higher than Dr Rich's estimate of 14%, but Dr Rich performed only one sampling. Contemporary practice in the United States calls for 10–12 biopsies to evaluate a man with an elevated PSA.

Dr Arnold Rich reported his observations in 1934. We are still struggling to understand the full implications of his findings and how best to treat this disease. With the advent of widespread PSA testing we have the potential of diagno
ing occult prostate cancer in as many as half of all new diagnoses. Clearly, we need better genetic markers that will help differentiate clinically significant disease from occult tumours. Imagine what Dr Rich might have reported if he knew about the structure of DNA!

References


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carcinomas of the prostate on screening by PSA (their detection seems not to be a feature of the use of DRE). These considerations are also likely to affect any new test that is developed of equivalent or superior sensitivity to PSA, unless it is based on a marker of progression, which in view of the issues I shall raise, seems to be urgently required.

Why should we be concerned about screening for prostate cancer? Currently there are three reasons, PSA screening has been widely promoted in several countries, with a marked increase in reported incidence of the disease, making it the most frequently treated cancer in men in many countries; mortality from prostate cancer is the second cause of cancer mortality in men in many countries; and there is so far no solid evidence that the screening being performed is having an impact upon such mortality. If that latter statement is based on a marker of progression, which in view of the considerations I shall raise, seems to be urgently required.

Rice was careful in his study only to count lesions as cancer if they had the classic features of malignancy. However, it is a truism, that until recently, pathologists have only had crude measures to assess the potential for progression, even rapid progression, expected in those cancers that will be most likely to metastasize early and result in death. By definition, none of the cancers identified by Rice had done so—hence the appropriateness of the term occult that he used, or the similar word latent, used by others. Subsequent studies have confirmed Rice’s observations, and have shown that in North America and Europe, about half of the men who die at the age of 70 or more have occult prostate cancer detectable at autopsy, while around 10–30% of men have these lesions at the age of 50–54, and about 30% of men harbour unsuspected prostate cancer by the end of the fifth decade of life. Some have suggested that if men lived to 150, nearly all will have them. However, the majority of men with detectable prostate cancer in life do not die of their disease, and this has become extremely obvious in the PSA era.

Many have claimed that the large majority of lesions detected following a positive PSA test have all the features of malignancy, and inferred that if these lesions were not treated, they would eventually kill the patient. This is often used as a justification for PSA screening, and increasingly men are surviving who are convinced, that but for the PSA test, they would be dead by now—a belief often buttressed by their urologists, who use the argument to offset, and minimize, the distress caused by the consequences of treatment—impotence and incontinence. The possibility that the detection and treatment of the cancer, and more so the undesired consequences of such treatment was entirely unnecessary, is swept aside and ignored. But we have no right to ignore such possibilities, so it is right to review the evidence that confirms that the PSA test does result in what we term overdiagnosis, and thus unnecessary detection and treatment, as initially inferred was likely through the studies of Rice and his successors.

Overdiagnosis is one of the four biases that affect evaluation of screening by assessment of survival of screen-detected cases, the others being lead time, length bias and selection bias. Overdiagnosis is possibly the least well understood, especially by pathologists, who insist that the cancers they report are real cancers, and not latent or non-progressive, and certainly not of borderline malignancy. This is of course true, because the definition of overdiagnosis is statistical, not biological. It is simply the detection of a cancer by screening that is not destined to present clinically in the subject’s lifetime. With all cancers detected by screening, overdiagnosis is probable, largely because of competing causes of death. For lung cancer, overdiagnosis, especially with highly sensitive tests such as low-dose helical computerized tomography, is inevitable because the majority who develop lung cancer are smokers, with a much higher propensity for death from other causes because of the smoking. Overdiagnosis is now accepted for breast cancer detected by mammography (perhaps about 10% of screen-detected cancers), and has now been conclusively demonstrated for prostate cancer.

The evidence to date largely derives from the Rotterdam component of the ERSPC trial, and assessment of trends in prostate cancer incidence in the US. The ERSPC trial commenced when screening with PSA was uncommon in The Netherlands, and thus contamination of the control group with PSA screening was probably unusual. Further, the investigators decided to use a lower cut-off point for PSA than that used in the US, and thus in the PLCO trial, 3 ng/ml as distinct from 4 ng/ml. Thus, they had a high detection rate for prostate cancer, and interestingly, a low interval cancer rate between the screens, planned for a 4-year interval compared with annual tests used in the US and in PLCO. Over a follow-up period that now incorporates the first two screening rounds at the planned 4-year interval, the excess of prostate cancers in the screening round compared with the baseline incidence in the control group was approximately 6-fold. Some of the excess is due to lead time, estimated from the same series as 11.2 years, but the rest is overdiagnosis, estimated by the investigators as ~48%. Indeed, these investigators’ model-based estimates suggested extending screening to the age of 75 would result in at least two cases of overdiagnosed cancer for every clinically relevant cancer detected.

What does this substantial level of overdiagnosis mean for screen-detected prostate cancer therapy and its consequences? Many in the Rotterdam trial were treated by radical prostatectomy, we do not know how many suffered from impotence and incontinence, perhaps 30%. So here is a considerable problem, in practice, forecast some time ago.

Moving from the Rotterdam trial—what about the routine use of PSA and its consequences, perhaps particularly in the US? Etzioni et al. estimated rates of prostate cancer overdiagnosis due to PSA testing based on the observed incidence of prostate cancer in the US from 1988 through 1998. They concluded that ~29% of prostate cancers among whites and 44% among blacks had been overdiagnosed.

The initial findings from the first screening round in PLCO have been published, but not as yet the corresponding detection rate from the usual care control group. It seems as if lower numbers of prostate cancers were detected in that first round than could have been anticipated from the Rotterdam results—perhaps because of a combination of different recruitment criteria and a higher cut-off level for PSA—as...
well as more caution in requesting biopsies than in the Rotterdam study (where there is a requirement that at least 80% of those with an abnormal PSA should proceed to biopsy, a requirement that cannot be enforced in standard North American practice). Perhaps already, urologists in the US are beginning to recognize the adverse impact of overdiagnosis, and are exercising commendable caution over early radical treatment. If the inferences to be drawn from the Andriole et al.’s paper can be extrapolated to the US, the overdiagnosis problem may be less than in the Rotterdam trial, but still there.

As inferred earlier, we may have approached our expectations for an ideal screening test from the wrong perspectives. Mere cancer detection is not the aim of screening, detection and effective treatment for progressive lesions that would otherwise result in death is. On these criteria PSA is clearly not an ideal screening test. We need to capitalize on the emerging knowledge on markers of progression and devise a screening test that will avoid overdiagnosis, and detect the cancers that otherwise will kill. And then when we have it, we must assess it properly—not by a simple comparison of test sensitivity of detected lesions in the same men, because the ideal test will always seem inferior if it avoids overdiagnosis, but by a randomized trial that will enable us to assess whether the new test removes from the future interval cancers that occur those that would otherwise kill. Perhaps this may be achieved by using the cumulative incidence of advanced disease as the endpoint, if we do not want to wait for the preferred endpoint, mortality from the disease.

References


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