LESS IS MORE

Risk Profiles and Treatment Patterns Among Men Diagnosed as Having Prostate Cancer and a Prostate-Specific Antigen Level Below 4.0 ng/mL

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Background: Despite controversy over the benefit of prostate-specific antigen (PSA) screening, little is known about risk profiles and treatment patterns in men diagnosed as having prostate cancer who have a PSA value less than or equal to 4.0 ng/mL.

Methods: We used data from the Surveillance, Epidemiology, and End Results system to describe patient characteristics and treatment patterns in the cases of 123 934 men with newly diagnosed prostate cancer from 2004 to 2006. Age-standardized treatment rates were calculated in 5-year age strata. Logistic regression was used to quantify the odds ratios (ORs) of men with low- and high-risk disease and the use of radical prostatectomy (RP) or radiation therapy (RT).

Results: Men with a PSA level of 4.0 ng/mL or lower represent 14% of incident prostate cancer cases. Fifty-four percent of men diagnosed as having prostate cancer and PSA levels lower than 4.0 ng/mL harbor low-risk disease (stage, ≤T2a, PSA level, ≤10 ng/mL, and Gleason score, ≤6), but over 75% of them received RP or RT. Men with screen-detected prostate cancer and PSA values lower than 4 ng/mL were 1.49 (95% confidence interval [CI], 1.38-1.62) and 1.39 (95% CI, 1.30-1.49) times more likely to receive RP and RT, respectively, and were less likely to have high-grade disease than men who had non–screen-detected prostate cancer (OR, 0.67; 95% CI, 0.60-0.76).

Conclusions: Most men diagnosed as having prostate cancer with a PSA threshold below 4.0 ng/mL had low-risk disease but underwent aggressive local therapy. Lowering the biopsy threshold but retaining our inability to distinguish indolent from aggressive cancers might increase the risk of overdiagnosis and overtreatment.

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More than 90% of all prostate cancers are diagnosed at a localized stage, and the 5-year relative survival rate for patients who are diagnosed with localized disease is almost 100%.[1,2] The relative 5-year survival for all stages combined increased from 69% to almost 99% during the period from 1975 to 2003.[1] The tremendous improvement in survival has been attributed to early detection and treatment. However, there have been concerns about the potential overdiagnosis and overtreatment of localized prostate cancer.[3-6] Despite these concerns, some researchers argue that the prostate-specific antigen (PSA) level is associated with a continuum of cancer risk and recommend lowering the 4-ng/mL threshold for biopsy.[7-10] (To convert PSA to micrograms per liter, multiply by 1.0.) Given our present inability to distinguish indolent cancers from aggressive cancers, lowering the biopsy threshold may increase overdiagnosis and overtreatment. For instance, a recent study estimated that overdiagnosis ranged from 23% to 42% of all screen-detected prostate cancer in the United States.[11] Relatively little is known about the risk profile and factors associated with treatment of prostate cancer in men whose PSA level is lower than 4 ng/mL. We undertook a nationwide study using 2004-2006 data from the Surveillance, Epidemiology, and End Results (SEER) database,[12] which contains the first available population-based collection of PSA levels and Gleason scores, to describe the risk profiles and treatment patterns of patients with prostate cancer and PSA levels below 4 ng/mL at the time of diagnosis.

See Invited Commentary at end of article

METHODS

The SEER 2004-2006 database from 16 SEER tumor registries was used to identify patients for this study. The SEER program covers approximately 26% of the US population and has a 98% completeness in case ascertainment.[12] We used *International Classification of Diseases for Oncology*, 3rd edition, site code C619 to identify newly diagnosed prostate cancer cases. Men were excluded from this study if they were 24 years or younger (n=96), had missing PSA values (n=24 679), or had a missing Gleason score and clinical stage or could not be classified into 1 of the 3 risk strata (n=2635). The study includes 123 934 subjects.

The PSA levels documented in the SEER data are the highest laboratory values reported prior to diagnostic biopsy or treatment. Demographic and clinical features including age at prostate cancer diagnosis; race; cancer stage; cancer grade; localized, regional, and distant stage; and tumor size were stratified by PSA level. Distant stage is defined as having a neoplasm that has spread to parts of the body remote from the primary tumor by (1) direct extension, (2) discontinuous metastasis to distant organs or tissues, or (3) via the lymphatic system to distant lymph nodes. The sizes of tumors were calculated from the diameter (d) of the primary tumor, based on the equation for calculating the volume (V) of a sphere ($V=(\pi/6)\times d^3$), and this estimation came from a subgroup of the SEER population (n=15 137). Men were categorized into 3 risk groups on the basis of the American Joint Committee on Cancer clinical stage, PSA level, and Gleason score[13]: low risk (stage, ≤T2a; PSA level, ≤10.0 ng/mL; and Gleason score, ≤6), intermediate risk (stage T2b; PSA level, 10.1-20.0 ng/mL; or Gleason score, 7), and high risk (stage, ≥T2c; PSA level, >20.0 ng/mL; or Gleason score, ≥8). Treatment following initial diagnosis for prostate cancer was categorized as attempted curative treatment or conservative management. Attempted curative treatment included radical prostatectomy (RP) and radiation therapy (RT) (ie, external beam radiation therapy and/or brachytherapy). The conservative management group was composed of men who were not treated with either RP or RT.

Treatment rates were calculated by age and risk stratification. Additionally, age-standardized treatment rates were calculated by PSA level, Gleason score, and cancer stage. Treatment rates were age standardized in 5-year age strata according to the direct method[14] and using prostate cancer cases in the SEER 2004-2006 data sample as the standard population. The association between PSA level at diagnosis and age at diagnosis was examined by 1-way analysis of variance using linear contrast. The independent distribution in Gleason score, cancer stage, and risk categories between different levels of PSA at the time of diagnosis were evaluated by the Mantel-Haenszel statistic for ordinal or cardinal outcomes. The distribution of attempted curative treatment stratified by PSA level, Gleason score, and cancer stage was evaluated using the Cochran-Mantel-Haenszel statistic.

We used logistic regression to quantify the odds ratio (OR) for clinical characteristics of high-grade cancer in men with tumor that identified by needle biopsy following an elevated PSA finding. We used multinomial logistic regression to measure the relative propensity for attempted curative treatment among men. Age, race, and year of diagnosis were included in these analyses as covariates. All analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Characteristics and risk profiles of the study cohort of 123 934 patients are summarized in **Table 1** and stratified into 4 categories based on the prebiopsy PSA value. Of these patients, 14.0% had PSA values lower than 4.0 ng/mL; 73.5% had values between 4.1 and 20.0 ng/mL; and 12.5% had values greater than 20 ng/mL. Compared with men in higher PSA groups, men with PSA values of 4 ng/mL or lower were younger and had lower Gleason scores. Of these patients with PSA values of 4 ng/mL or lower, 38% had screen-detected prostate cancer. Approximately 54% of patients with PSA levels of 4.0 ng/mL or lower at the time of diagnosis had low-risk cancers compared with only 48% of men with PSA values between 4.1 and 10.0 ($P<.001$). The percentage of patients who had intermediate- or high-risk cancer was positively associated with PSA level. Among patients who had PSA values greater than 20.0 ng/mL, 70% had tumor sizes larger than 0.5 cm^3, in contrast to 52%, 65%, and 71% among patients who had PSA levels from 0.0 to 4.0, 4.1 to 10.0, and 10.1 to 20.0 ng/mL, respectively.

Approximately 13% of the study cohort had PSA values higher than 20.0 ng/mL at the time of diagnosis. These men were older and had higher tumor grades and stages of disease than the remainder of the cohort. Their chance of having disease outside the prostate was 21% compared with only 1% for men with PSA values lower than 4.0 ng/mL and 1.1% for men with PSA values between 4.0 and 20.0 ng/mL.

More than 70% of men with PSA values lower than 20.0 ng/mL received either RP or RT. Radical prostatectomy was performed on 44% of men with PSA values of 4.0 ng/mL or lower, 38% of men with PSA values between 4.1 and 10.0 ng/mL, and 24% of men with PSA values between 10.1 and 20.0 ng/mL. Radiation therapy was performed on 33% of men with PSA values of 4.0 ng/mL or lower, 40% of men with PSA values between 4.1 and 10.0 ng/mL, and 41.3% of men with PSA values between 10.0 and 20.0 ng/mL.

Figure 1 presents the age-standardized percentage distribution of treatments stratified by cancer stage, Gleason score, and PSA level. Treatment patterns were similar across tumor stages, with a slightly lower rate of intervention with either RT or RP found in the group of men with T1 disease and a PSA value between 0 and 4.0 ng/mL (Figure 1A). Rates of attempted curative treatment were comparable among men with Gleason scores of 7 or between 8 and 10, but RP was slightly less common among men with Gleason 6 disease. Over half of the men with Gleason 2 to 5 disease received either RT or RP.

The percentage of men who did not receive any attempted curative treatment was 27%, 22%, and 36%, respectively for low-, intermediate-, and high-risk disease. The results by age groupings are presented in **Figure 2**. Conservative treatment strategies increased with patient age, especially for men older than 75 years, while RP dominated among men 65 years or younger. Radiation therapy was performed on approximately half of the men aged 65 to 74 years, while RP was performed on approximately one-third of men with intermediate- or high-risk disease and much less frequently on men with low-risk disease.

Table 2 lists the cancer features and uses of treatments among men with PSA levels of 4.0 ng/mL or lower. Men with screen-detected cancer were less likely to have high-grade tumors (OR, 0.67; 95% confidence interval [CI], 0.60-0.76), to have disease outside the prostate (OR, 0.30; 95% CI, 0.20-0.47), or to have tumor size larger than 0.5 cm^3 (OR, 0.75; 95% CI, 0.68-0.83). However, these men were 1.49 (95% CI, 1.38-1.62) times more likely

Table 1. Clinical Characteristics and Primary Therapy Among Men With Prostate Cancer PSA Value[a]

Characteristic or Therapy	PSA Value, ng/mL			
	0.0-4.0 (n=17 343)	4.1-10.0 (n=71 352)	10.1-20.0 (n=19 695)	>20.0 (n=15 544)
Cases	14.0	57.6	15.9	12.5
Patient age, mean (SD), y	63.9 (9.6)	65.8 (8.8)	69.6 (9.6)	70.8 (10.6)
Patient age group, y				
25-54	16.7	10.0	6.9	6.8
55-64	36.5	34.8	23.2	22.1
65-74	32.2	38.3	36.8	32.1
≥75	14.7	17.0	33.1	39.0
Race				
White	83.3	80.6	76.1	74.0
Black	10.6	11.5	13.6	16.4
Other	6.1	7.9	10.3	9.6
Gleason score				
2-5	3.5	2.2	2.2	1.5
6	56.4	50.5	35.5	19.1
7	30.4	36.9	39.5	34.5
3 + 4	23.1	27.0	25.9	20.2
4 + 3	6.9	9.4	12.9	13.8
8-10	8.5	9.9	20.9	39.6
Unknown	1.1	0.5	1.9	5.3
Clinical stage				
T1 (T1c)	43.3 (37.8)	62.6 (61.6)	54.4 (52.9)	38.3 (36.3)
T2	54.0	35.5	40.6	43.9
T3 or T4	2.4	1.7	4.2	13.0
Unknown	0.3	0.2	0.8	4.8
Distant[b]	1.0	0.6	3.1	20.5
Risk stratification, %				
Low	53.7	48.2		
Intermediate	26.0	32.7	67.3	
High	20.3	19.1	32.7	100.0
Tumor size, cm^3[c]	(n=956)[c]	(n=5656)[c]	(n=1200)[c]	(n=625)[c]
≤0.20	29.0	19.6	17.1	17.4
0.21-0.50	19.5	16.0	12.1	12.7
>0.50	51.5	64.5	70.8	69.9
Treatment				
Conservative management	23.1	21.6	34.7	56.0
Radical prostatectomy	43.9	38.0	24.0	12.5
Radiation therapy	33.0	40.1	41.3	31.5
EBRT	16.5	22.1	29.5	25.1
Brachytherapy	12.4	13.4	6.3	3.1
Both EBRT and brachytherapy	4.0	4.7	5.4	3.3

Abbreviations: EBRT, external beam radiation therapy; PSA, prostate-specific antigen.
SI conversion factor: To convert PSA to micrograms per liter, multiply by 1.0.
[a] Unless otherwise indicated, data are reported as percentage of patients. Differences across PSA values were statistically significant for all characteristics owing to our large sample size.
[b] Defined by historic stage and metastasis at diagnosis.
[c] Tumor size was provided in a SEER[12] subsample, and the size of the subsample is indicated in each PSA category.

to receive RP and 1.39 (95% CI, 1.30-1.49) times more likely to receive RT than those men with non–screen-detected cancer.

COMMENT

To our knowledge, this is the first large-scale US population–based study to document the risk profiles and treatment patterns among men with PSA levels of 4.0 ng/mL or lower who were diagnosed as having prostate cancer. In 2004 to 2006, 14% of prostate cancer cases were diagnosed at PSA levels of 4.0 ng/mL or lower. The patients in these cases were less likely to have high-grade cancer, and more than half were classified as having low-risk cancer. Despite their lower risk of having clinically significant disease, treatment rates for men with PSA values of 4.0 ng/mL or lower were comparable to those of men presenting with PSA values between 4.0 and 20.0 ng/mL. Treatments were especially common among men with screen-detected cancer. The finding that men in low-risk groups were treated intensively raises the concern of overtreatment, especially among older patients.

From the SEER database, we found that approximately a quarter of patients received conservative management as their primary intervention between 2004 and 2006. However, SEER registries lack explicit data regarding initial and longitudinal use of hormonal therapy. Based on our research group's earlier study,[15] 41% of patients older than 65 years who did not undergo RP or RT received androgen-

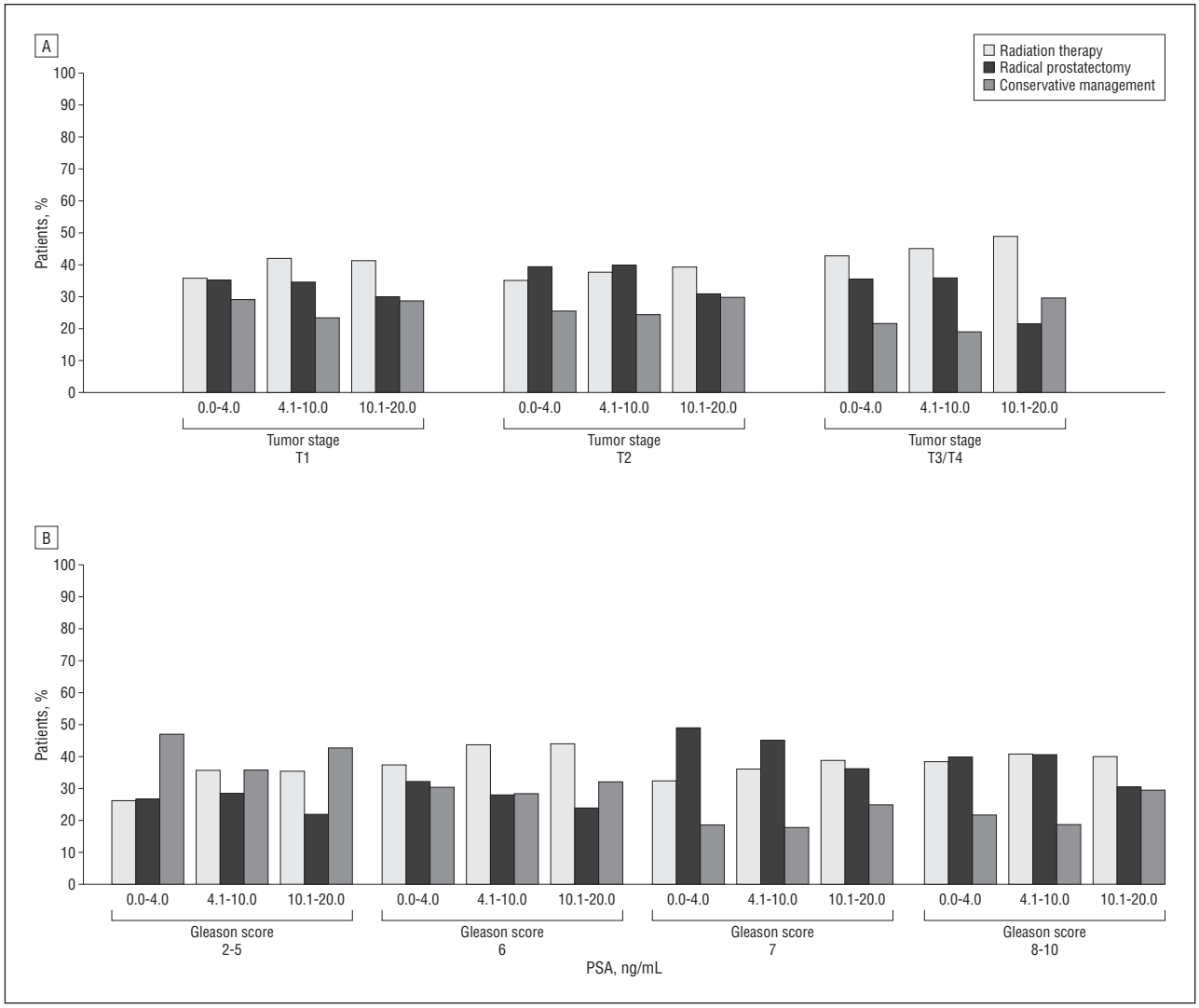

Figure 1. Age-standardized percentage distribution of treatment according to tumor stage, cancer grade, and prostate-specific antigen (PSA) level. A, Tumor stage and PSA level. B, Cancer grade and PSA level. Age standardization of treatment rate was performed according to the direct method using 5-year age strata and the prostate cancer cases in the SEER 2004-2006 database[12] as the standard population. Differences in receiving attempted curative therapy across the level of PSA value was statistically significant ($P < .001$) for all tumor stages and cancer grades. To convert PSA to micrograms per liter, multiply by 1.0.

deprivation therapy (ADT) within 6 months of diagnosis. We performed a subgroup analysis among men 65 years or older in SEER-Medicare records and found that 5.8% of men aged between 65 and 74 years and 19.8% of men 75 years or older received ADT. The use of ADT is comparable between patients with PSA levels above and below 4.0 ng/mL. The use of ADT is suspected to be lower among patients younger than 65 years. Therefore, the percentage of patients without any initial therapy would be even lower among older patients. Two previous studies reported treatment patterns before 2002 from SEER.[3,16] Their results show that the proportion of men who selected attempted curative treatment was strongly associated with patient age and tumor characteristics. However, our study demonstrates that Gleason score, PSA level, and risk stratification does not appear to substantially influence the decision to have attempted curative therapy.

Recently publicized results from the European Randomized Study of Screening for Prostate Cancer[17] show that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent 1 death from prostate cancer. Given that US patients are in general diagnosed at earlier stages and are more likely to receive attempted curative therapy, the number needed to treat to save 1 patient is likely to be higher in the United States than in Europe.

Based on the recent update of the Scandinavian Prostate Cancer Group Study Number 4 trial,[18] men 65 years or older treated with RP fared no better than men undergoing conservative management. Our results demonstrate that 66% of men aged between 65 and 74 years with low-risk disease and a PSA value of 4.0 ng/mL or lower received either RP or RT. These findings suggest that many contemporary men receiving treatment for localized prostate cancer are unlikely to benefit from the intervention. Furthermore, it has been documented that men who receive any treatment have increased risk of treatment-related adverse effects.[19-21] Therefore, it is critical that patients be counseled about treatment-associated adverse effects and benefits when they are deciding about therapy.[22-24]

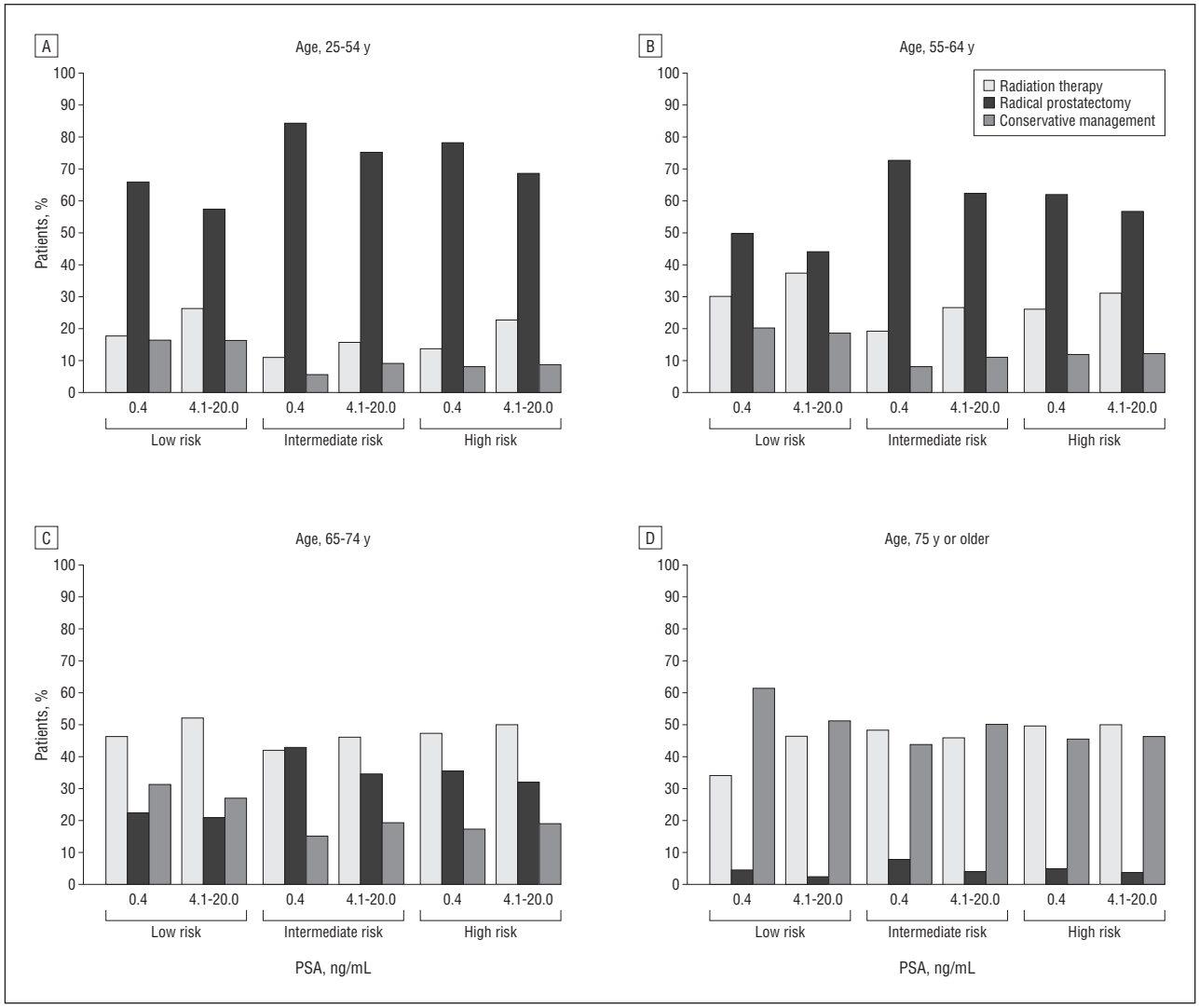

Figure 2. Percentage distribution of therapy stratified by age, prostate-specific antigen (PSA) level, and risk group. Patients were categorized into 3 risk groups on the basis of clinical stage, PSA level, and Gleason score: low risk (stage, ≤T2a; PSA level, ≤10.0 ng/mL; and Gleason score, ≤6), intermediate risk (stage T2b; PSA level, 10.1-20.0 ng/mL; or Gleason score, 7), and high risk (stage, ≥T2c; PSA level, >20.0 ng/mL; or Gleason score, ≥8).

Table 2. High-Risk Cancer Features and Use of Radical Prostatectomy or Radiation Therapy by Screen Status Among Men With PSA Levels of 4.0 ng/mL or Lower[a]

	High-Risk Features			Treatment[b]	
Characteristic	Gleason Score, 8-10	M1, Distant	Tumor Size, >0.5 cm^3	Radical Prostatectomy	Radiation Therapy
Screen-detected cancer, %	2.4	0.4	9.6	82.5	35.6
Non–screen-detected cancer, %	6.2	1.4	11.3	73.5	31.5
Screen-detected vs non–screen-detected cancer, OR (95% CI)	0.67 (0.60-0.76)	0.30 (0.20-0.47)	0.75 (0.68-0.83)	1.49 (1.38-1.62)	1.39 (1.30-1.49)

Abbreviations: CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.
SI conversion factor: To convert PSA to micrograms per liter, multiply by 1.0.
[a] Adjusted for age, race, and year of diagnosis.
[b] Multinomial logistic regression.

The number of men with "abnormal" PSA levels would double to approximately 6 million if the threshold were decreased from 4.0 to 2.5 ng/mL.[25] Estimates suggest that 32% of men with abnormal PSA levels would be diagnosed as having prostate cancer from their needle biopsy.[26] Based on the results in the present study, 82.5% of these 1.9 million men would receive attempted curative treatments, while only 2.4% would have high-grade cancer (Table 2). However, no evidence suggests that delaying biopsy until the PSA level reaches 4.0 ng/mL would result in an excessive number of potentially noncurable disease cases. Although abandoning an upper limit of nor-

mal for PSA level would allow physicians to detect more cancer, the benefits of diagnosing prostate cancer would likely be offset by treatment complications related to cancers that might never have caused harm.

Our analysis was limited by the nature of the data source. The SEER system collects information from all patients in 16 registries. The Gleason scores and PSA values recorded by the SEER system reflect the information that was used to make clinical decisions. The SEER system does not record information such as percentage of free PSA or the number of positive cores found on biopsy analysis. The major strength of our analysis derives from the large sample size that is population based and includes patients from defined geographic areas in all clinical settings rather than selected medical institutes.

Our study found that aggressive local therapy was provided to most patients diagnosed as having prostate cancer. These results underscore the fact that PSA level, the current biomarker, is not a sufficient basis for treatment decisions. Without the ability to distinguish indolent from aggressive cancers, lowering the biopsy threshold might increase the risk of overdiagnosis and overtreatment.

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