(10) Given the lack of consensus regarding the utility of DRE for prostate cancer screening, we sought to evaluate the relationship between PSA and DRE in a large, multi-institutionalcohort from the PLCO trial.

Our study has a number of important findings. First, suspicious DRE was associated with higher risk of CSPC across all PSA levels. Prior randomized trials demonstrated correlation between abnormal DRE and CSPC, though these studies generally did not investigate the interaction between DRE and PSA.(8, 17, 18) Cui et al. also demonstrated a relationship between DRE, PSA, and CSPC in the PLCO trial, though competing risks were not considered and the interaction of DRE and PSA was not evaluated.(19) The current study expands upon these data in demonstrating elevated risk of CSPC among men with suspicious DRE across all PSA categories.

Second, suspicious DRE was associated with a significantly increased relative and absolute risk of CSPC among men with elevated PSA (≥ 3 ng/mL). Men presenting with elevated PSA and suspicious DRE had a 9% higher cumulative incidence of CSPC compared to those with non-suspicious DRE. This risk increase is consistent with findings from Gosselar et al. that men in the ERSPC with abnormal DRE and PSA ≥ 3 ng/ml had increased risk of CSPC compared to those with normal DRE (positive predictive value 49% vs 22%).(8) Given this substantial risk difference, DRE can improve clinical decision-making for men with elevated PSA who are unsure whether to pursue prostate biopsy.

Third, DRE was of lesser clinical value in men with normal or equivocal PSA, in whom the absolute risk of CSPC is low. The role of DRE in this subgroup of patients has been hitherto unclear in the era of PSA screening. The ERSPC was initially designed to examine the utility of DRE in the setting of normal PSA, however a change in study protocol based upon preliminary data led to the avoidance of DRE (and prostate biopsy) in men with PSA < 3 ng/mL.(5) In the PLCO trial, we demonstrate that the *relative* risk of CSPC among men with non-elevated (normal or equivocal) PSA and suspicious DRE was 1.9–2.1 fold greater compared to those with non-suspicious DRE. However, the *absolute* risk difference between these groups was minor, merely 1% and 3%, respectively. While statistically significant, this difference is unlikely to influence clinical decision making.

The current study supports and expands upon previously published results from the Prostate Cancer Prevention Trial (PCPT).(20, 21) This data showed that the absolute risk of high grade cancer associated with a positive DRE is higher as PSA increases. For example, a 65 year old Caucasian male with no prior biopsy, PSA 2 ng/mL, and negative vs positive DRE has a 3% vs 5% risk of high grade cancer on biopsy, which translates to a 2% absolute risk increase for positive DRE. However, the same patient with a higher PSA 4 ng/mL and negative vs positive DRE has a 6% vs 9% risk of high grade cancer on biopsy, which translates to a 3% absolute risk increase for DRE. Our findings expand upon these data by demonstrating that differences in absolute risk associated with DRE persist beyond the immediate biopsy result and translate into long-term prognosis for development of high risk cancer.

Our findings, along with historical data, reaffirm the NCCN guidelines, suggesting that DRE may be best used as a follow-up and adjunct test in men with elevated PSA. Based on this data, we recommend that screening be conducted in two separate stages. First, primary care physicians would draw blood for PSA assays in men who have opted to undergo PSA testing after shared decision making. Second, in the setting of an elevated PSA (e.g. > 3 ng/mL, **or**

perhaps a lower cutoff in younger men if deemed appropriate), the patient would be referred to an urologist, at which point the urologist would conduct a DRE to inform the decision regarding pursuit of biopsy. This schema restricts the number of men undergoing an invasive test, ensures that the test is conducted by a specialist with appropriate experience, and avoids unnecessary referrals and testing in men with low PSA and positive DRE, who have a low risk of aggressive disease.

Our results must be interpreted within the context of the study design. First, we evaluated all screening encounters in aggregate in order to assess DRE and PSA as time-varying variables. However, this precluded any distinction between the prognostic significance of initial vs subsequent DRE, which has been previously demonstrated.(8) Second, DRE in the PLCO trial was performed by either physicians or screening clinicians (physician assistant or nurse) who were trained and supervised by a licensed physician, typically an urologist. (13, 22) It is unknown how the reproducibility and sensitivity of DRE performed by community urologists compares to use in the PLCO. Third, detection of CSPC in the PLCO trial is confounded by rate of biopsy, as no standard protocol for performance of biopsy existed within the trial. As noted previously, the 27% biopsy rate among men with positive DRE and normal PSA in the trial is protective against verification bias in the current study. That said, this low biopsy rate may have also resulted in under detection of CSPC in this cohort, thereby underestimating the clinical utility of DRE for men with normal PSA.(13) Fourth, due to the age restrictions of men in the PLCO trial, our data may not be generalizable to younger men who pursue screening. In these men, alternate PSA cutoffs may be appropriate, and the role of DRE must be further refined.

Conclusion

In a retrospective analysis of data from the PLCO trial, suspicious DRE was significantly associated with CSPC across all PSA levels. DRE demonstrated substantial prognostic utility for PSA >3, limited clinical utility when PSA <2, and some benefit in the setting of equivocal PSA 2–3. These findings provide support for the NCCN guideline recommendation to restrict DRE to men with higher PSA as a follow-up test to improve specificity. DRE should not be used as a primary screening modality. Further research is warranted on the value of DRE in men with equivocal PSA 2–3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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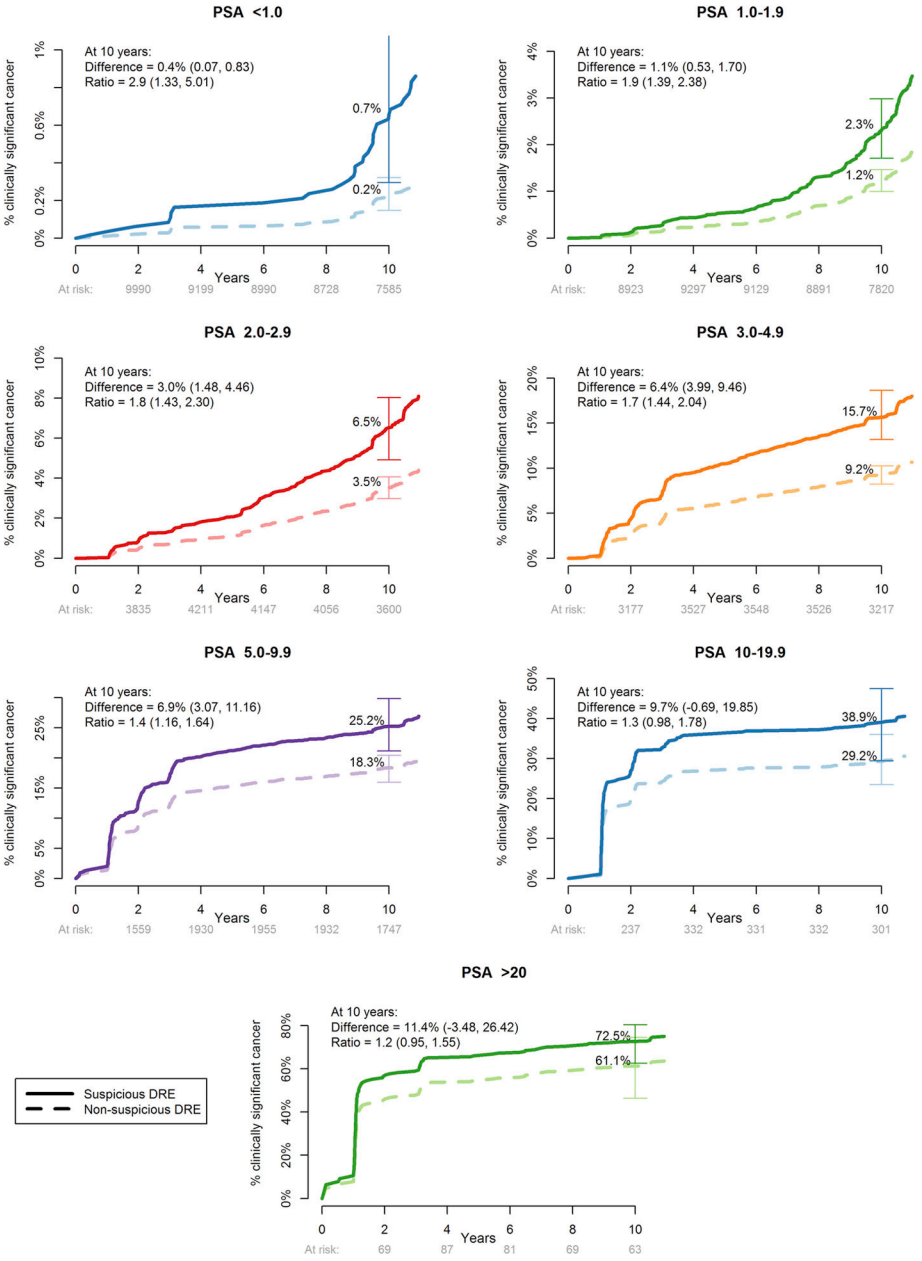

Figure 1 –.

Cumulative incidence of clinically significant prostate cancer (CSPC) by prostate-specific antigen (PSA) level at most recent screen

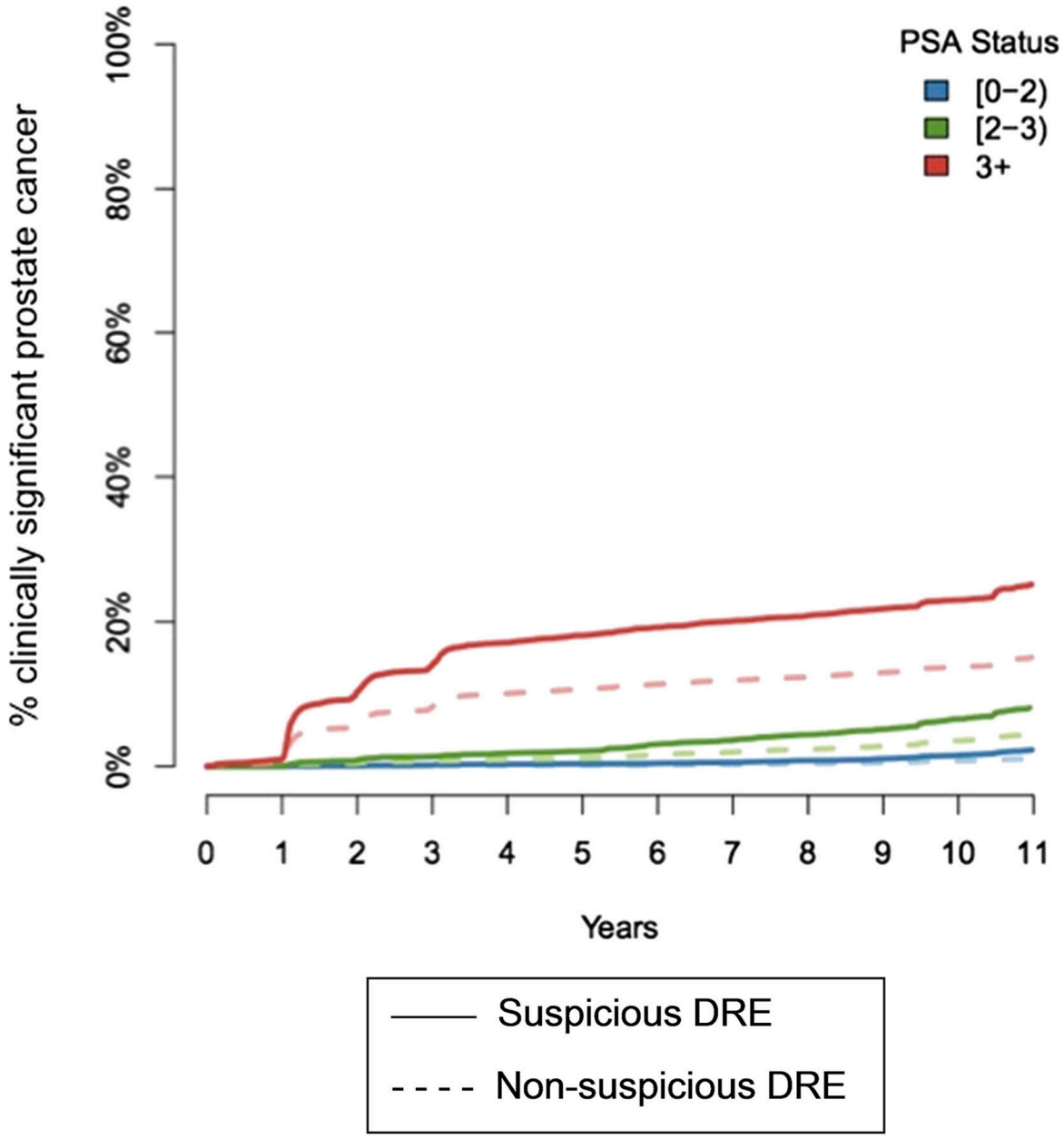

Figure 2 –.

Cumulative incidence of clinically significant prostate cancer (CSPC) according to clinical prostate-specific antigen (PSA) level grouping at most recent screen

Table 1:

Baseline characteristics and prostate cancer outcomes of men in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial who underwent digital rectal examination (N=35,350).

	Overall
N	35,350
Age	62 [58,67]
Race	
White, Non-Hispanic	31,084 [89%]
Black, Non-Hispanic	1,527 [4.3%]
Hispanic	726 [2.1%]
Other	1,692 [4.8%]
NA	321 [0.9%]
Disposition at end of study	
Censored	30,498
Death from other cause	4757
Prostate cancer death	95
Gleason score	
2–6	2,346 [6.6%]
7	1,296 [3.7%]
8+	417 [1.2%]
No cancer	31,291 [88%]

Continuous variables present median [interquartile range] and categorical variables present N [%].

Table 2:

Absolute and relative risk of clinically significant prostate cancer among men with suspicious digital rectal examination (DRE) stratified according to prostate-specific antigen (PSA) levels

	Cumulative cancer incidence			Cancer risk for suspicious vs non-suspicious DRE	
PSA (ng/mL)	Suspicious DRE	Non-suspicious DRE	p-value	Absolute (%)	Relative
<2	1.5(1.0–1.8)	0.7 (0.6–0.9)	<0.001	0.8(0.4–1.0)	2.1 (1 7–2.4)
>2, <3	6.5 (5.6–7.7)	3.5 (3.2–3.9)	<0.001	3.0(1.9–4.0)	1.9(1 5–2.2)
>3	23(21–25)	13(13–14)	<0.001	9.3(7.9–10)	1.7(16–1.8)

10-year cumulative incidence presented as % (95% confidence interval).