Evaluation of the Digital Rectal Examination as a Screening Test for Prostate Cancer

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Background: The utility of digital rectal examination (DRE) as a screening test for early detection of prostate cancer has not been established. Therefore, we evaluated the usefulness of DRE as a stand-alone screening test and in conjunction with measured serum prostate-specific antigen (PSA) levels of 0–3.9 ng/mL and transrectal ultrasonography (TRUS).

Methods: Our study population consisted of 10 523 men aged 54–76 years who were randomly assigned to the screening arm of the Rotterdam, The Netherlands, section of the European Randomized Study of Screening for Prostate Cancer. The underlying prevalence of detectable prostate cancer was estimated by logistic regression analysis and used for calculating the sensitivity of DRE as a test. Pathologic characteristics of 105 radical prostatectomy specimens were used to determine the aggressiveness of the tumors diagnosed (and missed) by DRE.

Results: The overall detection rate for prostate cancer in this population when serum PSA measurement, DRE, and TRUS were used was 4.5%, and the detection rate with DRE alone was 2.5%. The positive predictive value of DRE ranged from 4% to 11% in men with PSA levels of 0–2.9 ng/mL and from 33% to 83% in men with PSA levels of 3.0–9.9 ng/mL or more. Most tumors detected by DRE in men with PSA levels of less than 4.0 ng/mL were small (mean volumes = 0.24–0.83 mL), and most were well differentiated (Gleason scores of 6 or less). Minimal, moderate, and advanced cancers were seen in 42%, 42%, and 16% of men, respectively, with a PSA level of 4.0 ng/mL or less. DRE alone allowed detection of 264 (55.8%) of 473 cancers; 82 (17.3%) of the 473 cancers would have remained undetected by PSA-based screening alone (i.e., no follow-up procedures for PSA values of 0–3.9 ng/mL).

Conclusions: For PSA values of 0–3.9 ng/mL, the positive predictive value and sensitivity of DRE, tumor volume, and tumor grade were strongly dependent on PSA level. DRE has a poor performance in low PSA ranges.

Screening for prostate cancer is an accepted health-care policy in some countries, but screening is fiercely opposed in others (1–3). Reports from areas where screening is prevalent show that the routine of prostate-specific antigen (PSA)-based early detection leads to a drastic initial rise in prostate cancer incidence—because of all the subclinical cancers detected—followed by a decrease once saturation has been reached (4). The effect of PSA screening on mortality, if one occurs, will become visible much later. At present, the value of screening for prostate cancer is still uncertain with respect to mortality reduction and quality-of-life effects.

Large randomized trials provide a means to avoid important biases and provide sufficient statistical power to obtain reliable data. Such an effort is going on in a number of European countries through the European Randomized Study of Screening for Prostate Cancer (ERSPC), which has established close cooperation with the American Screening Project for Prostate, Lung, Colon, and Ovarian Cancer (5) and the Canadian randomized study of screening for prostate cancer (6).

This report is based on data from the screening arm of the Rotterdam, The Netherlands, section of the ERSPC. It is aimed at evaluating digital rectal examination (DRE) as a screening test for prostate cancer.

The value of DRE as a diagnostic screening test can be judged in several ways: by considering DRE as a stand-alone test, by looking at its incremental value, and by considering its value in conjunction with PSA values of 0–3.9 ng/mL and transrectal ultrasonography (TRUS).

This report uses all three approaches; its main purpose, however, is to determine the contribution of DRE as a single test relative to that of PSA levels and tumor characteristics.

Materials and Methods

European Randomized Study of Screening for Prostate Cancer

Data were obtained from the prevalence screen in the Rotterdam section of ERSPC for a 33-month period starting on July 1, 1994. The screening algorithm used was applied in a prospective fashion as part of the original protocol. The goals and structure of ERSPC are described elsewhere (7,8). A summary of the screening procedures and the participants is given in Fig. 1. Men of ages 54–70 years (in Rotterdam, the range was 54–76 years [one patient aged 54 years and one aged 76 years were included by accident]) are randomly assigned to screening or no screening. The main end point of the study is prostate cancer mortality. When this report was being written (March 1998), more than 30 000 men in Rotterdam, more than 110 000 men in Europe, and more than 190 000 men internationally through the International Prostate Screening Trial Evaluation Group had been randomly assigned.
Study Population and Screening Procedures

Participants are recruited from the population registry of Rotterdam and from surrounding communities. The invitation to participate is by letter. Written informed consent is required by Dutch law. The participation rate (i.e., the proportion of those who have been invited to participate and have in fact been randomly assigned to screening) varies around 45%. The participation rate is defined as the number of men who have been randomly assigned to screening divided by the number of men who were invited to participate. Process evaluation was carried out. Questionnaires administered to participants and refusers alike indicated that the frequency of prostatic symptoms in the two groups was equal. This finding suggests no selection bias on this account. Rescreening is carried out once after 4 years in the ERSPC protocol.

This study is based on 11,500 participants in the Rotterdam section of ERSPC who were randomly assigned to the screening arm during the period from 1994 through 1997, of whom 10,523 (92%) were actually screened. In February 1996, the protocol was changed so that men who had PSA levels of less than 1.0 ng/mL were not screened by DRE and TRUS. Of 3858 men with PSA values of less than 1.0 ng/mL, 1702 were recruited before this change and 2156 were recruited after this change (Fig. 1).

The screening algorithm called for a biopsy in all men who had at least one of the following results: an abnormal DRE, an abnormal TRUS, or a PSA level of 4.0 ng/mL or more. DRE findings were considered abnormal if nodularity, induration, or asymmetry was felt. TRUS findings were considered abnormal if hypoechogenic lesions were seen. In March 1997, a major protocol change was implemented. All men with PSA levels of 3.0 ng/mL or more were subjected to a biopsy. DRE and TRUS were omitted if an individual's PSA level was less than 3.0 ng/mL. Data obtained within the new protocol are not included in this report.

DREs, TRUSs, and biopsies were carried out by trained medical and paramedical personnel. Training periods for these personnel lasted 4–6 weeks, and their normal and abnormal findings were randomly crosschecked by experienced staff. Trainees were permitted to do independent examination only after they and their instructors had achieved an acceptable level of agreement on diagnosis. Still, for eight examiners involved, percentages of abnormal DRE findings and positive predictive values varied between 4% and 24% and between 13% and 34%, respectively. Prostatic biopsies were taken as sextant biopsies. The lateral biopsies were taken slightly more laterally than indicated in the original study by Terris et al. (9) so that the lateral aspects of the peripheral zone were covered. Transition-zone biopsies were not carried out. A seventh biopsy was directed toward hypoechogenic lesions if applicable.

Pathologic Examination of Biopsy Specimens and Radical Prostatectomy Specimens

After routine fixation in a buffered 4% formalin solution, biopsy cores were embedded separately in paraffin blocks. Biopsy cores were longitudinally sectioned at three 5-μm levels. Standard hematoxylin–eosin-stained histologic slides were prepared and examined histologically.

Radical prostatectomy specimens were fixed for 24 hours in a solution containing saline and buffered 4% formalin. After fixation, each specimen was step-sectioned at 4-mm intervals and totally embedded in paraffin blocks as described previously (10). From each paraffin block, standard hematoxylin–eosin-stained histologic slides were prepared for routine pathologic examination. Routine histopathologic examination included the determination of pathologic stage (tumor–lymph nodes–metastasis system [TNM], 1992) (11) and Gleason score (12). After histologic examination, all areas containing cancer were outlined on the slides. Gray-scale digital images of each histologic section were made with a digital camera, and then digital morphometric analysis was performed to measure each tumor area with the use of computer software for morphometry (Kontron Imaging System, model KS400; Kontron Elektronik GmbH, Eching, Germany). We determined tumor volume by adding all measured tumor areas and total slide areas (in millimeters squared) and multiplying them by 4 (the thickness in millimeters of the original slices). Earlier experiments had shown that no correction factor for the effects of fixation and paraffin embedding was required. To assign a clinical importance to the tumors, we categorized all tumors as described previously (10). In brief, tumors that were smaller than 0.5 mL and confined to the prostate without harboring high-grade cancer (Gleason pattern 4 or 5) were classified as “minimal.” Prostate-confined tumors and well-differentiated tumors (no Gleason pattern 4 or 5) that showed capsule penetration were classified as “moderate.” All other tumors, including those that showed invasion of the seminal vesicles or bladder neck, were classified as “advanced.”

Statistical Evaluation

Detection rate is defined as the number of cancers found in participants who were screened in one round, in this case during the prevalence screen. Positive predictive values (i.e., the proportion of those with a positive test who are diagnosed with prostate cancer) were calculated as described previously (13). Sensitivity and specificity were estimated by use of prevalence estimates as explained below. The definitions given by Essex-Sorlie (13) were applied. Sensitivity can be calculated only if the underlying prevalence of the disease under discussion is known. This information is not available when screening for prostate cancer. To estimate the underlying prevalence of cancers detectable by
screening, we performed logistic regression analysis on screening data. This analysis results in estimating the number of men who would have been diagnosed to have prostate cancer by their PSA levels, if everyone had been subjected to a biopsy examination.

We refer to this procedure as an a priori prevalence assessment (APPA). Clinical judgment suggests that, for each range of PSA levels, cancers predicted by an APPA would have the same characteristic volume and aggressiveness as those diagnosed, as long as identical biopsy procedures were used. APPA does not include cancers with a very small volume. Only small proportions of such cancers are detected because of the limited sampling by sextant biopsy.

The model applied is a simple logistic regression model using PSA, DRE, TRUS, and prostatic volume (TRUS estimated) as predictors for prostatic cancer. The model has been tested prospectively (Kranse R, Beemsterboer P, Rietbergen J, Habbema D, Hugosson J, Schröder FH: unpublished data). No interaction terms were added. These terms were studied but did not contribute significantly to the model. Validation was done by testing the model on a sample cohort from the Swedish partner in ERSPC (Göteborg). The model was shown to be applicable with remarkable accuracy to this independent population. The outcome of the model can be interpreted as the chance to detect prostate cancer in a sextant biopsy given the outcome of the screening tests and, therefore, can also be used to assess the chance to detect prostate cancer in those men who were not subjected to biopsy examination (extrapolation).

In the model, the outcome given as the number of cancers found by the large number of biopsies done in men with normal DRE and PSA values of 4.0 ng/mL or more was used. These biopsies provide information about the value of PSA without a suspicious DRE and/or TRUS. This knowledge is included in the model and is used in the extrapolation to a PSA range that is less than 4.0 ng/mL with a negative DRE and/or a negative TRUS. This model has been tested prospectively (Kranse R, Beemsterboer P, Rietbergen J, Habbema D, Hugosson J, Schröder FH: unpublished data). No interaction terms were added. These terms were studied but did not contribute significantly to the model. Validation was done by testing the model on a sample cohort from the Swedish partner in ERSPC (Göteborg). The model was shown to be applicable with remarkable accuracy to this independent population. The outcome of the model can be interpreted as the chance to detect prostate cancer in a sextant biopsy given the outcome of the screening tests and, therefore, can also be used to assess the chance to detect prostate cancer in those men who were not subjected to biopsy examination (extrapolation).

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Table 1. Results of screening from the European Randomized Study of Screening for Prostate Cancer, Rotterdam section, from 1994 through 1997 in 10,523 men*  

<table>
<thead>
<tr>
<th>PSA level, ng/mL</th>
<th>No. screened (a)</th>
<th>No. of biopsies (b)</th>
<th>Prostate cancer</th>
<th>DRE alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (c)</td>
<td>Detection rate, %†</td>
<td>No. (d)</td>
<td>No. of prostate cancers (e)</td>
</tr>
<tr>
<td>0–0.9</td>
<td>1702</td>
<td>183</td>
<td>4</td>
<td>0.12</td>
</tr>
<tr>
<td>1.0–1.9</td>
<td>3305</td>
<td>502</td>
<td>43</td>
<td>1.3</td>
</tr>
<tr>
<td>2.0–2.9</td>
<td>1314</td>
<td>217</td>
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<td>2.2</td>
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<td>&gt;10.0</td>
<td>217</td>
<td>196</td>
<td>113</td>
<td>52.1</td>
</tr>
<tr>
<td>Total</td>
<td>8367</td>
<td>2267</td>
<td>473</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*Results of screening of 10,523 men are presented. The use of all three tests is compared with the use of DRE alone. Because of a change in the protocol in February 1996, men with PSA levels of 0–0.9 ng/mL were no longer screened by TRUS and DRE. A total of 2,156 men with PSA values less than 1 ng/mL have entered the study since this time. PSA = prostate-specific antigen; TRUS = transrectal ultrasonography; DRE = digital rectal examination; PPV = positive predictive value.

†Detection rate = number of cancers/number of men screened (473/10,523 = 0.0449 and 264/10,523 = 0.025).
mance of DRE is strongly dependent on PSA levels and is poorest when the PSA level is less than 3.0 ng/mL, an area that is considered the domain of the DRE.

Sensitivity and Specificity of DRE

Table 2 shows that the overall sensitivity and specificity of DRE are 37% and 91%, respectively. This table introduces the parameter APPA, an estimate of the underlying prevalence of prostate cancer as a function of the PSA level. The APPA is based on a logistic regression analysis that considers DRE, TRUS, PSA, and prostatic volume. The sensitivity of the DRE increases with increasing PSA levels. The sensitivity of the DRE is 20% when the PSA level is less than 3.0 ng/mL. When the PSA level is 3.0 ng/mL or more, the sensitivity of the DRE becomes 46%. Sensitivity indicates the proportion of cancers detected by DRE of the cancers that would have been detected if every participant had been subjected to biopsy examination. Consequently, for the 1702 participants with PSA levels in the range of 0–0.9 ng/mL, 19 participants are assumed to have a cancer that could have been diagnosed with sextant biopsies (from the APPA), but only four of those cancers (21%) were detected by DRE followed by biopsy. With PSA values greater than or equal to 10.0 ng/mL, 128 of 217 participants in this group were expected to have prostate cancer with characteristics comparable to those of cancers that have been diagnosed. Sixty-seven (52%) of these 128 would be expected to have been diagnosed if DRE had been the only test used. The specificity remains greater than 83% over the total range of PSA values. The sensitivity data show a very low predictive capability for DRE in the low PSA ranges.

Tumor Volume and Grade

Roughly half of the patients whose cancers (230–240 cancers) were detected in this series have undergone radical prostatectomy. We have done complete morphometric and histologic analyses of tumor volumes and have determined the Gleason score for 105 of these tumors. In Table 3, the mean tumor volumes and Gleason scores and their ranges are listed separately by PSA level for 49 patients who had negative DRE results and for 56 patients who had positive DRE results. Tumor volumes show a weak but statistically significant correlation with PSA, which is also illustrated by Fig. 2. The correlation coefficient and two-sided P value are .57 and <.001, respectively. Very clearly, the smallest tumors are found in the very low PSA ranges, their tumor volume does not differ between men with positive DREs and negative DREs, and the volumes of most tumors are so small that detection by DRE is unlikely. If one considers palpable prostate cancer to be spherical, tumors with volumes of 0.02, 0.03, 0.07, and 0.5 mL would have diameters of 0.3, 0.4, 0.5, and 1.0 cm, respectively. Of 38 tumors from patients with PSA values in the range of

Fig. 2. A) Venn diagram of the results of screening by digital rectal examination (DRE), transrectal ultrasonography (TRUS), and prostate-specific antigen (PSA) in 10,523 men randomly assigned to screening. Two thousand two hundred sixty-seven biopsies detected 473 cancers (detection rate = 4.5%). Among 3858 men with serum PSA levels of 0–0.9 ng/mL, only 1702 underwent DRE and TRUS because of a policy change in 1996. B) Correlation between serum PSA level and prostate cancer volume in 105 participants after radical prostatectomy.
DISCUSSION

The usefulness of DRE in screening for prostate cancer is the main issue discussed in this report. Prior to the advent of PSA and TRUS, DRE was the only available screening test for prostate cancer. In clinical use, 40%–50% of all palpable abnormalities that were suspected of being prostate cancer, if subsequently subjected to biopsy examination, were found to be malignant (15). Such data cannot be applied to population-based screening. DRE is a strongly investigator-dependent test that requires time to master. In addition, the predictive value of the screening tests will be different in patients presenting with symptoms as opposed to the general population.

Since the decision to perform a biopsy in patients with PSA values of 3.0 ng/mL or more is often driven by the results of the PSA test, we have concentrated our efforts on the lower PSA ranges, where DRE is the mainstay of early diagnosis.

A review of the older literature (16) describes an average detection rate with DRE alone of 0.85% and a positive predictive value of 28%. Seventy-three percent of all cancers were detected in a clinically locally confined state. A number of older studies predating the PSA era and more recent reports deal with the usefulness of DRE as a screening test alone and in combination with other tests (17–24).

In spite of a very large number of participants and cancers already detected and in spite of our knowledge of tumor characteristics, definitive judgments on the value of individual screening tests or screening algorithms can be made only after the results of the definitive randomized screening studies are available. Statistical correlation with the main end point, which is prostate cancer mortality, will be of crucial importance. Also, data on important aspects of quality of life (such as difficulties with the screening process itself), the diagnostic and biopsy procedures, and cost are not available and cannot be judged at this time.

Predictive Value of DRE

Our data indicate that the DRE has a low positive predictive value in men with low PSA levels. This result is due to the low prevalence of the disease and the low sensitivity of the screening procedure. When PSA levels are less than 3.0 ng/mL, 11 biopsies are necessary to detect one cancer. If it were certain that those cancers detected in this PSA range pose a significant threat to the patient’s life, this burden might be acceptable (however, many of these cancers do not seem to pose such a threat). Selective screening for potentially aggressive lesions is important. Many prostate cancers detected in men with PSA levels of less than 4.0 ng/mL do not show the characteristics of aggressive disease by volume and grade of differentiation. A large proportion of the tumors detected may not be immediately clinically relevant and would probably be detected through subsequent screening, as suggested by Carter et al. (25). Since a PSA level of less than 4.0 ng/mL does not indicate the need for a biopsy, for PSA levels less than 4.0 ng/mL in this study, one might expect that cancers found by

| Table 2. Sensitivity and specificity of digital rectal examination (DRE)* |
|---------------------------------|-----------------|------------------|-----------------|-----------------|-----------------|
| PSA level, ng/mL                | No. of DREs (a) | No. of APPAs (b) | No. of PCs (c)  | Sensitivity (db) | Specificity, % |
| 0–0.9                          | 1702            | 19               | 109             | 4               | 21              | 94              |
| 1.0–1.9                        | 3305            | 119              | 296             | 29              | 24              | 92              |
| 2.0–2.9                        | 1314            | 97               | 128             | 14              | 14              | 91              |
| 3.0–3.9                        | 734             | 89               | 106             | 35              | 39              | 89              |
| 4.0–9.9                        | 1095            | 254              | 249             | 115             | 45              | 84              |
| >10.0                          | 217             | 128              | 82              | 67              | 52              | 83              |
| Total                          | 8367            | 706              | 970             | 264             | 37              | 91              |

*We screened 8367 men by use of the DRE and found that 970 men required biopsy examination. These biopsy examinations detected 264 prostate cancers (PCs). The a priori prevalence assessment (APPA) of prostate cancer as a function of prostate-specific antigen (PSA) level was used. The logistic regression model applied for determining APPA uses PSA, DRE, transrectal ultrasonography, and prostatic volume. These data give an estimate of the number of cancers that would have been found if all patients had received a biopsy examination.

| Table 3. Tumor volumes and Gleason scores as a function of prostate-specific antigen (PSA) level and digital rectal examination (DRE) results (n = 105) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| PSA range, ng/mL                | No. of DRE-negative cases | Tumor volume, mL† | Gleason score | No. of DRE-positive cases | Tumor volume, mL† | Gleason score |
| 0–0.9                          | 0               | 0.11 (0.002–0.23) | 6 (5–7) | 2               | 0.24 (0.04–0.43) | 6 (6–6) |
| 1.0–1.9                        | 4               | 0.49 (0.22–0.62) | 7 (7–7) | 13              | 0.36 (0.003–1.09) | 6 (5–7) |
| 2.0–2.9                        | 3               | 0.49 (0.22–0.62) | 7 (7–7) | 8               | 0.57 (0.04–1.80) | 7 (6–7) |
| 3.0–3.9                        | 4               | 0.57 (0.32–0.84) | 7 (7–7) | 4               | 0.83 (0.18–1.91) | 7 (7–7) |
| ≥4.0                           | 38              | 0.96 (0.005–4.34) | 6.5 (4–8) | 29              | 2.22 (0.16–13.48) | 7 (5–9) |
| Total                          | 49              | 0.83 (0.002–4.34) | 7 (4–8) | 56              | 1.38 (0.003–13.48) | 7 (5–9) |

*A DRE-negative result is defined as nonpalpable cancer.
†Data are the mean with the range in parentheses.
‡DRE-positive result is defined as palpable cancer.
DRE and/or TRUS are larger, clearly palpable, and visible tumors that do not produce much PSA, a feature often associated with poor differentiation. The contrary, however, is the case.

To improve the understanding of this situation further, the sensitivity of DRE as a function of PSA level was calculated by use of an estimate of the \textit{a priori} prevalence of prostate cancer obtained by logistic regression modeling (APPA). The proportion of these potentially diagnosable cancers, diagnosed by DRE, remains very low, perhaps because many of these tumors are too small to be palpable by DRE. In Table 2, sensitivity in this context indicates the number of cancers detected relative to those that would have been detected if every participant had been subjected to biopsy examination. A screening test that identifies only 20% of identifiable cancers has a very low predictive value. Consequently, for this test, the philosophic and ethical problem then is to determine the lower limit of the sensitivity that is acceptable. If screening could be made selective enough so that aggressive tumors could be identified with reasonable accuracy and so that nonaggressive lesions could be eliminated from immediate treatment, a lower sensitivity might be acceptable than in the present situation. The slight decrease of the specificity with increasing levels of PSA remains unexplained but could be related to benign prostatic hyperplasia. The presence of precursor lesions may be another explanation. The positive predictive value of the test combination overall is 473/2267 = 21%, and the sensitivity (Table 2) is 37%. This result compares unfavorably with the findings in regard to mammography in the Dutch National Screening trial, which had a positive predictive value of 45.4% with 2.2 biopsies per cancer detected (26). In the German mammography study, the sensitivity of mammography and physical examination was overall 73% (27). This is in line with the 68% sensitivity reported in the Health Insurance Plan trial in the United States (28).

As far as the ongoing screening study is concerned, the predictive value of a screening test has to be viewed in a different context as long as it remains uncertain which tumors will progress rapidly and which tumors will not. The final aim of the study, namely, to show or to exclude a difference in prostate cancer mortality, may be jeopardized by various exclusions. Thus, a change in screening strategies within protocols requires careful exclusion of the possibility that relevant tumors are eliminated from a given study. Still, with the combination of volume and grade of differentiation being likely, but for the most part unproven, prognostic parameters in this respect, the risk of missing potentially aggressive tumors remains.

Tumor Aggressiveness

Men with prostate cancer who have PSA levels, measured at an initial screening, of less than 3.0 ng/mL usually harbor prostate cancer that has a favorable prognosis. However, definitions of what might be nonaggressive disease have not been tested prospectively and are likely not to be applicable to the individual patient. Furthermore, the biologic potential of individual lesions may be unpredictable. It is a disturbing finding that, in our series of carefully studied radical prostatectomy specimens, up to 60% of cases contained poorly differentiated foci (Hoedemaeker RF, Rietbergen JB, Kranse R, van der Swast TH, Schröder FH: unpublished data). Without being able to correlate these findings to important end points, such as prostate cancer mortality, it will be impossible to determine exactly what may be a clinically unimportant prostate cancer or a tumor with a minimal risk that justifies a delay in diagnosis and treatment. Even more difficult will be the identification of such cancers on biopsy specimens because of the well-documented difficulty of identifying poorly differentiated disease. A study (29) indicated that undergrading with respect to Gleason scores 7–10 may be in the range of 50%. To develop biopsy techniques that are more representative of tumor composition and to improve judgment on aggressiveness are top research priorities in this field. Another source of uncertainty lies in the fact that only about half of the patients with diagnosed cancers in this study underwent radical prostatectomy, and selection bias cannot be excluded.

How to Continue?

This study presents evidence that the DRE has a very low predictive value with respect to diagnosing prostate cancer in men with PSA levels of less than 3.0 ng/mL and in large proportions of men with PSA levels between 3.0 and 3.9 ng/mL. Large numbers of biopsies are necessary to diagnose small numbers of tumors. This can be considered an inherent feature of screening. However, cancers found often have the characteristics of clinically nonaggressive tumors, and these cancers at the time of diagnosis are probably not life-threatening. In addition, the screening procedure is bothersome and not without danger for the participants. If at all possible, in those men who have PSA levels of less than 3.0 or 4.0 ng/mL, the DRE should be replaced with a more sensitive test. Research should concentrate on alternative technologies and algorithms. The predictive power of using the free/total ratio of PSA in men with low total PSA values has been insufficiently explored, but its use may be important to improve specificity and selectiveness of screening (30). Also, experimental confirmation of the correctness of model predictions of the underlying prevalence of prostate cancers needs to be obtained.

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NOTES

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