and she is aware of the potential risks and benefits, the legal imperative here suggests that once you have made the referral to MRI you must deal with all the findings, positive or otherwise.

Finally, he turns to his youngest son, an exceptional clinician (a surgeon and radiologist) and asks, “Doesn’t this lesion require the identical clinical attention that any other lesion found on MRI would dictate; do I have different clinical or ethical responsibilities in this particular case?”

The doctor appears conflicted about the situation, especially after hearing his siblings. He wants to entrust his patient’s care to these statistics, after all he has a degree in public health, but it doesn’t appear so simple, especially when he knows that delay in diagnosis of breast cancer is one of the most litigated claims in America. Look, he says, some of these “lesions” are dependent on menstrual cycles, so many represent benign proliferative disease. Yet, a few (admittedly very few) are cancer, and if it’s “my” cancer, it’s my problem. The mammographic examination and CBE didn’t show it the first time, just like some of those cancers metastatic to lymph nodes that are shown only on MRI. I’m not sure I can follow it with these more conventional tools the second time. Close follow-up, like my stock portfolio, may sound better than it really is. Therefore, the recommendation of the authors, that these lesions need not be subject to immediate biopsy, while likely a reasonable scenario in the future, requires additional clinical study for validation.

Dr. Gamliel reclines in his chair, finishes his fourth cup of wine, and tries to summarize:

Thank you my children, your collective wisdom has persuaded me that we are at a starting point, not an end point. Truly, it is too early to decide the appropriate management of these incidental findings. The protocols have not been standardized, the information not much better than anecdotal, and no longitudinal studies of these lesions are available to establish a reasonable approach from a clinical perspective. Perhaps you will help me write a multicenter grant for the study of these incidental lesions, with a focus on a well-standardized protocol for longitudinal study. May we hope that future serendipity will not throw us such a difficult curve ball.

**REFERENCE**


**NOTE**

1Dr. Gamliel is a fictitious character used to convey the editorial message.

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**Lest We Abandon Digital Rectal Examination as a Screening Test for Prostate Cancer**

*Joseph W. Basler, Ian M. Thompson*

Until the mid-1980s, early detection for prostate cancer had only one tool—digital rectal examination (DRE). The tool is subjective with high interobserver variability (1,2), upward of 10% of prostates are considered abnormal, but only about 1%-2% of men examined are found to have disease. Even then, two thirds or more of the cancers discovered are found to be pathologically advanced (3). Perhaps more worrisome is the fact that, in one study, many men who ultimately died of prostate cancer had a normal DRE at the time of diagnosis (4).

Enter prostate-specific antigen (PSA) testing. There is no question that PSA testing has improved our ability to detect prostate cancer at an earlier clinical stage. PSA testing has 1) dramatically increased the number of tumors detected, 2) detected a population of tumors [stage T1c (5) that are by most measures clinically important, and 3) streamlined our metastatic evaluation of prostate cancer (e.g., identifying a class of patients for whom bone scans and even lymph node dissections may be unnecessary). By using PSA derivatives such as lower PSA thresholds for biopsy (e.g., 2.5 ng/mL for all men), age- and race-adjusted cutoffs, free/total PSA ratio (<25%), PSA/transition zone volume density, etc., the majority of prostate cancers can probably be detected serologically.

So what do we do with our clinical relic of times past? Do we discard DRE and perform our early diagnosis en absentia: merely ask the patient to have a blood test and never examine the patient? Reporting in this issue of the Journal, Schröder et al. (6) would have us believe so. They screened 10,523 men aged 54-76 years with three tests—DRE, measurement of PSA levels, and transrectal ultrasonography (TRUS). Using estimated disease prevalence, they determined the performance characteristics of DRE and PSA. Across the board, the performance of PSA was superior to DRE. However, we are not yet ready to dismiss DRE because of concerns with the study of Schröder et al. and a body of evidence supporting the value of DRE. Perhaps you will help me write a multicenter grant for the study of these lesions, with a focus on a well-standardized protocol for longitudinal study. May we hope that future serendipity will not throw us such a difficult curve ball.

**REFERENCE**

There is no indication of how many patients had a previous evaluation with PSA and/or DRE before study entry. Without this information, we do not know if the study analyzed a prescreened population and, therefore, a group that was more likely to have been depleted of palpable or PSA-detectable tumors. In this setting, DRE would perform more poorly than in a population with no prescreening. 2) Because of two changes in the protocol, the actual detectable incidence of prostate cancer in patients with a low PSA level remains uncertain. 3) The criteria for a patient undergoing biopsy included a PSA level greater than or equal to 4.0 ng/mL, an abnormal DRE, or an abnormal TRUS (interpreted as meaning a hypoechoic lesion). While TRUS-detected lesions specifically underwent biopsies, no attempt was made to perform biopsies on palpable lesions. Since we know that many of the prostate cancers detected on serial biopsy are isoechoic and even expert interpretation of diagnostic TRUS is variable (7), this omission negatively impacts the sensitivity of DRE. 4) The biopsy rate is considerably lower for the patients in the lower PSA ranges than it is for the patients with PSA levels of 4.0 ng/mL or more. This suggests that the number of cancers in the low PSA ranges may be substantially underestimated in this lower PSA range. 5) Schröder et al. (6) claim a 100% compliance rate with the recommendations for biopsy; we note only 90% compliance with biopsies for men with PSA levels of 4 ng/mL or higher. This would suggest that biopsy rates of those who had lower PSA levels may be significantly less. 6) The definition of ‘‘minimal’’ prostate cancer is somewhat arbitrary and without substantiation. The work of Albertsen et al. (8) suggests that the 15-year mortality from untreated prostate cancer is low only for Gleason scores of 2–4 (4%–7%) and becomes progressively worse with the development of pattern 3, 4, or 5 disease (6%–30% for a Gleason sum of 5 and 6 and 42%–87% for a Gleason sum of 7–10). A more realistic classification would, therefore, include Gleason score 3 and above (sum >4), volume greater than 0.5 mL, and capsular penetration with the ‘‘advanced’’ category of tumors—a group of tumors that is readily found with DRE in the population with PSA levels less than 4.0 ng/mL.

From a technical standpoint, no clinical or pathologic staging of the cancers detected is given for either population (DRE-positive or DRE-negative). Also, it must be emphasized that Schröder et al. (6) reported on the ‘‘first-pass’’ screening results—essentially a ‘‘prevalence screen.’’ In such a clinical experience, we would expect to diagnose two groups of tumors that are glaringly missing: metastatic tumors and prostatic intraepithelial neoplasia. The lack of the former suggests that there may have been a prescreening phenomenon: the men in the study may have had periodic pretest study DREs (and perhaps a lower likelihood of pretest PSA tests), thus skewing the results against DRE. The lack of any reports of high-grade prostatic intraepithelial neoplasia is bothersome because, in most series, about 1%–5% of biopsies will demonstrate this lesion; 30%–50% of such patients will be found to have prostate cancer on a follow-up biopsy. It is possible that DRE may have detected some of such patients.

Although the overall positive predictive value of DRE was 27%, this value dropped substantially—to between 4% and 33%—in men with a ‘‘normal’’ PSA level (0–3.9 ng/mL). In men with a PSA level between 0 and 2.9 ng/mL, the positive predictive value was only 4%–11%. Had DRE been eliminated from the screening program, 82 tumors would have been ‘‘missed’’—17.3% of all tumors detected. It is interesting that no comment was made on the ability of TRUS to predict cancer. For instance, 74 biopsies were done for an abnormal TRUS in patients with PSA levels of 0–0.9 ng/mL, but no cancers were found. For PSA levels of 1–3.9 ng/mL, 370 biopsies were done for an abnormal TRUS, but only 40 cancers were detected (11% positive predictive value). This compares unfavorably to the approximately 15% positive predictive value for DRE in this range.

Since only approximately 50% of the patients with prostate cancer underwent radical prostatectomy and in less than half of these were pathologic findings (volume/Gleason score) analyzed, it is uncertain if the findings are applicable to the entire study population. Of those undergoing radical prostatectomy, Schröder et al. (6) found that none of the tumors missed by a PSA cutoff of 4.0 ng/mL were ‘‘advanced,’’ 41% were ‘‘minimal,’’ and 59% were ‘‘moderate.’’ However, a review of Table 3 of the report by Schröder et al. (6) shows average volumes of more than 0.5 mL starting in the DRE-positive group that had a PSA level of 2.0–2.9 ng/mL and at least some Gleason sum 7 (implying a grade 4 pattern) starting at a PSA level of 1.0–1.9 ng/mL. Applying the more conservative criteria for ‘‘important’’ tumors to the current series results in some cancers from all PSA ranges being considered ‘‘minimal’’ in both the DRE-positive and DRE-negative groups. Table 3 of the report by Schröder et al. (6) also shows that the tumors detected by DRE were on average larger and of intermediate or higher Gleason score. The only low-volume tumors (average <0.2 mL) that approached biological unimportance were in the DRE-negative group with PSA levels of 0.0–1.9 ng/mL. Contrary to the conclusions drawn by Schröder et al. (6), these data suggest that patients with an abnormal DRE but PSA levels of 2.0–4.0 ng/mL will have important tumor volumes and Gleason scores. This group of cancers had volumes of 0.5 mL or greater and Gleason scores greater than 4.

Although only 17% of DRE-detected tumors would have been missed with PSA-based screening, it is an unsubstantiated leap of faith that these tumors would be detected with serial follow-up examinations. Indeed, in a recent case–control study of men who died of prostate cancer and of control subjects, men with a DRE within 10 years of diagnosis had a 50%–70% lower likelihood of death due to prostate cancer (4). In addition, studies done in other screened populations indicate that the disease in a proportion (20%–25% at PSA levels of 4.0 ng/mL) of these men will progress to pathologically advanced disease (9). The disease in a number of men may progress to incurability while one waits for the PSA level to cross 4.0 ng/mL to find their cancer.

We and others (9,10) have found DRE to independently and significantly affect the prediction of prostate cancer risk. Additional evidence suggests that DRE may have different performance characteristics in distinct ethnic groups; the positive predictive value of DRE may be twice as high in African-American men as it is in Caucasian men (11). Such an advantage may not have been identified in the European trial and thus may not be generalizable to U.S. populations.
Notwithstanding these comments, Schröder et al. (6) should be congratulated for conducting a very important trial and for asking critical questions. DRE is certainly not a high-performance screening test (1/2). However, the facts that one quarter to one third of all prostate cancers are detected by DRE in the “normal” PSA range, that DRE is not viewed by patients as an impediment to screening, and that DRE is inexpensive and provides tumor staging information that is as good as TRUS make it a reasonable companion to PSA in current programs for prostate cancer screening. We echo the appeal by Schröder et al. for more sensitive methods of prostate cancer detection to either replace or supplement DRE.

Finally, the proof of the relevance of this issue will eventually be established upon the completion of the PLCO (prostate, lung, colorectal, ovarian) cancer screening trial sponsored by the National Cancer Institute. Until this trial is complete and until we have validated the observations of Schröder et al., we would continue to recommend both PSA and DRE for patients who desire screening for prostate cancer.

REFERENCES