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ORIGINAL RESEARCH

Ten-Year Trends in Digital Rectal Exam Results and Prostate Cancer Detection: Insights from the PLCO Trial

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Objective: Digital Rectal Examination (DRE) remains an important preventive measure in primary care settings, but a single screening may produce false positives. We sought to explore the trend of abnormal DRE (suspicious and non-suspicious) findings in men with and without prostate cancer.

Methods: We utilized data on 34,756 men (1,713 Black and 33,043 White) from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Serial DRE measurements were collected over a 10-year follow-up prior to prostate cancer diagnosis. DRE results were categorized as: normal, abnormal non-suspicious, and suspicious DRE. Generalized estimating equation (GEE) model was used to evaluate the trend in suspicious DRE findings over time.

Results: After adjusting for potential confounders, the interaction term of time to diagnosis and prostate cancer status was statistically significant indicating a 23.0% increase in the odds of suspicious DRE (OR=1.230, 95% CI: 1.193–1.268) and a 5.2% increase in the odds of non-suspicious DRE (OR=1.052, 95% CI: 1.033–1.072) per year closer to diagnosis. The positive predictive value of abnormal suspicious DRE was 4.74% at 10 years prior to diagnosis, 36.82% at 5 years prior to diagnosis, 60.63% at 2 years prior to diagnosis, and 90.48% at diagnosis. Older age and benign prostatic hyperplasia (BPH) were more likely to have increased suspicious DRE findings.

Conclusion: Our results suggest that incorporating serial DRE findings into screening strategies may reduce false positives and improve early detection of clinically significant prostate cancer. This study demonstrates a rising probability of abnormal DRE findings in men with prostate cancer, whereas no temporal change was observed in men without prostate cancer.

Keywords: prostate malignancy, DRE findings, prostate cancer detection, primary care physician

Introduction

Digital Rectal Exam (DRE) is a medical procedure where a lubricated gloved finger is inserted into the rectum to check for abnormalities, enlargements, lumps, tenderness, and hardness in the prostate, rectum, and pelvis.[1] Since the DRE only reaches the back wall of the prostate glands, the anomaly of the front and middle parts of the prostate gland cannot be ascertained. As these areas of the prostate are not accessible from outside the body, the utility of a single DRE has been questioned in screening for prostate cancer, as it is considered less reliable than Prostate Specific Antigen (PSA) blood test.[1–3] A meta-analysis of 8 studies with 85,798 participants showed that the positive predictive value (PPV) of DRE and PSA are approximately the same: 0.21 (95% CI = 0.13–0.33) and 0.22 (95% CI = 0.15–0.30), respectively, with no additional benefit observed when combining DRE and PSA (PPV = 0.22, 95% CI = 0.13–0.26).[4] This meta-analysis concluded that the cancer detection rate was lower for DRE than PSA.

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Since early-stage prostate cancer is typically asymptomatic, both DRE and PSA tests are used for screening. The existing guidelines for DRE screening were developed in conjunction with PSA testing through randomized trials to enhance biopsy decision-making. For instance, the US Preventive Services Task Force (USPSTF) recommends biennial DRE in conjunction with PSA testing for men with hypogonadism and for those with PSA less than 2.5 ng/mL.[5,6] The National Comprehensive Cancer Network (NCCN) recommends a prostate biopsy if the PSA value exceeds 3.0 ng/mL or if the DRE result is very suspicious.[7] The American Urological Association (AUA) advises that clinicians should consider performing DRE on patients with PSA levels of 2 ng/mL or higher to assess the risk of clinically significant cancer.[8] However, the USPSTF does not recommend DRE as a standalone screening for prostate cancer despite cases where DRE has found prostate cancers in men with normal PSA levels.[5] In contrast to the USPSTF, the German Statutory Early Detection Program has recommended stand-alone DRE for prostate cancer screening on 45+ years old male since 1971.[9] DRE is also a part of clinical assessment tools such as European Randomized Study of Screening for Prostate Cancer.[10] However, a multicentric randomized trial enrolling more than 46,000 men aged 45 years old to test for risk-adapted PSA screening for prostate cancer found that the stand-alone DRE screening for prostate cancer is poor because it also does not improve the detection of PSA-screen-detected prostate cancer and may not be recommended as a screening test for younger men.[9] According to this randomized trial, out of 57 men with a suspicious DRE at the age of 45 years old, only 3 had actual prostate cancers. The calculated DRE detection rate was 0.05% (3/6537) compared with the 4x higher detection by 0.21% PSA screening (48/23301).[9] The current study utilized trend analysis to detect abnormal DRE patterns, providing insights that may decrease the chance of false positives.

A meta-analysis of seven studies with 9,241 patients estimated the pooled sensitivity, specificity, and PPV of DRE to be 51%, 59%, and 41%, respectively.[11] This meta-analysis recommends against routine DRE screening in the primary care setting. However, the majority of primary care physicians in Canada are routinely using DRE in the primary care setting and 38% of 955 physicians believe that DRE provides a survival benefit.[12,13] In the United States, despite the impact of USPSTF guidelines on clinical practice, DRE is performed routinely by 84% of primary care physicians, particularly among men aged 50 and older.[14] Until now, DRE remains to be an acceptable procedure as a standard of care in urology clinics.[15]

We presented numerous studies that have shown stand-alone DRE has poor performance in detecting prostate cancer in primary care settings. We hypothesize that long-term follow-up such as serial DRE testing in which repeated suspicious results might improve DRE detection rate.[5,16] In this study, we utilized data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial[17] to evaluate whether long-term DRE screening offers crucial information for early detection of prostate cancer. This study examines 10-year trends of suspicious DRE findings among PLCO participants who were diagnosed or not diagnosed with prostate cancer. We theorize that the likelihood of suspicious DRE would change over time depending on prostate cancer status.

Materials and Methods

Study Population

A secondary analysis was conducted in the intervention arm from the PLCO Cancer Screening Trial.[17] For this prospective study, participants aged 55–74 years were recruited from the US general population and randomly assigned to the intervention arm or the control arm at 10 clinical centers between November 1993 and July 2001.[18] There was a nearly even split with 38,338 in the control arm that offered the standard care to participants and 38,340 in the intervention arm that underwent prostate cancer screening tests (total = 76,678). The PLCO trial was conducted in accordance with the Declaration of Helsinki. All participants were given informed consent, and the research was approved by the institutional review boards of all the 10 participating centers and the US National Cancer Institute (NCI). This study received approval (PLCO-1141) from the NCI to access deidentified data sets. PLCO trial design and methodology have been published previously.[19]

Study Inclusion and Exclusion

The PLCO Cancer Screening Trial includes participants who meet the eligibility criteria, and they receive either usual care as the control (N=38,338) or annual screening (N=38,340).[19] The usual care arm was excluded from the analysis due to the lack of DRE screening[19] and excluded missing race (N=914). Due to the small sample sizes of some ethnic groups, we restricted the study to black and white and excluded all other races. Therefore, our final analytic file contains 34,756 male participants.

Measurements

DRE Measurement

Participants in the screening arm were screened annually using DRE at four visits. Thus, there were four DRE exams (T0–T3) before and at diagnosis among the 34,756 participants who completed at least one of the screenings. To maintain quality assurance, a sample of men were selected for a second DRE by an independent examiner during the same screening session. In cases of discordant results, personalized screening outcomes and diagnostic paths were assigned for each patient.[19] Participants with a suspicious DRE were advised to seek diagnostic follow-up care from their primary care providers.[18] The DRE findings ranged from 1 (negative), 2 (abnormal, suspicious), 3 (abnormal, non-suspicious), 4 (inadequate screen), 8 (not done, expected), and 9 (not done, not expected). The DRE findings for this study were classified into: 0 (normal), 1 (abnormal non-suspicious), and 2 (abnormal suspicious). DRE codes 4, 8, and 9 were treated as missing. We analyzed the DRE findings over a 10-year period before and at the prostate cancer diagnosis (positive/negative). The 10-year follow-up adequately demonstrates changes in DRE findings, as men who underwent DRE within 10 years of diagnosis experienced a significant reduction of prostate cancer-specific mortality.[20] We defined the time at DRE result as the years before a positive or negative prostate cancer diagnosis (+ or -), where "0" represents the DRE result at the time of diagnosis (+ or -), and "-10" represents the DRE result "10" years prior to the diagnosis (+ or -). This calculation was based on days from randomization until the DRE test at each visit and days from randomization to a positive (+) or negative (-) prostate cancer.

Covariates

We included baseline data, such as participant age at randomization, body mass index (BMI) defined as weight (kg) divided by height (m^2), education level (college degree: no, yes), race (Black, White), marital status (married: no, yes), frequent urination (defined as urinating three or more times a night: no, yes), immediate family history of prostate cancer (no, yes), and enlarged prostate or benign prostatic hypertrophy (BPH) (no, yes). The PLCO screening trial confirmed prostate cancer diagnoses via medical record abstraction such as a self-report of prostate cancer, death certificate indicating prostate cancer, and relative information to the screening center of the participant's cancer. The assessment includes the question "does the participant have confirmed primary invasive prostate cancer diagnosed during the trial?": 0 = "no confirmed prostate cancer" and 1 = "confirmed prostate cancer".

Statistical Analyses

All data analyses were executed in SAS version 9.4 (SAS Institute Inc, Cary NC, United States). Numerical variables (age at randomization and baseline BMI) were presented as mean ± standard deviation (SD) and non-numerical variables (eg, race and education) were presented as count and percentage (Table 1). Proportions of normal, abnormal non-suspicious DRE, and abnormal suspicious DRE were compared across the sample characteristics using the Chi-square test (Tables 2–5). ANOVA test was used to compare age at randomization and baseline BMI across DRE findings (Tables 2–5). We modeled DRE results over a 10-year follow-up as binary outcomes: abnormal non-suspicious DRE vs normal DRE and abnormal suspicious DRE vs normal DRE. The trend in log odds ratio of abnormal DRE findings was modeled using repeated binary logistic regression via generalized estimating equation (GEE) with the exchangeable regression structure (LOGOR = EXCH). We examined the interaction effect, defined as the combination of follow-up year to diagnosis and prostate cancer status (+ or -) on the likelihood of having an abnormal non-suspicious DRE and an abnormal suspicious DRE, using normal DRE as the reference category. The model adjusted for age, education, marital status, baseline BMI, frequent urinating, family history, and BPH (Table 6). The results were presented in terms of

Table 1 Sample Characteristics (N = 34,756 Participants)

		n	%
Prostate Cancer	No	30476	87.7
	Yes	4280	12.3
DRE screening at the baseline visit (T0)	Normal	14998	49.0
	Abnormal DRE, non-suspicious	13268	43.3
	Abnormal DRE, suspicious	2361	7.7
DRE screening at visit 1 (T1)	Normal	12604	43.2
	Abnormal DRE, non-suspicious	14450	49.5
	Abnormal DRE, suspicious	2126	7.3
DRE screening at visit 2 (T2)	Normal	11334	40.0
	Abnormal DRE, non-suspicious	14806	52.2
	Abnormal DRE, suspicious	2220	7.8
DRE screening at visit 3 (T3)	Normal	10121	37.2
	Abnormal DRE, non-suspicious	14864	54.7
	Abnormal DRE, suspicious	2213	8.1
Race	White	33043	95.1
	Black	1713	4.9
College	No	20536	59.1
	Yes	14220	40.9
Married	No	5959	17.2
	Yes	28797	82.9
Frequent urination	No	31382	90.3
	Yes	3374	9.7
Immediate Family	No	31279	92.3
	Yes	2612	7.7
BPH	No	26965	77.7
	Yes	7760	22.4
		Mean	SD
Age at randomization		62.7	5.3
Baseline BMI		27.6	4.2

Abbreviations: DRE, Digital Rectal Examination; BPH, Enlarged prostate or benign prostatic hypertrophy.

Table 2 Assessing the Association Between DRE Findings and Sample Characteristics at the Baseline Visit (T0) (N= 34,756 Participants)

		DRE Screening at the Baseline Visit (T0)						
		Normal		Abnormal, Non-suspicious		Abnormal, Suspicious		p-value
		n	%	n	%	n	%	
Age at randomization, mean SD		62.4 ± 5.2		62.8 ± 5.4		64.2 ±5.3		<0.001
Race	White	14287	48.7	12,764	43.5	2260	7.7	<0.001
	Black	711	54.0	504	38.3	101	7.7	
College	No	8629	48.5	7832	44.0	1324	7.4	0.005
	Yes	6369	49.6	5436	42.3	1037	8.1	

(*Continued*)

Table 2 (Continued).

		DRE Screening at the Baseline Visit (T0)						
		Normal		Abnormal, Non-suspicious		Abnormal, Suspicious		p-value
		n	%	n	%	n	%	
Married	No Yes	2602 12396	51.4 48.5	2034 11,234	40.2 43.9	430 1931	8.5 7.6	<0.001
Baseline BMI, mean SD		27.5 ± 4.1		27.5 ± 3.9		26.9 ±4.0		<0.001
Frequent urination	No Yes	13744 1254	49.4 44.9	12,004 1264	43.1 45.3	2087 274	7.5 9.8	<0.001
Immediate Family	No Yes	13504 1166	49.0 49.3	11,927 989	43.3 41.9	2104 208	7.6 8.8	0.086
BPH	No Yes	12422 2560	52.5 36.9	9681 3581	40.9 51.7	1570 788	6.6 11.4	<0.001
PCa status	No Yes	13402 1596	50.1 41.3	11,547 1721	43.1 44.5	1814 547	6.8 14.2	<0.001

Table 3 Assessing the Association Between DRE Findings and Sample Characteristics at the First Visit (T1) (N= 34,756 Participants)

		DRE screening at visit 1 (T1)						
		Normal		Abnormal, Non-suspicious		Abnormal, Suspicious		p-value
		n	%	n	%	n	%	
Age at randomization, mean SD		62.2 ± 5.2		62.8 ± 5.4		64.1 ±5.4		<0.001
Race	White Black	11993 611	42.9% 49.8%	13,911 539	49.8% 43.9%	2048 78	7.3% 6.4%	<0.001
College	No Yes	7185 5419	42.7% 43.9%	8431 6019	50.1% 48.7%	1214 912	7.2% 7.4%	0.072
Married	No Yes	2177 10427	46.7% 42.5%	2158 12,292	46.3% 50.1%	327 1799	7.0% 7.3%	<0.001
Baseline BMI, mean SD		27.6 ± 4.2		27.5 ± 3.9		27.2 ±4.0		<0.001
Frequent urination	No Yes	11568 1036	43.5% 40.4%	13,140 1310	49.4% 51.1%	1909 217	7.2% 8.5%	0.003
Immediate Family	No Yes	11379 944	43.4% 42.3%	12,960 1115	49.4% 49.9%	1903 174	7.3% 7.8%	0.047
BPH	No Yes	10401 2188	46.0% 33.5%	10,753 3687	47.5% 56.4%	1461 665	6.5% 10.2%	<0.001
PCa status	No Yes	11409 1195	44.1% 36.4%	12,786 1664	49.4% 50.6%	1699 427	6.6% 13.0%	<0.001

adjusted odds ratio (aOR) and confidence intervals (CIs). CIs inclusive of 1.0 were considered non-significant association, while those without 1 were considered significant association. P-value (P) of less than or equal to 0.05 was considered statistically significant.

Table 4 Assessing the Association Between DRE Findings and Sample Characteristics at the second Visit (T2) (N= 34,756 Participants)

		DRE Screening at Visit 2 (T2)						
		Normal		Abnormal, Non-suspicious		Abnormal, SUSPICIOUS		p-value
		n	%	n	%	n	%	
Age at randomization, mean SD		62.1 ± 5.2		62.7 ± 5.3		63.9 ±5.3		<0.001
Race	White Black	10789 545	39.7 45.5	14,230 576	52.4 48.1	2143 77	7.9 6.4	<0.001
College	No Yes	6449 4885	39.4 40.7	8592 6214	52.5 51.7	1310 910	8.0 7.6	0.075
Married	No Yes	1979 9355	43.6 39.3	2194 12,612	48.3 52.9	365 1855	8.0 7.8	<0.001
Baseline BMI, mean SD		27.7 ± 4.2		27.5 ± 3.9		27.1 ±4.0		<0.001
Frequent urination	No Yes	10371 963	40.1 39.1	13,513 1293	52.2 52.4	2010 210	7.8 8.5	0.123
Immediate Family	No Yes	10261 838	40.2 39.0	13,291 1121	52.1 52.1	1981 192	7.8 8.9	0.47
BPH	No Yes	9301 2022	42.3 31.9	11,166 3628	50.8 57.2	1531 688	7.0 10.9	<0.001
PCa status	No Yes	10394 940	40.8 32.4	13,278 1528	52.2 52.6	1784 436	7.0 15.0	<0.001

Table 5 Assessing the Association Between DRE Findings and Sample Characteristics at the Third Visit (T3) (N= 34,756 Participants)

		DRE Screening at Visit 3 (T3)						
		Normal		Abnormal, Non-suspicious		Abnormal, Suspicious		p-value
		n	%	n	%	n	%	
Age at randomization, mean SD		61.9 ± 5.2		62.6 ±5.3		64 ±5.3		<0.001
Race	White Black	9608 513	36.9% 45.5%	14,333 531	55.0% 47.1%	2130 83	8.2% 7.4%	<0.001
College	No Yes	5648 4473	36.0% 38.8%	8698 6166	55.5% 53.5%	1323 890	8.4% 7.7%	<0.001
Married	No Yes	1788 8333	41.5% 36.4%	2168 12,696	50.3% 55.5%	353 1860	8.2% 8.1%	<0.001
Baseline BMI, mean SD		27.7 ± 4.3		27.5 ±3.9		27 ±3.8		<0.001
Frequent urination	No Yes	9289 832	37.3% 36.1%	13,599 1265	54.6% 54.9%	2005 208	8.1% 9.0%	0.192
Immediate Family	No Yes	9152 759	37.3% 37.0%	13,378 1112	54.6% 54.2%	1979 181	8.1% 8.8%	0.493

(*Continued*)

Table 5 (Continued).

		DRE Screening at Visit 3 (T3)						
		Normal		Abnormal, Non-suspicious		Abnormal, Suspicious		p-value
		n	%	n	%	n	%	
BPH	No	8409	39.7%	11,212	53.0%	1549	7.3%	<0.001
	Yes	1704	28.4%	3639	60.6%	663	11.0%	
PCa status	No	9374	37.9%	13,488	54.6%	1839	7.4%	<0.001
	Yes	747	29.9%	1376	55.1%	374	15.0%	

Table 6 GEE Analysis of Adjusted Odds Ratio of Abnormal DRE as Compared to Normal DRE

		Abnormal DRE non-suspicious			Abnormal DE Suspicious		
		OR	LCL	UCL	OR	LCL	UCL
Intercept		0.858	0.611	1.203	**0.019**	**0.011**	**0.034**
Age		**1.010**	**1.006**	**1.014**	**1.048**	**1.040**	**1.055**
Race	Black	**0.803**	**0.724**	**0.892**	**0.735**	**0.611**	**0.883**
	White	1.000			1.000		
College	Yes	**0.915**	**0.874**	**0.958**	**0.824**	**0.761**	**0.893**
	No	1.000			1.000		
Married	Yes	**1.204**	**1.135**	**1.278**	1.060	0.958	1.172
	No	1.000			1.000		
Baseline BMI		**0.988**	**0.983**	**0.994**	**0.976**	**0.967**	**0.986**
Frequent urination	Yes	0.983	0.908	1.064	1.013	0.890	1.152
	No	1.000			1.000		
Immediate Family	Yes	0.979	0.902	1.063	1.017	0.884	1.169
	No	1.000			1.000		
BPH	Yes	**1.579**	**1.491**	**1.672**	**1.689**	**1.541**	**1.852**
	No	1.000			1.000		
PCa status	Yes	**1.317**	**1.170**	**1.483**	**4.935**	**4.193**	**5.809**
	No	1.000			1.000		
T		**1.017**	**1.008**	**1.026**	1.015	1.000	1.030
T × PCa status=Yes		**1.052**	**1.033**	**1.072**	**1.230**	**1.193**	**1.268**
T × PCa status=No		1.000			1.000		

Note: Boldface indicates statistical significance (p=0.05).
Abbreviations: T, Time in years before diagnosis; BPH, Enlarged prostate or benign prostatic hypertrophy.

Results

Table 1 describes the characteristics of a subsample from the PLCO intervention arm (N=34,756). Of these, 12.3% (4280/34756) had prostate cancer with significantly higher estimates in Black men than in White men (15.1% vs 12.2%, P < 0.001).

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At the end of the follow-up, the percentage of abnormal suspicious DRE was significantly increased from 6.5% at 10 years prior to diagnosis to 27.2% at diagnosis.

The frequency distribution of normal, abnormal non-suspicious, and abnormal suspicious DRE by the sample characteristics at the baseline visit (T0), visit 1 (T1), visit 2 (T2), and visit 3 (T3) are displayed in Tables 2–5, respectively. In this subgroup analysis, we observed significant association between DRE findings and race, education, and BPH at all four visits. For instance, the percentage of abnormal DRE was lower among Black participants than White participants at all four visits. Age at randomization and baseline BMI were significantly different across DRE findings at all four visits. Specifically, age was positively associated with abnormal DRE findings, while baseline BMI was inversely associated with abnormal DRE findings.

Table 6 presents the results of the GEE analysis of the changes in DRE findings across time (follow-up years to diagnosis) by prostate cancer status. The interaction term (follow-up year to diagnosis × prostate cancer status) was statistically significant, indicating that the likelihood of abnormal DRE findings changes significantly over time between prostate cancer and non-prostate cancer participants. Each year closer to diagnosis, the prostate cancer participants were expected to increase the odds of abnormal non-suspicious DRE by 5.2% (aOR=1.052, 95% CI: 1.033–1.072) and abnormal suspicious DRE by 23.0% (aOR=1.230, 95% CI: 1.193–1.268). The probability of abnormal suspicious DRE increases sharply over time in participants with prostate cancer (Figure 1), while the probability of abnormal non-suspicious DRE increases gradually over time in participants with prostate cancer (Figure 2). There is no change in DRE overtime in participants who did not have prostate cancer.

Older age is associated with higher odds of abnormal DRE, where the odds of abnormal non-suspicious DRE tend to increase by 1.0% for every year increase in age (aOR=1.010, 95% CI: 1.006–1.014) and the odds of abnormal suspicious DRE tend to increase by 4.8% for every year increase in age (aOR=1.048, 95% CI: 1.040–1.055) (Table 6). The odds of abnormal non-suspicious DRE (aOR=0.803, 95% CI: 0.724–0.892) and abnormal suspicious DRE (aOR=0.735, 95% CI: 0.611–0.883) were significantly lower in Black participants compared to White participants. PLCO participants with a college degree had 8.5% lower odds of abnormal non-suspicious DRE (aOR=0.915, 95% CI: 0.874–0.958) and 17.6% lower odds of abnormal suspicious DRE (aOR=0.824, 95% CI: 0.761–0.893) when compared with PLCO participants without a college degree. Participants with higher BMI had lower odds of abnormal DRE, where the odds of abnormal

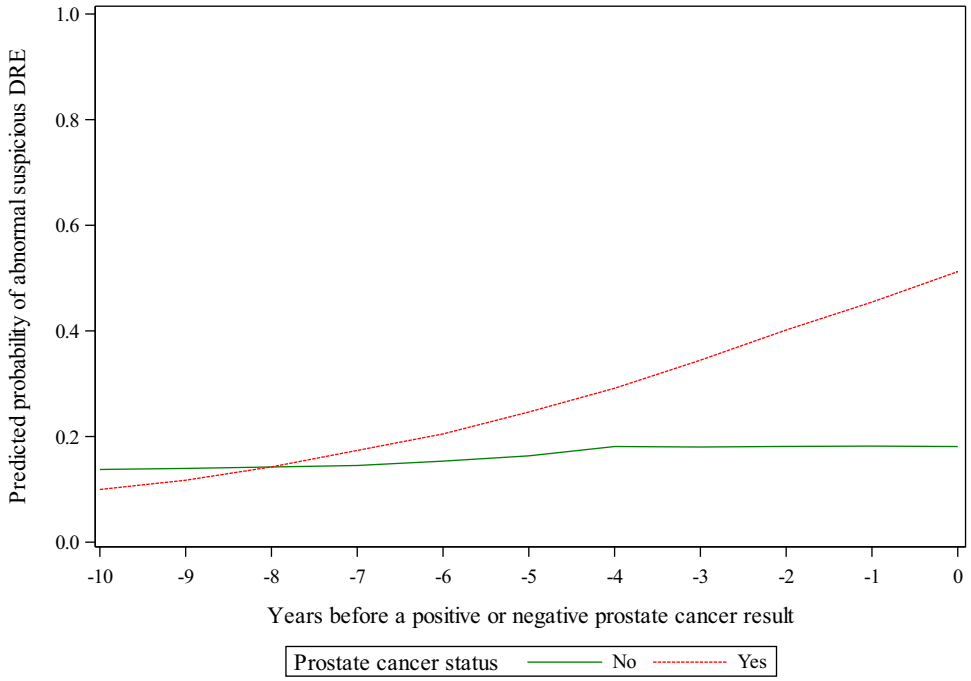

Figure 1 Predicted probability of an abnormal suspicious DRE by follow-up year to diagnosis and prostate cancer status. The probability of having an abnormal suspicious DRE goes up with prostate cancer vs no prostate cancer. Changes in trend observed 8 years before a positive or negative prostate cancer result.

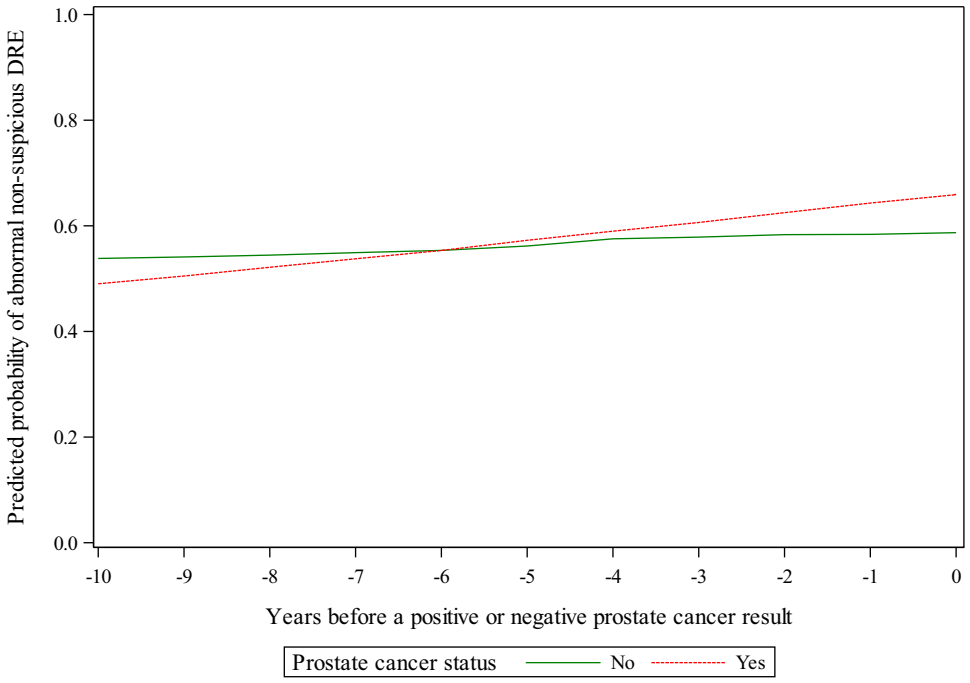

Figure 2 Predicted probability of an abnormal non-suspicious DRE by follow-up year to diagnosis and prostate cancer status.

non-suspicious DRE tend to decrease by 1.2% for every kg/m^2 increase in BMI (aOR=0.988, 95% CI: 0.983–0.994) and the odds of abnormal suspicious DRE tend to decrease by 2.4% for every kg/m^2 increase in BMI (aOR=0.976, 95% CI: 0.967–0.986). BPH associated with increased odds of abnormal non-suspicious DRE by 57.9% (aOR=1.571, 95% CI: 1.491–1.672) and increased odds of abnormal suspicious DRE by 68.9% (aOR=1.689, 95% CI: 1.541–1.852). Frequent urination and immediate family history of prostate cancer did not affect the odds risk of having abnormal DRE findings (Table 6).

Discussion

This study utilized secondary analysis of follow-up data on 34,756 men from the PLCO Screening Trial to explore changes in the likelihood of abnormal suspicious DRE by investigating the interaction term follow-up year to diagnosis × prostate cancer status. The overall crude prevalence of abnormal suspicious DRE increased over time from 6.5% at 10 years prior to diagnosis to 27.2% at diagnosis. Our GEE model provides evidence to support the research hypothesis by identifying an increasing trend in the likelihood of abnormal suspicious DRE (Figure 1) and abnormal non-suspicious DRE (Figure 2) among men with prostate cancer compared to men without prostate cancer.

We propose that there is still utility in performing DREs consistent with USPTF and AUA as we addressed an important gap in developing a model for long-term follow-up of DRE screening to reduce potential harms associated with a single DRE test.[5,6] Unlike studies that considered DRE as a one-time screening,[9] our study endorses the usage of long-term follow-up of DRE in primary care settings. A one-time DRE screening is not an effective approach as it misses true positive cases. For instance, Krilaviciute et al reported low detection for prostate cancer of 0.05%, while our study detection rate increases over time: 0.64% at 10 years prior to diagnosis, 6.32% at 5 years prior to diagnosis, 12.60% at 2 years prior to diagnosis, and 43.4% at diagnosis. The positive predictive value of abnormal suspicious DRE was 4.74% at 10 years prior to diagnosis, 36.82% at 5 years prior to diagnosis, 60.63% at 2 years prior to diagnosis, and 90.48% at diagnosis. This is similar to a previous study that reported a high chance of developing prostate cancer in men with suspicious DRE tests at the initial screening, second screening, and third screening.[21] This suggests that the long-term follow-up of DRE screening is an important and a reliable approach in detecting prostate cancer.

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Our study identified several other key factors influencing the likelihood of abnormal suspicious DRE. Black men had significantly lower likelihood of abnormal DRE than White men. The reasons for this difference are not fully understood, but it might be explained by the psychological fear regarding DRE impacting the screening practices and the likelihood of being screened across different race groups as Black men undergo DRE less often and have higher DRE screening fears than White men.[1,22] The DRE screenings rate was much lower for Black men as compared to White men due to the lack of recruitment of Black men.[23]

Our findings reveal a low BMI value is an indicator of abnormal DRE findings as we found an inverse correlation between baseline BMI and abnormal DRE. Studies suggest that obese men were less likely to have abnormal DRE findings[24] and less likely to have abnormal prostate cancer.[25] DRE in obese men presents unique considerations due to the increased tissue in the pelvic area. This may require skilled examiners to physically evaluate the prostate gland for presence of any abnormalities or loss of anatomic landmarks. Therefore, careful DREs in obese patients are vital to ensure effective DRE screening.

Our study showed that men with BPH were associated with greater odds of abnormal DRE than men without BPH. This finding has not been extensively explored, but a study found that abnormal DRE was an independent factor of incidental prostate cancer following BPH surgery.[26] We suggest that BPH nodules can mimic nodules caused by prostate cancer on DRE, which has also been shown on prostate MRIs. The current study suggests that older men were more likely to have abnormal DRE findings. Age significantly correlated with prostate cancer.[25] Older age may affect the structure of the prostate and can be interpreted as abnormal, which may contribute to false positive results.

Notwithstanding, our study comes with limitations secondary to the inherent nature of retrospective analysis. The study findings may not be generalizable to the African American population due to the greater representations of one race over another may have affected our results[23] as there are more white participants than black participants in the PLCO trial. Unlike the DRE, which has multiple assessments (T0–T3), the prostate cancer status was determined according to one assessment via medical record abstraction such as a self-report of prostate cancer, death certificates indicating prostate cancer, and relative informing the screening center of the participant's prostate cancer status. Inadequate DRE screening and not completed exams were treated as missing. Consequently, the authors were unable to use GEE analysis to assess the trends of prostate cancer changes within a period of 10 years prior to diagnosis.

The current study, however, has several strengths 1) the PLCO trial is a population-based study and serial DRE testing might represent the study populations, 2) the definition of DRE classification was clearly defined and reproducible to limit interpretation errors amongst clinicians performing DREs, 3) we show the importance of serial DREs overtime in raising the clinical suspicion of prostate cancer as well as its status as an important, feasible, and cost-effective adjunct to serum PSA screening in prostate cancer, and 4) our analysis has been adjusted for age at randomization, BMI, education level, race, marital status, frequent urination, immediate family history, and BPH.

Conclusion

Our results suggest that incorporating serial DRE findings into screening strategies may reduce false positives and improve early detection of clinically significant prostate cancer. This study demonstrates a rising probability of abnormal DRE findings in men with prostate cancer, whereas no temporal change was observed in men without prostate cancer. Long-term follow-up DRE findings can help identify the changes in the prostate gland due to aging to reduce the false positives associated with the PSA test.

Data Sharing Statement

Requests to access the PLCO datasets should be directed to the National Cancer Institute (NCI) Cancer Data Access System (CDAS): https://cdas.cancer.gov/plco/.

Ethics Statement

The PLCO study was approved by the Institutional Review Boards of participating centers and the NCI. The study participants provided written informed consent. Ethical approval was not required. The authors analyzed secondary data from the Prostate, Lung, Colorectal, and Ovarian cancer screening trial.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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