Uptake of Active Surveillance for Very-Low-Risk Prostate Cancer in Sweden

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Abstract

Importance—Active surveillance is an important option to reduce prostate cancer overtreatment, but it remains underutilized in many countries. Models from the United States show that greater use of active surveillance is important for prostate cancer screening to be cost-effective.

Objectives—To perform an up-to-date, nationwide, population-based study on use of active surveillance for localized prostate cancer in Sweden.

Design—Cross-sectional study in the National Prostate Cancer Register (NPCR) of Sweden from 2009 through 2014.

Setting—The NPCR has data on 98% of prostate cancers diagnosed in Sweden and has comprehensive linkages to other nationwide databases.

Participants—Overall, 32 518 men with a median age of 67 years were diagnosed with favorable-risk prostate cancer, including 4 693, 15 403 and 17 115 men with very-low-risk (subset of the low-risk group) (clinical stage, T1c; Gleason score, 6; prostate-specific antigen [PSA], <10 ng/ml; PSA density <0.15ng/mL/cm^3; and <8-mm total cancer length in 4 positive biopsy cores),

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low-risk (including all men in the very-low-risk group) (T1–T2; Gleason score, 6; and PSA, <10ng/mL), and intermediate-risk disease (T1–T2 with Gleason score, 7 and/or PSA, 10–20ng/mL).

Exposures—Diagnosis with favorable-risk prostate cancer

Major Outcome—Utilization of active surveillance

Results—The use of active surveillance increased in men of all ages from 57% (380 of 665) to 91% (939 of 1027) for very-low-risk prostate cancer and from 40% (1159 of 2895) to 74% (1951 of 2644) for low-risk prostate cancer, with the strongest increase occurring from 2011 onward. Among men aged 50 to 59 years, 88% (211 of 240) with very-low-risk and 68% (351 of 518) with low-risk disease chose active surveillance in 2014. Use of active surveillance for intermediate-risk disease remained lower, 19% (561 of 3030) in 2014.

Conclusions and Relevance—Active surveillance has become the dominant management for low-risk prostate cancer among men in Sweden, with the highest rates yet reported and almost complete uptake for very-low-risk cancer. These data should serve as a benchmark to compare the use of active surveillance for favorable-risk disease around the world.

Keywords

Brief Report

Low-risk prostate cancer has a prolonged natural history and can be safely managed with active surveillance and selective, deferred use of curative treatment. Despite this, recent US studies have reported that most low-risk prostate cancer is managed with immediate curative treatment,[1] often reducing quality of life. Moreover, a recent modeling study showed that prostate cancer screening is generally not cost-effective based on current US treatment patterns but would be cost-effective if low-risk prostate cancer were managed conservatively.[2] Although Sweden does not have a national screening program, more than 50% of Swedish men aged 55 to 69 years have been exposed to prostate-specific antigen (PSA) screening.[3,4]

Our group previously reported increasing use of active surveillance in Sweden through 2011.[5] The goal of the present study is to perform an updated analysis of nationwide use of active surveillance using comprehensive, population-based Swedish data through 2014.

The National Prostate Cancer Register (NPCR) includes 98% of all prostate cancer cases in Sweden.[6,7] Designated staff at each health care unit extract data on cancer features and treatment from the medical records to an online registration in NPCR and have distinguished "watchful waiting" from "active surveillance" since 2007. In addition, the Longitudinal Integration Database for Health Insurance and Labor Market Studies provided socioeconomic data, and the Patient Register provided information on comorbidities.[7]

The Umeå University Research Ethics Board approved the study, waiving patient written informed consent.

Descriptive statistics and the Mann-Kendall test for trend based on the Kendall rank correlation were used to examine active surveillance utilization from 2009 through 2014 by age and clinical risk category, classified as very-low-risk (clinical stage, T1c; Gleason score, 6; PSA, <10 ng/mL; PSA density <0.15 ng/mL/cm^3; <8-mm total cancer length in 4 positive biopsy cores[8]), low-risk (T1–T2; Gleason score, 6; and PSA, <10 ng/mL), and intermediate-risk disease (T1–T2 with Gleason score, 7 and/or PSA, 10–20 ng/mL). Subset analysis was performed for intermediate-risk cancer with Gleason, 6 and PSA, 10–20 ng/mL, and Gleason, 7 (3 + 4) and PSA less than 10 ng/mL, and using alternate risk classifications (CAPRA scores [Cancer and the Prostate Risk Assessment], Epstein criteria, and PRIAS criteria [Prostate Cancer Research International: Active Surveillance]). Multivariable logistic regression was performed within clinical risk categories to determine predictors of active surveillance, including variables not used in the risk categorization. All *P* values were 2 sided and *P* < .05 was considered statistically significant.

Between 2009 and 2014, 32 518 men, median age of 67 years, were diagnosed with favorable-risk prostate cancer (Table). Use of active surveillance and watchful waiting increased from 64% to 93% for very-low-risk disease, 50% to 79% for low-risk disease, and decreased from 26% to 25% for intermediate-risk cancer from 2009 to 2014. Use of active surveillance increased from 57% to 91% for very-low-risk cancer and from 40% to 74% for low-risk cancer (*P* < .001 for all comparisons), whereas use of watchful waiting decreased over time (Figure). The greatest increase in active surveillance for very-low-risk and low-risk cancer occurred after 2011. Classifying men using CAPRA scores, we found that active surveillance increased from 17% to 62% in men with CAPRA 0, 50% to 85% in CAPRA 1, 33% to 55% in CAPRA 2, and 22% to 29% in CAPRA 3. In men with CAPRA scores higher than 3, use of active surveillance was relatively stable (eFigure 1 in the Supplement).

Active surveillance increased over time in all age groups (<60, 60–69, and 70 years) (Figure). In men with very-low-risk cancer, active surveillance increased from 44% to 88% in those aged 50 to 59, 64% to 95% in those aged 60 to 69 years, and from 53% to 84% in those aged 70 years or older. In men with low-risk disease, active surveillance also increased, from 30% to 68% among those aged 50 to 59 years, from 43% to 79% in those aged 60 to 69 years, and from 44% to 67% in those aged 70 years or older. Even among men younger than 50 years, active surveillance increased, to 89% and 43% among men with very-low-risk and low-risk disease by 2014. Using the Epstein and PRIAS criteria for active surveillance yielded almost identical results, 93% and 90%, respectively, compared with 91% by the NPCR very-low-risk definition (eFigure 2 in the Supplement).

Active surveillance use among men in the intermediate-risk category remained low during the entire study period. However, use of active surveillance increased from 31% in 2009 to 53% in 2014 in the intermediate-risk subset with Gleason, 6 and PSA, 10–20 ng/mL. Use of active surveillance remained low in those with Gleason, 7 (3 + 4) and PSA, less than 10 ng/mL (17% in 2014) (eFigure 3 in the Supplement).

Within each clinical risk category, later year of diagnosis, diagnosis at a university hospital, older age, and status of not currently married were associated with the use of active surveillance, while comorbidity and educational level were not associated.

This population-based study shows the highest uptake of active surveillance ever reported: by 2014, 91% of Swedish men diagnosed with very-low-risk prostate cancer and 74% with low-risk disease initiated active surveillance. This use of active surveillance is substantially higher than that reported in the United States.[1,9,10] Potential facilitating factors for the rapid uptake of active surveillance in Sweden include 2007 national guidelines recommending active surveillance for men with low-risk prostate cancer and a life expectancy of 10 to 20 years. In 2014, the 20-year upper limit for life expectancy was abandoned, and active surveillance was recommended for all men with very-low-risk prostate cancer. Importantly, NPCR provides real-time feedback to units on their adherence to these national guidelines and also in annual reports publically available online.[11,12]. The creation in 2010 of 6 regional cancer networks, supporting cancer services from primary to tertiary care, likely also increased adherence to the guidelines. The Swedish health care system is dominated by equal-access, tax-funded care without financial incentives for clinicians to recommend curative treatment. Furthermore, there may also be cultural differences in attitudes toward conservative management between Sweden and other countries such as the United States with lower use of these strategies. However, use of conservative management in the United States also rapidly increased from 2010 through 2013, suggesting more widespread acceptance worldwide.

A limitation of our study is that the interpretation of the definition of active surveillance among some clinicians became less stringent for men 70 years or older, indicated by the fact that more than twice as many men younger than 70 years on active surveillance underwent a repeat biopsy compared with men 70 years or older (eTable in the Supplement).

Another limitation is that our study does not include follow-up data on active surveillance outcomes. However, the objective was to study initial treatment selection by contemporary cases, and our group previously demonstrated that the majority of Swedish men on active surveillance had not converted to curative treatment at 5 years.[13]

A strength of our study is that, unlike data from US registries that do not differentiate active surveillance from watchful waiting or low-risk from very-low-risk prostate cancer,[1,9] the Swedish NPCR provides population-based data on all of these features, and in addition, provides information on potential confounders including socioeconomic status and comorbidity from other nationwide databases. To our knowledge, there are no other reports from Europe on nationwide active surveillance use except our groups earlier Swedish data.[5]

In summary, active surveillance can preserve the benefits of screening while minimizing harm caused by overtreatment of indolent cancer.[2] The Göteborg randomized prostate cancer screening trial[14] showed the highest mortality reduction ever reported (44%) in a population in which almost half the screen-detected cancers were managed with active surveillance.[14] Our results show that treatment patterns can be changed on a national level within a few years. Active surveillance is now the dominant management strategy for low-risk prostate cancer across Sweden, and there is an almost complete uptake of active surveillance for very-low-risk cancer. These findings should encourage clinicians, healthcare authorities, and cancer network administrators in other countries to reduce the harms of screening by minimizing overtreatment of low-risk prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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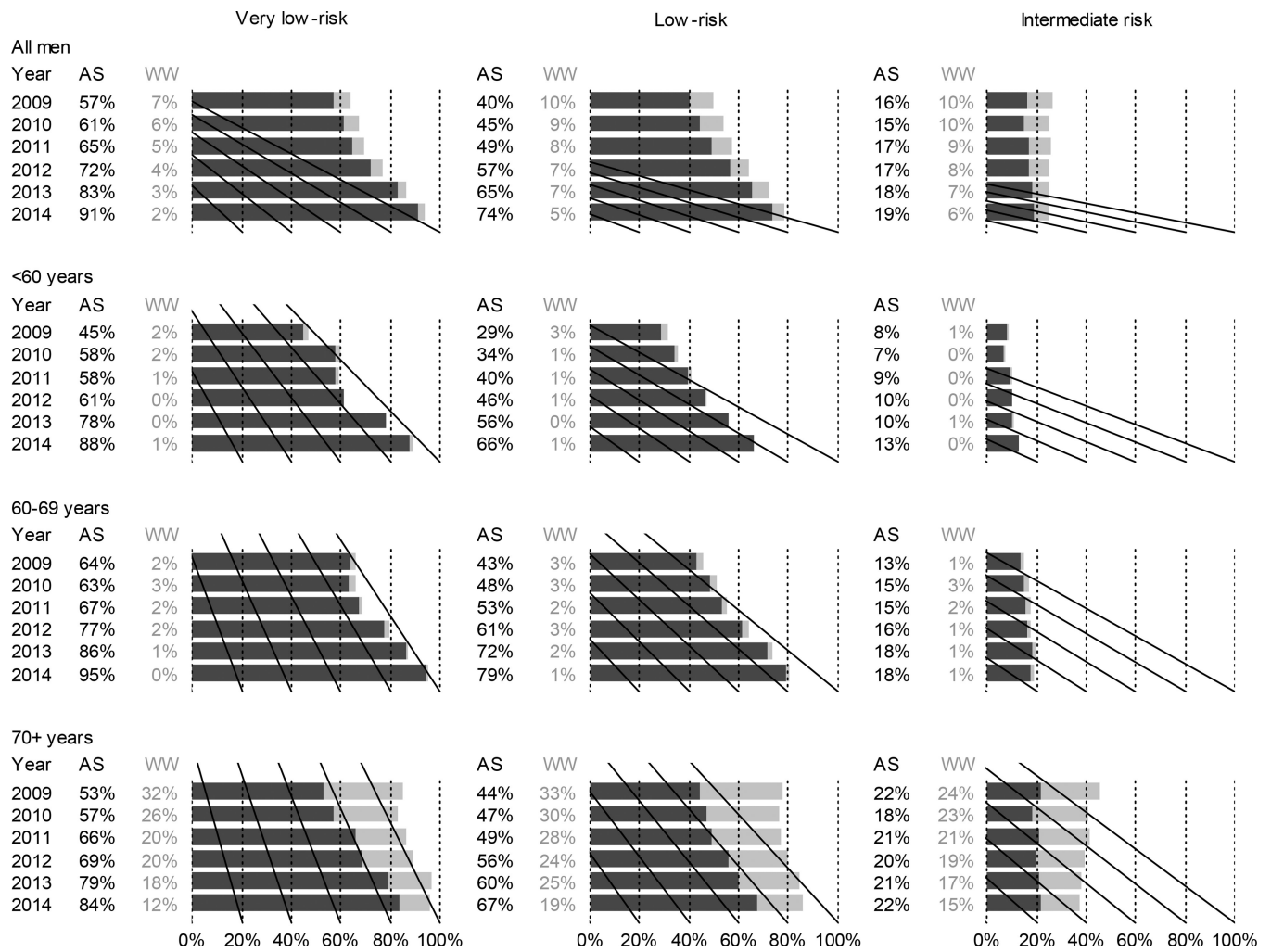
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Very low-risk

All men

Year	AS	WW
2009	57%	7%
2010	61%	6%
2011	65%	5%
2012	72%	4%
2013	83%	3%
2014	91%	2%

Low-risk

Year	AS	WW
2009	40%	10%
2010	45%	9%
2011	49%	8%
2012	57%	7%
2013	65%	7%
2014	74%	5%

Intermediate risk

Year	AS	WW
2009	16%	10%
2010	15%	10%
2011	17%	9%
2012	17%	8%
2013	18%	7%
2014	19%	6%

<60 years

Very low-risk:

Year	AS	WW
2009	45%	2%
2010	58%	2%
2011	58%	1%
2012	61%	0%
2013	78%	0%
2014	88%	1%

Low-risk:

Year	AS	WW
2009	29%	3%
2010	34%	1%
2011	40%	1%
2012	46%	1%
2013	56%	0%
2014	66%	1%

Intermediate risk:

Year	AS	WW
2009	8%	1%
2010	7%	0%
2011	9%	0%
2012	10%	0%
2013	10%	1%
2014	13%	0%

60-69 years

Very low-risk:

Year	AS	WW
2009	64%	2%
2010	63%	3%
2011	67%	2%
2012	77%	2%
2013	86%	1%
2014	95%	0%

Low-risk:

Year	AS	WW
2009	43%	3%
2010	48%	3%
2011	53%	2%
2012	61%	3%
2013	72%	2%
2014	79%	1%

Intermediate risk:

Year	AS	WW
2009	13%	1%
2010	15%	3%
2011	15%	2%
2012	16%	1%
2013	18%	1%
2014	18%	1%

70+ years

Very low-risk:

Year	AS	WW
2009	53%	32%
2010	57%	26%
2011	66%	20%
2012	69%	20%
2013	79%	18%
2014	84%	12%

Low-risk:

Year	AS	WW
2009	44%	33%
2010	47%	30%
2011	49%	28%
2012	56%	24%
2013	60%	25%
2014	67%	19%

Intermediate risk:

Year	AS	WW
2009	22%	24%
2010	18%	23%
2011	21%	21%
2012	20%	19%
2013	21%	17%
2014	22%	15%

Figure.

Use of active surveillance (AS) and watchful waiting (WW) in Sweden from 2009–2014. Results are shown by age group and clinical risk category: very low-risk (clinical stage T1c, Gleason score 6, PSA <10 ng/ml, PSA density <0.15ng/ml/cm^3, <8mm total cancer length in 4 positive biopsy cores)[8], low-risk (T1–T2, Gleason score 6 and PSA <10ng/ml), and intermediate-risk (T1–T2 with Gleason score 7 and/or PSA 10–20ng/ml).

Table

Demographic and Clinical Characteristics in the National Prostate Cancer Register of Sweden of Men Diagnosed With Favorable-Risk Prostate Cancer, 2009–2014

Characteristic	Participants, No. (%)			
	Very Low Risk[a] (n = 4693)	Low Risk[b] (n = 15 403)	Intermediate-Risk[c] (n = 17 115)	All Men (N = 32 518)
Calendar year				
2009	665 (14)	2895 (19)	3002 (18)	5897 (18)
2010	741 (16)	2683 (17)	2837 (17)	5520 (17)
2011	727 (15)	2582 (17)	2882 (17)	5464 (17)
2012	718 (15)	2214 (14)	2532 (15)	4746 (15)
2013	815 (17)	2385 (15)	2832 (17)	5217 (16)
2014	1027 (22)	2644 (17)	3030 (18)	5674 (17)
Age at diagnosis, y				
<50	67 (1)	282 (2)	161 (1)	443 (1)
50–59	1048 (22)	3136 (20)	2122 (12)	5258 (16)
60–69	2810 (60)	8330 (54)	8191 (48)	16 521 (51)
70	768 (16)	3655 (24)	6641 (39)	10 296 (32)
Charlson comorbidity index				
0	4096 (87)	12 895 (84)	13 560 (79)	26 455 (81)
1	356 (8)	1426 (9)	1964 (11)	3390 (10)
2	241 (5)	1082 (7)	1591 (9)	2673 (8)
Type of hospital				
University	660 (14)	2126 (14)	2311 (14)	4437 (14)
Nonuniversity	4033 (86)	13 277 (86)	14 804 (86)	28 081 (86)
Marital status[d]				
Married	2015 (71)	7216 (70)	7714 (69)	14 930 (69)
Divorced, widower, or never married	835 (29)	3155 (30)	3535 (31)	6690 (31)
Educational level[d,e]				
Low	676 (24)	2847 (27)	3692 (33)	6539 (30)
Middle	1151 (40)	4330 (42)	4483 (40)	8813 (41)
High	1016 (36)	3157 (30)	3016 (27)	6173 (29)
Missing data	8	40	62 (1)	102
PSA level at diagnosis, median (IQR), ng/mL	4.6 (3.7–5.9)	5.3 (4.0–7.0)	8.2 (5.4–12.0)	6.4 (4.5–9.3)
PSA density at diagnosis, ng/mL/cm³				
<0.15	4693 (100)	8155 (53)	4674 (27)	12 829 (39)
0.15	0	6358 (41)	11 419 (67)	17 777 (55)
Missing data	0	890 (6)	1022 (6)	1912 (6)
Clinical stage				
T1	4693 (100)	12 362 (80)	10 751 (63)	23 113 (71)
T2	0	3041 (20)	6364 (37)	9405 (29)

Characteristic	Participants, No. (%)			
	Very Low Risk[a] (n = 4693)	Low Risk[b] (n = 15 403)	Intermediate-Risk[c] (n = 17 115)	All Men (N = 32 518)
Gleason score				
<7	4693 (100)	15 403 (100)	3219 (19)	18 622 (57)
7	0	0	13 896 (81)	13 896 (43)
Positive cores, No.				
1	2597 (55)	5553 (36)	2753 (16)	8306 (26)
2–3	1908 (41)	5652 (37)	5794 (34)	11 446 (35)
4–6	188 (4)	2609 (17)	5534 (32)	8143 (25)
7	0	541 (4)	2312 (14)	2853 (9)
Missing data	0	1048 (7)	722 (4)	1770 (5)
Cancer extent in biopsies, mm				
<8	4693 (100)	10 121 (66)	6308 (37)	16 429 (51)
8–16	0	2083 (14)	3677 (21)	5760 (18)
16	0	1495 (10)	5717 (33)	7212 (22)
Missing data	0	1704 (11)	1413 (8)	3117 (10)
Primary treatment				
Active surveillance	3436 (73)	8389 (54)	2868 (17)	11 257 (35)
Watchful waiting	211 (4)	1200 (8)	1468 (9)	2668 (8)
ADT	13 (0)	172 (1)	1466 (9)	1638 (5)
Curative treatment	1033 (22)	5642 (37)	11 313 (66)	16 955 (52)

CCI = Charlson comorbidity index, PSA = Prostate-specific antigen, IQR = Interquartile range, ADT = Androgen deprivation therapy

[a]Very-low-risk disease defined as not N1/M1; clinical T1c; PSA, less than 10 ng/mL; Gleason 6 or lower; PSA density, less than 0.15 ng/mL/cm^3; 4 positive cores or fewer; and less than 8 mm of cancer in biopsies.[8]

[b]Low-risk disease defined as not N1/M1; clinical T1–T2; PSA, less than 10 ng/mL, Gleason 6 or lower. Low-risk category includes also all men in very-low- risk group.

[c]Intermediate-risk disease defined as Gleason grading group 3: not N1/M1; clinical T1–T2; PSA, 10–20 ng/mL; or Gleason 7 (3 + 4 or 4 + 3).

[d]Only available for men diagnosed between 2009 and 2012.

[e]Educational levels in years: low, compulsory school (<10 y); middle, upper secondary school (10–12 y); high, college, or university (>12 y).