Evidence

Études

From the Departments of *Medicine and of †Epidemiology and Biostatistics, McGill University, Montreal, Que.; ‡the Department of Medicine and §the Division of Clinical Epidemiology, Royal Victoria Hospital, Montreal, Que.; ¶the Division of Clinical Epidemiology and Community Studies, Sir Mortimer B. Davis–Jewish General Hospital, Montreal, Que.; and **Western Nuclear Medicine, Fairfield, Australia

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Screening for prostate cancer: estimating the magnitude of overdetection

Maurice McGregor,*‡ MD; James A. Hanley,*†§ PhD; Jean-François Boivin,†¶ MD, DSc; Richard George McLean, MB, BS**

Abstract

Background: No randomized controlled trial of prostate cancer screening has been reported and none is likely to be completed in the near future. In the absence of direct evidence, the decision to screen must therefore be based on estimates of benefits and risks. The main risk of screening is overdetection — the detection of cancer that, if left untreated, would not cause death. In this study the authors estimate the level of overdetection that might result from annual screening of men aged 50–70.

Methods: The annual rate of lethal screen-detectable cancer (detectable cancer that would prove fatal before age 85 if left untreated) was calculated from the observed prostate cancer mortality rate in Quebec; the annual rate of all cases of screen-detectable prostate cancer was calculated from 2 recent screening studies.

Results: The annual rate of lethal screen-detectable prostate cancer was estimated to be 1.3 per 1000 men. The annual rate of all cases of screen-detectable prostate cancer was estimated to be 8.0 per 1000 men. The estimated case-fatality rate among men up to 85 years of age was 16% (1.3/8.0) (sensitivity analysis 13% to 22%).

Interpretation: Of every 100 men with screen-detected prostate cancer, only 16 on average (13 to 22) could have their lives extended by surgery, since the prostate cancer would not cause death before age 85 in the remaining 84 (78 to 87).

Résumé

Contexte : Il n'a été fait rapport d'aucune étude contrôlée randomisée sur le dépistage du cancer de la prostate et il est peu probable qu'on en réalise avant longtemps. Comme il n'y a pas de données probantes directes, la décision de procéder à un dépistage doit donc être fondée sur des estimations des avantages et des risques. Le principal risque du dépistage est la surdétection — soit la détection de cancers qui, non traités, ne causeraient pas la mort. Dans cette étude, les auteurs estiment le taux de surdétection du cancer de la prostate qui pourrait découler d'un dépistage annuel chez les hommes âgés de 50 à 70 ans.

Méthodes : Le taux annuel de cancers mortels détectables par dépistage (cancer détectable qui serait mortel avant l'âge de 85 ans s'il n'était pas traités) a été calculé à partir du taux observé de mortalité attribuable au cancer de la prostate au Québec. On a calculé le taux annuel de tous les cas de cancer de la prostate détectables par dépistage à partir de deux études récentes sur le dépistage.

Résultats : Le taux annuel de cancers mortels détectables par dépistage s'est établi à 1,3 pour 1000 hommes. Le taux annuel estimé de tous les cas de cancer de la prostate détectables par dépistage est de 8,0 pour 1000 hommes. Le taux estimé de mortalité par cas chez les hommes de jusqu'à 85 ans a été de 16 % (1,3/8,0) (analyse de sensibilité : 13 % à 22 %).

Interprétation : Sur 100 hommes atteints d'un cancer de la prostate détecté par dépistage, de 13 à 22 (moyenne 16) seulement pourraient voir leur vie prolongée grâce à une intervention chirurgicale, puisque le cancer de la prostate ne causerait pas de décès avant l'âge de 85 ans chez les 78 à 87 (moyenne 84) hommes restants.

The question of whether to screen men for prostate cancer remains unresolved. Recent evaluations have concluded that screening might be beneficial among men under age 70 (if a favourable set of assumptions is used[1]), and others have concluded that it is unjustified[2,3] and that it should be discouraged[4] or left to the patient's preference.[5,6] The reason for this confusion is that no randomized controlled trial of screening for prostate cancer has yet been reported, nor is it likely that any such trial will be completed in the near future. Despite this, health authorities must decide whether screening should be advocated and paid for, and individual men and their doctors must decide whether screening should be done in the absence of symptoms.

Without direct evidence from trials, such decisions must be based on estimates. We must estimate the ability of prostate-specific antigen (PSA) screening to detect prostate cancer and the ability of treatment to prolong the life of patients in whom cancer is found. When the treatment itself entails significant morbidity, a third estimate becomes essential. How many cases of prostate cancer that do not require treatment (i.e., that would not cause death if left untreated) will be detected through screening and consequently receive unnecessary and potentially harmful treatment? Each such case represents overdetection.

Unfortunately, despite 2 large screening demonstration projects, overdetection has not been quantified explicitly for prostate cancer screening. To help fill this gap, we have estimated the annual rate of overdetection based on estimates of the incidence of lethal cancer and of the incidence of all cases of prostate cancer that would be detected through screening. Throughout, we have assumed that mortality rates based on Quebec data and detection rates based on US and Quebec screening studies are generalizable. For the purpose of our analysis the following terms were defined:

Screening: Annual PSA testing of asymptomatic men aged 50–70 years, with further investigation, including possible biopsy, if the PSA level is greater than 4 ng/mL. For our analysis, we considered only the steady-state situation after the first cycles of screening have eliminated prevalent cases of prostate cancer.

Screen-detectable cancer: Prostate cancer that would be detected by this screening strategy. The small tumours found at autopsy in 30%–40% of elderly men who die of other causes[7] are not relevant to our analysis.

Lethal cancer: Prostate cancer that would cause death if left untreated.

Overdetection: This was calculated by first estimating the case-fatality rate (CFR: the rate of screen-detected *lethal* cancer expressed as a proportion of the rate of *all* screen-detected cancer). The remaining proportion (100 – CFR) reflects the degree of overdetection.

Methods

In our analysis we did not consider morbidity due to prostate cancer. Reports of the outcomes of case series are not consistent as to their definitions of metastases; therefore, we used the more reliable outcome, mortality. (On the basis of the reported survival of patients with metastatic prostate cancer,[8] there would be on average about 3 years of worsening morbidity preceding each death from prostate cancer.)

To estimate overdetection we followed 4 steps: First, we calculated the rate of *lethal* prostate cancer entering the population from Quebec mortality statistics. We then calculated, from the literature, the proportion of these lethal cases that would be found through screening (lethal screen-detectable cancer). Third, from published screening studies we estimated the rate at which *all* cases of prostate cancer, lethal and non-lethal, would be found through periodic screening. Finally, we calculated the CFR and the rate of overdetection (100 – CFR) as rates that reflect the number of men with screen-detected prostate cancer who would and would not die of the disease if it was left untreated.

Rate of entry of lethal prostate cancer into the population

If no cases of lethal cancer were cured by treatment, and if all deaths from prostate cancer were reported, the mortality rate would reflect precisely the rate at which lethal cancer had entered the population several years previously. In Quebec, before the mid-1980s few men with prostate cancer received treatment with curative intent. Therefore, the rate of death from prostate cancer at the end of the 1980s is an approximate reflection of the rate of lethal cancer entering the population in earlier years.

We calculated the number of deaths from prostate cancer that would be observed in a theoretical cohort of men followed from age 50 to age 85 years. We did not consider deaths occurring after age 85 because we felt cancer that caused death after age 85 would likely not be detectable through a strategy that screens only to age 70. We used for our estimations the age-specific prostate cancer mortality rates reported for Quebec from 1988 through 1992.[9]

Detectability of lethal cancer by screening

The proportion of lethal cancer that would be detected by PSA testing was estimated from the available literature. Carter and colleagues,[10] through a retrospective analysis of stored blood samples, found that the PSA level was elevated in 78% of men with prostate cancer 5 to 7 years on average before the diagnosis was established. Because there

is a relation between invasiveness and PSA elevation,[11–14] PSA testing will probably detect lethal (more invasive) cancer more effectively than it will non-lethal cancer. In a retrospective study Gann and colleagues[15] found that, within 4 years of diagnosis, the PSA level was elevated (over 4 ng/mL) in 73% of all cases of prostate cancer, and in 87% of men with "aggressive" cancer. Similarly, Cohen and colleagues[16] found that the PSA level was elevated in 99.2% of 976 men with advanced cancer. Thus, as lethal prostate tumours develop, most will likely be associated with PSA elevation. However, in the strategy under consideration here, in which screening would end at age 70, some cases of late-developing cancer might be missed. The literature suggests detectability estimates ranging from 73% to 99.2%. For the purpose of our calculations we assumed that 85% of cases of lethal cancer might be detected through regular screening to age 70; we used detection rates of 75% and 95% in the sensitivity analysis.

Rate of detection through serial screening

The detection rate of prostate cancer through serial screening was estimated from data reported by Smith and colleagues[17] in 1996 (supplemented by personal communication from Smith to one of us [J.A.H.], Oct. 10, 1997]. This community-based study of serial screening with PSA measurement involved 10 248 male volunteers (99% white) aged 50 years or more who were screened every 6 months for at least 2 years. We combined the cases detected in 2 consecutive screens to determine an approximate annual rate of detection. After the initial screening cycles, the rate at which cancer was detected was maintained at about 8 new cases per 1000 men screened per year. The rate of detection was the same in the study by Labrie and colleagues,[18] in which 8029 men were screened annually using PSA testing. To allow for variations in compliance with screening and biopsy, geographic variations in tumour biology and different thresholds for investigating PSA elevations, we allowed for 25% variation in the annual detection rate (i.e., 6–10 per 1000 men screened) in the sensitivity analysis.

Results

We estimated that, in a cohort of 1000 men followed from age 50 to 85 years and experiencing the reported Quebec mortality rates, 23.9 (2.4%) will die of prostate cancer. This is equivalent to an entry rate into the population aged 50–70 of 1.35 new cases of lethal prostate cancer per 1000 men per year. After correction for possible underreporting and for possible deaths averted by effective treatment (see Appendix 1), we calculated an adjusted annual rate of 1.53 (sensitivity analysis [SA] 1.37–1.69) new cases of lethal cancer per 1000 men aged 50–70. These calculations are shown in Table 1.

Combining this corrected estimated annual rate of lethal prostate cancer with the estimated rate of detection through screening of 85% (SA 75%–95%), we estimated the annual rate of lethal screen-detectable cancer to be 1.30 per 1000 men (SA 1.03–1.61).

These estimates indicate that, in the absence of treatment, 1.30 of every 8 new cases of prostate cancer detected through screening will cause death by age 85, giving a CFR-85 of 16% ([1.3/8] × 100) (SA 13%–22%) (Table 2). Thus, of every 100 men with screen-detected prostate cancer left untreated, 16 (SA 13 to 22) would die from it before age 85, and the remaining 84 (SA 78 to 87) would either die from other causes or live past 85.

Table 1: Calculation of annual rate of entry of new cases of lethal prostate cancer in a cohort of 1000 men followed from age 50 to 85 years

	Age interval, yr						
	50–54	55–59	60–64	65–69	70–74	75–79	80–84
Average no. of men alive during age interval*	978	934	865	768	628	464	294
Age-specific prostate cancer mortality rate†	0.03	0.13	0.34	0.82	1.54	2.70	5.02
No. of deaths from prostate cancer in age interval‡	0.16	0.60	1.46	3.13	4.84	6.27	7.39

Derivation of the rate of new cases of lethal prostate cancer

Average no. of men aged 50–69 alive per year (978 + 934 + 865 + 768) ÷ 4	886
Annual rate of new cases of lethal prostate cancer per 1000 men (total no. of deaths from prostate cancer [23.9 (sum of row 3)] ÷ [886 × 20 years] × 1000)	1.35
Annual rate of new cases of lethal prostate cancer per 1000 men, corrected§	1.53

*As per Quebec Life Table, rescaled to begin with 1000 men alive at age 50.
†Reported in Quebec for 1988–1992; expressed as deaths per 1000 man-years, displayed to 2 decimal places.
‡Calculated as follows: average no. of men × age-specific mortality rate × 5 years. Total no. of deaths = 23.9.
§Corrected by 13.3% (sensitivity analysis [SA] 1.7%–25.0%) to allow for underreporting of prostate cancer on death certificates and for possible deaths averted because of effective treatment (see Appendix 1). The rate of reporting was increased by a mean of 10% (SA 0%–20%), and the number of deaths was increased by 20 deaths (or 3% [SA 1.5%–4.5%]) that may have been averted by successful treatment.

Interpretation

The concepts of overdetection, overdiagnosis and overdiagnosis bias have been used previously by authors, but no one has given a clear definition or calculated specific values for these parameters.[19–22] However, as defined here, overdetection can be estimated with some precision.

Our calculations indicate that only 16 (at most 22) of every 100 men undergoing radical prostatectomy for screen-detected prostate cancer might benefit from the operation. Although indirect, this estimate has considerable credibility because it is based on 2 fairly reliable input values: the mortality rate and the detection rate. We took the prostate cancer mortality rate in Quebec and, even though it is probably fairly accurate, further adjusted it upward to make allowance for the possible influence of previous therapy and underreporting of deaths from prostate cancer on death certificates. Any lesser adjustment would have resulted in an even lower CFR-85 than 16%. The estimated rate of detection through regular screening was based on the results of 2 recent extensive North American screening studies, whose results were in close agreement.

To compare with this estimated CFR-85, there are 3 published case series of men with clinically localized prostate cancer not treated by surgery or radiotherapy. We were able to derive a CFR-85 from the 10- or 15-year disease-specific survival rates reported in these studies (see Appendix 2). This approach resulted in CFR-85 estimates of 16%, 18% and 21%. Although they are based on less reliable data and a greater number of assumptions, the similarity of these results to our estimate is reassuring.

The estimated CFR-85 of 16% (SA 13%–22%) is an average value that applies to all cases of screen-detected, clinically operable prostate cancer aggregated over age and tumour grade. Older men, with more competing causes of death, will have higher overdetection rates than these average values. Thus, for any assumed efficacy of surgery, the probability of benefit will be greater for younger men.

Table 2: Sensitivity analysis of the annual estimated CFR-85 among men screened for prostate cancer*

Input variable (no. per 1000 men per year)		
Lethal cases of prostate cancer detected by screening	All cases of prostate cancer detected by screening	Estimated CFR-85, %
1.30	**8**	**16**
1.03	8	13
1.61	8	20
1.30	6	22
1.30	10	13

*CFR-85 = case-fatality rate calculated up to age 85. The best-estimate scenario is reflected in bold.

Similarly, since the overdetection rate is higher for low-grade cancers (Appendix 2) the probability of benefit will be greater for men with high-grade disease. Indeed, in the study of Lu-Yao and Yao[23] surgical benefit could be demonstrated only for tumours with high Gleason scores.

We have estimated here the ability of PSA screening to detect prostate cancer and the level of overdetection that could be expected. The ability of surgery to eradicate the tumours detected remains unknown. Even without this knowledge, however, our estimate of overdetection provides essential information for decision-making. The decision to screen an individual or a population must be guided by the estimated good and harm that may result from screening.

The potential good must, by definition, be limited to the men whose prostate cancer would have been fatal. Thus, if surgery were 100% effective, on average only 16 (at most 22) of every 100 men undergoing radical prostatectomy could benefit from the intervention. However, it is highly unlikely that all 16 men would actually benefit from surgery. Even in a regularly screened population 25% of the detected cases of cancer will be found at surgery to be pathologically advanced (histologically documented cancer extending beyond the prostate or resected prostatic tissue containing cancer at the margins).[17] Because advanced disease is more likely to be due to lethal than to non-lethal cancer, many of the 16% of lethal malignant tumours will probably be found at surgery to have spread beyond the capsule. Thus, overall the proportion of operations that can be expected to avert death from prostate cancer must be less than 16%.

Against this potential benefit of screening must be set its potential for harm. The complications of radical prostatectomy are not inconsiderable.[24–26] All men undergoing the procedure would be at risk for these complications, including the estimated 84% who would not benefit from surgery because their cancer would not be fatal if untreated.

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Correspondence to: *Dr. Maurice McGregor, Department of Medicine, Royal Victoria Hospital, Rm. M4.76, 687 Pine Ave. W, Montreal QC H3A 1A1; fax 514 843-1715; mcre@musica.mcgill.ca*

Appendix 1: Potential sources of underestimation of the rate of new cases of lethal prostate cancer based on the reported prostate cancer mortality rate for Quebec during 1988–1992

Some effective treatments given before the 1980s may have reduced the observed mortality rate used in the calculations

Radical prostatectomies were rare in Quebec in the 1970s. By 1984 they had reached a rate of 60 per year and increased rapidly thereafter. In most of the relevant time window (1978–1982) where successful treatment could have influenced the recorded mortality 10 years later, we assumed that on average 20 operations per year were carried out and that 50% (10) of these prevented death. The number of curative radiotherapy treatments administered in the years in question is unknown for Quebec, but given the reported patterns of care in the United States in that period,[27] we assumed that a comparable number of patients in Quebec received radiotherapy with curative intent. Assuming similar efficacy of treatment, a further 10 deaths might have been prevented. Thus, on the basis of these estimates, successful treatment by surgery and radiotherapy combined might have prevented 20 deaths per year. In sensitivity analyses we also explored the effect of 10–30 averted deaths on the final estimate.

Deaths from prostate cancer may have been underreported on death certificates

The mortality rates are based on information in death certificates. When causes are manually coded in order to prepare population mortality statistics,[28] priority is given to cancer as the underlying cause of death even if it is listed as the second or third underlying cause on the death certificate. In a follow-up of 648 consecutive cases of prostate cancer diagnosed during 1977–1984 the medical records of all 541 patients who had died were reviewed, and the investigators' own classifications of the cause of death were compared with those recorded on the death register.[29] There was agreement in 90% of cases and no evidence of systematic overreporting or underreporting of prostate cancer as the cause of death.

In a US study, an extensive comparison of death certificates and hospital records for patients with a definite diagnosis of cancer and for whom cancer was noted on the death certificate revealed that prostate cancer was overreported on the death certificate in 4% of cases and underreported in 5%.[30] In another US study of death certificates for men with prostate cancer who were admitted to hospital within a month before death, the rate of underreporting the prostate cancer on the death certificate was 5%–10%.[31] However, because death from prostate cancer is slow and symptomatic, in a society with free access to health care it is unlikely that many men will die of prostate cancer without the diagnosis becoming established during life. Thus, we assumed levels of underreporting of 10% and explored levels of 0% and 20% in the sensitivity analysis.

Appendix 2: Independent estimates of the case-fatality rate (CFR) based on published case series

We used as one input the disease-specific 10- or 15-year survival rate observed in case series of men with prostate cancer who had not been treated by surgery or radiotherapy.[23,32,33] These series were assembled in different ways and included men of different ages with cancer of different stages. Accordingly, the case series are not directly comparable to any series that might be found through regular screening of asymptomatic men. Partial adjustment for this is possible by applying the grade-specific mortality rates of each series and, as a second input, the all-other-cause mortality rates for Quebec men to the case mix of patient age and tumour grade that would be found in an annually screened population of men aged 50–70 years.

	Input variables		Estimated consequences‡	
Study	Tumour grade*	Cause-specific survival rate, %†	CFR-85	Mean CFR-85
Chodak et al[32]	1	87	15	18
(n = 828)	2	87	15	
	3	34	67	
Albertsen et al[33]	1	96	3	16
(n = 451)	2	72	22	
	3	50	40	
Lu-Yao and Yao[23]	1	93	8	21
(n = 18 338)	2	77	26	
	3	45	57	

*Grade: 1 = well differentiated, 2 = moderately differentiated, 3 = poorly differentiated.
†At 10 years for Chodak et al[32] and Lu-Yao and Yao;[23] at 15 years for Albertsen et al.[33] Mean ages at diagnosis: 70, 71 and 71.
‡The following estimates were used: (a) an average age at detection of 62 years,[34] with an assumed lead time of 5 years; (b) for mean CFR-85, a mix of 39:55:6 for grades 1:2:3, as in the report of Smith et al[17] (supplemented by personal communication from Smith to one of us [J.A.H.] Oct. 10, 1997); (c) for competing all-other-cause mortality, the level of all-other-cause mortality among Quebec men during 1988–1992, expressed as an exponential function of age fitted to the age-specific all-other-cause mortality rates; and (d) the rate of death from prostate cancer calculated as –ln[x-year cause-specific survival]/x; constant rate applied from 5 years after detection until age 85.