PSA: What Values Predict Increased Mortality Risk?

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Executive Summary: Studying 1.1 million male insurance applicants age 50 to 89 tested for PSA between 1991 and 2009, we found relative mortality did not increase until PSA values exceeded 6 ng/mL for age 50 to 59 and 10 ng/mL for age 60+. This relative risk remained stable out to 15 years of follow-up. Free PSA potentially added risk discrimination only for those age 50 to 59.

Introduction

Prostate specific antigen (PSA) is a glycoprotein produced in relatively large amounts by prostate tissue and in very small amounts elsewhere. It functions as an enzyme in dissolving seminal fluid coagulum, and thus may play a role in fertility.

Mean PSA values for applicants tested at CRL are 1.2 ng/mL (standard deviation "SD" 2.1) for men age 50 to 59, 1.9 ng/mL (SD 13.9) for men age 60 to 69, and 2.8 ng/mL (SD 19.8) for age 70 to 89; values for individuals vary substantially. Only in the absence of prostate tissue (in women and in men after complete removal of prostate tissue) or with use of prostate-suppressive medication, will the serum PSA level likely be below 0.2 ng/mL. PSA levels are elevated by inflammation (prostatitis) often without symptoms, by enlargement of the gland from BPH (benign prostatic hypertrophy which is common with aging), and by cancer.

PSA screening for cancer is commonly performed beginning at age 50 during health screening; most insurers also request PSA testing for men age 50 and over. A few insurers restrict PSA testing to higher face amounts or more limited ages. The commonly used reference range for PSA is 0 to 4 ng/mL, though some clinicians and insurers use a range of 0 to 2.5 for age <60 in an attempt to improve sensitivity of testing for prostate cancer at younger ages. Unfortunately, the PSA level is not a very accurate screening test for prostate cancer. For commonly used cut-

off values such as 2.5, 4 or 10 ng/mL, the sensitivity and/or specificity for prostate cancer are relatively low so that the positive and negative predictive values are limited.

Because prostate cancer may produce more PSA per gram of tissue than ordinary prostate tissue, PSA density (PSA level divided by the volume of prostate gland, usually measured by ultrasound) has been used in an attempt to improve the predictive value of PSA testing. Cancer may also cause PSA levels to rise rapidly over months; if serial measurements are available, a PSA velocity can be determined. Both approaches require additional testing not available for the insurance screening situation and even when measured, have not demonstrated consistent improvement in risk discrimination.[1]

In another approach to improve the accuracy of PSA testing for cancer screening, total PSA has been separated into the proportion in the serum that is chemically bound ("complexed") to another protein (anti-chymotrypsinogen) and the proportion that is "free" (not complexed). Studies have shown that the lower the free portion of PSA, the higher the likelihood of cancer rather than BPH or inflammation. Those with >=25% percent free PSA have a lower risk of prostate cancer. Unfortunately, the added predictive value of free PSA appears modest. In addition, the percentage of PSA that is free decreases as the serum sits at room temperature; the free PSA percentage from insurance processing (with 1-2 day delay) will often be lower than seen on a fresh blood specimen on repeat testing by an applicant's physician.

Prostate cancer growth is very androgen (male hormones) responsive. Removal of the testes (orchiectomy or castration) or use of anti-androgens such as Lupron or Casodex causes regression of the cancer for a high percentage of men; this response often persists for years. Smaller amounts of androgens are also produced in the adrenal glands. The ability of current treatment to suppress adrenal production (and certainty regarding the usefulness of that suppression) was limited until 2011, when the adrenal-specific anti-androgen abiraterone was released. Abiraterone appears to have substantial activity against prostate cancer even when other anti-androgen therapy alone is no longer effective. Additional (and hopefully less expensive) drugs in this class as well as androgen receptor inhibitors are anticipated.

Surgery (radical prostatectomy) and radiotherapy of the prostate gland are commonly used as initial therapy, but have imperfect long-term cure rates; they also cause substantial short- and long-term morbidity and even some mortality. Prostate cancer destined to remain localized and "well behaved" for extended periods is most easily cured/controlled by surgery or radiotherapy. Unfortunately, that is not the case with prostate cancer destined to cause morbidity and mortality which has often already escaped the gland by the time of diagnosis (though undetectable except for continued PSA levels >=0.2 ng/mL after treatment).

This combination of low specificity and sensitivity of PSA testing, limited efficacy and substantial side effects of surgery and radiotherapy, favorable impact of later hormonal therapy, and relatively benign natural course for many men has led the US Preventative Services Taskforce (USPSTF) to recently question the value to patients of PSA screening.[2] According to the USPSTF findings, PSA testing at age <75 is unclear in its benefits, and at age 75+ testing causes more harm than good. A Cochrane review came to similar conclusions.[3] One recent screening program found little benefit[4] and a second found some.[5]

However, insurance testing has a very different goal. Clinical testing should be performed only if it helps the patient. For insurers, the goal for testing is to simply identify increased mortality risk. Doing this requires a combination of adequate specificity of a test to avoid too many false positives for disease, and sufficient excess mortality associated with the targeted disease to be worthwhile to test for it. To establish the value of PSA testing to identify excess risk, the authors performed a long-term cohort all-cause mortality study of insurance applicants based on PSA levels.

How the Study Was Done

Researchers at CRL analyzed the mortality of applicants tested for PSA (including those tested for free PSA) from 1991 to 2009 with mortality follow-up by use of the Social Security Death Master File in 2010. PSA values lower than 0.2 ng/mL were excluded from our analysis because most would be from men post-radical prostatectomy for prostate cancer or from women whose sex was unknown to CRL at the time of testing (these samples are defaulted to "male" testing). The total number of applicants included in the study was 1,152,232, with 35,962 deaths observed

with a mean follow-up of 4 years (range 0 to 18 years). Applicants age 50 to 89 were studied; 25,803 (2.2%) also had free PSA performed.

All mortality analyses were conducted using Cox regression with age (even when also age-banded) and admitted smoking status as covariates utilizing IBM SPSS 19 software.

What the Study Found

Table 1 shows the distribution of PSA results by age bands (50 to 59, 60 to 69, 70 to 89) as well as the mortality by PSA level relative to those with PSA <=4 ng/mL (<=2.5 was the reference group for age 50 to 59). Excess mortality for age 50 to 59 begins at PSA >6 ng/mL. Relative mortality is only about 1.3 (130%) until the PSA is >20 where it increases to 2.7 (270%), but values this high occurred in only 0.06% of applicants in this age group. For age 60 to 69 and 70 to 89, excess mortality does not begin until the PSA value is >10 ng/mL, where risk climbs to a relative mortality of around 125%. At PSA >20 ng/mL for age 60+, relative risk increases to around 250% but levels >20 occurred in only 0.2% (age 60 to 69) and 0.6% (age 70 to 89) of applicants.

For age 50 to 59, PSA bands are further split into <=2.5 and 2.51-4 ng/mL, since the lower value of 2.5 ng/mL is sometimes used in this age band as a trigger for further evaluation. The mortality ratio for applicants with values in the 2.51-4 range is not significantly different from those <=2.5. In the 4.01-6 range, the mortality ratio is 1.1 (110%), but with 95% confidence intervals including values from 0.9 to 1.2, this should be considered as not significantly different from 1. Only for values >6 ng/mL is the relative mortality difference clear.

As shown in Figure 1, where relative mortality is plotted by year of follow-up by Cox analysis with age and smoking status as covariates, the relative mortality for PSA levels remains stable for age 60 to 69 through 15 years. This indicates that the favorable mortality seen for PSA values <=10 ng/mL does not increase over time. A similar pattern was seen for age 50 to 59 and 70 to 89 (not shown).

Distribution and relative mortality of the applicants who also had free PSA testing in addition to total PSA are shown in Table 2. Because the number of applicants with this test done and the associated number of deaths are much lower (leading to wide 95% confidence intervals), PSA values of 4.01-10 were combined into one group for this analysis. Even with this combined PSA group, the 95% confidence intervals are still much wider than what we found in our total PSA results, so less precision is possible regarding the exact relative risk between those with free PSA >25% and those <=25%.

As shown in Table 2, it is likely that there is a lower mortality risk for age 50 to 59 if free PSA is >25%, a level including only 18% of the free PSA values in our study. However, at age 60 and higher, there is no evidence of a difference in relative risk based on free PSA. Because no PSA values <=10 ng/mL have demonstrated increased risk for age 60+ and because free PSA has limited predictive ability, this observed lack of risk discrimination by free PSA is understandable.

What Do the Study Results Contribute to Risk Assessment?

Our study focused on relative mortality associated with PSA results in the way underwriters see them for life insurance applicants. We found that instead of using PSA cut-offs of 2.5 or 4 ng/mL to identify excess mortality risk, it may be possible to begin further evaluation or adverse action at much higher PSA values (>6 ng/mL for age 50 to 59 and >10 ng/mL for age 60+). This dramatically reduces the number of applicants needing such evaluation without adverse mortality impact. Because of the large numbers of applicants and long follow-up in our study, we were able to determine that the relative mortality we observed did not increase at a later time (at least to 15 years after testing).

The study also establishes a much narrower potential underwriting role for free PSA. For PSA values <=10 ng/mL, it may be useful only for men age 50 to 59. Even there, the test can only favorably impact 18% of the applicants (those with high free PSA). Of the other 82% who may be retested by their own physicians, some will likely retest with a higher free PSA because of the shorter period the retested sample sits at room temperature. Whether this tradeoff of identifying

a small portion at lower risk while overstating the risk to some applicants is of value, is a question facing each insurer.

Based on our review of existing literature, we believe that the low mortality seen in our study would remain low in those individuals with PSA values between 4 and 10 (or 2.5 and 6 ng/mL at younger ages) even if applicants were not further evaluated. This is based on the evidence that prostate cancer mortality is more dependent on natural history and the effectiveness of late hormonal therapy than on early surgery and radiation therapy. This is consistent with the opinion of the USPSTF, whose screening guidelines are highly regarded. However, if insurers raised action cut-off values, they may still choose to notify applicants of PSA values >4 ng/mL (or >2.5 ng/mL at younger age) even in the absence of underwriting action. That approach would capture much of any potential mortality improvement resulting from earlier therapy.

Conclusion

Underwriting review and potential action based on PSA can begin at PSA values >10 for male life insurance applicants age 60+ and >6 ng/mL for age 50 to 59 rather than at lower cut-off values without an increase in relative mortality. Free PSA potentially adds to risk discrimination only for age 50 to 59; that gain must be balanced against reporting falsely low levels of free PSA associated with any delay in testing, which can occur with insurance samples.

References

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Table 1. Distribution and relative mortality by PSA level

Age group	PSA (ng/mL)	% of tests	MR (Cox)	95% CI Lower	95% CI Upper
50 to 59	<=2.5 (ref)	91.9%	**1.0**	--	--
	2.51 to 4	5.5%	**1.0**	0.9	1.1
	4.01 to 6	1.6%	**1.1**	0.9	1.2
	6.01 to 10	0.7%	**1.3**	1.1	1.5
	10.01 to 20	0.2%	**1.2**	0.9	1.7
	>20	0.1%	**2.7**	1.7	4.1
60 to 69	<=4 (ref)	92.0%	**1.0**	--	--
	4.01 to 6	4.8%	**1.0**	0.9	1.1
	6.01 to 10	2.2%	**1.0**	0.9	1.1
	10.01 to 20	0.8%	**1.3**	1.1	1.5
	>20	0.2%	**3.8**	3.1	4.6
70 to 89	<=4 (ref)	84.2%	**1.0**	--	--
	4.01 to 6	8.6%	**1.0**	0.9	1.0
	6.01 to 10	4.8%	**1.0**	1.0	1.1
	10.01 to 20	1.9%	**1.2**	1.1	1.4
	>20	0.6%	**2.2**	1.9	2.6

Table 2. Distribution and relative mortality by free PSA for PSA values 4.01-10 ng/mL

Age group	Free PSA	% of tests	MR (Cox)	95% CI Lower	95% CI Upper
50 to 59	<=25% (ref)	82%	**1.0**	--	--
	>25%	18%	**0.7**	0.4	1.2
60 to 69	<=25% (ref)	73%	**1.0**	--	--
	>25%	27%	**1.0**	0.7	1.3
70 to 89	<=25% (ref)	59%	**1.0**	--	--
	>25%	41%	**1.1**	0.9	1.4

Figure 1. Cox regression survival by duration (in years) by PSA level, age 60 to 69

Note: Survival curves for PSA groups <=4 and 4.01-10 ng/mL overlap