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ORIGINAL ARTICLE

Unintended consequences of decreased PSA-based prostate cancer screening

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Abstract

Background In May 2012, the US Preventive Services Task Force issued a grade D recommendation against PSA-based prostate cancer screening. Epidemiologists have concerns that an unintended consequence is a problematic increase in high-risk disease and subsequent prostate cancer-specific mortality.

Materials and methods To assess the effect of decreased PSA screening on the presentation of high-risk prostate cancer post-radical prostatectomy (RP). Nine high-volume referral centers throughout the United States ($n = 19{,}602$) from October 2008 through September 2016 were assessed and absolute number of men presenting with GS ≥ 8, seminal vesicle and lymph node invasion were compared with propensity score matching.

Results Compared to the 4-year average pre-(Oct. 2008–Sept. 2012) versus post-(Oct. 2012–Sept. 2016) recommendation, a 22.6% reduction in surgical volume and increases in median PSA (5.1–5.8 ng/mL) and mean age (60.8–62.0 years) were observed. The proportion of low-grade GS 3 + 3 cancers decreased significantly (30.2–17.1%) while high-grade GS 8 + cancers increased (8.4–13.5%). There was a 24% increase in absolute numbers of GS 8+ cancers. One-year biochemical recurrence rose from 6.2 to 17.5%. To discern whether increases in high-risk disease were due to referral patterns, propensity score matching was performed. Forest plots of odds ratios adjusted for age and PSA showed significant increases in pathologic stage, grade, and lymph node involvement.

Conclusions All centers experienced consistent decreases of low-grade disease and absolute increases in intermediate and high-risk cancer. For any given age and PSA, propensity matching demonstrates more aggressive disease in the post-recommendation era.

Keywords Prostate cancer · Screening · USPSTF recommendation · High risk

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Abbreviations

PSA	Prostate-specific antigen
USPSTF	United States Preventive Services Task Force
GS	Gleason score
RP	Radical prostatectomy
SVI	Seminal vesicle invasion
LNI	Lymph node involvement
BCR	Biochemical recurrence
PCSM	Prostate cancer-specific mortality

Background

Prostate-specific antigen (PSA)-based prostate cancer (PCa) screening has been widely debated in the United States, given that diagnosis of clinically indolent disease could expose patients to unnecessary harms of overtreatment [1]. PSA-based screening was originally introduced without Level 1 evidence to guide its use and thus came under the scrutiny of the United States Preventive Services Task Force (USPSTF) in 2012 [1]. The resultant grade D recommendation in May 2012 was primarily dependent on two prospective, randomized trials: Prostate, Lung, Colorectal, and Ovarian (PLCO) and European Randomized Study for Screening of Prostate Cancer (ERSPC) [1, 2]. PLCO reported no significant mortality differences with screening and ERSPC determined nearly 1400 patients needed to be screened to prevent one death; accordingly, the USPSTF recommended against the use of PSA screening for all men. Extrapolation from these studies informed their conclusion that PSA-based screening would inevitably lead to a substantial overdiagnosis and overtreatment of men who would have otherwise remained asymptomatic [1–3].

The controversy surrounding the USPSTF recommendation is largely based on the flaws of the PLCO and ERSPC. The PLCO randomly assigned men to annual PCa screening versus usual care. While at first glance no difference in prostate cancer-specific mortality (PCSM) was found, a more in-depth analysis revealed a high rate of contamination (52%) via PSA testing in the usual care group [4]. The ERSPC, while not plagued by extensive cross-contamination (29%), was seriously flawed due to insufficient follow-up: the natural history from time of diagnosis to PCSM is 10–12 years [3]. Given the follow-up time in the ERSPC trial was only 7 years, the insignificant reduction of 1 PCSM per 1000 men screened was noted [4]. Interestingly, a sub-analysis of the Goteborg arm ($N = 20{,}000$) of ERSPC which had the lowest contamination (3%) showed a more than threefold difference: the number needed to screen was 293 and the number needed to treat was 12, representing a risk ratio of 44% ($P = 0.002$) [5, 6]. More recently, a study by Tsodikoc and colleagues concluded that the ERSPC and PLCO provided compatible evidence that screening reduces PCa mortality after adjusting for differences in study population and setting [7].

In response to the USPSTF's recommendation, professional entities have voiced their dissent. The American Urologic Association (AUA) and National Cancer Institute (NCI) maintain benefit of shared decision-making and risk-group stratification [8, 9], while academic institutions cite concern that high-grade tumors and metastatic disease may go undetected [10, 11]. Since 1992, PSA-based screening has been accompanied by a steady decline in PCSM, such that the incidence of fatal PCa declined by > 50% since the introduction of PSA [12]. While declines in PCSM and improvement in survival may not be singularly associated with screening practices, numerous reports attribute 45–70% of reduction in mortality outcomes to widespread PSA screening [13, 14]. Mathematical models by Gulati and colleagues found policy-based screening accounted for nearly 100% of reductions in incidence of metastatic PCa [13]. While eliminating screening would alleviate potential overtreatment, it could also increase number of high-risk patients, potentially increasing PCSM by 13–20%, along with associated increased costs due to secondary interventions such as radiation, chemotherapy and hormonal therapy [13].

Since 2012, population-based studies have linked the grade D recommendation to decreases of 18–39% in PSA testing and 28.7–64% in digital rectal examination [14–17]. Subsequently, incidence of early stage PCa has experienced a 16–28% decline [10], with the largest decrease in new diagnoses between 2011 and 2012 [14, 17]. Although the recommendation was intended to reduce the number of low-risk prostate cancers, epidemiologists are concerned of reverse-stage migration of high-risk, fatal cancers [18]. Herget and colleagues found that incidence of high-grade PCa declined slowly from January 2007 to August 2011 and was followed by a steep 10.8% decline post-recommendation [19]. Gulati and colleagues warn that risks of disease progression among untreated PCa are non-trivial and contribute to a near doubling in PCSM [20]. While publications have demonstrated substantial decreases in the incidence of early stage PCa post-USPSTF recommendation, there have been no studies examining the recommendation's downstream effect on PCa oncological outcomes [7, 21]. Further, the long natural history of PCa progression delays maturation of population-based databases and magnifies challenges with follow-up. Pathological metrics offer reliable early predictive risk stratification with high concurrence to population-based studies [22]. To address concern that decreased screening may lead to an increase in high-risk and local lymph node metastatic disease, we conducted a case series analysis of national trends in clinical and pathological metrics pre- and post-USPSTF recommendation.

Methods

Study data and population

We examined 19,602 patients who underwent robotic radical prostatectomy (RP) for treatment of PCa from October 2008 through September 2016 at nine high-volume institutions across the United States. Institutions with a history of stable referral patterns were selected. All data were prospectively collected and entered into electronic databases at respective institutions, under approved institutional review board (IRB) protocols. Prior to transmission, data were de-identified such that they were considered non-human participant research under US Department of Health and Human Services' Office for Human Research Protection and did not require IRB review or informed consent. Data use agreements were obtained per individual institutions' request. Centers collated and transmitted two datasets pre- and post-USPSTF recommendation without exclusion.

Study variables

Eleven data points per patient were requested: year of birth, year of surgery, ethnicity, preoperative PSA level (ng/mL), clinical Gleason score (cGS), pathological Gleason score (pGS), pathological T-stage, seminal vesicle invasion (SVI), lymph node involvement (LNI), positive surgical margin (PSM), 1-year biochemical recurrence rate (BCR).

Statistical analysis

Age and PSA are described as descriptive statistics (mean/SD for normally distributed variables and median/range for PSA due to non-normality). Trends in PSA were analyzed both as a continuous and categorical variable using either Kruskal–Wallis or Pearson chi-square tests. Age was treated as a continuous variable and tested via ANOVA and *F* test. Changes in the distribution of patients over time by stage, Gleason score, SVI, LNI and PSM were tested using Pearson chi-square tests. We estimated a 4-month interval for the recommendation's effect to manifest [9]. Therefore, the pre-USPSTF era was defined as October 2008–September 2012, and post-USPSTF was defined as October 2012–September 2016. For longitudinal analysis, data were analyzed in 12-month periods following the recommendation. We utilized Bonferroni adjustment to correct for multiple comparisons.

Propensity score matching was utilized to address possible confounding bias due to variation in referral patterns in these high-volume centers between pre- and post-USPSTF eras. Propensity scores were generated for a patient being referred in the post-USPSTF era based on the baseline characteristics of age and PSA. Generated propensity values were used as matching criteria to obtain 1:1 matched pairs between post-USPSTF and pre-USPSTF patients ($n = 15{,}758$). Using the age and PSA-matched data, logistic regression was used to generate the odds ratios for a post-USPSTF vs pre-USPSTF diagnosis associated with worse tumor characteristics (p-Stage = T3/T4; pGS ≥ 4 + 5; SVI; LNI; PSM). Post-USPSTF era was further subdivided into two periods 'POST-1' (Oct. 2012–Sept. 2014) and 'POST-2' (Oct. 2014–Sept 2016) and each was 1:1 matched with pre-USPSTF ($n = 7746$ and $n = 8700$, respectively). Odds ratios were generated for POST-1 and POST-2 diagnosis vs pre-USPSTF associated with having worse tumor characteristics.

Results

Pre-USPSTF (Oct. 2008–Sept. 2012) versus post-(Oct. 2012–Sept. 2016) metrics comparison

Table 1 shows clinical and pathological characteristics pre-($N = 11{,}051$) and post-($N = 8551$) USPSTF recommendation. Categorical analysis of the two eras showed a statistically significant rise in mean age from 60.8 to 62.0 ($P < 0.001$) and median PSA from 5.1 to 5.8 (ng/mL; $P < 0.001$) post-recommendation. The absolute number of patients with PSA levels greater than 10 and 20 ng/mL increased 24% from 888 (8.5% of total) to 1104 (13.2% of total) and 44% from 246 (2.4% of total) to 354 (4.2% of total), respectively, ($P < 0.0001$). Further, there was an increase in the absolute number and percent of total for higher grade clinical (cGS) and pathological (pGS) cancers ($P < 0.0001$). Also, in the post-screening era, there was a higher relative proportion and absolute number of SVI, LNI and PSM ($P < 0.001$). The proportion of men presenting with LNI prior to the USPSTF recommendation was 3.0% ($N = 325$), compared to 7.5% ($N = 625$) in the post-USPSTF era ($P < 0.001$).

Temporal trends between the two eras showed a 23% reduction in surgical volume post-USPSTF recommendation (from 11,051 to 8551), consistent at the nine institutions (Fig. 1a). Additionally, in the post-screening era there was a trend of increase in both mean age and median PSA on a per annual basis (Fig. 1b, c). During the 8-year study period, a rise in both absolute number and proportion of pGS4 + 5 became evident after the USPSTF recommendation (Fig. 2a). In addition to the increase in SVI, there was an increase in absolute number and proportion of cases with lymph node metastasis (Fig. 2b) in the post-USPSTF era ($P < 0.001$). Biochemical recurrence (BCR) data were available from five centers ($N = 10{,}927$). Pre-USPSTF recommendation, BCR was noted in 399/6474 (6.2%) of patients within the first year after surgery. Post-USPSTF recommendation,

Table 1 Baseline clinical and pathological characteristics of men undergoing radical prostatectomy in the pre- and post-USPSTF PSA-based screening eras

	Pre-USPSTF Oct. 2008–Sept. 2012 ($N=11,051$)		Post-USPSTF Oct. 2012–Sept. 2016 ($N=8551$)		*P* value
	Mean/Median	SD/range	Mean/Median	SD/range	
Age (mean, SD)	60.76	7.25	61.98	7.23	< 0.001
PSA (median, range)	5.10	0.06–500	5.79	0.00–418	< 0.001+
	No.	%	*N*	%	*P* value
Ethnicity					0.02
Caucasian	6572	59.5	4816	56.3	
Asian	109	1.0	141	1.6	
Hispanic	70	0.1	74	0.1	
African American	442	4.0	526	6.2	
Mixed/other	3391	30.7	2041	23.9	
Unknown	467	4.2	953	11.1	
PSA					< 0.0001
PSA ≤ 10	9266	89.1%	6895	82.5%	
10 < PSA ≤ 20	888	8.50%	1104	13.2%	
PSA > 20	246	2.4%	354	4.2%	
cGS					< 0.001
≤ 3 + 3	5223	47.4%	2667	31.3%	
3 + 4	3390	30.7%	3053	35.8%	
4 + 3	1233	11.2%	1392	16.3%	
4 + 4	769	7.0%	815	9.6%	
≥ 4 + 5	411	3.7%	598	7.0%	
pGS					< 0.001
≤ 3 + 3	3280	30.2%	1436	17.1%	
3 + 4	5033	46.3%	4065	48.3%	
4 + 3	1645	15.1%	1779	21.1%	
4 + 4	323	3.0%	411	4.9%	
≥ 4 + 5	590	5.4%	723	8.6%	
P-stage					< 0.001
pT2	8006	72.5%	5191	60.8%	
pT3/pT4	3040	27.5%	3342	39.2%	
SVI	779	7.1%	899	10.6%	< 0.001
LNI	325	3.0%	635	7.5%	< 0.001
SM+	1730	15.7%	1731	20.2%	< 0.001

cGS clinical Gleason score, *pGS* pathological Gleason score, *SVI* seminal vesicle invasion, *PSM* positive surgical margin

**P* values less than 0.007 were considered to be significant after Bonferroni adjustment

+Mann–Whitney test

BCR rose almost threefold to 784/4483 (17.5%) within the first year after surgery.

Stepwise trends post-recommendation (201–2016) versus average pre-(2008–2012)

A yearly stepwise increase was also observed in the 4 years following the recommendation (Fig. 2a, b). The absolute number of patients presenting with pGS ≥ 4 + 5 has increased 3–17% each year since 2012, while LNI has increased 17–21% annually. By the fourth-year post-recommendation, pGS ≥ 4 + 5 cancers had increased 1.5-fold and LNI had increased 3.4-fold, compared to the 4-year average pre-recommendation.

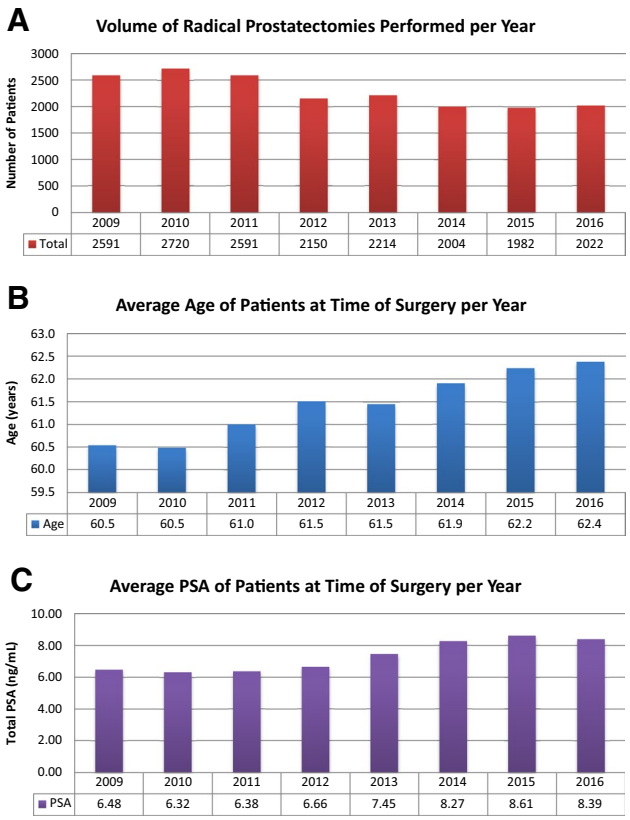


Fig. 1 Temporal trends of the USPTF grade D recommendation against PSA-based screening: **a** surgical volume, **b** age at time of surgery and **c** PSA at time of surgery

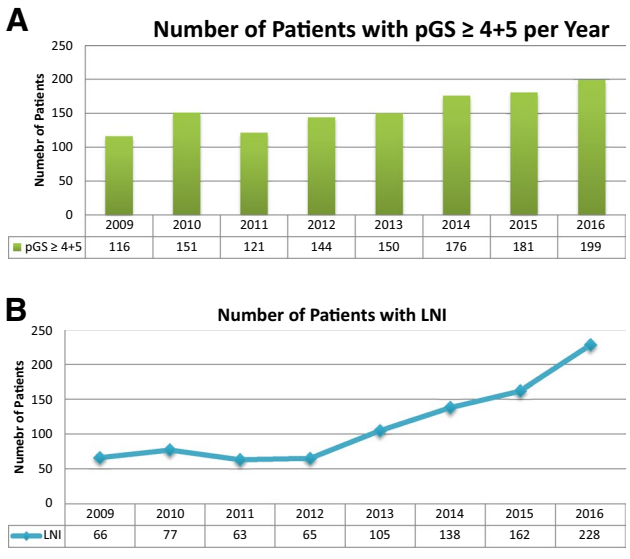


Fig. 2 Unintended consequences of the USPSTF grade D recommendation against PSA-based screening: **a** pGS ≥ 4 + 5 over 8 years and **b** LNI over 8 years

Propensity score matching for age and PSA

To discern whether the increase in high-risk disease was due to variation in referral patterns or inherent changes in disease aggressiveness, we performed propensity matching for age and PSA. After propensity score matching, a 1:1 matched dataset of 15,758 patients was generated; 7879 in post-USPSTF era and 7879 in pre-USPSTF era. Table 2 depicts significant increase in proportion with higher grade and stage disease in the post-recommendation era ($P < 0.001$) among age- and PSA-matched patients. Figure 3 shows significantly increased ORs for POST-1 and POST-2 diagnosis relative to pre-USPSTF associated with high-risk oncologic metrics, with ORs increasing from the first 2 years to the subsequent 2 years for each high-risk characteristic.

Discussion

Mature population-based data assessing the downstream clinical impact of the USPSTF grade D recommendation will not be available for years. Historically, approximately 70–80,000 or about one-third of men diagnosed with PC undergo RP as part of their treatment. We present the first large scale case series of oncological metrics from high-volume institutions throughout the United States pre- and post-USPSTF recommendation.

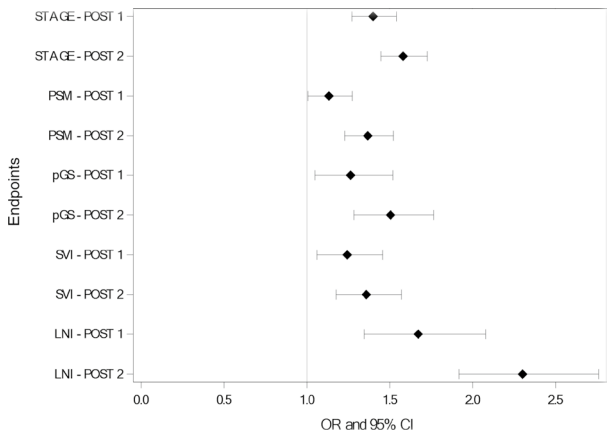
Since 2012, although the PSA has not risen dramatically, the absolute number of men with PSA > 10 and 20 has increased 1.45-fold. The primary anticipated benefit of limited screening was to decrease the harms of overdiagnosis, of which the most important are morbidities associated with overtreatment of screen-detected cancers that are unlikely to manifest in clinical harm to the patient (low volume: pT2; low-grade: pGS ≤ 3 + 3) [4, 23]. In conjunction with the 22.6% reduction in surgical volume post-USPSTF recommendation, there was a 56% decrease in absolute numbers of low-grade pGS3 + 3 cancers. Organ-confined disease dropped from 67 to 58% in the post-era. However, a potentially deleterious outcome of reduced screening is the risk over time of increasingly more aggressive disease. While changes in age and low-grade disease are congruent with the USPSTF recommendation, the presently noted increase in men with PSA > 10–20 is potentially a harbinger of unintended consequences [24]. There are two outcomes of interest which are interrelated, but of separate consequence: BCR and PCSM. Although not immediately life-threatening, BCR is burdensome for issues related to patient-based fear [25], of the side effects of secondary interventions (such as radiation, hormonal therapy, or chemotherapy) and costs [26, 27]. Independently or combined, metrics of preoperative PSA, positive surgical margins, extracapsular extension, or pGS 4 + 3/4 + 4 are more closely associated with BCR (35–47%)

Table 2 Pre- and post-USPSTF recommendation age, PSA, and tumor characteristics of matched dataset

Matched covariates	Pre-USPSTF Oct. 2008–Sept. 2012		Post-USPSTF Oct. 2012–Sept. 2016		
N	7879		7879		
Age (mean, SD)	61.53	7.06	61.60	7.13	
PSA (mean, SD)	6.95	5.58	7.01	5.64	
PSA (median, IQR)	5.60	4.40–7.80	5.60	4.40–7.90	
	N	%	*N*	%	*P* value
P-Stage					< 0.001
pT3/pT4	2346	29.8	2948	37.8	
pT2	5509	70.1	4852	62.2	
pGS					< 0.001
≥ 4 + 5	474	6.0	617	7.8	
< 4 + 5	7405	94.0	7262	92.2	
SVI	623	7.9	767	9.8	< 0.001
LNI	269	3.5	563	7.2	< 0.001
SM+	1289	16.4	1561	19.8	< 0.001

($n = 15{,}758$)

*P values less than 0.01 were considered to be significant after Bonferroni adjustment



	Post-USPSTF Overall Oct. 2012 – Sept. 2016 (N= 7879 per group)		Post-USPSTF Oct. 2008 – Sept. 2012 (N=7879)			
			Period 1: Oct. 2012 – Sept. 2014 (N= 3873 per group)		Period 2: Oct. 2014 – Sept. 2016 (N= 4350 per group)	
	OR	95%CI	OR	95%CI	OR	95%CI
p-Stage T3/T4	1.42	1.33-1.52	1.40	1.27-1.54	1.58	1.44-1.72
pGS ≥ 4+5	1.26	1.16-1.37	1.13	1.01-1.27	1.37	1.22-1.52
SM+	1.32	1.17-1.50	1.26	1.05-1.52	1.50	1.28-1.76
SVI	1.26	1.13-1.41	1.24	1.06-1.45	1.36	1.17-1.57
LNI	2.14	1.84-2.48	1.67	1.34-2.07	2.30	1.91-2.76

Fig. 3 Odds ratios for post-USPSTF recommendation era POST 1 period (Oct 2012–2014) and POST 2 period (2014–Sept 2016) relative to pre-USPSTF era (Oct 2008–Sept 2012) associated with worse tumor characteristics (p-Stage of T3/T4; pathological Gleason Score ≥ 4 + 5; seminal vesical invasion; lymph node involvement; positive surgical margin) in Age and PSA propensity matched dataset ($n = 15{,}758$)

than PCSM [28–32]. Of the nine centers, five had 1-year follow-up data on BCR. Compared to pre-recommendation patients, there has been a 2.8-fold increase in BCR within 1 year of surgery (6.2–17.5%).

In 2013 and 2017, Gulati and associates expressed a concern that a policy of reduced PSA screening would result in an upward shift of incidence in high-grade disease, recurrence rates, secondary interventions, and mortality patterns [13, 33]. The pathologic outcomes unique to RP allow important downstream clinical predictions not otherwise available, as pathological analysis of RP specimens allows assessment of whether the documented decline in PSA screening has increased the fundamental proportion of men with aggressive prostate cancer. The perioperative metrics most closely associated with PCSM are LNI, pGS9-10, and SVI [22, 34]. The USPSTF recommendation assumes that the reduction in overdiagnosis would result in only marginal and likely tolerable increase in the absolute number of high-risk cancers [12]. The increase in high-grade disease is consistent with the noted higher incidence of SVI and LNI in the post-USPSTF time period. In the face of waning surgical volume, the absolute number of patients with SVI and LNI has increased 1.4- and 3.4-fold by 2016, respectively. Perhaps more troubling is the exponential increase in the proportion of LNI immediately after 2012: growing from 3.1% (66/2149) patients in 2012 to 11.7% (228/1946) in 2016, or 3.8-fold.

To more precisely assess for an increase in aggressiveness since the recommendation, we performed propensity matching analysis adjusting for PSA and age in the pre- and post-recommendation eras. In this regard, propensity

matching addresses known confounders, especially variation in referral patterns for these high-volume centers. As seen in Table 2, there is a proportional increase in all factors predicting more aggressive disease. Forest plots of odds ratios shown in Fig. 3 depict the change from lower aggressiveness to significantly more aggressive disease in the post-recommendation era. Not only was a difference observed between pre- and post-eras, the proportion of high- and very-high-risk disease, especially LNI continues to increase in stepwise fashion.

Our study must be interpreted within the context of its design. The present investigation relies on case series analysis of nine high-volume centers distributed throughout the United States as a surrogate to population-based databases. Large population-based databases have inherent selection biases and inability to control for lead time bias associated with PSA screening [35]. Increased active surveillance (AS) and a potential increase in the use of RP are factors of which we were not able to specifically account. While these are most assuredly responsible for part of the proportional and absolute number reductions in men undergoing RP, the impact of increased AS and/or the uptake of RP cannot be singularly responsible for the increase in absolute number of high-risk patients. Similarly, selection bias is inherent in any observational study and potentially contributed an error, but is ostensibly consistent in both the pre- and post-recommendation eras. The only way to definitively demonstrate the pathologic changes would be to follow patients randomized to screening and non-screening who conformed to randomization and look at their long-term treatment and PCa outcomes. Lack of central pathology review is an inherent limitation of this multicenter study; however, pathology was reviewed by genitourinary pathologists from each of these high-volume academic institutions. Further, with such a diverse sampling, there should be a regression toward the mean that decreases variation in pathologists. The findings should be interpreted with consideration of variations in clinical practice (prior to referral and between referral centers) as well as surgical practices unique to each surgeon and center.

The present study is advantageous in its use of highly prognostic metrics and propensity matching for referral confounders in conjunction with early BCR results to show a temporal trend consistent with an epidemiologic increase in proportion and, more problematic, absolute number of high-risk cancers. The database comprised by the nine institutions included in this case series is an estimated 3.5% of all RARPs performed within the United States, with heterogeneous US geographical representation. While confirmation via population-based studies is necessary, present trends accurately reflect high-volume surgical practice patterns and PCa incidence and, therefore, will be in concordance.

Conclusions

Following the USPSTF's grade D recommendation against PSA-based PCa screening in 2012, a nationwide, epidemiological shift is strongly suggested with increased high-risk, advanced disease at the time of surgery. While the recommendation served its purpose of reducing surgical treatment for low-grade cancers, our study identified a previously predicted trend of increasing proportions of advanced disease. The 3.4-fold increase in the fourth year following the recommendation in patients with metastatic nodal disease will clearly impact PCSM. Also, the nearly threefold rise in absolute numbers of BCR within 12 months of surgery will no doubt lead to further unintended consequences associated with secondary interventions with their attendant side effects and costs. Our findings suggest an urgent need to collaboratively design better screening parameters that minimize overtreatment and maximize curative treatment outcomes.

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