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Article type : Original Article

Prostate Cancer Incidence across Stage, NCCN Risk Groups, and Age before and after USPSTF Grade D Recommendations against PSA Screening in 2012

Running Head: *Prostate Cancer Incidence Migration*

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Word Count: 1863

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FUNDING

Timothy R. Rebbeck, PhD, is funded by HHS grant CA184734; Brandon A. Mahal, MD, is funded by the PCF-ASTRO Award to End Prostate Cancer. Paul L. Nguyen, MD, is funded by the Prostate Cancer Foundation.

DISCLOSURES

Financial Disclosures and Possible Conflicts of Interest

Paul L. Nguyen, MD, has the following financial disclosures: Consulting—Nanobiotix, Bayer, Astellas, Ferring, Dendreon, Blue Earth, Genome Dx, Augmenix, Janssen; Research—Janssen and Astellas; Equity—Augmenix. Shuang G. Zhao, MD, reported funding from Genome Dx.

ACKNOWLEDGEMENTS/AUTHOR CONTRIBUTIONS

Data Access, Responsibility, and Analysis: Santino S. Butler (S.S.B.) and Brandon A. Mahal (B.A.M.) had full access to all the data and had final responsibility for the decision to submit this article for publication. *Concept and Design:* B.A.M., S.S.B. *Statistical analysis:* B.A.M., S.S.B. *Acquisition, analysis, interpretation of data:* All authors. *Drafting of the manuscript:* All authors. *Critical revision of the manuscript for important intellectual content:* All authors.

PRÉCIS FOR TABLE OF CONTENTS:

This report illustrates a recent “reverse migration” of prostate cancer away from indolent and toward more aggressive disease beginning in 2012. The incidence of localized disease has declined across age groups from 2012 to 2015—with the greatest relative declines occurring in low-risk disease—while the incidence of distant metastatic disease has gradually increased.

ABSTRACT:

Purpose: We sought to determine the extent to which United States Preventive Services Task Force (USPSTF) 2012 Grade-D recommendations against PSA-screening may have impacted recent prostate cancer (PCa) disease incidence patterns in the U.S. across stage, National Comprehensive Cancer Network (NCCN)-risk groups, and age.

Materials and Methods: SEER*Stat version 8.3.4 calculated annual PCa incidence rates from 2010-2015 for men aged ≥50 years, by AJCC stage at diagnosis (localized [T1-T4–N0M0] versus metastatic [M1]), NCCN-risk group (low versus unfavorable [intermediate or high-risk]), and age group (50-74 versus ≥75 years). Age-adjusted incidences per 100,000 persons, with corresponding year-by-year incidence ratios (IR), were calculated using the 2000 U.S. Census population.

Results: From 2010-2015, the incidence (per 100,000 persons) of localized PCa decreased from 195.4 to 131.9 (P_{trend}<0.001) and 189.0 to 123.4 (P_{trend}<0.001) among men aged 50-74 and ≥75 years, respectively. The largest relative year-by-year decline occurred between 2011 and 2012 in NCCN low-risk disease (IR 0.77, [0.75–0.79, P<0.0001] and IR 0.68 [0.62–0.74, P<0.0001] for men aged 50-74 and ≥75 years, respectively). From 2010-2015, the incidence of metastatic disease increased from 6.2 to 7.1 (P_{trend}<0.001) and from 16.8 to 22.6 (P_{trend}<0.001) among men aged 50-74 and ≥75 years, respectively.

Conclusions: This report illustrates recent PCa “reverse migration” away from indolent and toward more aggressive disease beginning in 2012. The incidence of localized disease declined across age groups from 2012-2015, with the greatest relative declines

occurring in low-risk disease. Additionally, the incidence of distant metastatic disease gradually increased throughout the study period.

KEY WORDS

Prostatic Neoplasms; PSA screening; Incidence; Prostate Cancer

MANUSCRIPT OVERVIEW

(1) Text pages, 17; (2) Tables, 0; (3) Figures, 2; (4) Supplemental Tables, 2

INTRODUCTION:

The PSA-screening era led to a drastic increase in prostate cancer detection, along with a migration toward more indolent disease at diagnosis.[1] However, following an October 2011 draft statement, the U.S. Preventive Services Task Force (USPSTF) made a formal Grade-D recommendation against PSA-screening for all men in 2012 (similar to 2008 Grade-D recommendations for men aged ≥75 years)[2,3] given questions about screening efficacy and concern that screening may lead to over-detection and treatment of indolent disease.[4,5] However, there has remained little consensus on an optimal screening paradigm and some specialists and cancer organizations continue to favor routine PSA-screening for younger healthy men.[6] Moreover, longer follow-up in PSA-screening trials has demonstrated the increasing efficacy of PSA-screening over time given the indolent nature of prostate cancer.[7,8] Therefore, in 2018 the USPSTF made a Grade-C recommendation supporting individualized PSA-screening decisions for men aged 55–69.[8]

Using contemporary population-based data, we sought to determine the extent to which 2012 USPSTF recommendations against PSA-screening may have impacted recent prostate cancer incidence patterns in the United States across stage, National Comprehensive Cancer Network (NCCN)[9] risk-groups, and age.

MATERIALS AND METHODS:

Statistical Analyses for Trends in Prostate Cancer Incidence by Stage, NCCN Risk Group, and Age

To illustrate trends in incidence patterns over time, SEER*Stat version 8.3.4 was used to calculate annual age-adjusted incidence rates of prostate cancer from 2010-2015

among men age ≥50 years in the SEER 18 Regs Custom Data (with additional treatment fields), Nov 2017 Sub (2010-2015) Database. The SEER 18 program collects and publishes cancer incidence data from 18 population-based cancer registries covering approximately 27.8% of the United States population (based on 2010 census). Trends in rates were compared using Cuzick's test. Incidence rates were calculated by stage at diagnosis (AJCC 7th edition T1-T4 N0M0 localized disease versus AJCC 7th edition distant Metastatic [M1] disease), and stratified by age group (50-74 years versus ≥75 years) based on USPSTF PSA-screening recommendations.[2,3] With the recent inclusion of validated and quality assured PSA data in SEER,[11] incidence rates were also calculated for localized NCCN-defined risk groups (low [PSA <10 ng/mL and cT1-2a and Gleason ≤6]; versus unfavorable [intermediate or high-risk] disease [PSA >10ng/mL or cT2b-T4 or Gleason 7-10])[9] in patients with known PSA, clinical tumor stage, and clinical Gleason score. The patient selection included all years (2010-2015) for which clinical information on NCCN risk factors is available in SEER.

Age-adjusted incidence rates and corresponding 95% confidence intervals (CIs) were expressed per 100,000 persons using the 2000 U.S. Census standard population, with adjustments for delays in reporting. To compare incidence rate changes across consecutive years, the Tiwari method was applied to define year-by-year incidence ratios (IRs) with associated 95% CIs and P-values, using the earlier year as reference (i.e. 2010 [referent] vs 2011).[12,13]

P-values were two-sided with α=0.05. The data are publicly available and deidentified and therefore considered exempt by the Dana-Farber/Harvard Cancer Center institutional review board.

RESULTS:

Trends in Prostate Cancer Incidence by Stage, NCCN Risk Group, and Age

From 2010-2015, there was a decrease in the annual incidence (per 100,000 persons) of localized prostate cancer from 195.4 to 131.9 (P_{trend}<0.001) and from 189.0 to 123.4 (P_{trend}<0.001) among men aged 50-74 and ≥75 years, respectively (Figure 1, Supplemental Table 1). Conversely, there was an increase in the incidence of metastatic disease from 6.2 to 7.1 (P_{trend}<0.001) and from 16.8 to 22.6 (P_{trend}<0.001) among men aged 50-74 and ≥75 years, respectively (Figure 1, Supplemental Table 1). There was also a decrease in the annual incidence of both localized NCCN low-risk and unfavorable (intermediate/high)-risk localized prostate cancer from 60.6 to 31.4 and from 104.2 to 84.3, respectively, among men aged 50-74 years—Among men aged ≥75 years, incidence rates similarly decreased from 26.1 to 11.6 and from 134.5 to 94.7, respectively (all P_{trend}<0.001) (Figure 1, Supplemental Table 1).

The largest relative year-by-year decline in incidence of localized disease occurred between 2011–2012, regardless of age or risk group (Figure 2, Supplemental Table 2). The incidence of low-risk disease began to decline in 2012 across age groups, although the decline was relatively greater among men aged ≥75 years (IR 0.68, 95% CI 0.62–0.74) compared to men aged 50-74 years (IR 0.77, 95% CI 0.75–0.79)—Notably, the subgroup with the largest relative year-by-year decline in incidence observed in this study occurred between 2011-2012 in low-risk disease among men aged ≥75 years

(Figure 2, Supplemental Table 2). The incidence of low-risk disease declined in each consecutive year from 2012-2015 among men aged 50-74 years (P<0.0001 for all IRs, Figure 2, Supplemental Table 2). For men aged ≥75 years however, incidence rates declined from 2012-2014 before stabilizing from 2014-2015 (Figure 2, Supplemental Table 2). Overall, from 2010-2015 there was a greater absolute decline in the incidence of low-risk disease among men aged 50-74 years (29.2 less cases per 100,000 men) compared to men aged ≥75 years (14.5 less cases per 100,000 men) (Figure 1, Supplemental Table 1).

The incidence of unfavorable (intermediate/high)-risk disease also began to decline between 2011–2012 across age groups, although the declines were relatively smaller compared to low-risk disease. Declining incidence rates in 2012 were again greater among men aged ≥75 years (IR 0.78, 95% CI 0.75–0.81) compared to men aged 50-74 years (IR 0.86, 95% CI 0.84–0.88). Notably, incidence rates declined in consecutive years until 2014 (P<0.01 for all IRs across age groups), before increasing from 2014 to 2015—from 79.3 to 84.3 (IR 1.06, 95% CI 1.04–1.08) and from 89.0 to 94.7 (IR 1.06, 95% CI 1.02–1.11) among men aged 50-74 and ≥75 years, respectively.

Metastatic disease incidence increased incrementally such that consecutive year-by-year IRs remained comparable for both age groups, with the exception of increases among men aged ≥75 years between 2011–2012 (IR 1.14, 95% CI 1.04–1.26) and between 2014–2015 (IR 1.13, 95% CI 1.04–1.23). However, when comparing 2015 to 2010, there were significant increases in metastatic disease across age groups (IR 1.14 [95% CI 1.06–1.23], and IR 1.34 [95% CI 1.23–1.47] for men aged 50-74 and ≥75 years, respectively).

DISCUSSION:

Utilizing contemporary population-based incidence data, this report illustrates recent prostate cancer "reverse migration" away from indolent and toward more aggressive presentation in the United States following USPSTF Grade-D recommendations against PSA-screening in 2012 (with draft statement released in October 2011 and official statement released in May 2012). The data demonstrate a significant decline in the

incidence of localized disease across age groups from 2010–2015, with the greatest declines observed between 2011–2012. Notably, the greatest relative declines in incidence rates were observed in NCCN low-risk localized disease where rates continued to decline throughout the study period, while the incidence of unfavorable (intermediate/high)-risk localized disease declined until 2014 before increasing from 2014–2015. Furthermore, there was a slow and gradual increase in the incidence of distant metastatic disease throughout the study period.

To the best of our knowledge, this is the first study to report on population-based incidence trends in localized (AJCC 7th edition N0M0) prostate cancer and across the NCCN risk groups used to guide clinical management. Prior studies were not able to benefit from the recent inclusion of validated and quality assured PSA data in SEER and therefore have been limited to describing trends in SEER summary stage which is not used in clinical practice,[13,14] or in AJCC M1 disease which cannot describe localized risk-group patterns.[15] By examining incidence rates by NCCN risk group, these findings are not only novel and clinically relevant, but also a more accurate reflection of the impact of PSA-screening recommendations based on the natural history of prostate cancer. Specifically, since 65.7% of all localized disease and 94.0% of NCCN low-risk disease were PSA screen-detected from 2010–2011 in SEER (unpublished data), USPSTF recommendations against screening would be expected to have an immediate impact on localized disease incidence, with the greatest impact on NCCN low-risk localized disease—as was demonstrated in this study—presumably through the decreased detection of indolent and asymptomatic disease. The declines in low-risk disease were a goal of USPSTF recommendations against screening. However, many men with potentially curable disease may end up presenting later on with more advanced and difficult-to-cure disease, as suggested by the slow increases in metastatic disease and increasing incidence of unfavorable-risk disease between 2014–2015.

Notably, Hu et al demonstrated that incidence rates of distant metastatic disease among men aged ≥75 years only increased by less than 1 per 100,000 persons from 2007 to

2013 (after USPSTF recommendations against PSA-screening for men aged ≥75 years in 2008),[15] while we demonstrate that these rates increased by 5.8 per 100,000 from 2010–2015. This is likely due to the fact that population increases in de novo metastases may not be expected until ≥6 years after development of disease in non-screened individuals based on the natural history of prostate cancer.[16–18] As such, the non-significant increases in metastatic disease (by ~1 case per 100,000 persons per year) for men aged 50–74 years between 2010–2015 would be expected to similarly continue increasing through 2018. Still, prostate cancer is a heterogenous disease and the missed screening of higher-risk cancers, which could progress more quickly to symptomatic presentation, may lead to increases in metastases at earlier timepoints at the population level. The public health ramifications of a trend towards excess metastatic prostate cancer incidence would likely include not only greater disease morbidity (e.g. metastatic bone pain, skeletal related events) and prostate cancer mortality, but also greater treatment-related toxicity—most notably from lifelong hormonal therapy—and higher overall health care costs.

Additionally, our study demonstrated that the largest decrease in localized prostate cancer incidence occurred between 2011-2012—suggesting that there may have been a decline in PSA screening throughout the year of 2012 after the highly publicized draft recommendations were made public in October 2011.

Overall, our results demonstrate disease “reverse migration” away from indolent and toward more aggressive presentation following 2011–2012 USPSTF Grade-D recommendations against PSA-screening. Additional factors that may have also contributed to these trends include changes in perceptions of PSA-screening risks and benefits, concern of prostate cancer overdiagnosis or overtreatment, and emphasis on informed decision-making. Patients with unknown clinical information on NCCN risk factors (i.e. PSA, Gleason score, T-stage) were not included in analyses stratified by NCCN risk group, which could underestimate overall absolute incidence rates within risk groups; notably, there was no difference in the completeness of data across the study period, therefore there is unlikely to be bias within the reported trends in relative ratios

across years. This study was also limited by lack of SEER data on regional differences in incidence. Lastly, this study was limited by short follow-up, and further studies will be required to assess the long-term impact of recommendations on prostate cancer incidence and mortality. Furthermore, future studies will need to determine whether 2018 USPSTF Grade-C recommendations again shift the prostate cancer landscape.

CONCLUSIONS: This report illustrates recent prostate cancer “reverse migration” away from indolent and toward more aggressive disease beginning in 2012. The incidence of localized disease declined across age groups from 2012-2015, with the greatest relative declines occurring in low-risk disease. Additionally, the incidence of distant metastatic disease gradually increased throughout the study period.

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FIGURE LEGEND

Figure 1. Age-adjusted† annual incidence rates (per 100,000 persons; error bars representing 95% CIs) of prostate cancer diagnoses in SEER*Stat U.S. Database stratified by age group (≥75 vs. 50-74 years of age) for **(A)** Localized disease (N0M0), **(B)** Metastatic disease (M1), **(C)** NCCN Low-risk localized disease‡, and **(D)** NCCN Unfavorable (Intermediate/High)-risk localized disease.‡

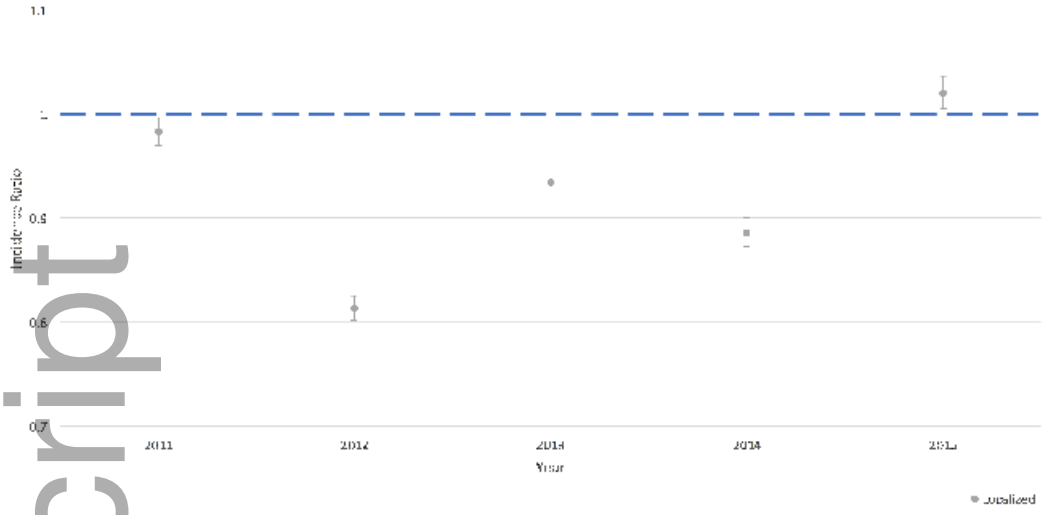
Figure 2. Incidence ratios§ comparing consecutive annual age-adjusted† incidence rates (with error bars representing 95% CIs) of prostate cancer diagnoses in SEER*Stat U.S. Database stratified by age group (≥75 vs. 50-74 years of age) for **(A-B)** Localized disease (N0M0), **(C-D)** Metastatic disease (M1), **(E-F)** NCCN Low-risk localized disease‡, and **(G-H)** NCCN Unfavorable (Intermediate/High)-risk localized disease.‡

† Age-adjusted incidence rate per 100,000 persons using the 2000 U.S. Census standard population.

‡ *Unknown NCCN-risk group accounts for remaining incidence of localized disease.*

§ Incidence ratios comparing consecutive year-by-year baselines: 2011 vs. 2010, 2012 vs. 2011, 2013 vs. 2012, 2014 vs. 2013, 2015 vs. 2014.

Abbreviations: CI, confidence interval; NCCN, National Comprehensive Cancer Network; SEER, Surveillance, Epidemiology, and End-Results; U.S., United States; vs., versus



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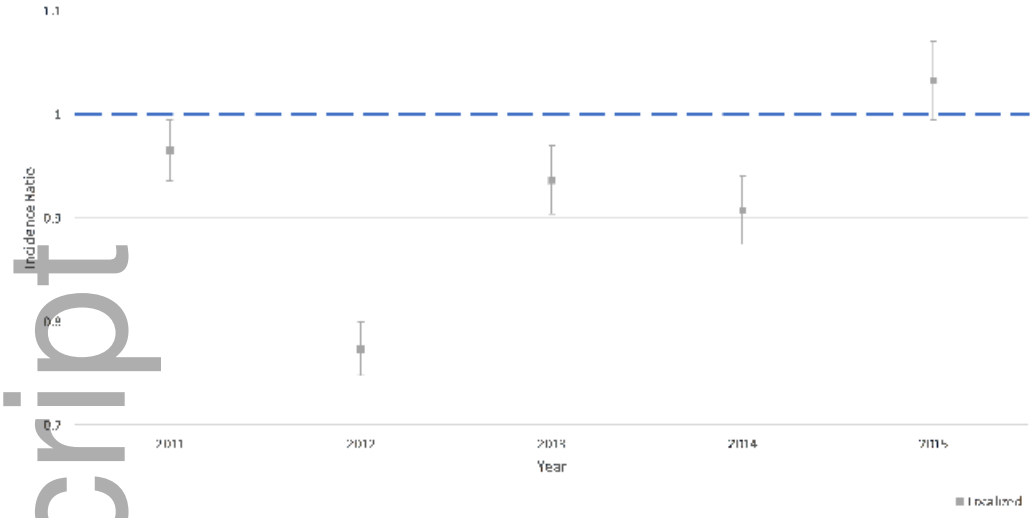

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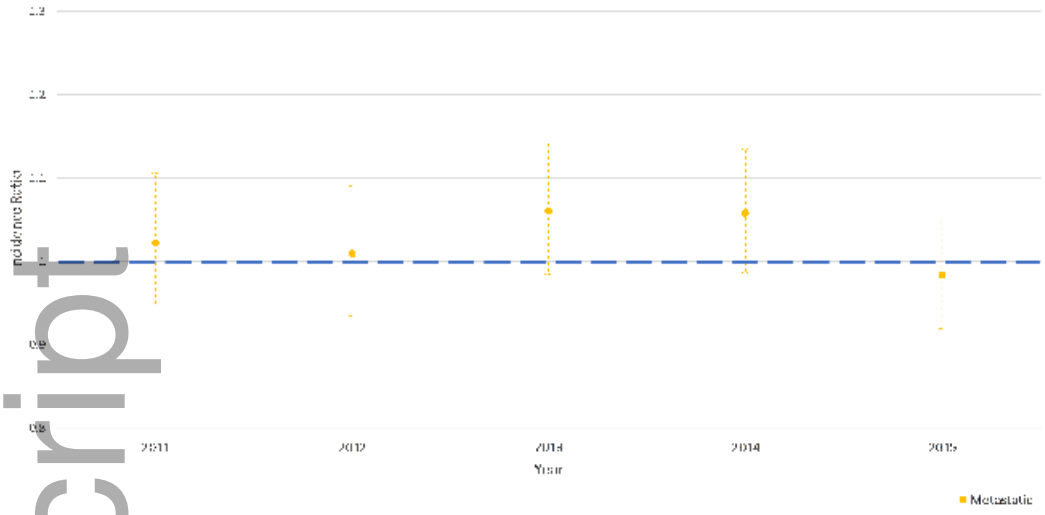

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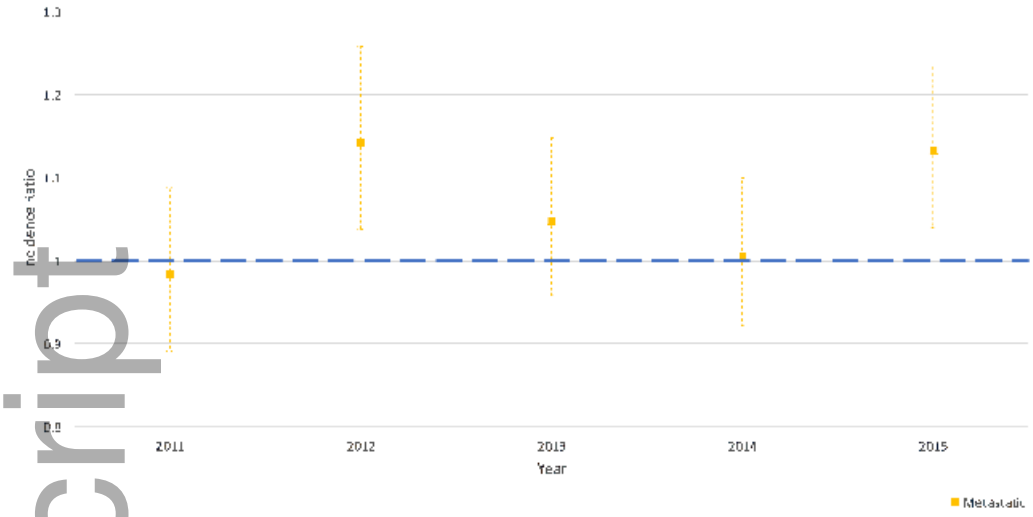

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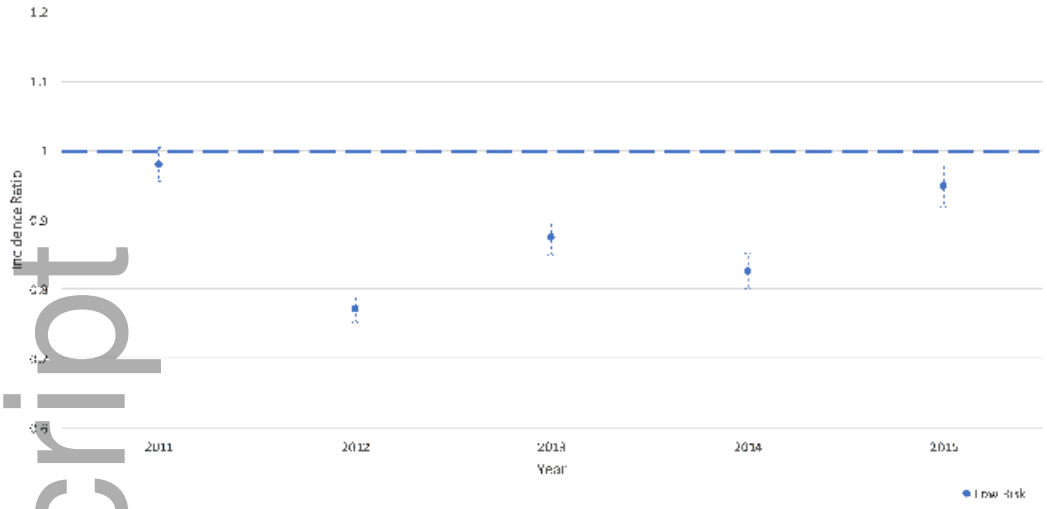

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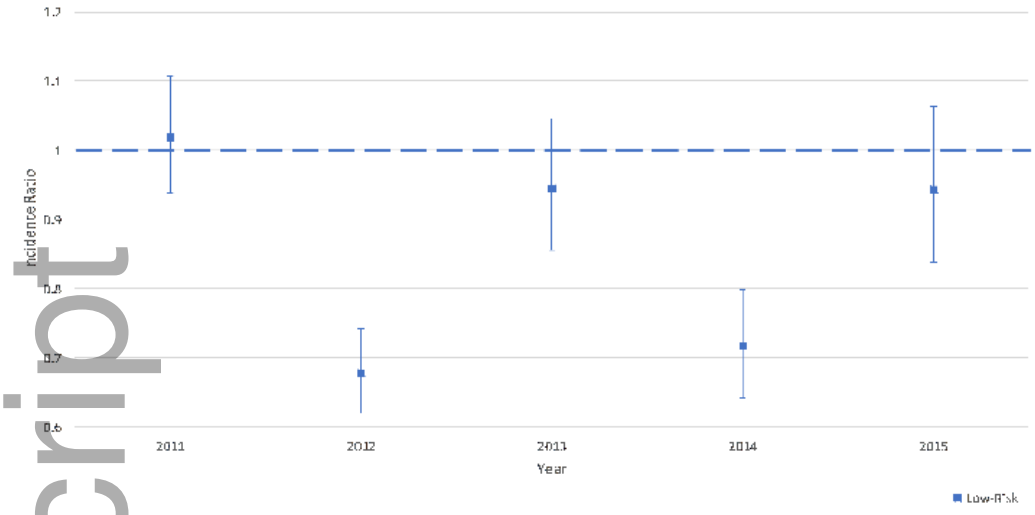

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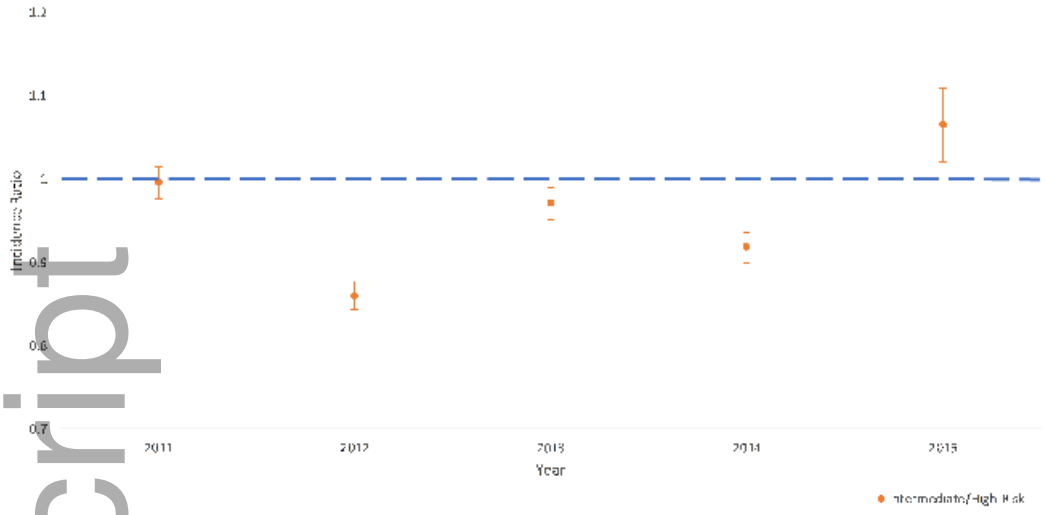

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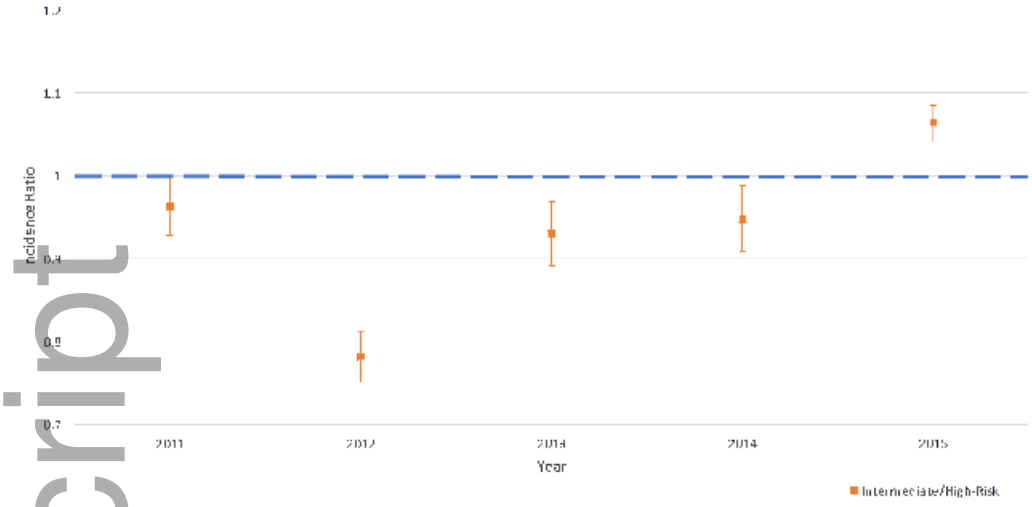

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