Prostate cancer screening: waiting for Godot

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Editorial

Éditorial

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The issue of prostate cancer screening continues to go around and around. All agree that a randomized clinical trial is needed to determine whether screening does more good than harm. However, everyone also agrees that the absence of evidence of benefits is not proof that benefits are absent. That prostate cancer is a significant health problem is undeniable. For Canadian men it is now the most commonly diagnosed malignant disease and is second only to lung cancer as a cause of cancer-related death.[1] The burden of this condition and the lack of definitive answers mean that there is not only an opportunity to provide further information short of a randomized controlled trial, but also a risk in doing so because the prostate cancer world is divided into 2 camps on the issue of screening: evangelists and snails.[2] The lack of definitive information has not been a barrier to thought on this matter. A search of the CANCERLIT database using the terms "prostate neoplasms" and "mass screening" revealed only 56 articles from 1983 to 1989, but 265 articles or comments from 1990 to 1994 and 362 from 1995 to May 1998.

Dr. Maurice McGregor and colleagues attempt to illuminate one area of this controversy by defining the extent of overdetection in a hypothetical screened population (page 1368). They conclude that 16 of every 100 cases of prostate cancer detected through screening would be fatal if left untreated. Their work takes the form of a thought experiment in which available information is synthesized to illuminate an area not previously examined. Similar thought experiments related to prostate cancer screening have been published previously[3,4] and have been followed by considerable debate.[5–7] Much of the controversy exists because there are no definitive data upon which to model these analyses. Consequently debate ensues about the assumptions used in these thought experiments.

What, then, are some of the assumptions upon which McGregor and colleagues base their observations? One assumption is that radical prostatectomy provides curative therapy for prostate cancer and that on average 20 operations per year were carried out in Quebec from 1988 to 1992. McGregor and colleagues estimate that 50% of these procedures prevented death. They also assume that the treatment patterns for curative radiation therapy in Quebec were similar to those in the United States during the same period and that curative radiotherapy was used in a comparable number of patients with similar results. The fact that the relative effectiveness of one therapy over the other or over a more conservative treatment has not been established leaves the extent to which either therapy can prevent death open to question. The authors performed a sensitivity analysis of their 2 study groups and determined that the total number of deaths averted could be from 0.5 to 1.5 times the number they predicted. Whereas this may seem reasonable, it does not take into account the fact that practice patterns for other conditions for which radiation therapy and surgery could be the primary modes of treatment are systematically different and seem to be related to local tradition.[8] If that scenario is true for prostate cancer, the assumption that radiotherapy use in Canada is comparable to that in the US is erroneous.

Perhaps the most difficult aspect of the report relates to the distribution of stage and grade of disease that a screening program would yield. McGregor and colleagues have used cause-specific survival rates from 2 series of conservatively managed patients[9,10] and a population-based registry[11] to estimate survival rates for a screened group of men. Although there is a great deal of similarity in the cause-

specific survival rates by tumour grade between these reports, the distribution of histologic grades in the study by Chodak and colleagues[9] differed substantially from that in the Surveillance, Epidemiology and End Results (SEER) report by Lu-Yao and Yao[11] (59.4%, 32.0% and 7.6% for grade 1, 2 and 3 tumours [*n* = 828] v. 29.6%, 47.5% and 16.6% [*n* = 59 876] in the SEER report).

What would the likely distribution of grade and stage be for a screened group of men? McGregor and colleagues have used data from the St. Louis screening study[12] to estimate the grade and, presumably, stage distribution of their hypothetical population. A worrisome feature of the St. Louis study is that 99% of the volunteers were white, something not in keeping with the demographics of the community or the higher burden of prostate cancer among black men. Therefore, to what extent can these data be generalized to this or any model of screening? Are the available data robust enough to predict both the extent of disease and the grade of prostate cancer that would be found in a screened population? If so, would the absolute mortality change or would survival rates be enhanced by factors unrelated to detection and therapy?

Are temporal trends of sufficient concern to raise questions about using historical data for the modelling? One report has demonstrated improvements in survival with successive cohorts of patients,[13] but this has been attributed primarily to the overdetection of non-lethal tumours and the effects of stage migration[14] rather than to any changes in therapy. The notion that overdetection is already an issue is buttressed by the similar mortality rates in different regions of the US despite different incidence rates.[15] Taken together, even without a formally functioning screening program, overdetection is already a fact. At the individual level, this occurs every time a man is told he has prostate cancer and is successfully cared for with conservative management.

Overdetection occurs when someone is informed of a condition that will never result in life-threatening illness during his or her lifetime. Do we know if all cases of in situ breast cancer will ultimately lead to invasive disease? If so, how quickly? Are all patients with a genetic marker for cancer or another serious illness destined to have that disease? Overdetection is certainly not an issue restricted to prostate cancer. Although there is the need to accept overdetection as a consequence of screening, irrespective of the disease or the test, what level of overdetection is acceptable?

The late Willet Whitmore is credited with asking, "Is cure possible when it is necessary and is cure necessary when it is possible?" Simply put, Whitmore recognized at least 2 classes of prostate cancer: one in which diagnosis and treatment are burdens because the disease will never cause a problem for the patient, and the other in which the clinical course of the disease defies any form of treatment and results in death. Most clinicians involved with prostate cancer believe there is a third group that can be cured with therapy. How large this group is and how confident clinicians are in distinguishing this group from the other 2 is difficult to address. The essence of the problem is that, however this issue is examined, short of a randomized clinical trial any speculation is just that and will likely not sway the evangelists, who believe that lives are being lost while we await the perfect trial, or the snails, who believe that promoting an activity in healthy individuals without convincing proof goes against the adage *primum non nocere* and that the standards should be much higher in advocating a course of action in well individuals than in those seeking relief from a problem.[2]

Current screening studies for prostate cancer may not be perfect, and with the advent of newer methods for classifying patient risk and for testing, their results may not be relevant in 10 years when they mature. It is hoped that levels of certainty about what works, and for whom, will improve dramatically. The required knowledge can be developed only with the proper research support, a fact noted by the near–universal recommendation of the National Prostate Cancer Forum in February 1997.[16] To date, the response to this recommendation from all levels of government has been a deafening silence. The only way we will stop waiting for Godot is to determine what is effective and what is not. Given the current burden of this disease and the increase that is looming as baby-boomers enter the age group in which incidence rates of prostate cancer rise steeply, the time to find answers is now. In the meantime, the best we can do is be honest with our patients about what we know and what we don't know regarding prostate cancer screening.[16–18]

Finally, what if the estimates of McGregor and colleagues are correct: that for every 100 men with prostate cancer diagnosed through screening, 16 might avert death? Is the opportunity to save 16 men out of every 100 worthwhile? Compared to what?

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