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The effect of the United States Preventive Services Task Force grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the US

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Abstract

Purpose: In October 2011, the United States Preventive Services Task Force (USPSTF) issued a draft guideline, discouraging the use of prostate-specific antigen (PSA) based screening for prostate cancer (grade D recommendation). Our objective was **t**o evaluate the effect of the USPSTF guideline on the number and distribution of new prostate cancer diagnoses in the US.

Materials and Methods: We identified incident cancers diagnosed between January 2010 and December 2012 in the 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 dropped by -1363 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%; $p<0.01$). By contrast, monthly colon cancer diagnoses remained stable. Diagnoses of low, intermediate, and high-risk prostate cancers decreased significantly, but new diagnoses of non-localized disease did not change. Subgroups of age, comorbidity, race, income, and insurance all experienced comparable decreases in incident prostate cancer following the draft guideline.

Conclusions: There was a 28% decline in incident diagnoses of prostate cancer in the year following the USPSTF draft recommendation against PSA screening. This

study helps quantify the potential benefits (reduced harms of overdiagnosis 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.

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Introduction:

In October 2011, the United States Preventive Services Task Force (USPSTF) published an evidence statement and draft recommendations regarding prostate-specific antigen (PSA) based screening for PCa.[1,2] In these documents and the final recommendation statement, the USPSTF concluded that harms of PSA-based screening outweigh benefits, yielding a "grade D" recommendation against screening.[3] The grade D recommendation is controversial because of uncertainty about the risk-benefit ratio of PCa screening. PCa remains the second leading cause of cancer death among men in the US, with nearly 30,000 deaths annually.[4] A clinical trial evidence and observational studies suggest a survival benefit for screening, while another trial shows no benefit to regular screening in a heavily pre-screened population.[5,6] Epidemiologically, PCa mortality has declined by about 40% since the advent of PSA-based screening in the late 1980's, and 40-70% of that decline may be attributable to screening.[7] However, the morbidity associated with radiation and surgery is substantial. Despite the fact that the number-needed-to-screen and number-needed to treat to save one life are similar to figures for mammography and fecal occult blood testing,[8-10] the uncertain benefit of PSA-based screening, combined with the morbidity associated with treatment led the USPSTF to recommend against regular screening.

The USPSTF recommendation may have changed screening practices among primary care providers, as evidenced by decreased utilization of PSA testing in some institutions and health systems.[11-13] However, it is not known how the change in

screening recommendations has affected PCa incidence. Therefore, we evaluated an all-payer, nationwide dataset to determine whether the number of incident cases per month changed substantially since the draft guideline, and whether observed changes disproportionately affected certain subgroups (age, race, socio-economic status), or resulted in a shift in disease burden at presentation.

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Methods:

Study population:

PCa patients, ages 18 and older, residing in the US 50 states or District of Columbia, with incident diagnosis in 2010-2012, were identified in the National Cancer Data Base (NCDB). The NCDB is a hospital-based registry, jointly sponsored by the Commission on Cancer (CoC) of the American Cancer Society, and the American College of Surgeons, which captures some 70% of new cancer diagnoses in the US, regardless of patient age or payer, via over 1500 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 the Facility Oncology Registry Data Standards manual (http://www.facs.org/cancer/coc/fordsmanual.html).

We eliminated data from hospitals suspected to have incomplete reporting, either 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. From the original 375,137 PCa cases submitted to the NCDB in 2010-2012, 354,842 (94.6%) unique, incident PCa cases from 1,343 facilities were identified, of whom 352,020 (99.2%) had non-missing month of diagnosis, making them eligible for analysis.

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

Study design:

We assessed changes in PCa diagnoses and a comparison outcome, colon cancer diagnoses, which did not experience a screening guideline change during the study period (Supplementary Table 1). We used an interrupted time series (ITS) with comparison series design in order 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. We used October 2011 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 performed ITS with segmented linear regression analysis using monthly aggregate incident cancer diagnosis counts, and 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 cancer types. From this model, we estimated level change, monthly trend change, and annual change in absolute number of cases for each cancer type. In order to assess 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, percent change over one year after the draft guideline, and we constructed hypothesis tests to evaluate statistical significance of these changes. (Supplementary material)

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. First, we assessed changes in PCa

diagnoses relative to other screening-detected malignancies – breast and lung cancer. Second, we restricted all of our analyses to age 50-74, the age range for which screening may be most relevant. Third, because of concerns regarding outlying PSA values, we assessed the number of cases that would be reclassified because of very low (<1) or very high (>98) PSA levels.

We used an a-priori level of statistical significance of $p<0.05$, and analyses were conducted using SAS 9.4 and R 3.1.2.

Results:

Patient characteristics are displayed in Table 1. Most new diagnoses were among men in their 60s, with approximately 19% non-white. There was a small predominance of intermediate-risk (32.2%) disease among localized cases, compared to low- (25.4%), and high-risk (27.0%), whereas 5.4% had non-localized disease at the time of diagnosis (10.1% missing.) Only 5% of had outlying PSA values (2% < 1.0, 3.0% 98 or higher); one percent of men had their risk stratum determined by an outlier PSA value.

Table 2 and Figure 1 depict changes in level and trend for incident PCa and colon cancer. In the period before the draft guideline, monthly PCa diagnoses ranged from 9442-12021, and diagnoses were increasing by approximately 45 cases/month, a 0.4% monthly increase. In October 2011, there was a significant, immediate reduction in estimated incident PCa diagnoses (-1373 cases), as well as a significant change in trend in the post vs. pre recommendation periods - a relative decline of

164 cases/month. This corresponds to a change of -12.2% (p<0.01) in incidence in the month immediately after the draft recommendations, with an ongoing rate of decline of -1.8% per month (p<0.01). One year after the draft guideline, new diagnoses had decreased by 27.9% compared to the projected trend from the pre-guideline period. Meanwhile, incident colon cancer diagnoses ranged from 5192-6042 before the draft guideline. Unlike PCa, colon cancer cases did not significantly change in level (absolute change=4; percent change=0.24%; p=0.95) or in monthly trend (absolute change=-27; percent change=-0.51%; p=0.18) after October 2011. Findings were similar in the sub-group of patients between age 50 and 74, as well as in comparisons between prostate vs. breast cancer and prostate vs. lung cancer (Supplemental Table 2, Supplemental Figures 1 and 2).

Table 2 shows level and trend changes as well as annualized change from subgroup models. Figure 2 displays these changes for disease risk groups. Diagnoses fell for all disease risk strata, but by different degrees. The initial drop in monthly diagnoses was -16.9% for low-risk, -12.9% for intermediate-risk, -10.1% for high-risk and -2.7% for non-localized disease, and the corresponding monthly changes thereafter were -2.7%, -1.9%, -1.4% and +0.1%, respectively (p-interaction<0.01). Thus, accounting for the initial level change and the monthly changes thereafter, at one year after the draft guideline, predicted diagnoses were down by 37.9%, 28.1%, 23.1% and 1.1% for low-risk, intermediate-risk, high-risk and non-localized disease.

Each stratum of age, comorbidity, race, insurance status, and income group underwent a similar decrease in level and monthly trend change after the guideline, and, therefore, the p-values for interaction were non-significant (Table 2).

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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 reduce the harms of screening, the most important of which are the morbidities associated with overtreatment of screen-detected cancers that are unlikely to manifest in clinical harm to the patient. Detection of 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, diagnoses of new low-risk cancers had fallen by 37.9%, and continued to fall more rapidly than other disease risk strata, suggesting that, in this regard, the USPSTF recommendation had its intended effect. Similarly, new diagnoses had fallen by 23.0-29.3% among men over age 70 and by 26.0% among infirm men, populations who are unlikely to live long enough to benefit from early detection, but are at-risk of 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 survival, disease-specific survival, development of metastases, and use of secondary

treatments.[20-24] Our study identified a drop of 28.1% in diagnoses of intermediate-risk disease and 23.1% in high-risk PCa one year after the draft guideline, suggesting that reduced screening could result in missing important opportunities to spare these men from progressive disease and cancer death. The observation period following the grade D recommendation was insufficient to determine the impact on the diagnosis of non-localized PCa, which is associated with a high treatment burden, quality of life decrements and mortality. However, we did observe a small upward slope in diagnoses of non-localized disease, and, in the context of declining rates of diagnosis 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 patient's life when he is no longer eligible for all available curative treatments. The decline in diagnoses one year after the draft recommendation did not vary across age and comorbidity strata (-22.3 to -29.2% decline), suggesting that younger, healthier men, who harbor intermediate- or high-risk disease and who 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 over-treatment.

Finally, we assessed the potential impact of the USPSTF recommendation on vulnerable populations. African-American men have a 60% higher risk of PCa

diagnosis and 150% increased risk of PCa mortality compared to whites.[4, 25] Our study showed that declines in diagnoses were comparable between whites and African Americans and across socio-economic strata, raising concern for missed diagnoses among high-risk and poorly-resourced populations.

The findings of this study must be interpreted within the context of the dataset and study design. The NCDB is a large cancer registry, which includes all ages and all payers, capturing up to 70% of US 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 US. We attempted to mitigate this limitation by comparing PCa diagnoses to other common cancers. We found that rates of other cancers remained relatively stable throughout this time period, suggesting that the change in PCa diagnoses reflects an effect of the USPSTF recommendation rather than secular trends or changes in cancer reporting within NCDB. Nonetheless, the incidence data in this study cannot be translated directly to national incidence, as the denominator is not precisely defined and the NCDB is a registry rather than a population-based dataset. Using the data from immediately after the draft guideline allowed for early identification of its results. However, by using this short time period after the draft guideline, we cannot assess downstream outcomes, such as effects on incidence on non-localized disease and PCa mortality, which we would expect to manifest some years later. Methodologically, in order to perform an interrupted time series analysis, we used data aggregated at monthly time points, which is a powerful method for assessing

trends within a population, but lacks the opportunity to control for individual-level covariates to account for confounding. However, it is unlikely that most characteristics changed over the study period, and we demonstrated that the incidence of other cancers did not change during this time period, even in the narrowed age group of 50-74.

The USPSTF grade D recommendation against PCa screening was intended to reduce the harms of screening, in the face of what was deemed a small potential benefit. While the policies over the previous two decades led to indiscriminate screening, resulting in a public health crisis of harms associated with over-diagnosis and over-treatment, 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 begin 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 a greater emphasis on shared-decision-making to facilitate individualized, patient-centered decisions regarding screening, which may provide a pathway for judicious use of screening for men at risk for PCa.[27]

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Conclusion:

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

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Figure Legends:

Figure 1. New diagnoses of prostate and colorectal cancer in NCDB 2010-2012
Red line: New prostate cancer diagnoses in NCDB 2010-2012, with 95% confidence bands. The dotted portion of the line is the continuation of the trend prior to the draft guideline.
Black line: New colorectal cancer diagnoses in NCDB 2010-2012, with 95% confidence bands. The dotted portion of the line is the continuation of the trend prior to the draft guideline.

Figure 2. New diagnoses of prostate cancer in NCDB 2010-2012 by disease risk stratum
The regression line and 95% confidence band for each disease risk stratum is displayed in a distinct color. The dotted portion of the line is the continuation of the trend prior to the draft guideline. The level change and monthly trend change are noted, along with p values.

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Table 1. Demographic and clinical characteristics of patients with prostate cancer

	N=352,020	%
Demographic characteristic		
Age		
18 to 49	12,133	3.4%
50 to 59	86,035	24.4%
60 to 69	153,935	43.7%
70 to 79	79,457	22.6%
≥80	20,460	5.8%
Charlson Comorbidity Index		
0	287,187	81.6%
1	53,658	15.2%
≥2	11,175	3.2%
Race		
White	281,456	80.0%
Black	55,748	15.8%
Other	14,816	4.2%
High school non-graduation rate[a]		
>=21%	54,080	15.4%
13-20%	85,441	24.3%
7-12%	114,554	32.5%
<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 Cancer Center	29,274	8.3%
Comprehensive Community	169,713	48.2%
Academic/Research Center	134,013	38.1%
Other	19,020	5.4%
Rurality		
Metro	284,113	80.7%
Urban	50,544	14.4%
Rural	7,077	2.0%
Missing	10,286	2.9%
Median Income Quartile[a]		
0-25th percentile	58,109	16.5%
26-50th percentile	77,500	22.0%
51-75th percentile	93,552	26.6%
76-100th percentile	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%

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West	17,524	5.0%
Pacific	39,625	11.3%
Disease characteristic		
PSA at presentation		
≤4	54,003	15.3%
4.1 to 10	180,117	51.2%
10.1 to 20	39,042	11.1%
>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	137,743	39.1%
7	128,605	36.5%
8 to 10	56,997	16.2%
No needle core biopsy/TURP	13,016	3.7%
Missing	15,659	4.4%
Clinical T-Stage		
T1 N0 M0[b]	225,749	64.1%
T2 N0 M0[b]	79,798	22.7%
T3 N0 M0[b]	7,800	2.2%
T4 N0 M0[b]	929	0.3%
Any T N+ or M+	18,909	5.4%
Missing	18,835	5.4%
Risk group		
D'Amico low-risk	89,266	25.4%
D'Amico intermediate-risk	113,323	32.2%
D'Amico high-risk	94,995	27.0%
Non-localized	18,909	5.4%
Missing	35,527	10.1%

[a] Measured at ZIP code level
[b] Includes Nx and Mx

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Table 2. Change in incident diagnoses of colon and prostate cancers, and in prostate cancer sub-groups

	Monthly slope before guideline change[a]		Level change immediately after guideline change[b]		Monthly slope change after guideline change relative to before guideline change[c]		Estimated change in monthly diagnoses one year after guideline change[d]	
Group	Absolute change	Percent change	Absolute change	Percent change	Absolute change	Percent change	Absolute difference	Percent difference
Cancer Type		p(int)=0.31[e]		p(int)=0.04		p(int)=0.03		
Prostate	39	0.4%	-1373	-12.2%	-164	-1.8%	-3181	-27.9%
Colon	3	0.1%	4	0.2%	-27	-0.5%	-298	-5.1%
Prostate Cancer Sub-group								
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%	-1134	-37.9%
Intermediate	26	0.8%	-437	-12.9%	-59	-1.9%	-1090	-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 to 49	-1	-0.2%	-27	-6.9%	-5	-1.7%	-79	-22.3%
50 to 59	6	0.2%	-240	-8.5%	-46	-2.1%	-743	-27.4%
60 to 69	22	0.5%	-634	-12.9%	-74	-1.8%	-1448	-28.6%
70 to 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%	-1175	-13.0%	-134	-1.9%	-2653	-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%	-1162	-12.7%	-134	-1.8%	-2639	-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%

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$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%	-1115	-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%	-1247	-28.9%
Medicare	24	0.5%	-668	-14.0%	-66	-1.7%	-1398	-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%

[a] Compares slope from February 2010 to January 2010
[b] Compares October 2011 to September 2011
[c] Compares slope from October/November 2011 to January/February 2010
[d] Compares predicted number of diagnoses in September 2012 based on pre-October 2011 trend to post-October 2011 trend
[e] 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

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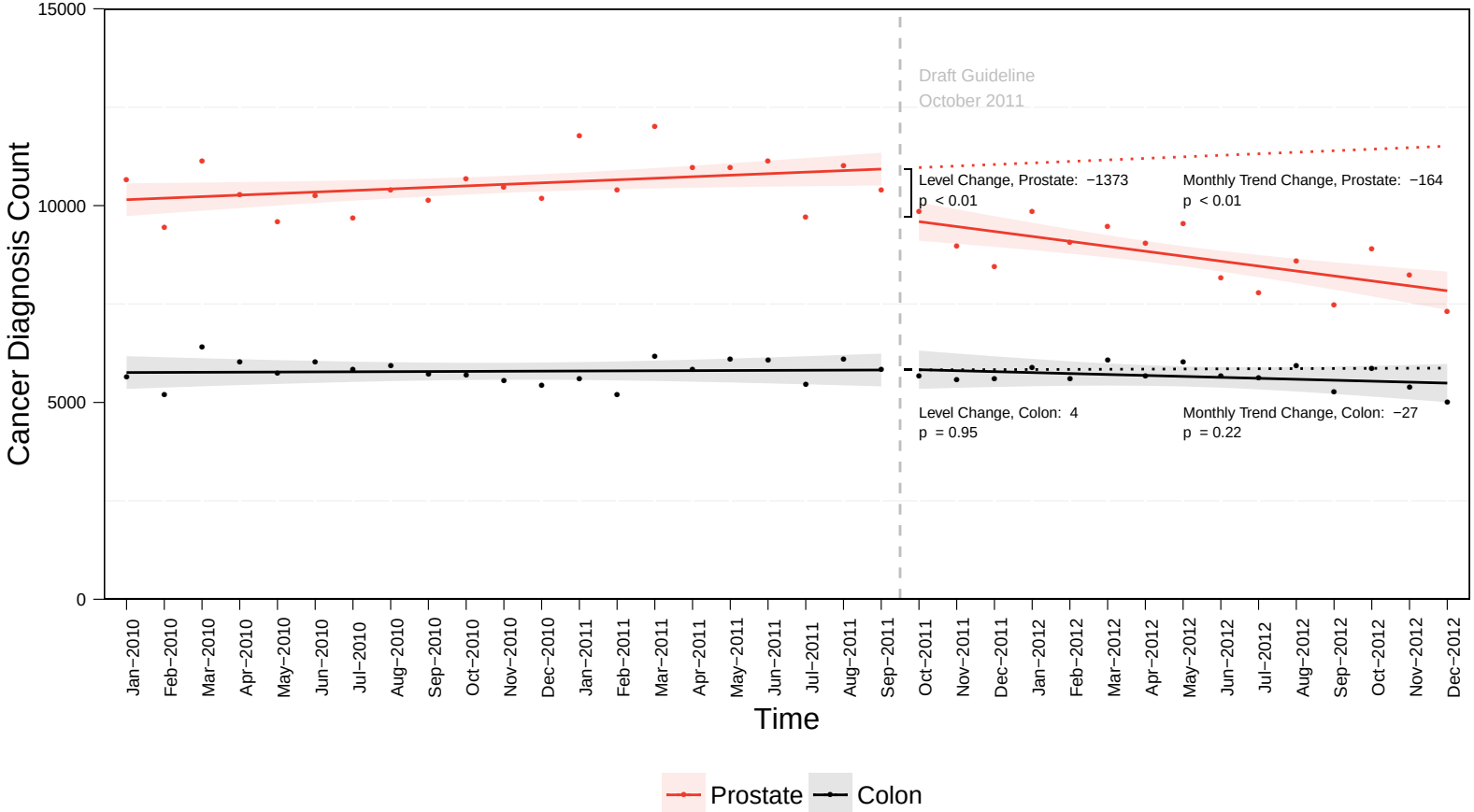
Cancer Diagnosis Count
15000
10000
5000
0
Draft Guideline
October 2011
Level Change, Prostate: −1373
p < 0.01
Monthly Trend Change, Prostate: −164
p < 0.01
Level Change, Colon: 4
p = 0.95
Monthly Trend Change, Colon: −27
p = 0.22
Jan−2010
Feb−2010
Mar−2010
Apr−2010
May−2010
Jun−2010
Jul−2010
Aug−2010
Sep−2010
Oct−2010
Nov−2010
Dec−2010
Jan−2011
Feb−2011
Mar−2011
Apr−2011
May−2011
Jun−2011
Jul−2011
Aug−2011
Sep−2011
Oct−2011
Nov−2011
Dec−2011
Jan−2012
Feb−2012
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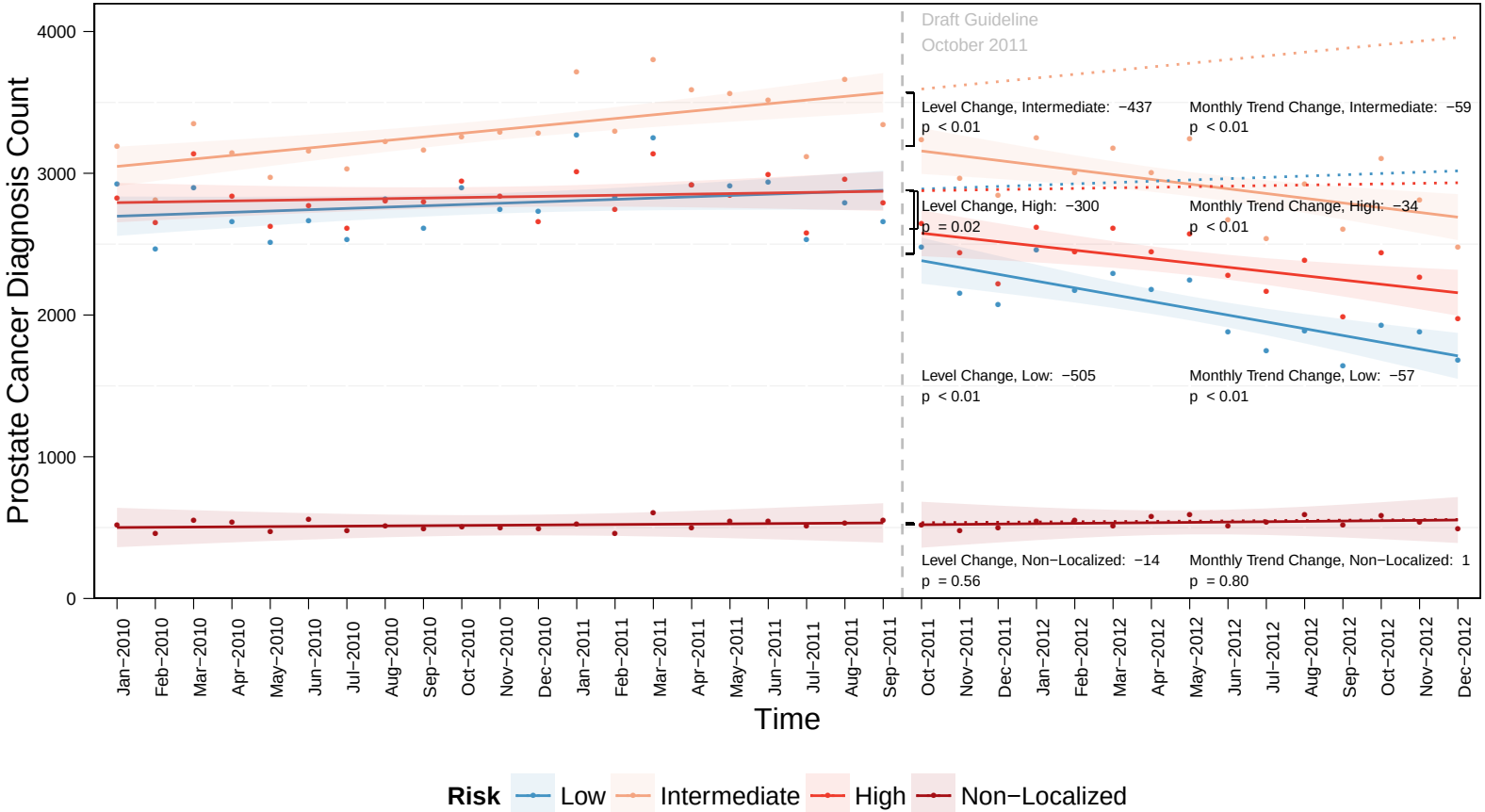
Nov−2012
Dec−2012
Time
Prostate
Colon


Prostate Cancer Diagnosis Count
4000
3000
2000
1000
0
Draft Guideline
October 2011
Level Change, Intermediate: −437
p < 0.01
Monthly Trend Change, Intermediate: −59
p < 0.01
Level Change, High: −300
p = 0.02
Monthly Trend Change, High: −34
p < 0.01
Level Change, Low: −505
p < 0.01
Monthly Trend Change, Low: −57
p < 0.01
Level Change, Non−Localized: −14
p = 0.56
Monthly Trend Change, Non−Localized: 1
p = 0.80
Jan−2010
Feb−2010
Mar−2010
Apr−2010
May−2010
Jun−2010
Jul−2010
Aug−2010
Sep−2010
Oct−2010
Nov−2010
Dec−2010
Jan−2011
Feb−2011
Mar−2011
Apr−2011
May−2011
Jun−2011
Jul−2011
Aug−2011
Sep−2011
Oct−2011
Nov−2011
Dec−2011
Jan−2012
Feb−2012
Mar−2012
Apr−2012
May−2012
Jun−2012
Jul−2012
Aug−2012
Sep−2012
Oct−2012
Nov−2012
Dec−2012
Time
Risk
Low
Intermediate
High
Non−Localized

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Abbreviations Used:

USPSTF – United States Preventative Services Task Force

PSA – Prostate-specific antigen

PCa – Prostate cancer

NCDB – National Cancer Data Base

CoC – Commission on Cancer

ITS – Interrupted time series

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Online-Only Supplement

Supplement to: Barocas DA, Mallin K, Graves AJ, Penson DF, Palis B, Winchester DP, and Chang S. The effect of the United States Preventive Services Task Force grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the US.

This Online-Only Supplement has been provided by the authors to give readers additional information about their work. It includes:

a) Guideline changes for prostate, colon, breast, and lung cancer during the 2010-2012 study period
b) Mathematical formulae for statistical models presented in the manuscript
c) Description of hypothesis tests generated from statistical models in the manuscript
d) Sensitivity analyses including:
    1. Breast and lung cancer as comparison series
    2. Cancer type analyses restricted to ages most likely to benefit from screening (50-74)

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a) Guideline changes for prostate, colon, breast, and lung cancer during the 2010-2012 study period

eTable 1: Cancer Screening Guidelines 2010-2012

Organization	Cancer			
	Prostate	Colorectal	Breast	Lung
U.S. Preventive Services Task Force				
2010 Baseline	men <75: Grade I; men ≥75: Grade D[1]	50-75: Grade A; 76-85: Grade C; ≥86: Grade D[2]	<50: Grade C; 50-74: Grade B; ≥75: Grade I[3]	Grade I [4]
Change 2010-2012	October 2011 (draft) and May 2012 (final): all men: Grade D[1]	none	none	none
National Comprehensive Cancer Network				
2010 Baseline	unclear	Age ≥50 and average risk: screening recommended (recommended options include: colonoscopy every 10 years, annual fecal-based tests, flexible sigmoidoscopy every 5 years, combination of annual fecal tests and sigmoidoscopy every 5 years, or CT colonography every 5 years [5]	Age ≥40 and average risk: annual screening mammography[6]	none
Change 2010-2012	February 2010: Offer PSA or DRE age ≥40[7]	none	none	February 2012: Screening via helical LDCT recommended for individuals with high-risk factors[8]
American Cancer Society				
2010 Baseline	unclear	Age ≥50 and average risk: screening recommended (options for detecting adenomatous polyps and cancer include: colonoscopy every 10 years, flexible sigmoidoscopy every 5 years,	Age ≥40: Annual screening mammography[10]	none

		DCBE every 5 years, or CT colonography every 5 years; options for detecting cancer include: annual gFOBT or FIT or sDNA of uncertain interval)[9]		
Change 2010-2012	March 2010: asymptomatic men with at least a 10-year life expectancy: informed decision about screening for prostate cancer with health care provider[11]	none	none	none
Professional Society*				
2010 Baseline	Age <=39: against screening; Age 40-69: recommend shared decision-making; Age ≥70: routine screening not recommended[12]	Age ≥50: Colonoscopy every 10 years or flexible sigmoidoscopy every 5-10 years or CT colonography every 5 years or annual FIT[13]	Age 40-49: screening mammography every 1-2 yrs; Age ≥50: annual screening mammography	none
Change 2010-2012	none	none	Aug 2011: Age ≥40: annual screening mammography [14,15]	Aug 2011: The National Cancer Institute reported results from National Lung Screening Trial (NLST), a randomized clinical trial that screened at-risk smokers with either low dose CT or standard chest x-ray. Screening individuals with low dose CT scans could reduce lung cancer mortality by 20 percent compared to chest x-ray. This prompted 2012 changes in NCCN and ALA guidelines[16] April 2012 ALA: Low-dose CT screening recommended for individuals with high-risk factors[17]

*Prostate: American Urological Association; Colorectal: American College of Gastroenterology; Breast: American College of Obstetrics and Gynecology; Lung: American Lung Association

b) Statistical Models:

1. Model 1: Cancer type model (percent change)
   $E(Y_{ij}) = B_0 + B_1X_1 + B_2X_{i2} + B_3X_{i3} + B_4X_{i4} + B_5(X_1*X_{i2}) + B6(X_1*X_{i3}) + B7(X_1*X_{i4}) + e_i$
   Where:
   Y_i = Ln(count of prostate and colon cancer diagnoses during monthly interval i)
   X_1 = Cancer type (1=Prostate; 0=Colon)
   X_{i2} = Month (1-36)
   X_{i3} = Post indicator (0=before month 21 [before USPSTF PSA guideline change]; 1=during and after month 21 [during after USPSTF PSA guideline change])
   X_{i4} = Months starting in post period during and after USPSTF PSA guideline change (0 during months 1-21; 1-15 during months 22-36)

2. Model 2: D'Amico risk stratum model (percent change)
   $E(Y_{ij}) = B_0 + B_1X_1 + B_2X_{i2} + B_3X_{i3} + B_4X_{i4} + B_5(X_1*X_{i2}) + B6(X_1*X_{i3}) + B7(X_1*X_{i4}) + e_i$
   Where:
   Y_i = Ln(count of prostate cancer diagnoses during monthly interval i)
   X_1 = D'Amico risk stratum (Low; Intermediate; High; Non-localized)
   X_{i2} = Month (1-36)
   X_{i3} = Post indicator (0=before month 21 [before USPSTF PSA guideline change]; 1=during and after month 21 [during after USPSTF PSA guideline change])
   X_{i4} = Months starting in post period during and after USPSTF PSA guideline change (0 during months 1-21; 1-15 during months 22-36)

3. Model 3: Age group model (percent change)
   $E(Y_{ij}) = B_0 + B_1X_1 + B_2X_{i2} + B_3X_{i3} + B_4X_{i4} + B_5(X_1*X_{i2}) + B6(X_1*X_{i3}) + B7(X_1*X_{i4}) + e_i$
   Where:
   Y_i = Ln(count of prostate cancer diagnoses during monthly interval i)
   X_1 = Age group (18-49; 50-59; 60-69; 70-79; ≥80)
   X_{i2} = Month (1-36)
   X_{i3} = Post indicator (0=before month 21 [before USPSTF PSA guideline change]; 1=during and after month 21 [during after USPSTF PSA guideline change])
   X_{i4} = Months starting in post period during and after USPSTF PSA guideline change (0 during months 1-21; 1-15 during months 22-36)

4. Model 4: Charlson-Deyo comorbidity group model (percent change)
   $E(Y_{ij}) = B_0 + B_1X_1 + B_2X_{i2} + B_3X_{i3} + B_4X_{i4} + B_5(X_1*X_{i2}) + B6(X_1*X_{i3}) + B7(X_1*X_{i4}) + e_i$
   Where:
   Y_i = Ln(count of prostate cancer diagnoses during monthly interval i)
   X_1 = Charlson-Deyo comorbidity group (0; 1; ≥2)
   X_{i2} = Month (1-36)
   X_{i3} = Post indicator (0=before month 21 [before USPSTF PSA guideline change]; 1=during and after month 21 [during after USPSTF PSA guideline change])
   X_{i4} = Months starting in post period during and after USPSTF PSA guideline change (0 during months 1-21; 1-15 during months 22-36)

5. Model 5: Race model (percent change)
   $E(Y_{ij}) = B_0 + B_1X_1 + B_2X_{i2} + B_3X_{i3} + B_4X_{i4} + B_5(X_1*X_{i2}) + B6(X_1*X_{i3}) + B7(X_1*X_{i4}) + e_i$
   Where:
   Y_i = Ln(count of prostate cancer diagnoses during monthly interval i)
   X_1 = Race (white, black, other)
   X_{i2} = Month (1-36)
   X_{i3} = Post indicator (0=before month 21 [before USPSTF PSA guideline change]; 1=during and after month 21 [during after USPSTF PSA guideline change])
   X_{i4} = Months starting in post period during and after USPSTF PSA guideline change (0 during months 1-21; 1-15 during months 22-36)

6. Model 6: Income model (percent change)
   $E(Y_{ij}) = B_0 + B_1X_1 + B_2X_{i2} + B_3X_{i3} + B_4X_{i4} + B_5(X_1*X_{i2}) + B6(X_1*X_{i3}) + B7(X_1*X_{i4}) + e_i$
   Where:
   Y_i = Ln(count of prostate cancer diagnoses during monthly interval i)
   X_1 = Income group (<$30,000; $30,000-$34,999, $35,000-$45,999, ≥$46,000)
   X_{i2} = Month (1-36)
   X_{i3} = Post indicator (0=before month 21 [before USPSTF PSA guideline change]; 1=during and after month 21 [during after USPSTF PSA guideline change])
   X_{i4} = Months starting in post period during and after USPSTF PSA guideline change (0 during months 1-21; 1-15 during months 22-36)

7. Model 7: Insurance model (percent change)
   $E(Y_{ij}) = B_0 + B_1X_1 + B_2X_{i2} + B_3X_{i3} + B_4X_{i4} + B_5(X_1*X_{i2}) + B6(X_1*X_{i3}) + B7(X_1*X_{i4}) + e_i$
   Where:
   Y_i = Ln(count of prostate cancer diagnoses during monthly interval i)
   X_1 = Insurance group (Private/Managed care; Medicare; VA/Military; Medicaid; Not insured)
   X_{i2} = Month (1-36)
   X_{i3} = Post indicator (0=before month 21 [before USPSTF PSA guideline change]; 1=during and after month 21 [during after USPSTF PSA guideline change])
   X_{i4} = Months starting in post period during and after USPSTF PSA guideline change (0 during months 1-21; 1-15 during months 22-36)

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c) Hypothesis tests:

1. Model 1
    a. Does the monthly slope before guideline (baseline trend) vary by cancer type?
    H0: $X_1*X_{i2} = 0$; HA: $X_1*X_{i2} \neq 0$
    P = 0.31; fail to reject H0 and conclude that baseline trend does not vary by cancer type
    b. Does the level change immediately after guideline vary by cancer type?
    H0: $X_1*X_{i3} = 0$; HA: $X_1*X_{i3} \neq 0$
    P = 0.04; reject H0 and conclude that level change immediately after guideline varies by cancer type
        i. Among prostate cancer, does the level change immediately after guideline differ from 0?
        P < 0.01; Prostate cancer level change differs from 0.
        ii. Among colon cancer, does the level change immediately after guideline differ from 0?
        P = 0.95; Colon cancer level change does not differ from 0.
    c. Does the monthly slope after guideline relative to before guideline (trend change) vary by cancer type?
    H0: $X_1*X_{i4} = 0$; HA: $X_1*X_{i4} \neq 0$
    P = 0.03; reject H0 and conclude that trend change varies by cancer type
        i. Among prostate cancer, does the monthly slope after guideline relative to before guideline differ from 0?
        P < 0.01; Prostate cancer slope change differs from 0.
        ii. Among colon cancer, does the monthly slope after guideline relative to before guideline differ from 0?
        P = 0.18; Colon cancer slope change does not differ from 0.

2. Model 2
    a. Does the monthly slope before guideline (baseline trend) vary by risk stratum?
    H0: $X_1*X_{i2} = 0$; HA: $X_1*X_{i2} \neq 0$
    P = 0.31; fail to reject H0 and conclude that baseline trend does not vary by risk stratum
    b. Does the level change immediately after guideline vary by risk stratum?
    H0: $X_1*X_{i3} = 0$; HA: $X_1*X_{i3} \neq 0$
    P = 0.30; fail to reject H0 and conclude that level change immediately after guideline does not vary by risk stratum
        i. Among low-risk individuals, does the level change immediately after guideline differ from 0?
        P < 0.01; Low-risk level change differs from 0.
        ii. Among intermediate-risk individuals, does the level change immediately after guideline differ from 0?
        P < 0.01; Intermediate-risk level change differs from 0.
        iii. Among high-risk individuals, does the level change immediately after guideline differ from 0?
        P = 0.02; High-risk level change differs from 0.
        iv. Among individuals with non-localized disease, does the level change immediately after guideline differ from 0?
        P = 0.56; Non-localized level change does not differ from 0.
    c. Does the monthly slope after guideline relative to before guideline (trend change) vary by risk stratum?
    H0: $X_1*X_{i4} = 0$; HA: $X_1*X_{i4} \neq 0$
    P < 0.01; reject H0 and conclude that trend change varies by risk stratum
        i. Among low-risk individuals, does trend change differ from 0?
        P < 0.01; Low-risk trend change differs from 0.
        ii. Among intermediate-risk individuals, does trend change differ from 0?
        P < 0.01; Intermediate-risk trend change differs from 0.
        iii. Among high-risk individuals, does trend change differ from 0?
        P < 0.01; High-risk trend change differs from 0.
        iv. Among individuals with non-localized disease, does trend change differ from 0?
        P = 0.80; Non-localized trend change does not differ from 0.

3. Model 3
    a. Does the monthly slope before guideline (baseline trend) vary by age group?
       H0: $X_1*X_{i2} = 0$; HA: $X_1*X_{i2} \neq 0$
       P = 0.53; fail to reject H0 and conclude that baseline trend does not vary by age group
    b. Does the level change immediately after guideline vary by age group?
       H0: $X_1*X_{i3} = 0$; HA: $X_1*X_{i3} \neq 0$
       P = 0.57; fail to reject H0 and conclude that level change immediately after guideline does not vary by age group
    c. Does the monthly slope after guideline relative to before guideline (trend change) vary by age group?
       H0: $X_1*X_{i4} = 0$; HA: $X_1*X_{i4} \neq 0$
       P = 0.94; fail to reject H0 and conclude that trend change does not vary by age group

4. Model 4
    a. Does the monthly slope before guideline (baseline trend) vary by comorbidity group?
       H0: $X_1*X_{i2} = 0$; HA: $X_1*X_{i2} \neq 0$
       P = 0.93; fail to reject H0 and conclude that baseline trend does not vary by comorbidity group
    b. Does the level change immediately after guideline vary by comorbidity group?
       H0: $X_1*X_{i3} = 0$; HA: $X_1*X_{i3} \neq 0$
       P = 0.47; fail to reject H0 and conclude that level change immediately after guideline does not vary by comorbidity group
    c. Does the monthly slope after guideline relative to before guideline (trend change) vary by comorbidity group?
       H0: $X_1*X_{i4} = 0$; HA: $X_1*X_{i4} \neq 0$
       P = 0.76; fail to reject H0 and conclude that trend change does not vary by comorbidity group

5. Model 5
    a. Does the monthly slope before guideline (baseline trend) vary by race?
       H0: $X_1*X_{i2} = 0$; HA: $X_1*X_{i2} \neq 0$
       P = 0.77; fail to reject H0 and conclude that baseline trend does not vary by race
    b. Does the level change immediately after guideline vary by race?
       H0: $X_1*X_{i3} = 0$; HA: $X_1*X_{i3} \neq 0$
       P = 0.64; fail to reject H0 and conclude that level change immediately after guideline does not vary by race
    c. Does the monthly slope after guideline relative to before guideline (trend change) vary by race?
       H0: $X_1*X_{i4} = 0$; HA: $X_1*X_{i4} \neq 0$
       P = 0.79; fail to reject H0 and conclude that trend change does not vary by race

6. Model 6
    a. Does the monthly slope before guideline (baseline trend) vary by income group?
       H0: $X_1*X_{i2} = 0$; HA: $X_1*X_{i2} \neq 0$
       P = 0.95; fail to reject H0 and conclude that baseline trend does not vary by income group
    b. Does the level change immediately after guideline vary by income group?
       H0: $X_1*X_{i3} = 0$; HA: $X_1*X_{i3} \neq 0$
       P = 0.99; fail to reject H0 and conclude that level change immediately after guideline does not vary by income group
    c. Does the monthly slope after guideline relative to before guideline (trend change) vary by income group?
       H0: $X_1*X_{i4} = 0$; HA: $X_1*X_{i4} \neq 0$
       P = 0.90; fail to reject H0 and conclude that trend change does not vary by income group

7. Model 7
    a. Does the monthly slope before guideline (baseline trend) vary by insurance?
       H0: $X_1*X_{i2} = 0$; HA: $X_1*X_{i2} \neq 0$
       P = 0.98; fail to reject H0 and conclude that baseline trend does not vary by insurance

b. Does the level change immediately after guideline vary by insurance?
   H0: $X_1 * X_{i3} = 0$; HA: $X_1 * X_{i3} \neq 0$
   P = 0.83; fail to reject H0 and conclude that level change immediately after guideline does not vary by insurance
c. Does the monthly slope after guideline relative to before guideline (trend change) vary by insurance?
   H0: $X_1 * X_{i4} = 0$; HA: $X_1 * X_{i4} \neq 0$
   P = 0.77; fail to reject H0 and conclude that trend change does not vary by insurance

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d) Sensitivity analyses including

1. Breast and lung cancer as comparison series among patients age ≥18

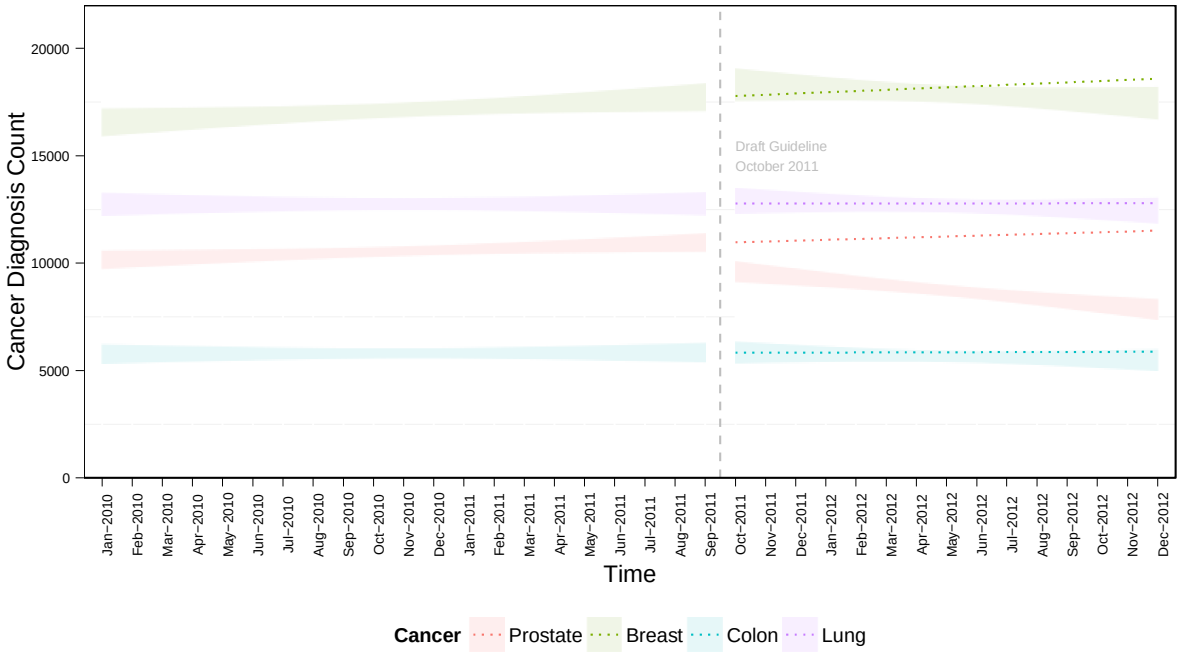
2. Cancer type analyses restricted to ages most likely to benefit from screening

eTable 2. Sensitivity analyses

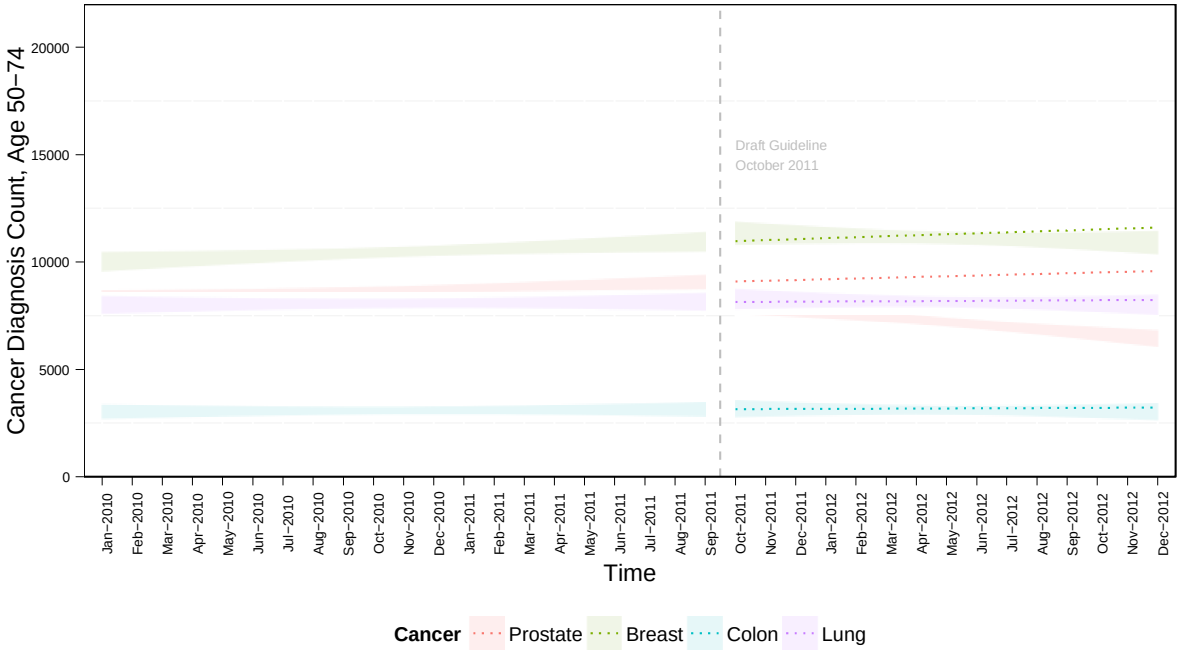
Group	Monthly slope before guideline change*		Level change immediately after guideline change**		Monthly slope change after guideline change relative to before guideline change***		Estimated change in monthly diagnoses one year after guideline change	
	Absolute change	Percent change	Absolute change	Percent change	Absolute change	Percent change	Absolute difference	Percent difference
Cancer Type (original comparison)		**p(int)=0.31**		**p(int)=0.04**		**p(int)=0.03**		
Prostate	**39**	**0.4%**	**-1373**	**-12.2%**	**-164**	**-1.8%**	**-3181**	**-27.9%**
Colon	**3**	**0.1%**	**4**	**0.2%**	**-27**	**-0.5%**	**-298**	**-5.1%**
Cancer Type		p(int)=0.91		p(int)=0.01		p(int)=0.05		
Prostate	39	0.4%	-1373	-12.2%	-164	-1.8%	-3181	-27.9%
Breast	57	0.3%	502	2.9%	-118	-0.7%	-791	-4.3%
Cancer Type		p(int)=0.22		p(int)=0.03		p(int)=0.01		
Prostate	39	0.4%	-1373	-12.2%	-164	-1.8%	-3181	-27.9%
Lung	1	0.0%	133	1.1%	-34	-0.3%	-236	-1.8%
Cancer Type - Age 50-74		p(int)=0.45		p(int)=0.04		p(int)=0.02		
Prostate	35	0.4%	-1129	-12.1%	-142	-1.9%	-2692	-28.4%
Colon	5	0.2%	5	0.2%	-15	-0.5%	-160	-5.0%
Cancer Type - Age 50-74		p(int)=0.92		p(int)=0.01		p(int)=0.04		
Prostate	35	0.4%	-1129	-12.1%	-142	-1.9%	-2692	-28.4%
Breast	45	0.4%	363	3.4%	-75	-0.7%	-467	-4.1%
Cancer Type - Age 50-74		p(int)=0.28		p(int)=0.02		p(int)=0.01		
Prostate	35	0.4%	-1129	-12.1%	-142	-1.9%	-2692	-28.4%
Lung	7	0.1%	121	1.6%	-25	-0.3%	-154	-1.9%

* compares slope from February 2010 to January 2010
** compares October 2011 to September 2011
*** compares slope from October/November 2011 to January/February 2010
**** p(int) is 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.

eFigure 1: Predicted and expected number of cancer cases by cancer type



eFigure 2: Predicted and expected number of cancer cases by cancer type, Age 50-74



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