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SERIAL PROSTATE SPECIFIC ANTIGEN SCREENING FOR PROSTATE CANCER: A COMPUTER MODEL EVALUATES COMPETING STRATEGIES

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ABSTRACT

Purpose: We compare prostate specific antigen (PSA) screening strategies in terms of expected years of life saved with screening, number of screens, number of false-positive screens and rates of over diagnosis, defined as detection by PSA screening of patients who would never have been diagnosed without screening.

Materials and Methods: A computer model of disease progression, clinical diagnosis, PSA growth and PSA screening was used. Under baseline conditions, when screening is not considered, the model replicates clinical diagnosis and disease mortality rates recorded by the Surveillance, Epidemiology and End Results Program of the National Cancer Institute in the mid 1980s.

Results: Biannual screening with PSA greater than 4.0 ng./ml. was projected to reduce the number of screens and false-positive tests by almost 50% relative to annual screening while retaining 93% of years of life saved. With annual screening use of an age specific bound for PSA to consider a test positive instead of the standard 4.0 ng./ml. was projected to reduce false-positive screens by 27% and over diagnosis by a third while retaining almost 95% of years of life saved. Sensitivity analyses did not change the relative efficacy of biannual screening.

Conclusions: Under the model assumptions biannual PSA screening is a cost-effective alternative to annual PSA screening for prostate cancer. With annual screening use of an age specific bound for PSA positivity appears to reduce false-positive results and over diagnosis rates sharply relative to a bound of 4 ng./ml. while retaining most of the survival benefits.

KEY WORDS: prostate-specific antigen, mass screening, cost-benefit analysis, computer simulation

How often should healthy men have a PSA test for prostate cancer? This question demands attention because of the enormous costs associated with population screening[1] and the high prevalence of clinically insignificant yet potentially screen detectable prostate cancer in the population.[2] Despite these drawbacks, the test is perceived in some circles as an effective early diagnosis tool,[3] although its impact on prostate cancer mortality has yet to be demonstrated in a controlled study. To date analyses of the costs and benefits of prostate cancer screening have focused mainly on whether to do 1-time screening.[4–6] The question is now more theoretical than practical because many older men have already had a PSA test.[7,8] The salient question is how to proceed in terms of future screening. The American Cancer Society recommends annual screening with PSA and digital rectal examination for men 50 years old or older who have at least a 10-year life expectancy and for younger men at high risk for the disease.[9] However, several recently published studies have suggested that annual PSA screening may not be needed for everyone. Carter et al suggested that a 2-year PSA testing interval may be adequate among men with no cancer suspected on digital rectal examination and an initial PSA of less than 2 ng./ml.[10] Pearson et al further suggested that PSA testing may not be necessary for 10 to 15 years among men with PSA lower than 1 ng./ml. at age 65 years.[11] These studies based these recommendations on the frequency of PSA growth to levels at which cure is perceived to be relatively unlikely. For instance, Carter et al estimated that men with an initial PSA of 2.0 ng./ml. or less rarely have a level above 5.0 within 2 years.[11] They concluded that biannual screening of such cases would miss only a few of the curable cases that would be detected with annual screening. A direct evaluation of the costs and mortality benefits of this strategy relative to annual screening was not performed, although the authors noted that such an approach is likely to lead to substantial cost savings.

Recognizing that the choice of an optimal inter-screening interval is a complex function of cost and benefit, we used a computer model to predict the clinical benefits and liabilities of several alternative serial PSA screening strategies. The clinical liabilities, which are largely responsible for generating costs, are the tests, false-positive tests (unnecessary biopsies and complications thereof) and over diagnosed cases, that is those that would never have been diagnosed without screening and, therefore, incur the costs of diagnosis and treatment unnecessarily. We present results in terms of these components of cost rather than dollar amounts, which we believe provides a more informative assessment of the relative strengths and weaknesses of the competing strategies. The benefits are the years of life gained due to screening.

Accurately predicting years of life gained requires estimating the survival time of patients without screening and the survival time after screen detection for those diagnosed on screening. Although data quantifying the survival benefits due to PSA screening are not available, we make the basic assumption that screening impacts survival by advancing the date of diagnosis, thereby allowing disease to be detected while still curable. This assumption is common to practically all cancer screening models, although definitions of curable disease may vary. Our definition is similar to that of Barry et al, namely disease pathologically confined to the prostate gland.[5] Quality adjusted survival gains were not considered due to the lack of data on population based utilities for assessing quality of life in prostate cancer patients.

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There are several compelling reasons for using a computer modeling approach. Principal among them is the lack of data from clinical trials to assess the relative merits of competing screening strategies. However, in the absence of clinical trials, if we are willing to accept certain basic assumptions and results from the literature, and follow the implications, the computer model is the most efficient tool to deduce logically the public health consequences.

METHODS

Markov models describe the movements of a population through defined states according to various population level transition rates that are constant with time and independent of disease history.[12] Our model population consists of an initial cohort of healthy 30-year-old men followed until death or age 95 years, whichever comes first. For each individual in this hypothetical cohort the computer generates a data record representing the relevant aspects of life history, including prostate cancer status, age at death due to causes other than prostate cancer and PSA at each age. For individuals with disease ages at onset, key points in the histological and clinical progression, diagnosis and prostate cancer death are also generated. The model is programmed in GAUSS[13] and running time is 1.5 to 2 hours for an initial cohort of 200,000 men. When describing the model structure we use the term clinical presentation to refer to diagnosis without PSA screening and the term screening to imply PSA screening. Figure 1 summarizes the main components of the model, and tables 1 and 2 present the input data used for the baseline model.

Model structure. Natural History: The natural history component is responsible for determining which individuals will have histological cancer and at what age. Natural history of prostate cancer is described in terms of progression through pathological stages as classified by the American Urological Association.[14] Unlike previous models,[4,5] we do not explicitly model tumor grade. Including grade would require several additional modeling assumptions which would be difficult or impossible to validate, including the correlation between stage lengths and tumor grade, and the association between grade and PSA growth rates. In addition, little is known about whether and how tumor grade might change with time. Thus, our model is stage based. Age specific rates of disease onset[15] are used as input and the computer determines which men have disease at each age. For these cases the computer

TABLE 1. *Age specific mortality rates[17,35] and rates of onset of stage A1 prostate cancer[15]*

Age	% All Causes Mortality	% Prostate Ca Mortality	% Asymptomatic Onset*
30–34	0.002087	0.00	0.000754
35–39	0.002488	0.00	0.001098
40–44	0.002956	0.000002	0.001604
45–49	0.004520	0.000008	0.002376
50–54	0.007463	0.000036	0.003535
55—59	0.012215	0.000116	0.005346
60–64	0.019398	0.000312	0.008327
65–69	0.029087	0.000712	0.013039
70–74	0.046021	0.001392	0.020303
75–79	0.069881	0.002460	0.031163
80–84	0.108257	0.004085	0.049490
85+	0.185761	0.006168	Not used

* At the start of the age interval.

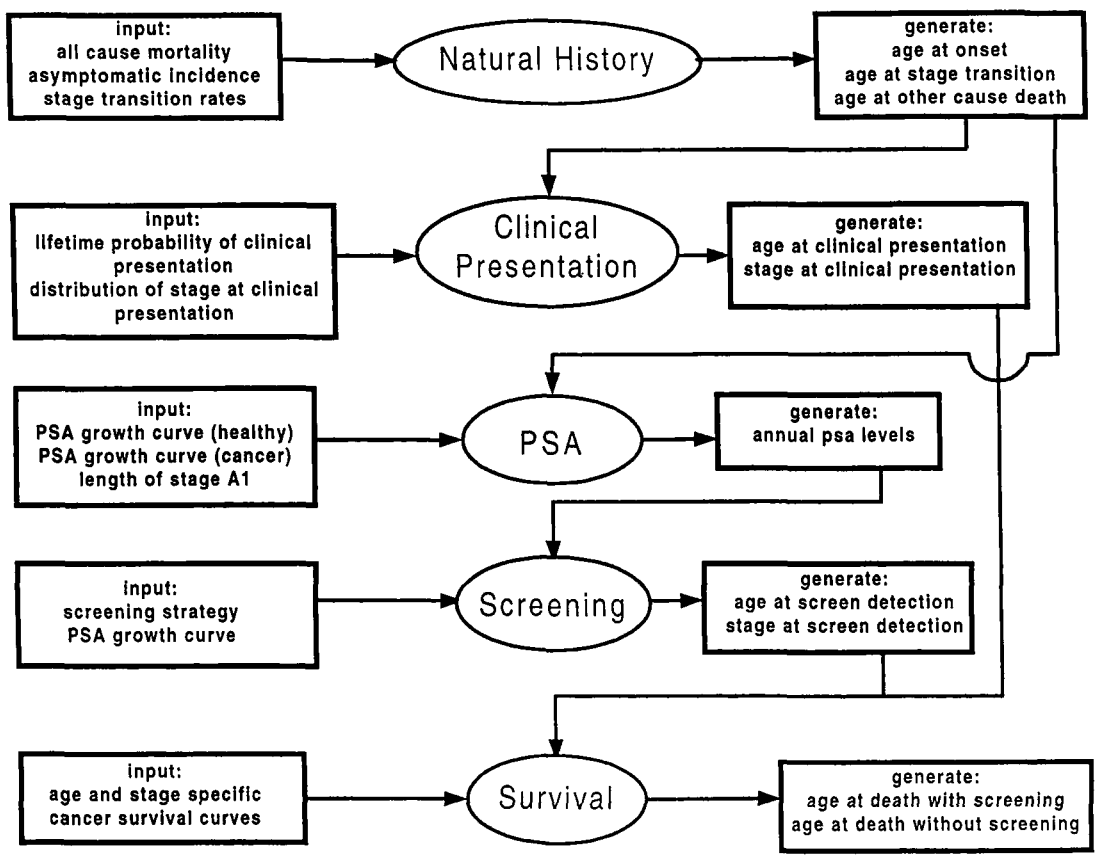

FIG. 1. Main components of computer model, and main data input and output for each module. Relevant aspects of life histories of 200,000 hypothetical healthy 30-year-old men are generated through series of modules for natural history, clinical presentation, PSA, screening and survival.

TABLE 2. *Mean duration of pathological stages[16] and distribution of clinically detected cancers[19]*

Stage*	Mean Duration (yrs.)	Proportion
A1	24.5	
		0.21
A2	5.3	
B	5.3	0.34
C	2.8	0.20
D1	2.4	
		0.25
D2	3.3	

* Distributions are exponential.

converts transition rates between stages from Cowen et al[16] to stage durations which vary from case to case according to exponential distributions. For all individuals age at death due to causes other than prostate cancer is also determined using age specific death rates from United States life tables.[17] Figure 2 represents the data generated by the model for a hypothetical individual. This patient has disease onset at age 53 years and a stage A1 duration of 15 years. Subsequent pathological stages B, C, D1 and D2 have durations of 4, 3, 4 and 2 years, respectively. Death from causes other than prostate cancer occurs at age 80 years.

Clinical Presentation Without Screening: Once individuals destined to have prostate cancer are identified, the model determines who would have presented with prostate cancer without screening, and the age and stage at clinical presentation. The likelihood of clinical presentation and the stage at diagnosis depend on data from the pre-PSA era used in the model. The age at clinical presentation depends on the assigned stage and natural history. To determine the number of patients presenting clinically the model takes as input the lifetime probability of a clinical diagnosis of prostate cancer, which can be computed from data on the age specific clinical incidence of prostate cancer.[18] We used a baseline value of 11% to reflect a lifetime probability compatible with clinical incidence for 1984 to 1988 as recorded by the Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute. The number of patients destined to present clinically is computed by multiplying the lifetime probability of clinical diagnosis by the number of individuals in the original cohort. Thus, for example 22,000 individuals of an initial cohort of 200,000 will present clinically. Individuals who will have stage D2 are automatically selected into the set of those who will present clinically. Once the target number of clinical cases has been determined, the input stage distribution[19] is used to compute the number diagnosed with each clinical stage.

Like Cowen et al[16] we defined clinical stages similarly to pathological stages except that for cases proceeding directly from a given pathological stage X to D1 clinical stage X is defined as the sum of the time in pathological stage D1 and X. Thus, for example the duration of clinical stage C is the sum of the durations of pathological stages C and D1. For cases that progress directly from pathological stage B to D1 clinical B is the sum of the durations of pathological stages B and D1. For cases that progress directly from pathological stage A2 to D1 clinical stage A consists of pathological stages A1, A2 and D1 combined. This correspondence between clinical and pathological staging systems assumes that mortality differences between clinical and pathological stages are primarily due to the inclusion of cases with positive lymph nodes in the former. Thus, if 22,000 cases are clinically diagnosed and 20% have clinical stage C, then roughly 4,400 clinical cases are assigned a diagnosis time within the clinical stage C duration. The computer randomly selects these 4,400 stage C cases from among all whose natural history

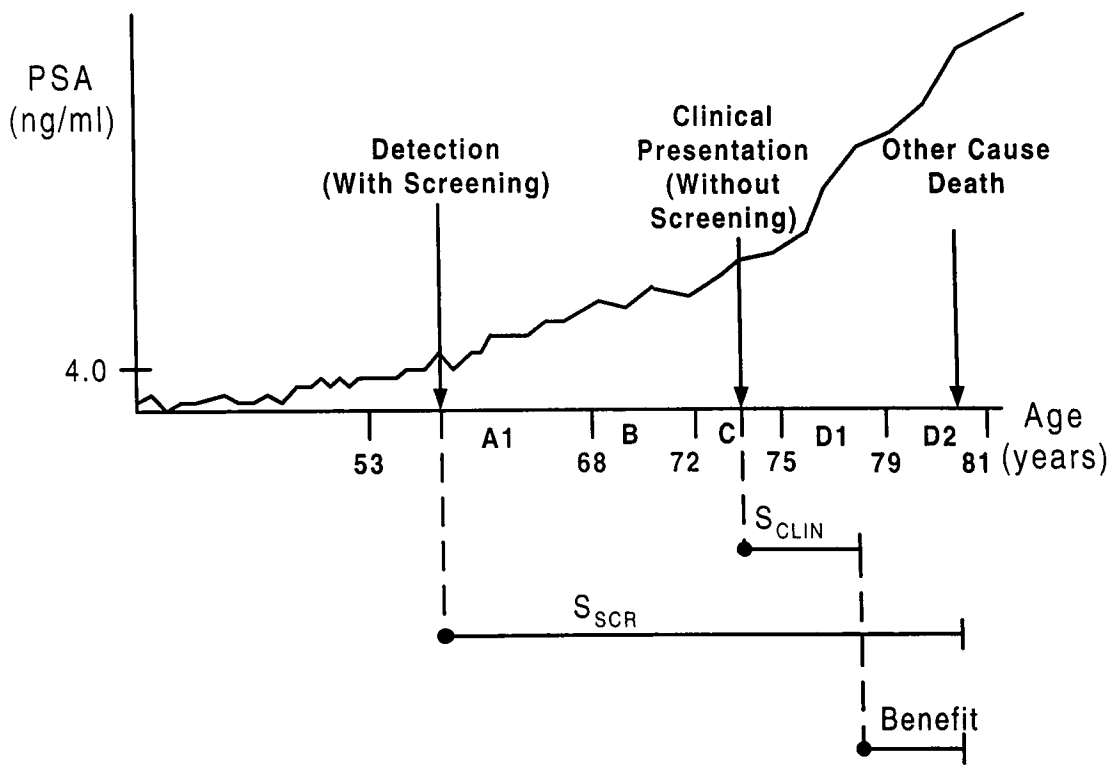

FIG. 2. Schema of hypothetical individual in model. Clinical presentation is at age 74 years for clinical stage C with subsequent prostate cancer death at age 78 years. However, with screen detection at age 56 years clinical stage A cancer is effectively cured and patient dies at age 80, which is his assigned age of other cause of death. Thus, benefit of prostate cancer screening is effectively 2 years of life saved. S_{CLIN}, time to prostate cancer death following clinical detection. S_{SCR}, time to death following screen detection. *BENEFIT*, difference between age at death following screen detection and age at death following clinical presentation without screen detection.

includes a transition to stage C. The age at diagnosis is then randomly generated from within the clinical stage C duration. The individual represented in figure 2 was selected to present clinically with stage C and, thus, age at clinical presentation (74 years) was randomly selected from the age interval of 72 to 79 years, the clinical stage C duration.

PSA Measurements: Based on disease status and natural history, annual PSA is calculated for each individual in the initial cohort. For men without histological cancer PSA at age 45 years is generated according to a distribution that matches the percentiles of PSA in healthy men between 40 and 49 years old.[20] Then, 1 PSA measurement per year is generated for each individual so that PSA increases by 3.2% per year.[20] A small random error (mean 0, standard deviation 0.05) is added to the logarithm of each generated PSA measurement to represent within person variability,[21] and between person variability is accounted for using a distribution for PSA values at age 45 years.

For disease cases PSA is generated similarly to healthy cases until the time of disease onset. However, at the time of transition to stage A1 the average annual change in PSA increases to 17.5%.[21] The individual rate of increase in PSA after the transition differs from person to person, and is assumed to depend on an inverse fashion on the length of stage A1. Specifically, annual change in PSA after transition to stage A1 is generated from a statistical distribution with mean 17.5% (interquartile range 10 to 20%). The exact percentile within this distribution is given by 1 minus the percentile of the individual stage A1 duration within the population distribution of stage A1 durations. Based on this model, PSA velocities are lower for cases with longer stage A1 durations. For example, a case with a stage A1 duration of 24 years (61st percentile within the stage A1 distribution) will have an approximately 11.8% annual rate of change in PSA (39th percentile within the PSA rate of change distribution), whereas a case with a stage A1 length of 5 years (18th percentile within the stage A1 distribution) will have an approximately 23% annual rate of change in PSA (82nd percentile within the PSA rate of change distribution). Within person variability is modeled similarly to healthy men, by incorporating a small random error with mean 0 and standard deviation 0.05 into each PSA measurement.

Screening Strategies: Once PSA has been assigned, the impact of 5 screening strategies is tested. The number of positive screens is determined based on PSA greater than 4.0 ng./ml. with annual screening (fixed bound), PSA greater than α ng./ml. with annual screening when α is the age specific bound proposed by Oesterling et al,[20] PSA greater than 4.0 ng./ml. with biannual screening, an age specific bound with biannual screening and PSA greater than 4.0 ng./ml. with screening every 5 years. For all strategies definitive diagnosis on biopsy is assumed to follow a positive test, and clinical intervention is assumed to follow a definitive diagnosis of prostate cancer.

Prostate Cancer Mortality: The clinical presentation and screening components of the model lead to 2 diagnostic scenarios for each prostate cancer case, namely clinical presentation without screening and diagnosis with screening. Each scenario has an associated age and stage at diagnosis, and the model generates a time to prostate cancer death. In the absence of screening prostate cancer death rates among clinical presentations follow those recorded by SEER before the PSA era.[22] Death rates are based on the relative survival curves output by SEER defined by age (within a 5-year interval) and stage at diagnosis.[23] The relative survival curves estimate 1 minus cumulative disease specific mortality for patients diagnosed from 1973 through 1987 inclusive (fig. 3). SEER data are used to represent the survival experience in the population, that is corresponding to the mix of treatment decisions and responses to treatment at the population level.

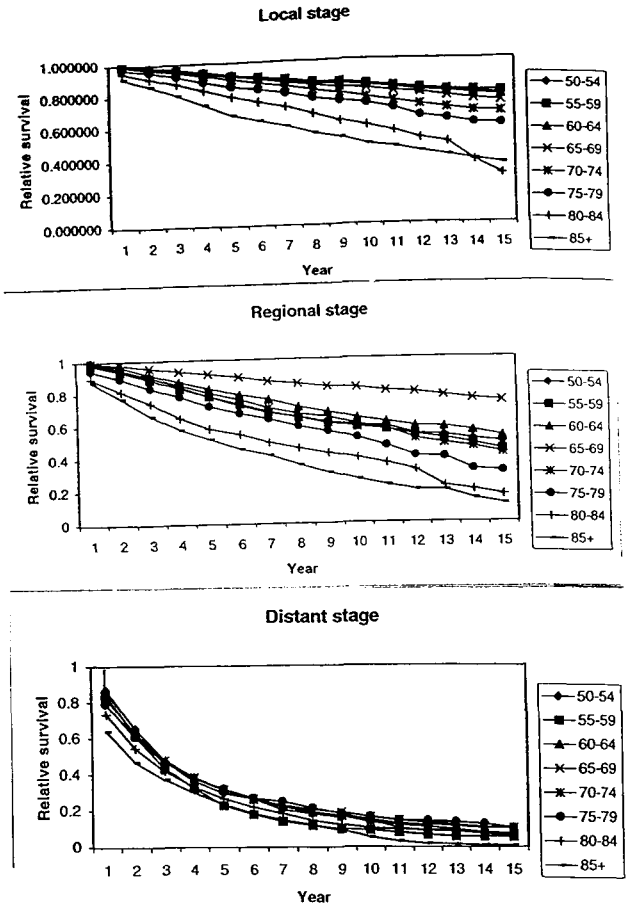

FIG. 3. SEER relative survival rates among prostate cancer patients diagnosed between 1973 and 1987 inclusive by age and stage of disease.

The model clinical stages are converted to SEER stages as A and B—local, C—regional and D—distant.

Our model of mortality with screening is a simple cure/no cure model, which has precedence in the literature.[5,24] Patients with pathologically localized disease (stages A1, A2 and B) on screening are considered cured and assigned the other cause date of death, otherwise the time of prostate cancer death is unchanged regardless of whether screening advances the date of diagnosis. Consider the hypothetical patient represented in figure 2. Without screening this patient would be diagnosed at approximately age 74 years with clinical stage C disease, and would die of prostate cancer at age 78 years. However, with annual screening he is diagnosed at approximately age 56 years with pathological stage A1 disease. Under the model assumptions, he subsequently has full life expectancy and dies at age 80 years, the assigned time of death from causes other than prostate cancer. Thus, the survival benefit due to screening is 2 years of life saved.

Model validation. Since computer models necessarily simplify complex real-life processes, it is important to validate the output against published data whenever possible. For validation of clinical incidence we compared the annual age specific clinical incidence computed by the model with the clinical incidence from SEER for 1984 to 1988 (fig. 4, *A*). The average sojourn time (from disease onset to clinical diagnosis) was between 10 and 11 years, which compares well with published estimates.[15,25] For joint validation of the natural history and clinical presentation modules, we compared the model generated asymptomatic prevalence of prostate cancer with the autopsy prevalence of latent disease[2] based on the

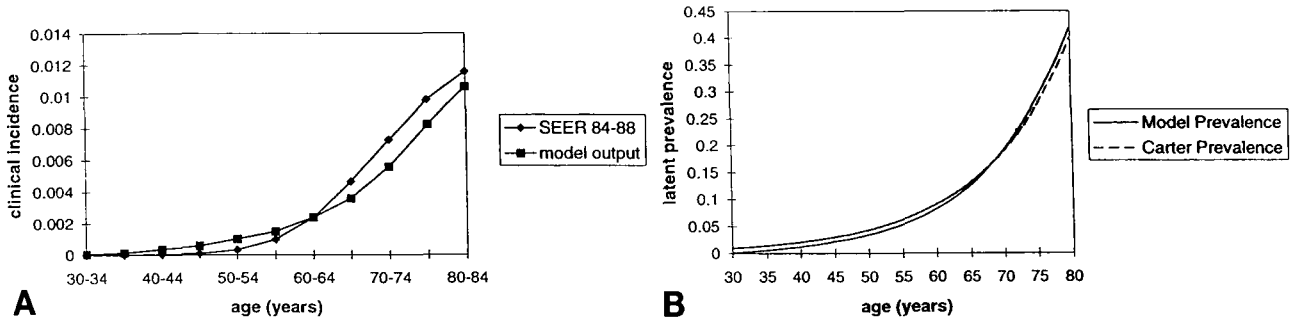

FIG. 4. Model validation. *A*, age specific clinical incidence. *B*, prevalence of asymptomatic disease

single largest study of autopsy prevalence which combined results from 4 United States studies (fig. 4, *B*). The model prevalence of asymptomatic disease was computed as the ratio of the number of individuals with undiagnosed, preclinical prostate cancer to the number alive and without prior clinical diagnosis at each age.

We validated the assumptions underlying the assignment of PSA by comparing the sensitivity, specificity, positive predictive values and cancer detection rates associated with a single screen against published estimates. For cancer detection rate and positive predictive value we used results from prospective screening studies. Specifically, we modeled a single screen at ages corresponding to the study of Richie et al.[26] A true positive screen was defined as a positive screen and positive biopsy. The model cancer detection rate and positive predictive value were 5.6 and 35.8%, respectively, which compared well with those observed by Richie et al (4.7 and 31.4%). For sensitivity and specificity we validated results against the retrospective study of Gann et al,[27] since prospective studies cannot provide unbiased estimates of these quantities unless all subjects undergo biopsy regardless of screening outcome. They considered patients with prostate cancer diagnosed within 10 years from entry to the Physicians' Health Study with a sample of age matched controls. Serum samples drawn at entry to the study were retrospectively assayed for PSA. For any given followup time (for example 4 years) sensitivity was estimated by computing the proportion of patients with prostate cancer diagnosed during this time who had positive tests. Similarly, specificity was estimated by computing the proportion of patients not diagnosed during this time who had negative tests. By programming a single screen and defining true positive as diagnosed clinically within 4 years of a positive test, we generated sensitivity estimates comparable to those of Gann et al and similarly generated specificity estimates.[27] Our model generated specificity validated well (88 versus 91.0% in their study) and sensitivity was 50%, which was lower than their 73% rate. Thus, for sensitivity our results may be considered conservative in that they are slightly biased against screening.

Finally, we examined the distribution of stage at screen detection against the results of the 4-year screening study reported by Smith and Catalona.[28] We simulated a 4-year screening study among men 60 years old, which was the average age in their study. Although our proportion of clinically localized cases at screen detection was similar to theirs (93 versus 97%), the pathological stage distribution of our screen detected cases was more heavily weighted towards localized disease (89 versus only 71%) and stage A1 tumors (71 versus only 30%). Detecting too many stage A1 tumors in the model could lead to overestimation of over diagnosis rates and possibly survival benefits. Therefore, we performed sensitivity analyses to examine whether shifting the point at which PSA growth accelerates changed the relative merits of the various screening schedules. For validation of prostate cancer mortality figure 5, *A* displays the model generated prostate cancer mortality without screening with the mortality from SEER for 1984 to 1988.

RESULTS

Based on an initial cohort of 200,000 men for each screening strategy we computed the total number of tests, number of false-positive tests, average years of life saved per person with a clinical diagnosis (approximately 25% of all men) and years of life saved per person entering the screening program at age 50 years. Since the model without screening represents a level of clinical diagnosis comparable to the period of 1984 to 1988, the years of life saved rate is interpretable as the survival benefit achieved if PSA screening were added to the standard of diagnostic care at that time. Results are presented in table 3 and figure 5. Additional outcome measures include the number of deaths prevented by screening, the percentage of patients with a clinical diagnosis and cancer detected by screening, and a measure of over diagnosis

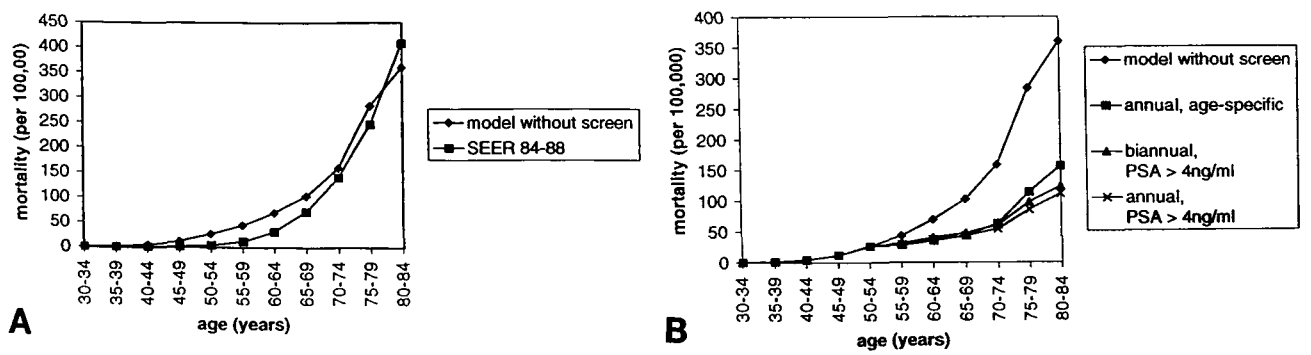

FIG. 5. Age specific prostate cancer mortality. *A*, SEER 1984 to 1988 and model without screening. *B*, model with and without screening for 3 screening strategies.

TABLE 3. *Comparison of 5 alternative screening strategies for 50 to 80-year-old men*

Strategy	Annual Fixed*	Biannual Fixed*	Annual Age Specific†	Biannual Age Specific†	5-Yr. Fixed*
Total No. screens	4,176,230	2,166,529	4,216,466	2,185,121	953,211
No. false-pos. screens	291,668	148,991	212,313	59,123	62,679
% Clinically detected‡	63.0	59.8	54.8	51.2	52.9
% Over diagnosis§	24.7	23.1	16.8	15.4	20.5
Total yrs. life saved	31,172.6‖	28,928.6	29,385.7	26,927.14	23,493.5
Yrs. life saved 1 pt./clinical presentation	1.5	1.4	1.4	1.3	1.1
Yrs. life saved/screening detection	0.17	0.155	0.16	0.14	0.13
No. deaths prevented	4,143	3,893	3,641	3,369	3,270

Annual probability of progression from stage A1 to A2 or B is 0.02[16] and lifetime probability of clinical diagnosis is 11%, which resulted in 7,895 prostate cancer deaths without screening.

* Fixed upper bound (4.0 ng./ml.) for a positive PSA test.

† Age specific bound of Oesterling et al.[20]

‡ Patients with prostate cancer with a clinical diagnosis date and screening detection.

§ Number of patients with prostate cancer with screening detection and without clinical presentation, divided by the total number of those with stage A1 (approximately 80,000 men).

‖ Mean for 10 runs was 31,122 (standard deviation 553).

based on the number of patients with cancer detected by screening who would never have presented clinically without screening. Using 4.0 ng./ml. as the cutoff for a positive PSA test (fixed bound) screening every 2 years reduced the number of screens and false-positive screens by almost 50% relative to annual screening. These gains were achieved while detecting almost 95% of cases that would have been detected with annual screening, and retaining 93% of the years of life saved. The biannual schedule also reduced the extent of over diagnosis by about 7%. Screening with a fixed bound every 5 years led to even more dramatic reductions in numbers of tests and false-positive tests (less than 25% of the corresponding values with annual screening), and reduced over diagnosis by 17% but the years of life saved relative to annual screening was only 75%.

Table 3 also clarifies the comparison between tests that use a fixed and age specific bound. Annual screening with an age specific bound was potentially preferable to annual screening with a fixed bound, reducing the number of false-positive screens by approximately 27% and the extent of over diagnosis by a dramatic third while retaining almost 95% of the years of life saved. Biannual screening with the age specific bound revealed greater reductions in years of life saved relative to annual screening than fixed bound screens but similar improvements in numbers of screens and false-positive screens are apparent. Figure 5 plots the age specific prostate cancer mortality corresponding to several annual and biannual screening programs. All screening programs decreased disease specific mortality considerably. Relative to no screening, the annual and biannual strategies performed similarly (table 3).

We conducted a sensitivity analysis to assess the impact of our assumptions about select model parameters on the results. We considered the annual rate of progression from stage A1 to A2 or B, since this parameter was noted by Cowen et al to have a particularly important effect.[16] We considered the lifetime probability of clinical disease and the annual change in PSA in patients with disease, and for the latter used a value of 33% in the sensitivity analysis, like Morrell et al.[29] We considered the possibility that not all localized cases would be cured following screen detection. Finally, we allowed PSA growth rates among cancer cases to begin accelerating some time after the start of stage A1.

Table 4 displays results of annual and biannual screening strategies with constant PSA. Clearly, small changes in the lifetime probability of clinical diagnosis and the duration of stage A1 led to small changes in the absolute estimates of benefits and components of cost due to screening. In contrast, the estimate of PSA increase from Morrell et al[29] was quite different from the model baseline of 17.5%, and led to substantially more years of life saved at the expense of more over diagnosis. Reducing the number of localized cases cured following screen detection led to corresponding reductions in benefit. Moving the PSA acceleration point forward reduced years of life saved and over diagnosis considerably.

In all sensitivity analyses the relative differences between the various strategies were similar. Annual screening strategies provided few gains in survival compared to biannual strategies. In addition, strategies using an age specific bound performed substantially better in terms of components of cost than those using a fixed bound with little difference in years of life saved (results not shown).

DISCUSSION

We assessed the relative benefits of several serial PSA screening strategies as well as drawbacks in terms of number of tests, number of false-positive tests and rates of over diagnosis. Our results are in agreement with previous studies suggesting that biannual screening is likely to be a cost-effective alternative to annual screening. The model relies on several critical assumptions, including disease progression pathways and rates, PSA growth rates relative to natural history and the mechanism for how screening might improve

TABLE 4. *Sensitivity analysis results for annual and biannual screening strategies with a fixed bound for PSA*

	Annual Screening		Biannual Screening	
	Yrs. Life Saved	% Over Diagnosis	Yrs. Life Saved	% Over Diagnosis
Baseline	31,173	25	28,928	23
Lifetime prostate Ca (clinical diagnosis) probability 0.10	29,713	26	27,227	24.5
Prostate Ca (stage A1 to A2) probability 0.015	30,553	26	27,561	24
Annual PSA change 33%	42,231	34	39,208	32
75% Stage A/B cured	23,033	25	21,303	23
50% Stage A/B cured	15,287	25	14,194	23
PSA accelerates after 25% stage A1	27,820	19	25,211	18
PSA accelerates after 50% stage A1	23,600	16	20,888	15

Models the increase in PSA due to cancer beginning after 25 or 50% of the time spent in stage A1 has passed. Baseline has annual probability of progression from stage A1 to A2 or B set to 0.002 and lifetime probability of clinical diagnosis to 0.11, PSA in disease cases increasing on average by 17% per year and 100% of pathologically localized cases cured following screening detection.

survival. Consequently, it has been extensively validated against published data. The model is flexible in that given the basic structure further refinements can be easily added depending on the availability of relevant data. For example, a rough estimate of costs for comparing screening programs can be derived from the outcomes (screens, false-positive screens and over diagnoses), which are the primary cost generators associated with any screening program. In general further information will be needed to generate the costs, including the likelihood of treatment for over diagnosed cases and of each type of complication (and associated costs) following treatment. Coley et al provided some estimates of these quantities but given the basic model results, individual assumptions can be specified for generating costs.[30] Other possible additions include adjustment for quality of life, incorporation of treatment decisions if modeling treatment options are of interest and further screening strategies, possibly using other biomarker based measures like the ratio of free-to-total PSA. The model is based as much as possible on published data which have influenced the structure. For example, we have not explicitly modeled disease grade or tumor size. Including these characteristics would necessitate making assumptions about how they correlate with each other and PSA growth with time.

A potential limitation is that for baseline scenarios the model projected an apparently greater proportion of screen detected A1 tumors than the reported clinical experience.[28] This difference could be due to nomenclature and/or the assumption that total PSA begins to increase concurrently with the onset of histological cancer. The model definition of stage A1[16] includes tumors ranging from "insignificant" to stage T1c.[31] The model could be developed further by using sojourn times and PSA as criteria to define stage T1c, which would decrease some of this apparent discrepancy. Fewer cases of screen detected A1 tumors would also be generated if the increase in PSA had been modeled to begin sometime after the onset of histological cancer, which would be supported by the longitudinal study of Pearson et al.[32] We accounted for this possibility in sensitivity analyses by delaying the onset of the increase in PSA until 25 to 50% of the time for A1 to elapse. However, modeling this delay did not substantially change the projected relative efficacy of biannual compared to annual screening, although it did reduce the absolute number of years of life saved and rate of over diagnosis (table 4). Thus, the baseline assumptions appear adequate for our purposes, that is for comparing the relative merits of various screening schedules. However, these modeling issues need refinement before more formal cost-effectiveness or utility analyses can be performed.

Although we explicitly model white men, we expect that the relative performance of the screening strategies would be similar for black men. A model for black men would have slightly different input parameters, such as lifetime probability of clinical diagnosis and stage specific relative survival. However, other key parameters, such as PSA rates of change and rates of progression between stage, have not been estimated separately for white and black men. Whittemore et al noted that PSA growth curves were similar in black and white men.[21]

It is instructive to compare our estimates of survival benefit attributable to a single screen to those in previous studies.[4,5] Specifically, we compared our expected years of life saved with screening at ages 65 and 75 years using a fixed bound to estimates in these studies. For 65-year-old men we obtained 453 days of life saved per person with cancer screen detected and treated. For 75-year-old men, the corresponding estimate was 139 days. In comparison Barry et al estimated benefit at 555 days per 65-year-old man with cancer screen detected and treated, and 149 days per 75-year-old man.[5] These benefits pertain to screening with PSA and digital rectal examination relative to no screening at all. In contrast, our survival benefits pertain to adding screening with PSA to the standard of diagnostic care in the mid 1980s, which may have included digital rectal examination and may explain the discrepancy between the results of the 2 models, although they are remarkably similar considering the different structures. In terms of benefits per person screened our model yielded estimates of 17 days for 65 and 75-year-old men. These estimates are substantially higher than those obtained by Krahn et al,[4] namely 1 to 2 days of improvement in life expectancy per 60 or 70-year-old man screened. However, we note that the survival models used by Krahn et al are different from ours with and without screening.

Our results represent perfect compliance to biopsy and treatment recommendations, and a biopsy error rate of 0. Thus, our estimates represent the maximal benefits and costs of screening. Naturally, reduced compliance rates will affect results, particularly if compliance depends on PSA. Our estimates of years of life saved are also slightly inflated because we did not explicitly model relatively infrequent surgical mortality in radical prostatectomy cases. Considering this incidence in the model would slightly diminish the small differences in years of life saved among different strategies, particularly between age specific and fixed bound strategies. In our model the age specific bound led to slightly fewer patients with screen detected localized disease, who are typically candidates for radical prostatectomy. Thus, these strategies would be subject to proportionately less surgical mortality.

The importance of the model assumptions about how screening affects disease specific mortality cannot be overemphasized. Our cure/no cure survival model is optimistic for pathologically localized cases, assuming that all such cases are cured with screening. If the probability of cure is less than 100%, the potential years of life saved are reduced, but this change does not alter the relative performance of annual and biannual screening. However, the cure/no cure survival model does not provide any benefits for shifts from distant to regional stage, which may potentially be important given the differences between the stage specific relative survival curves (fig. 3). Stage shift models have been previously used in projecting the cost-effectiveness of cancer screening.[33,34] Both types of models describe theoretical mechanisms for how screening might work to reduce disease specific mortality. A computer model translates these descriptions of mechanisms for screening efficacy into meaningful measures of survival benefit (for example, years of life saved) in a defined population. No model, however well done, is able to replace a controlled clinical trial of screening for prostate cancer. We do not propose our model as a replacement for clinical trials but as a tool for learning more about the disease process, understanding the role of screening in observed disease incidence and mortality, and guiding decision making towards sensible and cost-effective public health policy so long as results from such trials are unavailable.

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EDITORIAL COMMENT

Computer models of the natural history of cervical cancer, with the introduction of various screening strategies into the model, have been used to help define rational guidelines for cervical cancer screening. This approach is important since it is not practical to test various strategies (for example screening intervals) in a prospective trial. The authors used a stage driven computer simulation of prostate cancer to evaluate years of life saved with serial screening, and the downstream costs in terms of number of tests, false-positive tests and over diagnoses (table 3 in article). Their model predicts that screening every other year would reduce unnecessary testing (PSA tests and presumably biopsies by reducing false-positive tests) while maintaining years of life saved.

A number of critical assumptions regarding disease progression and PSA progression are necessary to create the model, and these assumptions drive the estimates of years of life saved and the over diagnosis of cancer with screening. For example, the authors correctly point out that their model projects a greater proportion of cancers that may not behave like most screen detected cancers, which explains the predicted rates of over diagnosis (table 3 in article). However, even if the model to some extent overestimates or underestimates years of life saved or detection of unimportant cancers with screening, it does not limit the ability to make comparisons between different screening strategies. In the absence of data from screening trials further studies like this may help define strategies that reduce unnecessary testing while maintaining the detection of curable prostate cancer.[1]

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