Effect of the USPSTF Grade D Recommendation against Screening for Prostate Cancer on Incident Prostate Cancer Diagnoses in the United States

Daniel A. Barocas,*,† Katherine Mallin, Amy J. Graves, David F. Penson, Bryan Palis, David P. Winchester and Sam S. Chang‡

From the Department of Urologic Surgery (SSC), and Center for Surgical Quality and Outcomes Research, Vanderbilt University Medical Center (DAB, AJG, DFP), Nashville, Tennessee, and National Cancer Data Base, American College of Surgeons (KM, BP, DPW), Chicago, Illinois

Purpose: In October 2011 the USPSTF (U.S. Preventive Services Task Force) issued a draft guideline discouraging prostate specific antigen based screening for prostate cancer (grade D recommendation). We evaluated the effect of the USPSTF guideline on the number and distribution of new prostate cancer diagnoses in the United States.

Materials and Methods: We identified incident cancers diagnosed between January 2010 and December 2012 in NCDB (National Cancer Database). We performed an interrupted time series to evaluate the trend of new prostate cancers diagnosed each month before and after the draft guideline with colon cancer as a comparator.

Results: Incident monthly prostate cancer diagnoses decreased by −1,363 cases (12.2%, p <0.01) in the month after the USPSTF draft guideline and continued to decrease by 164 cases per month relative to baseline (−1.8%, p <0.01). In contrast monthly colon cancer diagnoses remained stable. Diagnoses of low, intermediate and high risk prostate cancers decreased significantly but new diagnoses of nonlocalized disease did not change. Subgroups of age, comorbidity, race, income and insurance showed comparable decreases in incident prostate cancer following the draft guideline.

Conclusions: There was a 28% decrease in incident diagnoses of prostate cancer in the year after the USPSTF draft recommendation against prostate specific antigen screening. This study helps quantify the potential benefits (reduced harms of over diagnosis and overtreatment of low risk disease and disease found in elderly men) and potential harms (missed opportunities to diagnose important cancers in men who may benefit from treatment) of this guideline.

Key Words: prostatic neoplasms, mass screening, prostate-specific antigen, guideline, diagnosis

Abbreviations and Acronyms

CoC = Commission on Cancer

PCa = prostate cancer

PSA = prostate specific antigen

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* Correspondence: Center for Surgical Quality and Outcomes Research, Vanderbilt University Medical Center, A-1302 Medical Center North, Nashville, Tennessee 37232 (telephone: 615-322-3807; FAX: 615-322-8990; e-mail: dan.barocas@vanderbilt.edu).

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‡ Financial interest and/or other relationship with Bayer, Astellas, Janssen and Tolmar.

In October 2011 USPSTF published an evidence statement and draft recommendations regarding PSA based screening for PCa.[1,2] In these documents and the final recommendation statement USPSTF concluded that the harms of PSA based screening outweigh the benefits, yielding a grade D recommendation against screening.[3] The grade D recommendation is controversial because of uncertainty about the risk-to-benefit

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ratio of PCa screening. PCa remains the second leading cause of cancer death among men in the United States with nearly 30,000 deaths annually.[4] Clinical trial evidence and observational studies suggested a survival benefit for screening while another trial showed no benefit to regular screening in a heavily prescreened population.[5,6]

Epidemiologically PCa mortality has decreased by about 40% since the advent of PSA based screening in the late 1980s and 40% to 70% of that reduction may be attributable to screening.[7] However, the morbidity associated with radiation and surgery is substantial. The number needed to screen and number needed to treat to save 1 life are similar to values for mammography and fecal occult blood testing.[8–10] However, the uncertain benefit of PSA based screening combined with the morbidity associated with treatment led USPSTF to recommend against regular screening.

The USPSTF recommendation may have changed screening practices among primary care providers as evidenced by decreased PSA testing in some institutions and health systems.[11–13] To our knowledge it is unknown how the change in screening recommendations has affected the PCa incidence. Therefore, we evaluated an all payer, nationwide data set to determine whether the number of incident cases per month has changed substantially since the draft guideline and whether observed changes disproportionately affected certain subgroups (age, race and socioeconomic status) or resulted in a shift in disease burden at presentation.

METHODS

Study Population

In NCDB we identified patients 18 years old or older with PCa who resided in the 50 United States or District of Columbia with an incident diagnosis in 2010 to 2012. NCDB is a hospital based registry jointly sponsored by the American Cancer Society CoC and the American College of Surgeons, which captures some 70% of new cancer diagnoses in the United States regardless of patient age or payer via more than 1,500 participating CoC accredited facilities.[14] Any patient who touches a CoC hospital for any part of diagnosis or treatment is captured. Trained abstractors collect demographic and clinical information, cancer stage, grade, PSA, and treatment using FORDS (Facility Oncology Registry Data Standards, http://www.facs.org/cancer/coc/fordsmanual.html).

We eliminated data from hospitals suspected to have incomplete reporting because the hospital was not accredited during the entire study period or the hospital reported a decrease of 20% or more in total cancer cases in 2012 compared to prior years. Of the original 375,137 PCa cases submitted to NCDB in 2010 to 2012 we identified 354,842 unique, incident PCa cases (94.6%) from a total of 1,343 facilities. Of these cases 352,020 (99.2%) had nonmissing month of diagnosis, making them eligible for analysis.

We obtained demographic characteristics, including age (18 to 49, 50 to 59, 60 to 69, 70 to 79, and 80 years or greater), Charlson-Deyo comorbidity (0, 1 or 2+),[15] race (white, black or other), insurance status (private/managed care, Medicare, Medicaid, other government or not insured), facility type (community cancer center, comprehensive community, academic/research center or other), rurality (metropolitan, urban or rural), region (Northeast, South, Midwest, West or Pacific), and ZIP Code™ level median income (0% to 25%, 26% to 50%, 51% to 75%, or 76% or greater) and median high school nongraduation rate (less than 7%, 7% to 12%, 13% to 20%, or 21% or greater). We included PCa characteristics, including PSA at presentation (less than 4, 4.1 to 10, 10.1 to 20 or greater than 20 ng/ml), biopsy Gleason score (6 or less, 7 or 8 to 10), clinical T stage (T1 N0 M0, T2 N0 M0, T3 N0 M0, T4 N0 M0 or any T N+ M+) and D'Amico risk group (low, intermediate, high or nonlocalized).[16]

Study Design

We assessed changes in PCa diagnoses with colon cancer diagnoses as a comparison outcome. The latter did not show a screening guideline change during the study period (supplementary table 1, http://jurology.com/). We used an interrupted time series with a comparison series design to assess changes in aggregate monthly counts of incident cancers.[17,18] We examined whether significant changes in level and trend occurred after the USPSTF grade D draft recommendation. October 2011 served as the cutoff date because clinicians were expected to have changed screening behavior in response to the draft recommendations, which were widely publicized and publicly debated.

Statistical Analysis

We used an interrupted time series with segmented linear regression analysis of monthly aggregate incident cancer diagnosis counts. We assessed the Durbin-Watson statistic to identify potential autocorrelation among successive monthly time points. Our primary model included monthly incident prostate and colon cancer cases as the dependent variable. Independent variables included cancer type (prostate or colon), baseline trend (monthly data from January 2010 to December 2012), level change after the draft guideline (before or after October 2011), trend change after the draft guideline (trend after October 2011 relative to before October 2011) and interaction terms between cancer type and baseline trend, level change and trend change to determine whether differences in level and trend existed between the cancer types. From this model we estimated level change, monthly trend change and annual change in the absolute number of cases for each cancer type. To assess the statistical significance of these changes across equivalent units of measurement we performed a similar statistical model using the natural log of cancer case counts. From this model we estimated percent change in level and trend and percent change during 1 year after the draft guideline. We constructed hypothesis tests to evaluate the statistical significance of these changes (supplementary material, http://jurology.com/).

We stratified our analyses across factors that affect life expectancy (age and comorbidity) as well as race, socioeconomic status (income and insurance status) and disease risk stratum using appropriate interaction terms.

We performed several sensitivity analyses. 1) We assessed changes in PCa diagnoses relative to those of other screening detected malignancies, including breast and lung cancer. 2) We restricted all analyses to ages 50 to 74 years, the age range for which screening may be most relevant. 3) Because of concerns regarding outlying PSA values, we assessed the number of cases that would be reclassified because of very low (less than 1 ng/ml) or very high (greater than 98 ng/ml) PSA.

We used an a priori level of statistical significance of $p < 0.05$. Analyses were done with SAS®, version 9.4 and R, version 3.1.2 (https://www.r-project.org/).

RESULTS

Table 1 lists patient characteristics. Most new diagnoses were in men in the seventh decade of life and approximately 19% of the men were nonwhite. There was a small predominance of intermediate risk disease in localized cases compared to low and high risk (32.2% vs 25.4% vs 27.0%). Nonlocalized disease was present at diagnosis in 5.4% while staging data were missing in 10.1% of cases. Only 5% of men had outlying PSA values, including 2% with PSA less than 1.0 ng/ml and 3.0% with PSA 98 ng/ml or higher. In 1% of men the risk stratum was determined by an outlier PSA value.

Table 2 and figure 1 show changes in level and trend for incident PCa and colon cancer. In the period before the draft guideline the number of monthly PCa diagnoses ranged from 9,442 to 12,021 and diagnoses were increasing by approximately 45 cases per month, which was a 0.4% monthly increase. In October 2011 there was a significant and immediate reduction in estimated incident PCa diagnoses of −1,373 cases as well as a significant change in trend in the periods before vs after the recommendation, representing a relative decrease of 164 cases per month. This corresponded to a change of −12.2% ($p < 0.01$) in incidence in the month immediately after the draft recommendations with an ongoing rate of decrease of −1.8% per month ($p < 0.01$). One year after the draft guideline the number of new diagnoses had decreased by 27.9% compared to the projected trend from the preguideline period.

Meanwhile the number of incident colon cancer diagnoses ranged from 5,192 to 6,042 before the draft guideline. Unlike PCa the colon cancer cases did not significantly change after October 2011 in level (absolute change 4 or 0.24%, $p = 0.95$) or in monthly trend (absolute change −27 or −0.51%, $p = 0.18$). Table 2 also shows the p value of the interaction term between group and monthly baseline slope, group and level change, and group and monthly slope change.

Findings were similar in the subgroup of patients between ages 50 and 74 years, and in comparisons between prostate vs breast cancer and prostate vs lung cancer (supplementary table 2, and supplementary figs. 1 and 2, http://jurology.com/).

Table 2 lists level and trend changes as well as the annualized change in subgroup models. Figure 2 shows these changes in disease risk groups. Diagnoses decreased for all disease risk strata but by different degrees. The initial decrease in monthly diagnoses was −16.9% for low risk, −12.9% for intermediate risk, −10.1% for high risk and −2.7% for nonlocalized disease. The corresponding monthly changes thereafter were −2.7%, −1.9%, −1.4% and 0.1%, respectively (p-interaction <0.01). Thus, when accounting for the initial level change and the monthly changes thereafter, at 1 year after the draft guideline the number of predicted diagnoses had decreased by 37.9%, 28.1%, 23.1% and 1.1% for low risk, intermediate risk, high risk and nonlocalized disease, respectively.

Each stratum of age, comorbidity, race, insurance status and income group showed a similar decrease in level and monthly trend change after the guideline. Therefore, p values of interaction were nonsignificant (table 2).

DISCUSSION

We found a 28% reduction in new PCa diagnoses at CoC accredited hospitals in the year following the USPSTF grade D recommendation against PCa screening. We further sought to elucidate whether the reductions were distributed throughout the population in a manner consistent with the goals of the grade D recommendation.

For example the primary anticipated benefit of limiting screening was to decrease the harms of screening, of which the most important are the morbidities associated with overtreatment of screen detected cancers that are unlikely to manifest in clinical harm to the patient. Detection and treatment of indolent cancers exposes patients to harms such as erectile dysfunction, incontinence and radiation cystitis with little likelihood of benefit.[19] Our study shows that 12 months after the draft guidelines were published the number of diagnoses of new low risk cancers had decreased by 37.9% and they continued to decrease more rapidly than other disease risk strata. This suggests that in this regard the USPSTF recommendation had its intended effect. Similarly the number of new diagnoses had decreased by 23.0% to 29.3% among men older than 70 years and by 26.0% among infirm men. These are populations of men unlikely to live long enough to benefit from

Table 1. *Demographic and clinical characteristics of 352,020 patients with PCa*

	No. Pts (%)
Age:	
18—49	12,133 (3.4)
50—59	86,035 (24.4)
60—69	153,935 (43.7)
70—79	79,457 (22.6)
80 or Greater	20,460 (5.8)
Charlson comorbidity index:	
0	287,187 (81.6)
1	53,658 (15.2)
2 or Greater	11,175 (3.2)
Race:	
White	281,456 (80.0)
Black	55,748 (15.8)
Other	14,816 (4.2)
ZIP Code high school nongraduation:	
21 or Greater	54,080 (15.4)
13—20	85,441 (24.3)
7—12	114,554 (32.5)
Less than 7	95,018 (27.0)
Missing	2,927 (0.8)
Insurance status:	
Private/managed care	132,997 (37.8)
Medicare	150,829 (42.8)
Other government	18,548 (5.3)
Medicaid	8,934 (2.5)
Not insured	7,443 (2.1)
Missing	33,269 (9.5)
Facility type:	
Community Ca center	29,274 (8.3)
Comprehensive community	169,713 (48.2)
Academic/research center	134,013 (38.1)
Other	19,020 (5.4)
Rurality:	
Metropolitan	284,113 (80.7)
Urban	50,544 (14.4)
Rural	7,077 (2.0)
Missing	10,286 (2.9)
Median ZIP Code income quartile:	
0—25th	58,109 (16.5)
26th—50th	77,500 (22.0)
51th—75th	93,552 (26.6)
76th—100th	119,722 (34.0)
Missing	3,137 (0.9)
Region:	
Northeast	74,393 (21.1)
South	128,016 (36.4)
Midwest	92,462 (26.3)
West	17,524 (5.0)
Pacific	39,625 (11.3)
PSA at presentation (ng/ml):	
4 or Less	54,003 (15.3)
4.1—10	180,117 (51.2)
10.1—20	39,042 (11.1)
Greater than 20	38,818 (11.0)
Test ordered, no results	7,082 (2.0)
Test not performed	6,599 (1.9)
Missing	26,359 (7.5)
Biopsy Gleason score:	
6 or Less	137,743 (39.1)
7	128,605 (36.5)
8—10	56,997 (16.2)
No needle core biopsy/transurethral prostate resection	13,016 (3.7)
Missing	15,659 (4.4)
Clinical T stage:	
T1 N0 M0*	225,749 (64.1)
T2 N0 M0*	79,798 (22.7)
T3 N0 M0*	7,800 (2.2)
T4 N0 M0*	929 (0.3)
Any T N+ or M+	18,909 (5.4)
Missing	18,835 (5.4)
Risk group:	
D'Amico low	89,266 (25.4)
D'Amico intermediate	113,323 (32.2)
D'Amico high	94,995 (27.0)
Nonlocalized	18,909 (5.4)
Missing	35,527 (10.1)

*Including Nx and Mx.

early detection but who are at risk for harms of treatment.

However, a policy to withhold screening is also expected to result in failure to detect higher risk cancers during the window of curability. Timely treatment of intermediate and high risk localized disease is associated with superior overall and disease specific survival, development of metastases and secondary treatments.[20—24] Our study revealed a 28.1% reduction in diagnoses of intermediate risk disease and a 23.1% reduction in diagnoses of high risk PCa 1 year after the draft guideline. This suggests that decreased screening could result in missing important opportunities to spare these men from progressive disease and cancer death. The observation period after the grade D recommendation was insufficient to determine the impact on the diagnosis of nonlocalized PCa, which is associated with a high treatment burden, quality of life decrements and mortality. However, we observed a small upward slope in diagnoses of nonlocalized disease. In the context of decreasing rates of diagnoses of intermediate and high risk localized disease our findings raise concern for increasing rates of advanced disease in coming years.

Similarly it would be undesirable to delay diagnosis to a time in the life of the patient when he is no longer eligible for all available curative treatments. The reduction in diagnoses 1 year after the draft recommendation did not vary across age and comorbidity strata (−22.3% to −29.2% decrease), suggesting that younger, healthier men who harbor intermediate or high risk disease and would be candidates for aggressive local therapy may not have a timely diagnosis under this policy. On the other hand those with low risk disease would be spared the harms of over diagnosis and overtreatment.

Finally we assessed the potential impact of the USPSTF recommendation on vulnerable populations. Black men are at 60% higher risk for PCa diagnosis and at 150% increased risk for PCa mortality compared to white men.[4,25] Our study showed that decreases in diagnoses were comparable between white and black American men, and across socioeconomic strata, raising concern for missed diagnoses among high risk and poorly resourced populations.

Table 2. *Change in incident diagnoses of colon and prostate cancers, and in prostate cancer subgroups*

Group	Monthly Slope before Guideline Change*		Level Change Immediately after Guideline Change†		Monthly Slope Change after Guideline Change Relative to before Guideline Change‡		Estimated Change in Monthly Diagnoses 1 Yr after Guideline Change§	
	Absolute Change	% Change	Absolute Change	% Change	Absolute Change	% Change	Absolute Difference	% Difference
Cancer type:		p(int)=0.31‖		p(int)=0.04		p(int)=0.03		
Prostate	39	0.4	−1,373	−12.2	−164	−1.8	−3,181	−27.9
Colon	3	0.1	4	0.2	−27	−0.5	−298	−5.1
Prostate cancer subgroup:								
Disease risk stratum:		p(int)=0.31		p(int)=0.30		p(int)<0.01		
Low	9	0.3	−505	−16.9	−57	−2.7	−1,134	−37.9
Intermediate	26	0.8	−437	−12.9	−59	−1.9	−1,090	−28.1
High-risk	4	0.1	−300	−10.1	−34	−1.4	−674	−23.1
Non-localized	2	0.3	−14	−2.7	1	0.1	−6	−1.1
Age group:		p(int)=0.53		p(int)=0.57		p(int)=0.94		
18–49	−1	−0.2	−27	−6.9	−5	−1.7	−79	−22.3
50–59	6	0.2	−240	−8.5	−46	−2.1	−743	−27.4
60–69	22	0.5	−634	−12.9	−74	−1.8	−1,448	−28.6
70–79	10	0.4	−416	−16.5	−32	−1.5	−763	−29.2
80+	2	0.3	−56	−8.7	−8	−1.6	−148	−23.0
Comorbidity count:		p(int)=0.93		p(int)=0.47		p(int)=0.76		
0	32	0.4	−1,175	−13.0	−134	−1.9	−2,653	−28.9
1	6	0.4	−133	−7.4	−25	−1.8	−407	−23.1
≥2	1	0.3	−66	−14.4	−5	−1.4	−122	−26.0
Race:		p(int)=0.77		p(int)=0.64		p(int)=0.79		
White	28	0.3	−1,162	−12.7	−134	−1.8	−2,639	−28.5
Black	10	0.6	−190	−11.1	−26	−1.8	−478	−26.7
Other	2	0.5	−22	−5.8	−4	−1.4	−65	−18.3
Income quartile:		P(int)=0.95		p(int)=0.99		p(int)=0.90		
<$30,000	5	0.3	−214	−11.6	−22	−1.5	−461	−25.1
$30,000-34,999	9	0.4	−317	−12.9	−33	−1.7	−678	−27.0
$35,000-45,999	13	0.5	−351	−11.7	−48	−2.0	−882	−28.7
≥$46.000	15	0.4	−455	−11.9	−60	−1.9	−1,115	−28.5
Insurance:		p(int)=0.98		p(int)=0.83		p(int)=0.77		
Private/managed care	15	0.4	−479	−11.2	−70	−2.0	−1,247	−28.9
Medicare	24	0.5	−668	−14.0	−66	−1.7	−1,398	−27.9
VA/Miltary	2	0.3	−75	−12.0	−8	−1.8	−165	−27.7
Medicaid	1	0.4	−19	−6.3	−4	−1.7	−61	−21.5
Not Insured	1	0.3	−16	−6.9	−2	−1.0	−36	−15.9

* Compares slope from February 2010 vs January 2010.
† Compares October 2011 vs September 2011.
‡ Compares slope from October/November 2011 vs January/February 2010.
§ Compares predicted number of diagnoses in September 2012 based on pre-October 2011 trend to post-October 2011 trend.
‖ p(int) refers to the p value for the interaction term between group and monthly baseline slope; between group and level change; and between group and monthly slope change.

The findings of this study must be interpreted in the context of the data set and study design. NCDB is a large cancer registry that includes all ages and all payers. It captures up to 70% of American cancer diagnoses each year, making it a powerful tool for clinical epidemiology. However, it is not population based in the sense that it is not weighted to reflect the demographic distribution of persons in the United States. We attempted to mitigate this limitation by comparing PCa diagnoses to diagnoses of other common cancers. We found that rates of other cancers remained relatively stable throughout this period, suggesting that the change in PCa diagnoses reflects an effect of the USPSTF recommendation rather than secular trends or changes in cancer reporting in NCDB. Nonetheless, the incidence data in this study cannot be translated directly to national incidence as the denominator is not precisely defined and NCDB is a registry rather than a population based dataset.

Using data from immediately after the draft guideline allowed for early identification of its results. However, since we used this short period after the draft guideline, we could not assess downstream outcomes such as effects on the incidence of non-localized disease and PCa mortality, which we would expect to manifest some years later. Methodologically to perform an interrupted time series analysis we used data aggregated at monthly time points. This is a powerful method to assess trends in a population but it lacks the opportunity to control for individual level covariates to account for confounding. However, it is unlikely that most characteristics changed during the study period. We found that the incidence of other cancers did not change during this period even in the narrowed age group of 50 to 74 years.

The USPSTF grade D recommendation against PCa screening was intended to reduce the harms of

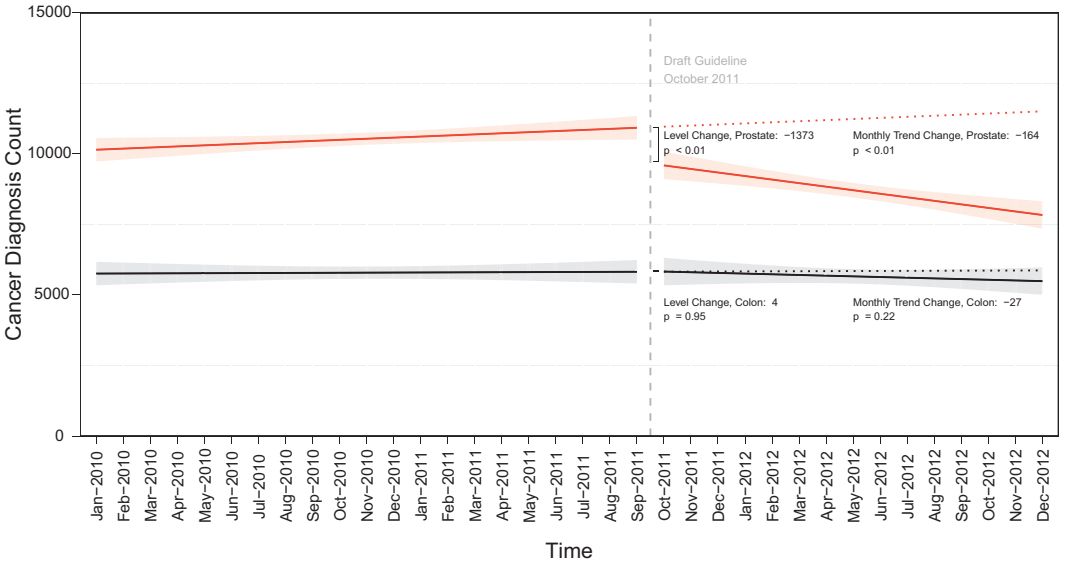

Figure 1. New cancer diagnoses in NCDB from 2010 to 2012. Red curves indicate PCa with 95% confidence bands. Black curves indicate colorectal cancer with 95% confidence bands. Dots indicate continuation of trend before draft guideline.

screening in the face of what was deemed a small potential benefit. While policies in the previous 2 decades led to indiscriminate screening, resulting in a public health crisis of harms associated with over diagnosis and overtreatment, the grade D recommendation risks ushering in an era of indiscriminate delays in PCa diagnoses, which could have deleterious effects on downstream outcomes. Our findings have begun to quantify those potential benefits and harms of the USPSTF recommendation against PSA based screening for PCa. While some such as the Canadian Task Force on Preventive Health Care[26] have followed along with USPSTF, opponents of the USPSTF grade D recommendation have placed greater emphasis on shared decision making to facilitate individualized, patient centered decisions regarding screening, which may provide a pathway for judicious screening in men at risk for PCa.[27]

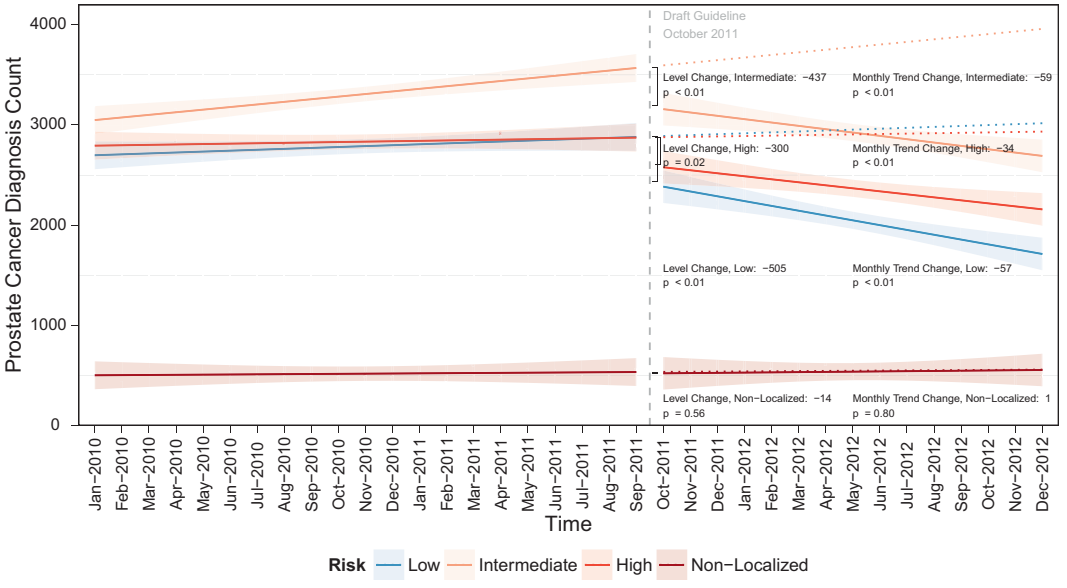

Figure 2. New PCa diagnoses in NCDB from 2010 to 2012 by disease risk stratum, including level and monthly trend changes, and p values. Curves indicate regression line and 95% confidence band for each disease risk stratum. Dots indicate continuation of trend before draft guideline.

CONCLUSIONS

PCa diagnoses decreased by 28% in the first year after the USPSTF grade D draft recommendation against PCa screening. While some effects of this guideline may be beneficial in terms of decreasing harms of over diagnosis and overtreatment, the reduction in intermediate and high risk cancer diagnoses raises concern for delayed diagnoses of important cancers, which are associated with inferior cancer outcomes. Future research should focus on PCa screening paradigms that minimize harms and maximize the potential benefits of screening as well as account for individual patient risk factors and preferences.

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