Survey of Prostate Specific Antigen testing and the incidence of prostate-cancer in Kronoberg County 2007-2015

Thomas Wåxnäs, ST-läkare, Kirurgkliniken

thomas.waxnas@kronoberg.se

Handledare: Henrik Kjölhede, med,dr,

Sahlgrenska universitetssjukhus, Göteborg

Abstract

Background

Unstructured PSA testing is believed to increase in the developed world. This is confirmed in a Swedish study from Stockholm County, a metropolitan area. The incidence in rural areas in Sweden is not studied.

Results

From the year 2007 until 2015, a total of 37 542 men had 164 349 PSA tests in Kronoberg County. The total population at the end of 2016 were 194 628. We decided the age span 40-79 to be clinically interesting. A mean of 10% of all men aged 40-49 had a PSA test during the study. 20% in the age span 50-59, 28% of 60-69 and 27% of men aged 70-79. When stratified to level of first PSA, not taking age into account, those with a first sample of <1 μg/L had a resampling rate in one and two years of 16% and 38%, respectively.

Conclusion

The rate of PSA-retesting is high in all PSA-intervals, even in the group with PSA<1, about 60% had retested during the study.

The total rate of PSA testing seems not to increase over time.

Keywords: Prostate cancer, Screening, PSA

Contents

Background

In Sweden, prostate cancer is the most common type of cancer [1]. The majority of cases are diagnosed after an elevated level of Prostate-specific antigen (PSA) is detected in blood tests [2]. It is so far, the only widely adopted biomarker for prostate cancer (PCa) although some new clinically promising markers are emerging [3].

PSA was first described by Wang et al. and is a protein exclusively made by prostate cells [4]. Further studies showed that PSA is overexpressed from prostate cancer cells. This has led to increased use of PSA in the developed world and to earlier detection of PCa [5].

Two large randomized controlled trials have investigated the use of PSA as a means of systematic screening; the Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO) [6] and the European Randomized Study of Screening for Prostate Cancer (ERSPC) [7]. PLCO could not detect a difference in prostate cancer mortality when comparing a systematic versus opportunistic screening. ERSCP on the other hand showed a 20% reduction in prostate-specific mortality after 11-year follow-up. A commonly voiced explanation for this difference is that a large amount of the men included in PLCO still took PSA tests both before and during the study, and hence the control-arm was contaminated [8]. During the time of the ERSPC the opportunistic screening in Europe was much smaller, but this study as well suffered from contamination. In conclusion, there is some level of evidence that supports a systematic screening for PCa. Still, to our knowledge, no nationwide authority has recommended a systematic screening for the public, such as the mammography program in Sweden [9]. One reason for this might be the extensive morbidity that further diagnostics and treatment of PCa leads to [10-13].

This duality of PCa means that general screening would find a lot of clinically insignificant cancer while on the other hand more of the aggressive cancers could be found before becoming symptomatic [14,15].

The extent and outcome of unstructured PSA testing is not that well investigated. A study performed in the urban area of Stockholm [16] showed that 46-77% of men aged 40-79 years and without a previously known PCa had at least one PSA test in the years 2003 to 2011 and that 40-

58% took a new PSA test in two years, with a higher rate in higher age strata. The frequency of retesting was higher for men with elevated results, but in the group with PSA below 1 it was also common to resample every one or two years. This is in stark contrast with the minimal risk that men with such a low PSA will be diagnosed with PCa in the following 6 years [17] Limitations is that this study is performed in a highly urbanized area, and at the time of the study there where a large amount of private practice urology clinics. Ciatto et al made a similar study in Italy and found that 25% of males aged 45-79 years tested PSA any given year, and half of those took the test again the following year [18].

In Sweden, the current praxis is to inform a man who asks about a PSA test about his right for a PSA test after written and oral information of risks and benefits [19].

While the Stockholm study was performed in a highly urbanized area in Sweden with more than 2 million inhabitants, of which almost half lived in the city, Kronoberg County is a rural area with about 200 000 inhabitants in the southern parts of Sweden with Växjö being the largest city with a population of 65 000 [20]. The aim of this study was to determine the incidence of PSA-testing in Kronoberg County, explore the patterns of retesting and the proportion of diagnosed PCa in various PSA intervals.

Materials and methods

Ethics

The collection and handling of data for this study was approved by the Regional Ethics Review Board in Linköping, Sweden (2016/547).

Data acquisition

SA tests analysed by the Department of Clinical Chemistry in Kronoberg from 2007 to 2015 were obtained with information on analysis result, date, patient identity and what caregiver ordered the test. Every prostate biopsy result was obtained from the Department of Pathology with the same details as the PSA tests. These two departments analyse all tests taken in Kronoberg County. Men with a first PSA ordered from the Department of Oncology or the Department of Surgery were excluded from the study, since they were likely to be under investigation or treatment for PCa.

In order to exclude patients with a previously known PCa, we extracted all such diagnoses according to ICD-10 classification of C61.9 in the digital medical records system Cambio Cosmic, which is used by all caregivers in Kronoberg, and regional data from the National Prostate Cancer Register (NPCR), which contains information on all patients diagnosed with PCa. The date of prostate cancer diagnosis was set as the date registered in the NPCR, or if not available as the first date with a positive biopsy result or registered diagnosis in the medical records. Patients with a PCa diagnosis date before the start of the study period were excluded from the study. Finally, the study focused on men aged 40 to 79 years at the time of the first PSA, since this is the clinically most relevant age group.

Information regarding the number of men living in Kronoberg County and their distribution in different age strata was obtained from Statistics Sweden (SCB).

Statistics

The number of men who took a PSA test during the follow-up were described as both absolute numbers and as a proportion of the total male population for any given year. The number of men that also performed prostate biopsy is accounted for as well as the numbers of men that were diagnosed with PCa. Time to retesting, time to biopsy and time to diagnosis was analyzed with a Kaplan-Meier plot as one minus survival. Analyses were done using R version 3.5.0 (R Foundation, Vienna, Austria)

Results

Demographics

From the year 2007 until 2015, a total of 37 542 men had 164 349 tests. The following were excluded: 195 had a previous PCa diagnosis and 136 were ordered from other regions, and so did not have any further data available for analysis. For 2 223 men, the first registered PSA tests were ordered from either the Department of Surgery/Urology or the Department of Oncology within the region, indicating a previously known or treated PCa. After exclusions, 34 988 men with 124 464 PSA results were available for analysis. The male population aged 40-79 years was 41 664 in 2007, with a steady increase to 44 454 in 2015. Table 1 shows the male population in the age span 40-79 for each year on the 31st of December.

The number of unique PSA testing events compared to the male population, stratified by age group and year, is presented in Table 2 and visually in Figure 1. There was no evidence of increased testing in any of the age groups.

Prevalence of PSA testing 2007-2015

The number of unique PSA testing events compared to the male population, stratified by age group and year, is presented in Table 2 and visually in Figure 1. There was no evidence of increased testing in any of the age groups.

Table 1. Prevalence of PSA testing 2007-2015. n PSA indicates number of men that took a first PSA without known PCa. n men indicate the number of men residing in Kronoberg. The percentage is the incidence of PSA testing in each age strata per year.

	40-49			50-59			60-69			70-79		
Year	n PSA	n men	%	n PSA	n men	%	n PSA	n men	%	n PSA	n men	%
2007	863	12 134	7,1%	2 448	11 997	20,4%	2 843	10 927	26,0%	1 866	6 606	28,2%
2008	938	12 327	7,6%	2 459	11 820	20,8%	2 993	11 295	26,5%	1 809	6 629	27,3%
2009	1 403	12 326	11,4%	2 723	11 684	23,3%	3 443	11 608	29,7%	1 957	6 766	28,9%
2010	1 404	12 413	11,3%	2 555	11 529	22,2%	3 457	11 865	29,1%	1 931	6 893	28,0%
2011	1 349	12 425	10,9%	2 394	11 417	21,0%	3 412	12 096	28,2%	1 974	7 031	28,1%
2012	1 378	12 473	11,0%	2 231	11 342	19,7%	3 400	12 114	28,1%	1 953	7 312	26,7%
2013	1 221	12 440	9,8%	2 164	1 1376	19,0%	3 334	12 070	27,6%	1 972	7 678	25,7%
2014	1 168	12 449	9,4%	2 046	11 504	17,8%	3 304	11 916	27,7%	2 162	8 123	26,6%
2015	1 239	12 544	9,9%	2 149	11 643	18,5%	3 471	11 742	29,6%	2 335	8 525	27,4%

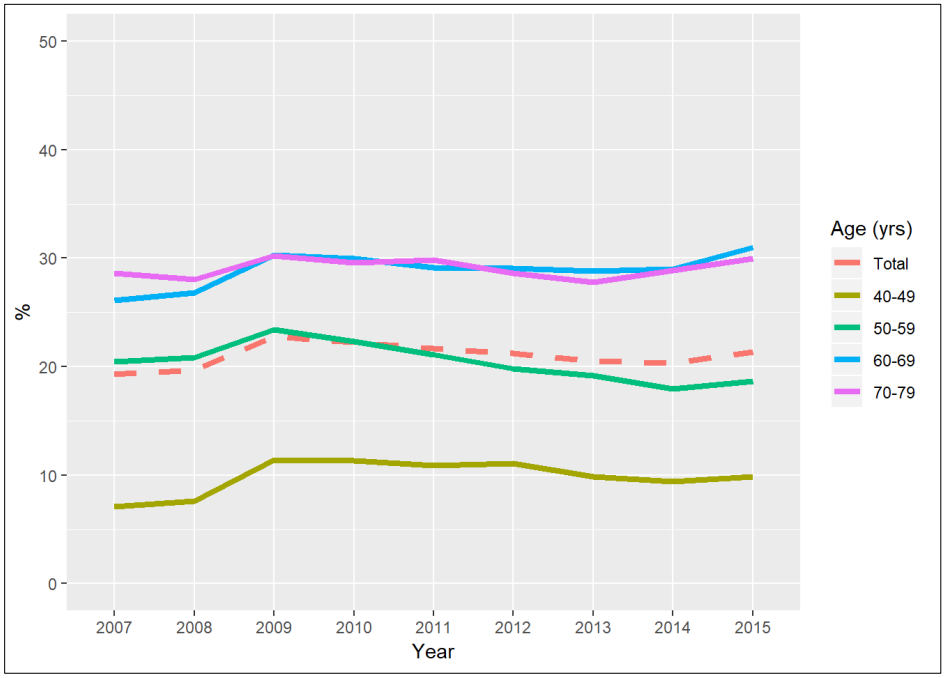

Figure 1. Part of the male population that took a PSA test every year This shows the percentage in each age strata that took at least one PSA test for each given year.

PSA-retesting

For the 13966 men with an initial PSA < 1.0 ng/ml, 8607 (62%) retested during the study period (figure 2). After one year 16,5% of them had retested and after two years 38%. In the groups of 10 411 men with an initial PSA 1.0 – 2.9 and 4 612 men with initial PSA 3.0 – 9.9 ng/ml, 6903 (66%) and 4047 (88%), respectively, retested. The retesting frequency after one and two years were 20,6%, 43% and 70,5%, 81,6% respectively. Finally, of the 1132 men with initial PSA > 10 ng/ml, 1067 (94%) retested PSA during the study.

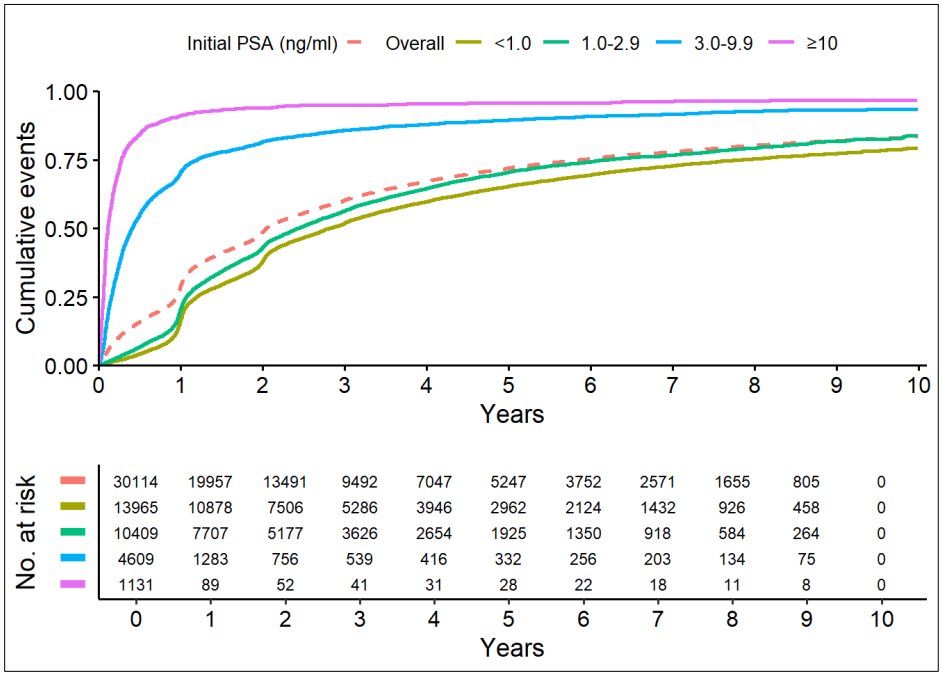

Figure 2. Cumulative incidence for time between first and second PSA sample for all men stratified according to level of first PSA.

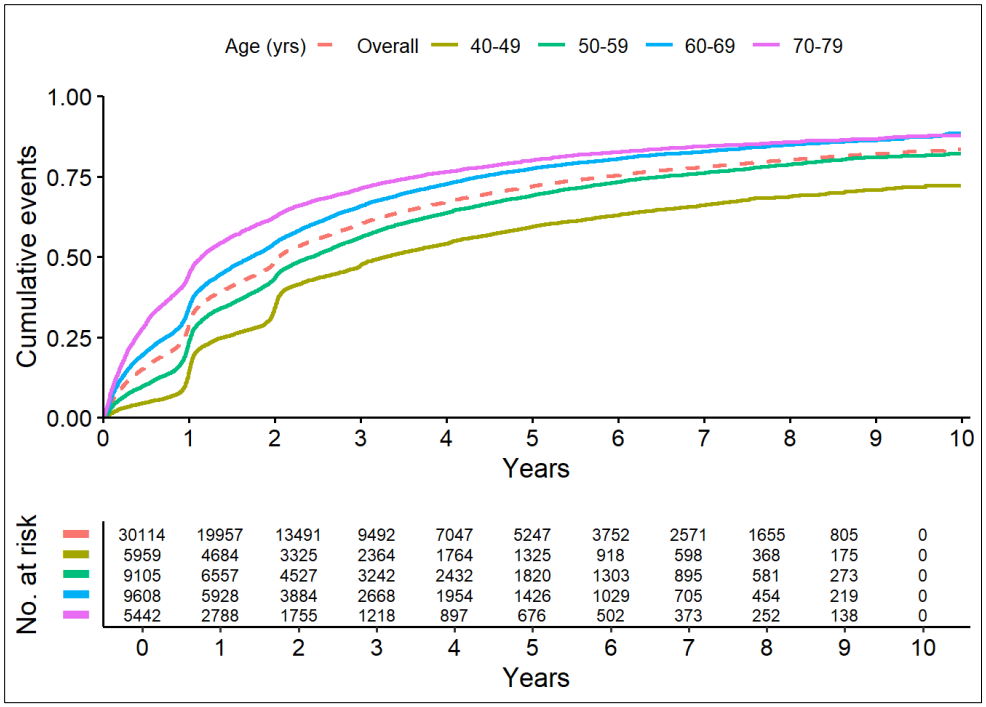

Figure 3. Cumulative incidence for time between first and second PSA sample for all men stratified by age.

Time to biopsy

Of the 13 966 men with an initial PSA < 1.0 ng/ml, 76 (0,5%) had at least one biopsy during the study period (Figure 4). In the groups of 10 411 men with an initial PSA 1.0 – 2.9 and 4 612 men with initial PSA 3.0 – 9.9 ng/ml, 900 (8,6%) and 1927 (42%), respectively, were biopsied. Finally, in the group of 1 132 men with PSA > 10 ng/ml, 661 (58%) had a biopsy taken.

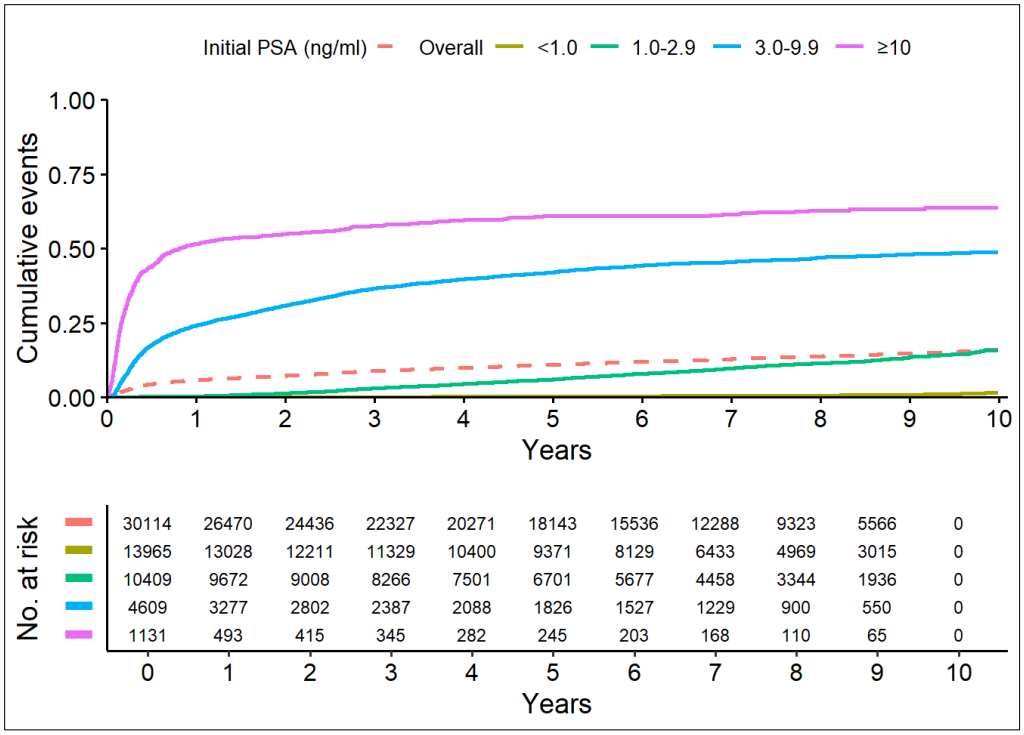

Figure 4. Cumulative incidence of time from first PSA to a prostate biopsy, stratified according to level of first PSA.

Time to diagnosis

For the 13 966 men with an initial PSA < 1.0 ng/ml, 103 (0.7%) were registered with a diagnosis of PCa during the study period (Figure 5). In the groups of 10 411 men with an initial PSA 1.0 – 2.9 and 4 612 men with initial PSA 3.0 – 9.9 ng/ml, 523 (5.0%) and 1 083 (23%), respectively, were registered with PCa. Finally, in the group of 1 132 men with PSA > 10 ng/ml, 612 (54%) were diagnosed with PCa.

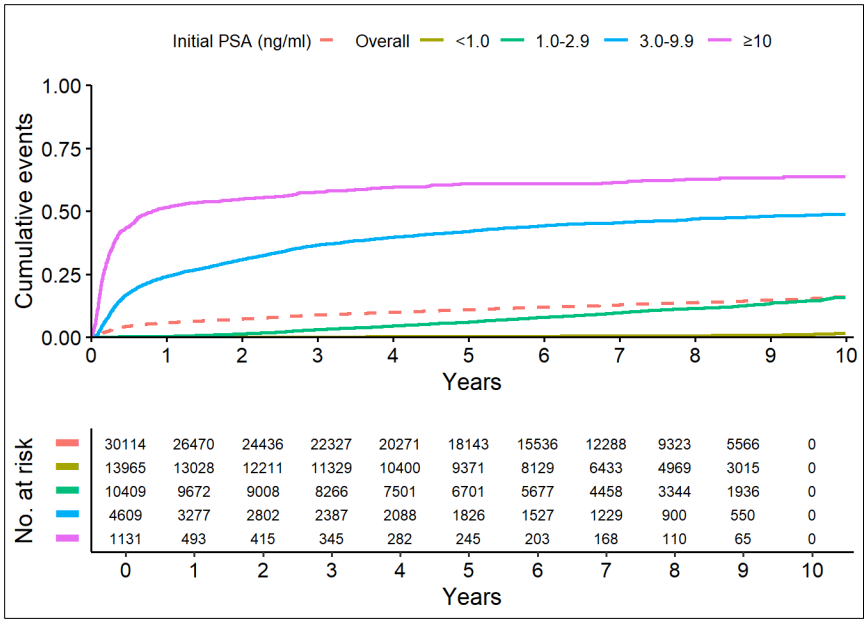

Figure 5. Cumulative incidence of PCa diagnosis, stratified according to level of first PSA.

Discussion

This study was aiming to describe the PSA testing patterns in a rural area in Sweden. A similar study was performed out of the STHLM0 cohort and mentioned before. Our results show similarities. The most obvious is the pattern of annual and biannual resampling of PSA in the lower PSA strata <1 and 1-3.

The age group that took the most tests and had the highest prevalence of PSA testing was 60-69. It is common to perform re-testing of PSA, even when the first PSA is very low.

Men with a first PSA of less than one has a very low risk of being diagnosed with prostate cancer during the follow-up of this study.

As is evident in figure 3, there is a significant level of annual and bi-annual testing of PSA, even in those with a first PSA of less than 1. This is indicated by the stepwise, annual changes in the Kaplan-Meier diagram.

Prostate cancer is the most common cancer in Sweden and thus the discussion about a screening program is necessary. Especially since opportunistic screening seems to be quite evident. Every unnecessary PSA test takes time and recourses and as is discussed in many articles, not every prostate cancer diagnose is of any grave threat to the patient and all we might succeed to do in some cases is to create fear and discomfort.

Roughly 10% of all men aged 40-49yr tested at least once for PSA every year and between 25-30% in the older categories 60-79yr. On the other hand, in the age strata of 50-59yr, some 80 percent do not test at all. This indicates a clear bias and possible unequal distribution of public resources.

How many of these tests were unnecessary? This is of course impossible to answer but the broader implications of our results are that men with a very low first PSA still exhibit frequent resampling to a high degree, which may not be very cost-effective. Our findings support the recommendations in the Swedish national practice guidelines for prostate cancer, that a PSA <1

does not warrant resampling until 6 years. Since we have showed that a substantial number of men with a primary PSA lower than 1 is still testing and retesting annually, the current strategy of free at will testing after information might not be working. A viable alternative could be structured information to all men aged 50 – 70 years, detailing the potential advantages and disadvantages of PSA testing.

The risk of developing a prostate cancer that is diagnosed is quite low in the group of men with a first PSA of <1 during the follow-up time. The rate is growing according to higher first PSA value.

The fact that the number of biopsies performed in the group of 13966 men with initial PSA <1 totaled 76 and still 103 got a PCa diagnosis, ICD 10 C61.9, might seem confusing. In our view this is likely because we failed to exclude them. They may have had prostate cancer before enrolling in the study, or moved in from another county. This possible overinclusion supports our notion of PCa being rare in this PSA strata.

The strengths of this study are that we have all available data in our region and very few are lost to follow-up. All data regarding both PSA tests and biopsies are taken from a single laboratory. All data regarding prostate cancer is extracted from one electronic medical records system that covers virtually all citizens in Kronoberg.

One weakness is that the demographics is an estimate since we cannot know for sure how many men that lived in Kronoberg County every year were living here before and whether or not they had PSA tests where they lived before so there might be contamination to some extent. Another weakness is that we don't know the extent of migration and cannot specify exactly the lost to follow-up. It was also not possible to study why the men who took a PSA test did so.

Conclusions

This study confirms that the rate of PSA testing and retesting in Kronoberg County are on par with what was showed in the STHLM0 study. It is a clear trend that annual and bi-annual testing is taking place even in younger men and men with a very low PSA result and this is likely unnecessary.

Competing interests

The authors declare that they have no conflicts of interest.

Funding

This study was performed with funding from the regional research and development department, FoU Kronoberg

Authors' contributions

Conception and design:	HK
Acquisition of data:	HK, TW
Analysis and interpretation:	HK
Drafting and revising manuscript:	HK, TW

References

[1] http://www.socialstyrelsen.se/statistik/statistikefteramne/cancer>datum

[2] Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med 1987; 317: 909-916.*

[3] Ström, P et al. The Stockholm-3 Model for Prostate Cancer Detection: Algorithm Update, Biomarker Contribution, and Reflex Test Potential. *European Urology , Volume 74 , Issue 2 : 204 – 210.*

[4] Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate specific antigen. *Invest Urol 1979; 17: 159–163.*

[5] W.J. Catalona, J.P. Richie, F.R. Ahmann, et al.Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol, 151 (1994): 1283-1290.*

[6] Andriole GL, Crawford ED, Grubb III RL, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst 2012;104:125–32.*

[7] Schröder FH, Hugosson J, Roobol MJ, et al. The European Randomized Study of Screening for Prostate Cancer – Prostate Cancer Mortality at 13 Years of Follow-up. *Lancet. 2014;384(9959):2027-2035.*

[8] Gulati R, Tsodikov A, Wever EM, et al. The impact of PLCO control arm contamination on perceived PSA screening efficacy. *Cancer Causes Control 2012;23:827-35.*

[9] https://www.socialstyrelsen.se/SiteCollectionDocuments/screening-brostcancer-rekommendation.pdf>datum

[10] Lundstrom KJ, Drevin L, Carlsson S, Garmo H, Loeb S, Stattin P, et al. Nationwide population based study of infections after transrectal ultrasound guided prostate biopsy. *The Journal of urology. 2014;192(4):1116-22*

[11] Van Hemelrijck M, Garmo H, Holmberg L, Bill-Axelson A, Carlsson S, Akre O, et al. Thromboembolic events following surgery for prostate cancer. *European urology. 2013;63(2):354-63.*

[12] Steineck G, Bjartell A, Hugosson J, Axen E, Carlsson S, Stranne J, et al. Degree of preservation of the neurovascular bundles during radical prostatectomy and urinary continence 1 year after surgery. *European urology. 2015;67(3):559-68.*

[13] Wallerstedt A, Carlsson S, Steineck G, Thorsteinsdottir T, Hugosson J, Stranne J, et al. Patient and tumour-related factors for prediction of urinary incontinence after radical prostatectomy. *Scandinavian journal of urology. 2013;47(4):272-81.*

[14] Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schroder FH, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *Journal of the National Cancer Institute. 2003;95(12):868-78.*

[15] Aus G, Robinson D, Rosell J, Sandblom G, Varenhorst E, South-East Region Prostate Cancer G. Survival in prostate carcinoma--outcomes from a prospective, population-based cohort of 8887 men with up to 15 years of follow-up: results from three countries in the population-based National Prostate Cancer Registry of Sweden. *Cancer. 2005;103(5):943-51.*

[16] Nordström T, Aly M, Clements MS, et al. Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, Despite no recommendations for PSA screening: results from a population-based study, 2003-2011. *Eur Urol 2013; 63: 419-25.*

[17] Aus G, Damber JE, Khatami A, Lilja H, Stranne J, Hugosson J. Individualized screening interval for prostatecancer based on prostate-specific antigen level: results of a prospective, randomized, populationbasedstudy. *Arch Intern Med.2005;165(16):1857-61.*

[18] Ciatto S, Houssami N, Martinelli F, Giusti F, Zappa M. PSA use and incidence of prostate biopsy in the Tuscany region: is opportunistic screening discounting biopsy in subjects with PSA elevation? *Tumori. 2008;94(4):518–22.*

[19] http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19489/2014-8-4.pdf>datum

[20] Statistics Sweden, http://www.scb.se>datum