African Journal of Urology

REVIEW

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Digital rectal exam in prostate cancer screening: a critical review of the ERSPC Rotterdam study

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Abstract

The history of prostate cancer screening has evolved from relying on the Digital Rectal Exam to the introduction of PSA test. Initially, DRE was the cornerstone for diagnosing aggressive PCa, but the advent of PSA testing allowed for proactive detection. Distinctions between screening for the general population and early detection for individuals are vital. The French Onco-Urology Recommendations cite the European Randomized Study of Screening for Prostate Cancer (ERSPC), highlighting a 21% reduction in mortality using total PSA for screening, endorsing DRE in combination with PSA for early detection. However, a comprehensive analysis of the ERSPC study raises questions about DRE's role in screening. Studies indicate weak correlations between DRE and PCa diagnosis, especially with low PSA values. DRE's reproducibility is also a concern. As the ERSPC study progressed, DRE's significance diminished, and PSA became the primary screening tool. Other trials omitted DRE from their protocols, emphasizing PSA's dominance. While some studies advocate for DRE in specific contexts, its overall utility in screening is questionable. It can be uncomfortable, has low sensitivity and specificity, and may lead to unnecessary biopsies. Controversies persist regarding its role in follow-up tests after the initial screening. In summary, the analysis of various publications suggests that DRE has limited value in subsequent PCa screening procedures, particularly in regions where screening has evolved beyond its initial use. PSA's dominance underscores the diminishing role of DRE in modern PCa screening practices.

Keywords Prostate cancer screening, Digital rectal exam, European Randomized study of screening for prostate cancer, Guidelines and recommendations

Historically, before the era of prostate-specific antigen (PSA), the primary concern within the urological community was the timely diagnosis of aggressive prostate cancer (PCa). The Digital Rectal Exam (DRE) served as the cornerstone of this diagnostic approach, and the question of screening rarely arose during that period. The introduction of the PSA test as a reliable tool for detecting PCa at a sub-clinical stage paved the way for proactive cancer detection, even in the absence of symptoms. This marked the inception of modern PCa screening. The distinction between screening for the general population and early detection for individuals is essentially epidemiological. In practice, it involves asymptomatic individuals for whom we provide tools to detect a cancer that has remained latent until now.

In the French Onco-Urology Recommendations for the period 2020–2022, as outlined by the Prostate Committee of the AFU (French Urology Association) [1], the section on screening references a significant study conducted by the European Randomized Study of Screening for Prostate Cancer group (ERSPC), Rotterdam updated in 2014 with 16 years of follow-up [2]. This study, initially published in The Lancet, provided an update on follow-up data after 13 years, not 16 years as indicated. Subsequently, in 2019, another study,

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which we will discuss later, was published in European Urology, presenting the data from 16 years of follow-up. In their report, the authors of the AFU Oncology Committee [1] highlight the favorable outcomes of the ERSPC, which showed a 21% reduction in mortality within the screening group when utilizing total PSA as a screening tool. Furthermore, in the context of early detection, the panel strongly recommends the use of DRE in conjunction with PSA, assigning it a high recommendation grade [1]. In support of this recommendation, they reference a prior study conducted by the ERSPC group and published in 2008 [3].

It appears to us that if DRE is recommended for early detection, it should be endorsed with the same level of recommendation for screening. Our primary objective is to analyze the ERSPC study comprehensively and to monitor the various publications and updates associated with this study, beginning from its inception. This analysis will help us better understand the role of DRE in the screening process.

Several experts consider the ERSPC study to be the most significant study conducted in the field of PCa screening to date [1]. This trial involved 182,160 men aged 50–74, of whom 162,388 were in the age range of 55–69. The participants were randomly assigned to two groups: one for screening and another as a control group. The study was primarily conducted across eight European countries, including Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, and Switzerland [4]. In addition, other countries participated in the study through randomization by the International Prostate Screening Trial Evaluation Group [5].

The trial commenced at the end of 1993 [6], with recruitment concluding in 2003 [4]. The first screening rounds took place between November 1993 and May 2000, between January 1998 and June 2004 for the second, and between March 2002 and August 2007 for the third [6]. Post-2003, screening activities continued in the Netherlands, Sweden, Italy, Switzerland, and France. However, Belgium, Finland, and Spain discontinued screening after completing three rounds [4].

In the Netherlands, Transrectal Ultrasound was used from 1993 to 1996 for men with a PSA level between 1.0 and 4.0 ng/ml. In Finland, this practice was adopted from 1996 to 1998. Since 1996, most centers have used a PSA cut-off value of 3.0 ng/ml to determine the positivity of a screening test. Subsequently, DRE was performed before the biopsy [7]. The screening protocol generally followed this sequence: between June 1994 and January 1996, a biopsy was conducted in cases of an abnormal DRE, transrectal ultrasound findings, or a PSA ≥ 4 ng/ml. From February 1996 to January 1997, transrectal ultrasound and DRE were no longer performed for individuals with a PSA < 1 ng/ml [5].

Upon analyzing this methodology, it becomes evident that DRE held a secondary role in the screening process. Furthermore, the ERSPC investigators sought to address the ongoing controversy surrounding DRE. In a publication titled “The Role of DRE in Screening” the authors concluded that, despite the study’s limitations, an abnormal or suspicious DRE was associated with a higher risk of having cancer. Notably, this risk became more pronounced when an abnormal DRE was coupled with a PSA level of ≥ 3 ng/mL, leading to the detection of more aggressive cancers with Gleason scores exceeding 7 [3].

The significance of this study [3] was so profound that it has become a key reference in the guidelines of several urological societies, including the AFU 2016–2018 [8], the Canadian Urological Society 2017 [9], and even the EAU 2015 [10]. However, it is worth noting that the EAU panel primarily references this study [3] within the context of diagnosis rather than screening. Specifically, it is noted that an abnormal DRE, when combined with an elevated PSA level, doubles the risk of positive biopsies (48.6% vs. 22.4%) in the diagnosis chapter. In contrast, the AFU and Canadian panels incorporate this study [3] to discuss the role of DRE in both screening and diagnosis. It is important to acknowledge that these guidelines address different patient populations".

To comprehensively trace the different stages of the ERSPC Rotterdam trial, we will dissect and analyze various publications by the investigators, with a particular focus on the role of DRE.

Chronologically, Schröder et al., specifically evaluating the utility of DRE as a screening tool, conducted one of the early analyses of this study. Notably, their findings revealed a strong correlation between PSA levels in the range of 0–3.9 ng/mL and the positive predictive value, sensitivity of DRE, tumor volume, and tumor grade.

As a result, DRE appears to make a modest contribution, characterized by a low positive predictive value—indicating a weak correlation between DRE results and prostate cancer diagnosis [5]. This observation finds support in the study by Lodding et al. [11], which similarly concluded that there is either a weak correlation or, in some cases, no correlation at all between DRE findings and the diagnosis of prostate cancer, particularly for individuals with low PSA values [5, 11].

Moreover, it is noteworthy that as of the date of the publication in 1998, for at least 2 years prior (since 1996), only a few centers continued to perform DRE as part of the screening protocol. This raises questions about the scientifically proven necessity of DRE in screening, as it had already been phased out in some centers by this time, well before 1996 or 1998.

In another analysis published in 1999 in the International Journal of Oncology [12], it was found that DRE, even when performed by a medical assistant, did not provide a clear advantage in screening for individuals with PSA levels < 2 ng/ml. The study suggested that biopsy should not be recommended based solely on DRE findings. This recommendation was influenced by the examiner-dependent nature of DRE, which makes it challenging to standardize and reproduce as a consistent procedure [12].

Furthermore, Smith and Catalona (1995) noted that the reproducibility of DRE results was only moderate, even among urologists [13]. We firmly believe that DRE is a medical procedure, and its lack of reproducibility even among urologists raises concerns about its reliability in a broader context.

The utility of DRE was further scrutinized by Vis et al. [14] in the context of screening for PSA levels ≤ 3.9 ng/ml. Their findings suggested that for individuals with lower PSA values, the use of DRE alone could be replaced by relying solely on PSA levels. In fact, their study indicated that for PSA values ≤ 3 ng/ml, it would require 289 DRE exams to detect a single case of clinically significant prostate cancer. For PSAs ranging from 0.0 ± 2.9 to 3.0 ± 3.9 ng/ml, a substantial portion of the cancers identified through suspicious DRE results—72.2% (26 out of 36) and 38.5% (5 out of 13), respectively—were found to be tumors measuring < 0.5 ml. According to the authors, it is improbable that DRE would have been effective in detecting these small tumors, which they refer to as false positives. These findings align with conclusions from a prior study by Hoedemaeker et al. [15] ".

Tumors detected by DRE in individuals with a PSA ≤ 4 ng/ml were found to have low pathological stages, with a significant portion (43%) classified as 'minimal tumors'. A minimal tumor was defined as one with a volume of less than 0.5 ml, the absence of Gleason patterns 4 or 5, and confinement to the prostate [12]. In the same year, 2001, the ERSPC investigators published an analysis of screening without DRE in the journal Urology [16]. By lowering the PSA threshold to 3 ng/ml or more as an indicator for biopsy, without the requirement of DRE, the study reported a significant improvement in the positive predictive value (from 18.2% to 24.3%). Moreover, the number of biopsies needed to diagnose prostate cancer decreased from 5.2 to 3.4.

In 2007, Gosselaar et al. [17] published the results of their comparative analysis of tumor characteristics in PCa cases detected by screening, either through DRE or by PSA, with PSA levels between 2 ng/mL and 3.9 ng/mL. The study indicated that DRE tends to selectively detect high-grade cancers but misses many of them. Furthermore, it was observed that DRE cannot substitute for PSA, especially for individuals with low PSA values.

One argument for continuing to use DRE was that patients screened via DRE were more likely to adhere to biopsy recommendations, with only 4% refusing the biopsy, compared to those screened by PSA (15.5%). However, the authors questioned the scientific rationale for this argument, suggesting that it may not justify DRE as a screening tool. In conclusion, their findings underscored the predictive value of PSA, emphasizing the need to develop new diagnostic tests for aggressive tumors.

A year later, these authors conducted a study [3] to assess the role of DRE in the screening program for individuals aged between 55 and 75 years. During the study period (May 1997 to October 2006), all subjects underwent DRE before a biopsy was recommended for those with PSA levels ≥ 3.0 ng/ml. Their findings indicated that the risk of having cancer upon biopsy was higher in men with suspicious DRE compared to those with normal DRE results. Specifically, the combination of an abnormal DRE and a PSA level ≥ 3.0 ng/mL significantly increased the detection of prostate cancer with a Gleason score > 7. As a result, the authors suggested that rectal DRE, which was previously performed for everyone, should be replaced with more selective screening approaches to reduce the risk of unnecessary biopsies and overdiagnoses.

In 2009, the same research team published an article in European Urology [6] titled 'DRE and the Diagnosis of PCa' which presented an analysis of results after eight years of follow-up. Their conclusion was unequivocal: an initial suspicious DRE did not influence the likelihood of detecting cancer or clinically significant cancer in subsequent screenings. Furthermore, they emphasized that DRE data should not impact the screening rates for future populations.

For instance, during the second screening round (January 1998 to June 2004) with a 4-year follow-up, only 2% of cancers were detected based on an initial abnormal DRE, while 1% were detected in individuals with an initial normal DRE. In the third screening round (March 2002 to August 2007), with an 8-year follow-up, 3% of cancers were detected in individuals with an initial abnormal DRE, compared to 2% in those with an initial normal DRE [6].

After 11 years of follow-up, the ERSPC investigators evaluated mortality outcomes [4], emphasizing reliance on screening results rather than the tools themselves. In their findings, they highlighted that when employing PSA screening alone, preventing one death required screening 1,055 individuals and detecting 37 cases of cancer.

Two years later [2], the investigators provided an update on the data from the 13-year follow-up of the

ERSPC study. Despite the positive results regarding mortality, the question of screening remained controversial, primarily due to the drawbacks, particularly overdiagnosis. The authors noted that this study served to confirm and strengthen previous findings in a population screened primarily using PSA as the main screening tool. Interestingly, in outlining the methodology, the authors emphasized that PSA had been the primary screening tool throughout the study, and notably, they did not mention DRE in this article.

The results, as analyzed in relation to PSA alone, suggest that the contribution of DRE is so negligible that it has been disregarded. This interpretation is supported by two sentences in their article: 'It is possible that the follow-up is still too short to see the long-term effect of PSA screening, given the long natural history…' and 'Despite the evidence of the effectiveness of PSA screening in reducing PCa mortality in our study…'. In their clear conclusion, they recommend the use of PSA as the primary screening tool in studies of this nature, despite some criticisms regarding the need for longer follow-up periods to fully assess its impact.

At 16 years of follow-up [7], the ERSPC authors conducted an update of their data to assess whether PSA screening reduces mortality (the benefit of screening) and to evaluate the disadvantages of long-term screening. Once again, the results regarding mortality were reinforced, emphasizing the need for repeated screening. The role of DRE had become a thing of the past, as previously described in the study's protocol.

Furthermore, several other randomized clinical trials also do not consider DRE as a screening tool. For instance, the Göteborg randomized controlled trial (RCT) [18] recruited 20,000 subjects aged between 54 and 64 years, with the screening group (9950) undergoing biannual PSA tests until the age of 69. In this trial, a PSA level $\geq$ 2.5 ng/ml was the indication for biopsy.

Another Canadian RCT, conducted by Labrie et al. in 2004 [19], evaluated the impact of PCa screening on mortality after an 11-year follow-up period. At the outset of screening, all patients underwent both a PSA test and a DRE. However, over the years of follow-up, patients received only one PSA test. The authors did not provide specific commentary on this choice, but it is evident that they did not find any advantage in repeating the DRE.

Similarly, a UK RCT known as the CAP study, published in 2018 [20], involved 400,000 subjects aged between 50 and 69 years. This study prescribed only one PSA assay for screening purposes. The primary aim was to assess PCa-specific mortality while minimizing the risk of overdiagnosis or overtreatment, with a median follow-up of 10 years. Notably, DRE was not mentioned or included in the screening protocol for this study.

In contrast to some other studies, one of the noteworthy clinical trials that emphasized the role of DRE is the prostate cancer screening study conducted by the PLCO group [21]. The investigators advocated for DRE as an essential component of screening alongside PSA. In this study, while PSA was repeated for six years, DRE was recommended for four years. Despite the criticisms and concerns about contamination (involving predisposed subjects who had not undergone screening tests), the authors did not find, after 7–10 years of follow-up, a statistically significant difference in specific mortality between the two randomization arms. This retrospective analysis led to the conclusion that DRE did not provide any additional benefit beyond PSA, particularly in light of the ongoing debate surrounding its utility.

Another study referenced by the ERSPC investigators is that of Borden et al. [22]. In this prospective and monocentric study, DRE was identified in multivariate analysis as a predictive factor for high-grade cancerous lesions ($G \geq 7$). However, the authors did not provide information about the clinical history of their patients, specifically whether DRE or PSA tests were conducted as part of a screening or diagnostic process. In addition, to support their findings, they cited two studies [23, 24] that demonstrated the utility of DRE and its inclusion in predictive cancer nomograms. It is important to note that these referenced studies are likely focused on diagnostic rather than screening procedures. Furthermore, Borden et al. suggested that DRE should have a significant role in patients with low PSA levels. We know, based on various large clinical studies [5, 11], that at a certain stage, DRE loses its significance as a screening tool. In their study, they also highlight the issue of non-reproducibility of DRE, which is acknowledged as a limitation in any study. They also mention the non-reproducibility of the DRE as a limitation of any study, while noting that in their study, DRE was performed by a single urologist. It is worth noting that in their study, all patients were referred to the center either due to elevated PSA levels or abnormal DRE, which could introduce subjectivity and influence into the evaluation process.

Another crucial point that requires clarification is related to the AFU panel's [1] reference to the ERSPC study [7]. The AFU panel recommends establishing a screening rhythm for early detection of prostate cancer based on this study and suggests personalizing this rhythm on a case-by-case basis according to the PSA level.

Controversies surrounding the role of DRE in PCa screening remain unresolved, especially as it pertains to its place in subsequent tests during follow-up, compared to its initial use. It is puzzling why DRE was omitted from the follow-up step when it is expected to serve the same

purpose, whether in the first test or subsequent screenings. In addition, DRE can act as a barrier to participation in screening, as demonstrated by Nagler et al. [25]. Their study found that 22% of subjects questioned refused to participate in screening that included DRE alongside PSA. Furthermore, the use of DRE exposes individuals to an uncomfortable examination with minimal gain, as previously described (detecting only 2% of clinically significant PCa) and the possibility of false positives [6, 26]. Its low sensitivity and specificity have been underscored by a recent meta-analysis [27], with significant limitations, including non-reproducibility (both inter and intra-variability). A study published in 2009 [28] even demonstrated that 70% of initially abnormal DRE results had returned to normal one year later.

In conclusion, through the analysis of the various publications (especially the ERSPC-Rotterdam study), we believe that DRE has no place in subsequent screening procedures, particularly in countries where screening has not been done before.

Abbreviations

PSA	Prostate Specific Antigen
DRE	Digital Rectal Exam
PCa	Prostate Cancer
AFU	French Association of urology
ERSPC	European Randomized Study of Screening for Prostate Cancer
EAU	European Association of Urology
RCT	Randomized Controlled Trial

Acknowledgements
Not applicable.

Author contributions
The author declares that he is the sole author of this manuscript. The author read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The author declares that he has no competing interests.

Received: 30 October 2023 Accepted: 3 September 2024
Published online: 18 September 2024

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