Trends in Diagnosis of Gleason Score 2 Through 4 Prostate Cancer in the National Cancer Database, 1990–2013

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• ***Context.***—**The incidence of prostate cancer with Gleason scores 2 through 4 has been decreasing for decades, largely because of evolving criteria for Gleason scores, including the 2005 International Society of Urological Pathology recommendation that scores of 2 through 4 should rarely, if ever, be diagnosed based on needle biopsy. Whether trends in assigning Gleason scores 2 through 4 vary by facility type and patient characteristics is unknown.**

Objective.—**To assess trends in prostate cancer grading among various categories of treatment facilities.**

Design.—**Analyses of National Cancer Database records from 1990 through 2013 for 434 612 prostate cancers diagnosed by core needle biopsy, including multivariable regression for 106 331 patients with clinical T1c disease diagnosed from 2004 through 2013.**

Results.—**The proportion of prostate core needle biopsies with Gleason scores 2 through 4 declined from 11 476 of 53 850 (21.3%) (1990–1994) to 96 of 43 566 (0.2%) (2010–2013). The proportions of American Joint Committee on Cancer category T1c needle biopsies assigned Gleason scores 2 through 4 were 416 of 12 796 (3.3%) and 9 of 7194 (0.1%) during 2004 and 2013, respectively. Declines occurred earliest at National Cancer Institute–designated programs and latest at community programs. A multivariable logistic model adjusting for patient demographic and clinical variables and restricted to T1c cancers diagnosed in needle biopsies from 2004 through 2013 showed that facility type is independently associated with the likelihood of cancers in such specimens being assigned Gleason scores of 2 through 4, with community centers having a statistically significant odds ratio of 5.99 relative to National Cancer Institute–designated centers.**

Conclusions.—**These results strongly suggest differences in Gleason grading by pathologists practicing in different facility categories and variations in their promptness of adopting International Society of Urological Pathology recommendations.**

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Histologic grade is a valuable factor used in assessing prognosis and selecting treatment for patients with many forms of cancer, and this is especially true regarding the Gleason score for men with prostate cancer.[1–4] Like any other surgical pathology result, the clinical utility of tumor grade requires that it be determined with accuracy and precision. One challenge in achieving accurate and precise Gleason scores is that the criteria for assigning Gleason patterns and for combining them into Gleason scores have evolved during the decades since this system was first introduced.[1–6] As long as new morphologic criteria are adopted consistently and promptly, patients can benefit from their improved prognostic and predictive power. On the other hand, if new criteria are not uniformly disseminated and adopted, inconsistency in assigning Gleason scores may result in suboptimal tailoring of treatment regimens by clinicians.

Previous studies of Surveillance, Epidemiology, and End Results registries and the National Cancer Database (NCDB) data showed a decline occurring from the 1970s to the 1990s in the proportion of prostate cancers classified as well differentiated or low grade (defined at that time as Gleason scores 2–4).[6,7] During the late 1990s, a clear consensus emerged among leaders in the prostate pathology community that some lesions previously interpreted as prostate cancer with Gleason scores 2 through 4 may have represented benign conditions such as adenosis or atypical adenomatous hyperplasia. Additionally, some other prostate cancers with Gleason scores 2 through 4 had been undergraded and were actually higher-grade cancers (Gleason scores 5 and 6).[1,5,8] Articles such as "Gleason Score 2–4 Adenocarcinoma of the Prostate on Needle Biopsy: A Diagnosis That Should Not Be Made"[8] reflected a decline in the use of Gleason scores in that range and an increase in higher Gleason scores—a phenomenon known as "grade inflation."[1,6,8–16] Although this shift in grade distribution

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coincided with the introduction of widespread screening with the prostate-specific antigen (PSA) test, analyses of registry data and studies based on review of past cases indicate that changes in specimen interpretation are the main cause.[5,6]

A more complete understanding of trends in prostate cancer grade inflation in core needle biopsy specimens has important implications for quality measurement and improvement in prostate pathology, as well as broader relevance to the design of quality surveillance systems that could use data from cancer registries to rapidly identify clinically significant variations in pathology practice patterns. Although the shift in grading patterns has been well documented, no previous study has examined variations in prostate cancer grade trends by facility type and patient characteristics. We examined these trends among patients diagnosed in 1990–2013 using the NCDB, a hospital-based registry of patients diagnosed or treated at more than 1500 Commission on Cancer (CoC)–approved facilities in the United States.[17–20]

METHODS

Study Participants

Data were from the NCDB,[17–20] a hospital-based registry that captures approximately 58% of prostate cancer cases diagnosed in the United States[21] and contains standardized data elements on patient demographics, stage at diagnosis, and facility-level factors. Information is abstracted from medical records and entered into the NCDB according to its standardized data dictionary, the *Facility Oncology Data Standards Manual*.[18] The Morehouse University Institutional Review Board in Atlanta, Georgia, determined that this study was exempt from review.

We initially selected patients diagnosed with a malignant prostate neoplasm from 1990 through 2013, diagnosed and reported by the same CoC-accredited facility, who underwent core biopsy but had no surgical treatment.

Outcome and Independent Variables

The primary outcome of interest was whether or not the cancer was classified as Gleason score 2 to 4 versus 5 to 10. Registry coding procedures for prostate cancer grade evolved during the study period. From 2004 through 2009, the NCDB recorded numerical Gleason scores as collaborative stage site-specific factor 6, but did not have separate fields to record scores from core biopsy and prostatectomy specimens; therefore, the score recorded would be based on the core biopsy if no prostatectomy was performed, but would be based on the resected gland if prostatectomy was performed. Starting in 2010, the NCDB recorded Gleason scores for prostate biopsies and prostatectomy specimens separately (as site-specific factors 8 and 10, respectively). The NCDB also recorded categorical grades of low, intermediate, and high/undifferentiated (defined during the period of data collection as Gleason scores of 2 through 4, 5 through 7, and 8 through 10, respectively).[18] For patients diagnosed from 2004 to 2013, we used the numerical Gleason scores recorded in the NCDB; this approach provided the greatest degree of transparency in assuring that categorical grades reflected the NCDB's definitions based on Gleason scores. For patients diagnosed prior to 2004, we used the categorical grade variable in our analyses.

Because separate Gleason scores were not recorded for biopsy and prostatectomy specimens until 2010, for the sake of consistency we excluded patients treated by prostatectomy from this study.

Our primary independent variable of interest was facility type. Four facility types were studied (others were excluded because of small numbers and/or heterogeneity): community cancer programs, comprehensive community cancer programs, academic cancer programs, and National Cancer Institute (NCI)–designated cancer programs. Criteria for cancer center classification are described in detail elsewhere.[22,23] Briefly, the spectrum from community to comprehensive community to academic to NCI-designated cancer programs generally reflects greater comprehensiveness of diagnostic and treatment services, numbers of patients treated, participation in clinical research, and involvement in postgraduate training of physicians. Our interest in this variable is based on prior reports of differences in prostate cancer grading between pathologists in academic and nonacademic facilities, based on review of consultation cases.[12] We also examined potential variables that might be associated with grade and facility type, such as the clinical American Joint Committee on Cancer (AJCC) T category, the AJCC M category, PSA level (available from 2004 through 2013) grouped as quartiles, patient age, and patient race/ethnicity.

Data Analyses

Bivariate statistical analyses were performed with SPSS Statistics version 20 (SPSS, Armonk, New York) and multivariable logistic analyses were performed with SAS, version 9.3 (SAS, Cary, North Carolina). Chi-square tests and the corresponding 2-tailed *P* values with a significance level at .05 were used to examine potential associations of Gleason scores 2 through 4 with the independent variables noted above.

Adjusted multivariable models predicting Gleason scores 2 through 4 versus 5 through 10 were used to estimate odds ratios (ORs) and 95% CIs using marginal logistic models, which accounted for clustering at the facility level (correlation of characteristics among patients treated at a particular hospital).[24]

In addition to analyses for the period from 1990 through 2013, we also performed subset analyses of cases diagnosed from 2004 through 2013 because a larger number of cases per year and the availability of information regarding additional covariates (such as PSA level) permitted more detailed analyses. During this period, the definitions for AJCC category clinical T1c (which comprised more than half of cases) remained constant, allowing us to restrict analyses to this large and homogeneous group of cases. Identification of cases during this period with Gleason scores of 2 through 4 was based on a quantitative Gleason score variable, rather than the low-grade, intermediate-grade, high-grade, and undifferentiated categories of earlier time periods.

RESULTS

Study Participants and Characteristics, All Stages, 1990–2013

Of the initial 635 991 cases diagnosed by prostate biopsy but not treated with prostatectomy from 1990 through 2013, 434 612 cases remained in the analytic sample after exclusions (Table 1). Table 1 also shows the exclusions that reduced the initial sample of 147 285 patients diagnosed by prostate biopsy but not treated with prostatectomy from 2004 through 2013 to a final analytic sample of 106 331 cases.

Table 2 summarizes the characteristics of the analytic sample for cases diagnosed from 1990 through 2013. Most of these 434 612 patients were aged between 70 and 99 (190 327; 43.8%) or 60 and 69 years (144 932; 33.3%), and most were non-Hispanic white (339 747; 78.2%). Fewer cases were recorded during the first 5 years (1990–1994) of this time period. A majority (233 477; 53.7%) were AJCC clinical T1 lesions, and a majority (241 040; 55.5%) were reported to the NCDB by comprehensive community programs. There were statistically significant differences in all patient sociodemographic and clinical characteristics by facility type. For example, there was a greater proportion of T1 patients diagnosed at NCI-designated and academic facilities than at community or comprehensive community facilities.

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Table 1. Exclusion Criteria for Prostate Cancer Cases, National Cancer Database 1990–2013 and 2004–2013

Included and Excluded Cases	1990–2013	2004–2013
Initial cases diagnosed by prostate core biopsy but not treated with prostatectomy, diagnosed and reported at same facility	635 991	NA
Initial clinical T1c cases diagnosed by prostate core biopsy but not treated with prostatectomy, diagnosed and reported at same facility	NA	147 285
Exclude histology not adenocarcinoma, NOS, or acinar adenocarcinoma	8978	1502
Exclude age <40 or >100 years	278	38
Exclude missing race	54 681	11 969
Exclude missing sex	138	36
Exclude missing census region	1942	133
Exclude missing facility type	20 845	2077
Exclude "other" or pediatric facility type	40 469	9437
Exclude missing AJCC clinical T categories, nonstandard category, or T0	66 816	NA
Exclude missing AJCC clinical M categories or nonstandard category	5159	2948
Exclude missing grade (low, intermediate, high, or undifferentiated) for cases 1990–2003	31 144	NA
Exclude missing Gleason score for cases 2004–2013	2027	7861
Exclude missing PSA level	NA	11 977
Final	434 612	106 331

Abbreviations: AJCC, American Joint Committee on Cancer; NA, not applicable; NOS, not otherwise specified; PSA, prostate-specific antigen.

Table 2. Patient Characteristics by Facility Type Among Men With Prostate Biopsies, National Cancer Database 1990–2013[a]

	CCP, No. (%)	CCCP, No. (%)	ACADP, No. (%)	NCIP, No. (%)	All Facilities, No. (%)
Age group, y ($P < .001$)					
40–49	535 (0.8)	2111 (0.9)	1437 (1.4)	411 (1.5)	4494 (1.0)
50–59	5796 (9.2)	24 515 (10.2)	13 725 (13.3)	3884 (14.1)	47 920 (11.0)
60–69	19 238 (30.4)	79 472 (33.0)	36 491 (35.5)	9731 (35.4)	144 932 (33.3)
70–79	28 314 (44.8)	109 350 (45.4)	41 851 (40.7)	10 812 (39.3)	190 327 (43.8)
80–89	8768 (13.9)	24 337 (10.1)	8890 (8.6)	2501 (9.1)	44 486 (10.2)
90–99	611 (1.0)	1255 (0.5)	428 (0.4)	149 (0.5)	2443 (0.6)
Race/ethnicity ($P < .001$)					
Non-Hispanic white	50 912 (80.5)	200 212 (83.1)	68 932 (67.0)	19 691 (71.6)	339 747 (78.2)
Hispanic	1446 (2.3)	7069 (2.9)	4679 (4.6)	815 (3.0)	14 009 (3.2)
Black	9423 (14.9)	28 911 (12.0)	25 067 (24.4)	6104 (22.2)	69 505 (16.0)
Asian and PI	1070 (1.7)	3475 (1.4)	3141 (3.1)	651 (2.4)	8337 (1.9)
Other	411 (0.6)	1373 (0.6)	1003 (1.0)	227 (0.8)	3014 (0.7)
Region ($P < .001$)					
Northeast	15 419 (24.4)	53 260 (21.1)	40 870 (39.7)	4524 (16.5)	114 073 (26.2)
Midwest	20 680 (32.7)	52 472 (21.8)	25 403 (24.7)	11 079 (40.3)	109 634 (25.2)
South	20 050 (31.7)	89 278 (37.0)	27 785 (27.0)	6228 (24.1)	143 741 (33.1)
West	7113 (11.2)	46 030 (19.1)	8764 (8.5)	5257 (19.1)	67 164 (15.5)
Year group ($P < .001$)					
1990–1994	8829 (14.0)	31 030 (12.9)	11 648 (11.3)	2343 (8.5)	53 850 (12.4)
1995–1999	14 681 (23.2)	54 558 (22.6)	21 362 (20.8)	5397 (19.6)	95 998 (22.1)
2000–2004	18 712 (29.6)	73 474 (30.5)	30 436 (29.6)	7337 (26.7)	129 959 (29.9)
2005–2009	14 940 (23.6)	63 855 (26.5)	25 775 (25.1)	6669 (24.3)	111 239 (25.6)
2010–2013	6100 (9.6)	18 123 (7.5)	13 601 (13.2)	5742 (20.9)	43 556 (10.0)
T category ($P < .001$)					
T1	32 719 (51.7)	126 794 (52.6)	58 027 (58.0)	15 937 (58.0)	233 477 (53.7)
T2	25 491 (40.3)	97 758 (40.6)	37 620 (36.6)	9366 (34.1)	170 235 (39.2)
T3	3729 (5.9)	13 053 (5.4)	5526 (5.4)	1755 (6.4)	24 063 (5.5)
T4	1323 (2.1)	3435 (1.4)	1649 (1.6)	430 (1.6)	6837 (1.6)
M Category ($P < .001$)					
Mx	59 240 (93.6)	230 573 (95.7)	96 736 (94.1)	25 692 (93.5)	412 241 (94.9)
M1	4022 (6.4)	10 467 (4.3)	6086 (5.9)	1796 (6.5)	22 371 (5.1)
Total	**63 262**	**241 040**	**102 822**	**27 488**	**434 612**

Abbreviations: ACADP, academic cancer program; CCCP, comprehensive community cancer program; CCP, community cancer program; NCIP, National Cancer Institute–designated cancer program; PI, Pacific Islander.

[a] The χ^2 tests and the corresponding 2-tailed P values represent differences in facility type by patient characteristics.

Bivariate Associations With Gleason Scores 2 Through 4, Core Biopsies, All Stages, 1990–2013

From 1990 through 2013, 27 137 of these 434 612 cancers (6.2%) were characterized as Gleason scores 2 through 4 (Table 3). During this period, the proportion of prostate cancers in the analytic sample classified as Gleason scores 2 through 4 decreased significantly ($P < .001$) and substantially, from 11 476 of 53 850 (21.3%) during 1990–1994 to 96 of 43 566 (0.2%) during 2010–2013. The following variables

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Table 3. Patient and Facility Characteristics by Prostate Cancer Gleason Score (2–4 Versus 5–10), Prostate Biopsies, National Cancer Database 1990–2013[a]

	Gleason Score, No. (%)	
	2–4	5–10
Age, y ($P < .001$)		
40–49	179 (4.0)	4315 (96.0)
50–59	2134 (4.5)	45 786 (95.5)
60–69	8538 (5.9)	13 6394 (94.1)
70–79	13 289 (7.0)	177 038 (93.0)
80–89	2868 (6.4)	41 628 (93.6)
90–99	129 (5.3)	2314 (94.7)
Race/ethnicity ($P < .001$)		
Non-Hispanic white	22 478 (6.6)	317 269 (93.4)
Hispanic	730 (5.2)	13 279 (94.8)
Black	3438 (4.9)	66 067 (95.1)
Asian and PI	395 (4.7)	7942 (95.3)
Other	96 (3.2)	2918 (96.8)
Region ($P < .001$)		
Northeast	6879 (6.0)	107 194 (94.0)
Midwest	7332 (6.7)	102 302 (93.3)
South	9234 (6.4)	134 507 (93.6)
West	3692 (5.5)	63 472 (94.5)
Year group ($P < .001$)		
1990–1994	11 476 (21.3)	42 374 (78.7)
1995–1999	10 089 (10.5)	85 909 (89.5)
2000–2004	4273 (3.3)	125 686 (96.7)
2005–2009	1203 (1.1)	110 036 (98.9)
2010–2013	96 (0.2)	43 470 (99.8)
AJCC T category ($P < .001$)		
T1	14 269 (6.1)	219 208 (93.9)
T2	11 670 (6.9)	158 565 (93.1)
T3	1010 (4.2)	23 053 (95.8)
T4	188 (2.7)	6649 (97.3)
AJCC M category ($P < .001$)		
Mx	26 609 (6.5)	385 632 (93.5)
M1	528 (2.4)	21 843 (97.6)
Facility type ($P < .001$)		
CCP	5789 (9.2)	57 473 (90.8)
CCCP	15 150 (6.3)	225 890 (93.7)
ACADP	5315 (5.2)	97 507 (94.8)
NCIP	883 (3.2)	26 605 (96.8)
Total	**27 137** (6.2)	**407 475** (93.8)

Abbreviations: ACADP, academic cancer program; AJCC, American Joint Committee on Cancer; CCCP, comprehensive community cancer program; CCP, community cancer program; NCIP, National Cancer Institute–designated cancer program; PI, Pacific Islander.

[a] The χ^2 tests and the corresponding 2-tailed P values represent differences in facility type by patient characteristics.

were also significantly ($P < .001$) associated with the proportion of cases classified as Gleason scores 2 through 4 in this bivariate analysis: patient age at diagnosis, race/ethnicity, geographic region of patient's residence, AJCC T category, AJCC M category, and facility type. The proportions of cases assigned Gleason scores 2 through 4 were highest among patients aged 70 to 79 years (13 289 of 190 327; 7.0%) and those aged 80 to 89 years (2868 of 44 496; 6.4%). Cancers were most likely to be classified as Gleason scores 2 through 4 among non-Hispanic whites (22 478 of 339 747; 6.6%). Differences by geographic region, albeit statistically significant, were less prominent than those for other variables.

Of 233 477 AJCC T1 cancers, 14 269 (6.1%) were classified as Gleason scores 2 through 4, more than double the corresponding proportion for T4 cancers (188 of 6837; 2.7%). The proportions of cancers with Gleason scores 2 through 4 also varied more than twofold by AJCC M category: 26 609 of 412 241 (6.5%) for Mx and 528 of 22 371 (2.4%) for M1. Differences among facility categories were greater than for any other variable, with almost a 3-fold difference in the proportions of cancers assigned Gleason scores 2 through 4 reported by community programs (5789 of 63 262; 9.2%) versus NCI-designated programs (883 of 27 488; 3.2%), and with intermediate values reported by comprehensive community programs (15 150 of 241 040; 6.3%) and academic programs (5315 of 102 822; 5.2%).

Trends in Percentages of Prostate Cancers With Gleason Scores 2 Through 4, Core Biopsies, All Stages, 1990–2013

The temporal trends from 1990 through 2013 in percentages of prostate cancer cases classified as Gleason scores 2 through 4 by each facility type are shown in Figure 1. During all time periods, the percentages of cases with Gleason scores 2 through 4 were lowest among NCI-designated programs and highest among community programs. The absolute differences between these 2 facility categories were greatest during the first (1990–1994) and second (1995–1999) periods: 9.0 and 9.2 percentage points, respectively. There were smaller differences between the comprehensive community programs and academic programs. During subsequent years, the percentages of cases with Gleason scores 2 through 4 converged, and values were less than 0.5% for all facility types during 2010–2013.

Relative Frequency of Reporting Facilities' Percentages of Prostate Cancers With Gleason Scores 2 Through 4, Core Biopsies, All Stages, 2000–2004

Figure 2 illustrates the relative frequency of reporting facilities' percentages of cancers diagnosed on needle biopsy from 2000 through 2004 that were classified as Gleason scores 2 through 4, according to the category of the reporting facility. Because percentages based on a very small number of cases are imprecise, we included only those centers with at least 5 cases during this time interval. This resulted in excluding 37 of 368 community programs (10.1%), 31 of 588 comprehensive community programs (5.3%), 6 of 192 academic programs (3.1%), and 1 of 40 NCI-designated programs (2.5%). This low threshold for case volume was chosen to avoid excluding too many of the smaller community programs. However, we also conducted a sensitivity analysis in which we increased the volume threshold to 25 cases, which produced results that are very similar to those shown in Figure 2. In 18 of 39 NCI-designated programs (46.2%), fewer than 1% of cases were classified as Gleason scores 2 through 4 during this period. Only 115 of 331 community programs (34.7%), 209 of 557 comprehensive community programs (37.5%), and 68 of 186 academic programs (36.6%) had such a small percentage of cases with Gleason scores 2 through 4. At the other extreme, no NCI-designated programs had more than 8% of cases classified as Gleason scores 2 through 4; in contrast, 85 community programs (25.7%), 71 comprehensive community programs (12.7%), and 26 academic programs (14.0%) classified more than 8% of their cases as Gleason

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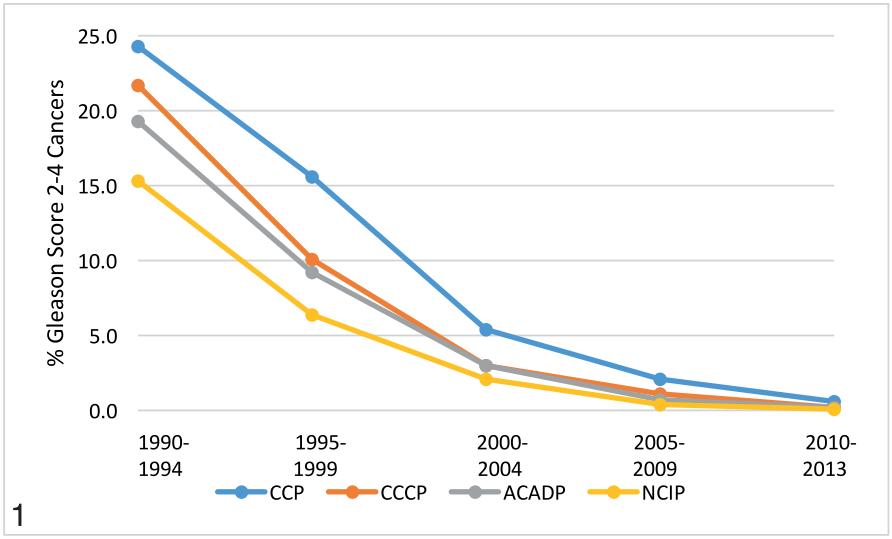
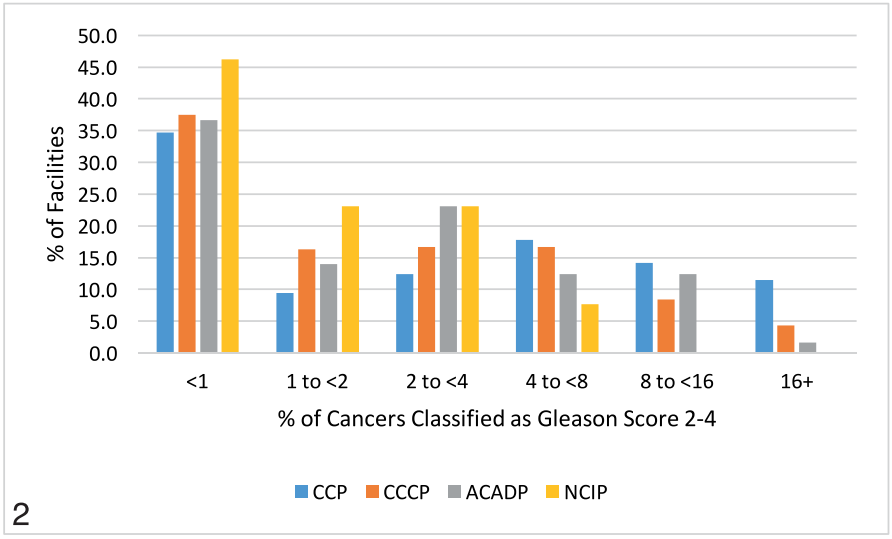
Figure 1. *Percentage of cases with Gleason scores 2 through 4 among core biopsies with prostate cancer. Abbreviations: ACADP, academic (teaching/research) cancer programs; CCCP, comprehensive community cancer programs; CCP, community cancer programs; NCIP, National Cancer Institute–designated cancer programs.*

Figure 2. *Relative frequency of the percentage of facilities of each category according to their percentage of prostate cancers in core biopsies from 2000 through 2004 classified as Gleason scores 2 through 4. For example, 46.2% of NCIPs and 34.5% of CCPs classified less than 1% of their cases as Gleason scores 2 through 4 during this period. Similarly, 0% of NCIPs and 11.3% of CCPs classified 16% or more of their cases as Gleason scores 2 through 4. Abbreviations: ACADP, academic (teaching/research) cancer programs; CCCP, comprehensive community cancer programs; CCP, community cancer programs; NCIP, National Cancer Institute–designated cancer programs.*





scores 2 through 4. More than 16% of cases were classified as Gleason scores 2 through 4 by 38 community programs (11.5%), 24 comprehensive community programs (4.3%), and 3 academic programs (1.6%).

Study Participants and Characteristics, Category T1c Prostate Cancer, 2004–2013

Reasons for the decrease in reporting of Gleason scores 2 through 4 among all stages combined from 1990 through 2013 could be multifactorial, including biopsy of lower-grade cancers because of PSA-screening detection of stage T1c cancers, along with recommendations by prostate cancer pathology experts to not report Gleason scores 2 through 4 on biopsy. In order to tease out whether the latter factor impacted the reporting of Gleason scores 2 through 4, a subset analysis of only T1c cases was performed. Table 4 shows the demographic and clinical characteristics of patients diagnosed in the 4 categories of facilities from 2004 through 2013. Similar to findings shown in Table 2 for the period from 1990 through 2013, values of all variables differed significantly by facility type, but the absolute magnitudes of these differences were not very large.

Bivariate Associations With Prostate Cancer With Gleason Scores 2 Through 4, Core Biopsies, Category T1c, 2004–2013

During 2004–2013, 1238 of the 106 331 AJCC category T1c cancers (1.2%) were characterized as Gleason scores 2 through 4 (Table 5). During this period, the percentage of T1c prostate cancers in the analytic sample classified as Gleason scores 2 through 4 decreased significantly ($P < .001$) and substantially, from 416 of 12 796 (3.3%) during 2004 to 9 of 7194 (0.1%) during 2013. Race/ethnicity ($P = .04$), geographic region ($P < .001$), PSA level ($P < .001$), and facility type ($P < .001$) were also significantly associated with the percentage of T1c cases classified as Gleason scores 2 through 4 in this bivariate analysis (Table 5). The percentages of cases with Gleason scores 2 through 4 were highest among patients residing in the South (660 of 37 358; 1.8%) and lowest among those in the West (76 of 14 362; 0.5%). Relative to those cases with PSA levels in the lowest quartile, those in the highest quartile were half as likely to have Gleason scores 2 through 4. Differences among facility categories were far greater than for any other variable, with more than an 8-fold difference in the percentages of cancers with Gleason

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Table 4. Patient Characteristics by Facility Type, Prostate Biopsies With T1c Cancer, National Cancer Database 2004–2013[a]

	CCP, No. (%)	CCCP, No. (%)	ACADP, No. (%)	NCIP, No. (%)	All Facilities, No. (%)
Age group ($P < .001$)					
40–49	156 (1.1)	663 (1.2)	548 (2.0)	169 (2.0)	1536 (1.4)
50–59	1859 (13.7)	8093 (14.3)	5063 (18.3)	1736 (20.2)	16 751 (15.8)
60–69	5106 (37.6)	21 913 (38.8)	11 140 (40.4)	3542 (41.1)	41 701 (39.2)
70–79	5189 (38.2)	21 774 (38.5)	9277 (33.6)	2663 (30.9)	38 903 (36.6)
80–89	1225 (9.0)	3949 (7.0)	1509 (5.5)	475 (5.5)	7158 (6.7)
90–99	51 (0.4)	146 (0.3)	57 (0.2)	28 (0.3)	282 (0.3)
Race/ethnicity ($P < .001$)					
Non-Hispanic white	10 378 (76.4)	45 072 (79.7)	17 153 (62.2)	5911 (68.6)	78 514 (73.8)
Hispanic	357 (2.6)	1682 (3.0)	1393 (5.0)	266 (3.1)	3698 (3.5)
Black	2459 (18.1)	8398 (14.9)	7889 (28.6)	2102 (24.4)	20 848 (19.6)
Asian and PI	244 (1.8)	999 (1.8)	831 (3.0)	245 (2.8)	2319 (2.2)
Other	148 (1.1)	387 (0.7)	328 (1.2)	89 (1.0)	952 (0.9)
Region ($P < .001$)					
Northeast	2882 (21.2)	12 378 (21.9)	11 417 (41.4)	1580 (18.3)	28 257 (26.6)
Midwest	4117 (30.7)	12 473 (22.1)	6641 (24.1)	3063 (35.6)	28 257 (26.6)
South	5093 (37.5)	22 482 (39.8)	7389 (26.8)	2394 (27.8)	37 358 (35.1)
West	1434 (10.6)	9205 (16.3)	2147 (7.8)	1576 (18.3)	14 362 (13.5)
Diagnosis year ($P < .001$)					
2004	1559 (11.5)	7419 (13.1)	3112 (11.3)	706 (8.2)	12 796 (12.0)
2005	1651 (12.2)	7263 (12.8)	3046 (11.0)	792 (9.2)	12 752 (12.0)
2006	1809 (13.3)	8331 (14.7)	3200 (11.6)	803 (9.3)	14 143 (13.3)
2007	1749 (12.9)	8313 (14.7)	3380 (12.2)	827 (9.6)	14 269 (13.4)
2008	1678 (12.4)	7732 (13.7)	3136 (11.4)	763 (8.9)	13 309 (12.5)
2009	1372 (10.1)	6257 (11.1)	2919 (10.6)	903 (10.5)	11 451 (10.8)
2010	907 (6.7)	2890 (5.1)	1810 (6.6)	853 (9.9)	6460 (6.1)
2011	953 (7.0)	3102 (5.5)	2386 (8.6)	984 (11.4)	7425 (7.0)
2012	916 (6.7)	2466 (4.4)	2190 (7.9)	960 (11.1)	6532 (6.1)
2013	992 (7.3)	2765 (4.9)	2415 (8.8)	1022 (11.9)	7194 (6.8)
AJCC M category ($P < .001$)					
Mx	13 338 (98.2)	55 794 (98.7)	26 990 (97.8)	8444 (98.0)	104 566 (98.3)
M1	248 (1.8)	744 (1.3)	604 (2.2)	169 (2.0)	1765 (1.7)
PSA quartile ($P < .001$)					
1 (0–4.8)	3260 (24.0)	14 310 (25.3)	7051 (25.6)	2125 (24.7)	26 746 (25.2)
2 (4.9–6.4)	3046 (22.4)	14 063 (24.9)	6484 (23.5)	2064 (24.0)	25 657 (24.1)
3 (6.5–10)	3428 (25.2)	14 741 (26.1)	6807 (24.7)	2157 (25.0)	27 133 (25.5)
4 (10.1+)	3852 (28.4)	13 424 (23.7)	7252 (26.3)	2267 (26.3)	26 795 (25.2)
Total	**13 586**	**56 538**	**27 594**	**8613**	**106 331**

Abbreviations: ACADP, academic cancer program; AJCC, American Joint Committee on Cancer; CCCP, comprehensive community cancer program; CCP, community cancer program; NCIP, National Cancer Institute–designated cancer program; PI, Pacific Islander; PSA, prostate-specific antigen level.

[a] The χ^2 tests and the corresponding two-tailed P values represent differences in facility type by patient characteristics.

scores 2 through 4 reported by community (334 of 13 586; 2.5%) and NCI-designated programs (27 of 8613; 0.3%), and with intermediate values reported by comprehensive community (706 of 55 832; 1.2%) and academic programs (171 of 27 594; 0.6%).

Trends in Percentages of Prostate Cancers With Gleason Scores 2 Through 4, Core Biopsies, Category T1c, 2004–2013

Figure 3 illustrates the temporal trends from 2004 through 2013 in percentages of T1c prostate cancer cases classified as Gleason scores 2 through 4 by each reporting facility type. As in the results for earlier time periods and analyses of all T categories shown in Figure 1, in this analysis of T1c cases from 2004 through 2013 the percentage with Gleason scores 2 through 4 was consistently highest among community programs and lowest among NCI-designated programs.

Independent Associations With Prostate Cancer With Gleason Scores 2 Through 4, Core Biopsies, Category T1c, 2004–2013

A multivariable marginal logistic regression including potential confounding covariates such as patient age, race, geographic region, year of diagnosis, AJCC M category, and PSA level grouped as quartiles demonstrated an independent, significant association between facility type and the proportion of prostate cancers with Gleason scores 2 through 4 (Table 6). Relative to NCI-designated programs, the odds of a diagnosis of prostate cancer with Gleason scores 2 through 4 at community and comprehensive community programs were significantly higher, OR = 5.99 (95% CI, 2.58–13.91) and OR = 2.65 (95% CI, 1.20–5.86), respectively. The only other covariates with statistically significant differences between Gleason score categories were geographic region, year of diagnosis, and PSA quartile. Among these covariates, only the year of diagnosis had a greater effect than facility type on likelihood of cancer being

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Table 5. Patient and Facility Characteristics by Prostate Cancer Gleason Score (2–4 Versus 5–10), Biopsies With American Joint Committee on Cancer (AJCC) Category T1c Cancer, National Cancer Database 2004–2013[a]

	Gleason Score, No. (%)	
	2–4	5–10
Age group ($P = .23$)		
40–49	23 (1.5)	1513 (98.5)
50–59	172 (1.0)	16 579 (99.0)
60–69	476 (1.1)	41 225 (98.9)
70–79	472 (1.2)	38 431 (98.8)
80–89	93 (1.3)	7065 (98.7)
90–99	2 (0.7)	280 (99.3)
Race/ethnicity ($P = .04$)		
Non-Hispanic white	954 (1.2)	77 560 (98.8)
Hispanic	36 (1.0)	3662 (99.0)
Black	225 (1.1)	20 623 (98.9)
Asian and PI	17 (0.7)	2302 (99.3)
Other	6 (0.6)	946 (99.4)
Region ($P < .001$)		
Northeast	262 (0.9)	27 995 (99.1)
Midwest	240 (0.9)	26 114 (99.1)
South	660 (1.8)	36 698 (98.2)
West	76 (0.5)	14 286 (99.5)
Year of diagnosis ($P < .001$)		
2004	416 (3.3)	12 380 (96.7)
2005	247 (1.9)	12 505 (98.1)
2006	207 (1.5)	13 936 (98.5)
2007	131 (0.9)	14 138 (99.1)
2008	85 (0.6)	13 224 (99.4)
2009	92 (0.8)	11 359 (99.2)
2010	21 (0.3)	6439 (99.7)
2011	16 (0.2)	7409 (99.8)
2012	14 (0.2)	6518 (99.8)
2013	9 (0.1)	7185 (99.9)
AJCC M category ($P = .06$)		
Mx	1226 (1.2)	103 340 (98.8)
M1	12 (0.7)	1753 (99.3)
PSA quartile ($P < .001$)		
1 (0–4.8)	539 (2.0)	26 207 (98.0)
2 (4.9–6.4)	219 (0.9)	25 438 (99.1)
3 (6.5–10)	220 (0.8)	26 913 (99.2)
4 (10.1+)	260 (1.0)	26 535 (99.0)
Facility type ($P < .001$)		
CCP	334 (2.5)	13 252 (97.5)
CCCP	706 (1.2)	55 832 (98.8)
ACADP	171 (0.6)	27 423 (99.4)
NCIP	27 (0.3)	8586 (99.7)
Total	**1238** (1.2)	**105 093** (98.8)

Abbreviations: ACADP, academic cancer program; CCCP, comprehensive community cancer program; CCP, community cancer program; NCIP, National Cancer Institute–designated cancer program; PI, Pacific Islander; PSA, prostate-specific antigen level.

[a] The χ^2 tests and the corresponding two-tailed P values represent differences in facility type by patient characteristics.

interpreted as Gleason scores 2 through 4. Relative to cases diagnosed in 2013, those diagnosed during all years prior to 2011 had a significantly lower OR, and the OR for cases diagnosed in 2004 was 24.33 (95% CI, 11.21–52.79).

DISCUSSION

This study of NCDB records demonstrated a decline between 1990 and 2013 in the percentage of prostate core needle biopsies (for all stages combined) classified as Gleason scores 2 through 4 and a decline in the percentage of AJCC category T1c needle biopsies from 2004 through 2013 assigned Gleason scores 2 through 4. These declines occurred earliest at NCI-designated programs and latest at community programs. A multivariable analysis of cases restricted to T1c cancers diagnosed in needle biopsies from 2004 through 2013 showed that facility type was strongly and independently associated with the likelihood of cancers in such specimens being assigned Gleason scores of 2 through 4. These results indicate differences in patterns of specimen interpretation by pathologists practicing in different facility categories. Despite a recommendation by the International Society of Urological Pathology[2] published in 2005 and disseminated in journal articles[8] prior to that time that Gleason scores of 2, 3, or 4 should rarely if ever be diagnosed on needle biopsy, adoption of that recommendation occurred slowly and inconsistently.

This analysis and prior reports based on the NCDB; the Surveillance, Epidemiology, and End Results program; the Swedish National Prostate Cancer Register; and retrospective review of cases from one or more institutions indicate that changes in prostate cancer grading by pathologists were underway before 2005.[5,6,10,12] Among prostate cancers across all stages, 11 476 of 53 850 (21.3%) diagnosed in core needle biopsies from 1990 through 1994 were classified as Gleason scores 2 through 4, in contrast to 96 of 43 566 (0.2%) from 2010 through 2013. The percentages of cases with Gleason scores 2 through 4 across all stages (Figure 1) indicate that the decline in use of Gleason scores 2 through 4 from 1990 to 2005 occurred approximately 5 years earlier at NCI-designated programs than at community programs. For T1c cases (Figure 3) diagnosed between 2004 and 2013, that difference was approximately 4 years.

In bivariate analyses of stage-unrestricted cases from 1990 through 2013 (Table 3) and T1c cases diagnosed during 2004–2013 (Table 5), likelihood of being assigned Gleason scores 2 through 4 was associated with several demographic and clinical variables (in addition to year of diagnosis and facility type as noted above). However, in multivariable analyses of T1c cases diagnosed during 2004–2013, the only variables independently associated with Gleason scores 2 through 4 were geographic region, year of diagnosis, PSA quartile, and facility type. In this multivariable model, ORs (with NCI-designated programs as the referent category) for a diagnosis of prostate cancer with Gleason scores 2 through 4 were 5.99 (95% CI, 2.58–13.91) for community programs, 2.65 (95% CI, 1.20–5.86) for comprehensive community programs, and 1.60 (95% CI, 0.74–3.49) for academic programs.

The clinical significance of these results is that undergrading of some prostate cancer needle biopsies appears to have occurred while the proportion of cases with Gleason scores 2 through 4 was declining more rapidly at NCI-designated programs and academic programs than it did at community programs and comprehensive community programs. This could have led to undertreatment based on an inaccurately favorable assessment of prognosis. A high percentage of cases interpreted as Gleason scores 2 through 4 at some facilities also raises the possibility that at least some of these (especially those interpreted prior to widespread use of immunohistochemical stains for decreasing false-positive rates) might actually have been benign lesions.

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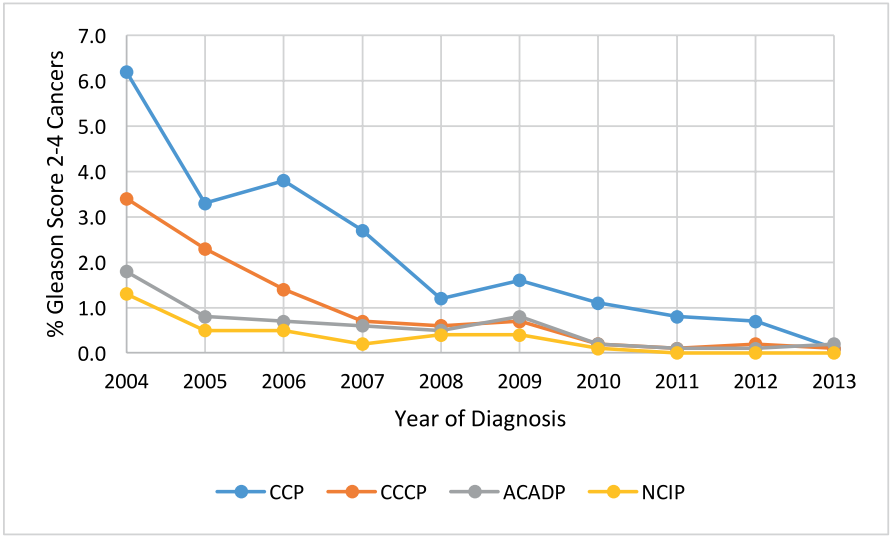

Figure 3. *Percentage of cases with Gleason scores 2 through 4 among core biopsies with category T1c prostate cancer, 2004–2013. Abbreviations: ACADP, academic (teaching/research) cancer programs; CCCP, comprehensive community cancer programs; CCP, community cancer programs; NCIP, National Cancer Institute–designated cancer programs.*

More broadly, our observations of changes in prostate cancer grading from 1990 through 2013 are consistent with prior studies showing that diffusion of many other medical innovations can occur slowly and inconsistently, which may adversely influence clinical outcomes.[25,26]

The gold standard for quality measurement in surgical pathology is comparing the initial pathologist's interpretation (diagnosis, grade, etc) with subsequent interpretation by an expert consultant or the consensus diagnosis of peers.[27,28] However, such programs are resource intensive and can only be applied to a small proportion of cases. One approach for prioritizing quality measurement and quality improvement programs for surgical and medical therapies is to focus on treatments with highly variable use in different geographic regions or practice settings.[29] Similarly, large differences in patterns of anatomic pathology specimen interpretation that persist after statistically controlling for patient-level factors may offer clues regarding potentially harmful variations in pathology practice, and might be helpful in prioritizing quality measurement and quality improvement activities.

Analyses of NCDB data have also been used to help institutions assess how their aggregate medical oncology, radiation oncology, and surgical oncology practice patterns compare with quality benchmarks of other participating institutions.[19,20] This could be applied to some aspects of surgical pathology with the approach we used in creating Figure 2. That figure indicated that from 2000 to 2004, a substantial number of pathologists had not yet adopted the advice of Epstein[8] in his 2000 article, "Gleason Score 2–4 Adenocarcinoma of the Prostate on Needle Biopsy: A Diagnosis That Should Not Be Made." Although facilities with the highest proportions of prostate cancers classified as Gleason scores 2 through 4 tended to be community programs, there were also some comprehensive community programs and a few academic programs (but no NCI-designated programs). Substantial undergrading of prostate cancer by general pathologists relative to interpretations of academic urologic pathologists was reported[30] in 2001 and to a lesser degree[12] in 2008; these findings are consistent with differences in percentages of Gleason scores 2 through 4 cases we found among cancers diagnosed at community and comprehensive community programs (relative to NCI-designated programs) during those years. It is expected that new practices will be assimilated more promptly by academic subspecialists than by generalists responsible for a broad range of services. The long-term goal of this research is to encourage the development of registry-based systems that provide facility-based or pathologist-based feedback on deviations from expected distributions of grade or diagnosis that may reflect failure to keep up with changes in diagnosis and classification of cancers. If it had been feasible in 2000 to provide specific feedback to pathologists outside of NCI-designated programs, it seems likely they would have more rapidly adopted the expert recommendations for prostate cancer grading. To the best of our knowledge, however, this registry-based approach has not been used for anatomic pathology quality measurement programs, although doing so seems feasible and potentially beneficial.

The main strength of this study is that the NCDB provided high quality demographic and clinical information regarding hundreds of thousands of men with prostate cancer diagnosed by core needle biopsy. This large sample size permitted us to minimize the risk of uncontrolled confounding by including demographic, clinical, and facility factors in multivariable analyses. However, our use of the NCDB also introduced several limitations. First, for cases diagnosed from 1990 through 2009, histologic grade was recorded for only one specimen; if patients were diagnosed by core biopsy and subsequently treated by prostatectomy, grade was recorded for only the latter specimen. Consequently, we had to restrict our analyses to patients who did not undergo surgical treatment, which limited our sample size. For consistency, we maintained that restriction for cases diagnosed from 2010 through 2013. Second, PSA level (an important variable we felt should be included in the multivariable model) was not recorded in the NCDB until 2004, and the accuracy of PSA data in registry records is imperfect.[31]

A limitation of the NCDB for analyzing long-term trends is that the hospitals reporting to the NCDB are not consistent over time. In its early years, the NCDB accepted voluntary data submissions from hospitals that were not CoC accredited, and CoC-accredited hospitals were not required to report data. In 1996, NCDB stopped accepting data submissions from nonaccredited facilities, implemented the requirement for data submission by CoC-accredited

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Table 6. Adjusted Odds Ratio of Prostate Cancer Being Assigned Gleason Scores 2 Through 4, Biopsies With American Joint Committee on Cancer (AJCC) Category T1c Cancer, National Cancer Database 2004–2013[a]

	Odds Ratio	95% CI	*P*
Age group, y			
40–49	Referent		
50–59	2.03	0.46–8.96	.35
60–69	1.38	0.33–5.80	.66
70–79	1.49	0.35–6.28	.59
80–89	1.49	0.35–6.29	.59
90–99	1.67	0.39–7.13	.49
Race/ethnicity			
Non-Hispanic white	Referent		
Hispanic	1.04	0.63–1.71	.88
Black	0.95	0.72–1.25	.71
Asian and PI	1.04	0.59–1.83	.89
Other	0.64	0.21–1.94	.43
Region			
Northeast	1.70	0.86–3.38	.13
Midwest	1.77	0.84–3.72	.13
South	3.25	1.57–6.75	.002
West	Referent		
Year			
2004	24.33	11.21–52.79	<.001
2005	13.90	6.04–31.99	<.001
2006	10.24	4.65–22.55	<.001
2007	6.38	2.74–14.88	<.001
2008	4.29	1.98–9.30	<.001
2009	5.54	2.52–12.16	<.001
2010	2.35	1.03–5.36	.04
2011	1.61	0.63–4.08	.32
2012	1.67	0.64–4.34	.30
2013	Referent		
AJCC M category			
Mx	Referent		
M1	0.89	0.45–1.74	.73
PSA quartile			
1	2.18	1.40–3.40	<.001
2	0.92	0.72–1.19	.54
3	0.85	0.69–1.06	.15
4	Referent		
Facility type			
CCP	5.99	2.58–13.91	<.001
CCCP	2.65	1.20–5.86	.02
ACADP	1.60	0.74–3.49	.23
NCIP	Referent		

Abbreviations: ACADP, academic cancer program; CCCP, comprehensive community cancer program; CCP, community cancer program; NCIP, National Cancer Institute–designated cancer program; PI, Pacific Islander; PSA, prostate-specific antigen level.

[a] Results are based on a multivariable log-binomial model.

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programs, and implemented new data definitions and codes. This implementation of standard data items, codes, definitions, and data collection procedures greatly increased the consistency of data included in the NCDB. Although fewer cases were reported to the NCDB during the early 1990s in comparison with subsequent years, and data quality review procedures became more stringent over time, population-based data from the Surveillance, Epidemiology, and End Results program showed similar declining trends in diagnoses of prostate cancers with Gleason scores 2 through 4 during the years in question, supporting the validity of our analyses during this period.[6] Furthermore, the analysis of relative frequency of the percentage of facilities of each category according to their percentage of prostate cancers classified as Gleason scores 2 through 4 is based on the period from 2000 through 2004, and our multivariable model (Table 6) is restricted to cases diagnosed from 2004 through 2013. The low-grade, intermediate-grade, and high-grade/undifferentiated categories recorded in the NCDB prior to 2004 and defined during that period as Gleason scores 2 through 4, 5 through 7, and 8 through 10, respectively, posed a challenge to this investigation and prevented examination of long-term trends in use of individual Gleason scores. Although this limitation does not diminish the validity or our research regarding trends in Gleason scores 2 through 4, we should note that clinical use of these grade categories, especially the intermediate-grade group, is no longer valid and prohibits meaningful grade evaluation of this group given the dissimilarity and wide prognostic differences between Gleason scores 5 and 7, as reflected in the new grade group system. This system compresses Gleason scores into 5 grade groups: grade group

1 (Gleason score ≤6), grade group 2 (Gleason score 3 + 4 = 7), grade group 3 (Gleason score 4 + 3 = 7); grade group 4 (Gleason score 8), and grade group 5 (Gleason score 9–10).[3,32–34]

Despite these limitations, this study of NCDB prostate cancer records convincingly demonstrates substantial inconsistency in practices of Gleason grading, and suggests that more widespread use of similar techniques could contribute to quality measurement and quality improvement programs for some aspects of oncologic pathology. Our recent analyses of NCDB records also showed significant variations by facility category, and among facilities within each category, in the cytologic diagnosis of small cell lung cancer and pancreatic cancer, which suggest a potential application of such analyses to improving collection of pulmonary and pancreatic specimens by pulmonologists, gastroenterologists, and radiologists, as well as improving interpretation of these specimens by pathologists.[35,36] Registry data are increasingly being used for clinical quality monitoring and improvement. Although this approach is not a panacea for pathology quality monitoring and improvement, we conclude that it can nonetheless make a significant contribution.

The variations in the use of Gleason scores 2 through 4 described in this article were most prominent between 1990 and 2000, and have become much less so during the past few years. Nonetheless, the recent endorsement of the 2014 International Society of Urological Pathology grading criteria in publications from the World Health Organization and the AJCC makes this topic especially timely.[3,32,37] To facilitate prompt and consistent adoption of this new framework, we propose several recommendations. Laboratory information systems and cancer registry systems should be updated so that findings can be reported and captured using the recommended terminology. Registry organizations, pathology organizations such as the College of American Pathologists, cancer-related specialty organizations, cancer centers, laboratories, and health services researchers should collaborate to develop practical mechanisms for benchmarking quality indicators relevant to adoption of new nomenclature. Finally, during implementation of new systems for cancer grading (or staging), pathologists and treating clinicians should be especially careful in clearly indicating the frameworks they refer to in various types of clinical, public health, and research communications.

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Prepare Submissions Now for the CAP18 Abstract Program

Abstract and case study submissions to the College of American Pathologists (CAP) 2018 Abstract Program will be accepted beginning at noon Monday, January 8 through 5 p.m. Central time Friday, March 9, 2018.

Accepted submissions will appear on the *Archives of Pathology & Laboratory Medicine* Web site as a Web-only supplement to the September 2018 issue. Awards will be presented to the winners of the Top 5 Junior Member Abstract Program.

The CAP18 meeting will be held October 20–24 in Chicago. Visit the *Archives* Web site (www.archivesofpathology.org) for additional abstract program information as it becomes available.