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Cohort Profile Update: The National Prostate Cancer Register of Sweden and Prostate Cancer database—a refined prostate cancer trajectory

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The original cohort

Prostate Cancer data Base Sweden (PCBaSe) 2.01,2 is based on linkages of different national health care registers with the Swedish National Prostate Cancer Register, and contains more than 110 000 registered cases since 1998. It also includes a selection of two control series of men free of prostate cancer (PCa) at the time of samples, as well as information on brothers of men diagnosed with PCa.

What is the reason for the new data collection?

PCBaSeTraject includes new linkages, so that we cannot only study primary treatment but also the entire PCa treatment trajectory. Prostate cancer has become a chronic disease in a large proportion of afflicted men, since its fatality rate is low, but statistical cure is never attained.3 Thus, many men with PCa receive multiple subsequent treatments and their treatment trajectory often spans decades. In PCBaSeTraject, the PCa treatment trajectory is delineated by use of data on primary treatment in the National Prostate Cancer Register (NPCR) of Sweden, verified by data obtained by linkages with the Prescribed Drug Registry4 (i.e. use of androgen deprivation therapy (ADT)) and the National Patient Registry (i.e. surgical procedures and hospital admissions). In addition, data were collected on radiotherapy (RetroRad) from oncology information systems and local databases at radiotherapy departments for treatments performed before 2008 (Figure 1).

What will be new areas of research?

Previously all our studies were limited to treatment at time of diagnosis. The new focus of PCBaSeTraject is to outline the full treatment trajectory for a nationwide, population-based cohort of men with PCa. PCBaSeTraject will also continue to serve as a platform for studies on patterns of care, outcomes and adverse effects of treatment in post-authorization surveillance studies.

Who is in the cohort?

PCBaSeTraject focuses specifically on men diagnosed with PCa between 1992 and 2012 with available information on their complete treatment trajectory. It is an update of PCBaSe 3.0, which is already an update of PCBaSe 2.0.
through inclusion of two additional years of follow-up. However, since the Prescribed Drug Registry started on 1 July 2005, ADT prescriptions could only be captured as of 1 January 2006, allowing for a 6-month run-in period. Therefore, only men who were alive and living in Sweden on 1 January 2006 were eligible (n = 116,962) for PCBaSeTraject. We excluded: 6146 men who, according to the National Prostate Cancer Register (NPCR), received ADT as primary treatment but had no corresponding filled prescription; 938 men who had undergone curative treatment according to NPCR, but with no corresponding information in other registers; 1948 men who had received ADT according to the Prescribed Drug Registry in the run-in period (July 2005–January 2006), without ADT as primary treatment in NPCR and thus unknown date of ADT initiation; and 1008 men with missing information on treatment in the NPCR as well as in other registers. A total of 106,922 men with PCa with complete and coherent information on treatment were included in the final study population (Figure 2, Table 1). In addition, a comparison cohort of PCa-free men matched by birth year and county of residence was selected from the background population, as previously described in detail.

What has been measured?

PCBaSeTraject is designed to capture information on the treatment trajectory following the order of treatments: conservative treatment (CT) → radical prostatectomy → radiotherapy → anti-androgens (AA) → gonadotropin-releasing hormone (GnRH) agonists, in which any treatment may be omitted. Information about conservative treatment was collected from NPCR and the NPCR Follow-up study in three categories (Figure 3): active surveillance [i.e. regular follow-up with prostate-specific antigen (PSA) testing and repeated biopsies with the intent to convert to curative treatment if signs of progression occur]; watchful waiting [i.e. a treatment strategy where ADT is used if symptomatic progression occurs]; and unspecified conservative treatment
Men in PCBaSe 3.0 diagnosed 1992-2012 (n=144 218)

Complete follow-up 1 Jan 2006 – 31 Dec 2012 (n=116 962)

Complete follow-up and complete ADT information (n=110 816)

Complete follow-up, complete ADT information, and complete curative treatment information (n= 110 793)

To study with complete treatment and follow-up information (n= 106 922 )

Dead/Emigrated before 1/1 2006 (n=27 256)

ADT treatment initiated before 1 Jan 2006 according to NPCR without verified or contradicting continuation according to the Drug Registry (n=6 146)

Unspecified curative treatment initiated before 1 Jan 2006 according to NPCR not verified in other sources (n=23)

Unspecified non curative treatment initiated before 1 Jan 2006 according to NPCR (n=915)

Missing treatment in NPCR before 1 Jan 2006 (n=1 008)

Secondary ADT with unknown date of initiation or contradicting treatment paths (n=1 948)

NPCR: National Prostate Cancer Register, ADT: androgen deprivation therapy.

Figure 2. Flow chart of patient selection for PCBaSeTraject.

(CTUNS) which is a mixture of active surveillance and watchful waiting because the NPCR did not make the distinction between these two types of conservative treatment before 2007. Men registered in the NPCR with active surveillance were only considered to be on active surveillance if they met the inclusion criteria from the Study on Active Monitoring in Sweden (SAMS), i.e. low-risk cancer in men below age 70. Men registered in the NPCR with watchful waiting, who underwent radical prostatectomy or radiotherapy within 2 years of diagnosis were reclassified as curative treatment. Curative treatment initiated more than 2 years after diagnosis, for men originally registered with watchful waiting, were registered as non-standard procedures. Watchful waiting was reclassified to primary ADT when GnRH agonists were used less than 2 months after diagnosis (Figure 3).
Table 1. Characteristics of men with prostate cancer in PCBaSeTraject

|                      | Conservative treatment | Radical prostatectomy | Curative radiation therapy | Anti-androgens | GnRH agonists | All study subjects |
|----------------------|------------------------|-----------------------|----------------------------|----------------|--------------|-------------------|
| Age, Mean (SD)       | 71.5 (8.1)             | 63.0 (6.1)            | 66.5 (5.9)                  | 75.5 (7.1)     | 76.7 (8.0)   | 69.8 (8.9)        |
| < 65                 | 6273 (22.0)            | 17932 (60.8)          | 6474 (37.8)                 | 445 (8.3)      | 2337 (8.9)   | 33461 (31.3)      |
| 65–74                | 12267 (43.0)           | 11144 (37.8)          | 9639 (56.3)                 | 1893 (35.4)    | 7584 (28.7)  | 42527 (39.8)      |
| 75–84                | 8808 (30.9)            | 418 (1.4)             | 1014 (5.9)                  | 2606 (48.7)    | 12777 (48.4) | 25623 (24.0)      |
| 85+                  | 1181 (4.1)             | 17 (0.1)              | 4 (0.0)                     | 402 (7.5)      | 3707 (14.0)  | 5311 (5.0)        |
| Age in years, n (%)  |                        |                       |                            |                |              |                   |
| < 65                 | 6273 (22.0)            | 17932 (60.8)          | 6474 (37.8)                 | 445 (8.3)      | 2337 (8.9)   | 33461 (31.3)      |
| 65–74                | 12267 (43.0)           | 11144 (37.8)          | 9639 (56.3)                 | 1893 (35.4)    | 7584 (28.7)  | 42527 (39.8)      |
| 75–84                | 8808 (30.9)            | 418 (1.4)             | 1014 (5.9)                  | 2606 (48.7)    | 12777 (48.4) | 25623 (24.0)      |
| 85+                  | 1181 (4.1)             | 17 (0.1)              | 4 (0.0)                     | 402 (7.5)      | 3707 (14.0)  | 5311 (5.0)        |
| Educational level, n (%) |                     |                       |                            |                |              |                   |
| High                 | 6087 (21.3)            | 9025 (30.6)           | 4257 (24.8)                 | 1057 (19.8)    | 3606 (13.7)  | 24032 (22.5)      |
| Middle               | 10685 (37.5)           | 12023 (40.7)          | 6804 (39.7)                 | 1884 (35.2)    | 8408 (31.8)  | 39804 (37.2)      |
| Low                  | 11505 (40.3)           | 8315 (28.2)           | 5967 (34.8)                 | 2343 (43.8)    | 13954 (52.8) | 42084 (39.4)      |
| Missing              | 252 (0.9)              | 148 (0.5)             | 103 (0.6)                   | 62 (1.2)       | 437 (1.7)    | 1002 (0.9)        |
| Stage group,a n (%)  |                       |                       |                             |                |              |                   |
| Low risk             | 14626 (51.3)           | 12226 (41.4)          | 3534 (20.6)                 | 261 (4.9)      | 502 (1.9)    | 31149 (29.1)      |
| -Very low riskb      | 1824 (25.5)            | 510 (11.6)            | 93 (7.3)                    | 3 (3.2)        | 4 (4.0)      | 2434 (18.7)       |
| -Not very low riskb  | 4623 (64.5)            | 3440 (78.3)           | 1099 (86.1)                 | 81 (87.1)      | 82 (81.2)    | 9325 (71.6)       |
| -Low risk UNSb       | 715 (10.0)             | 441 (10.0)            | 85 (6.7)                    | 9 (9.7)        | 15 (14.9)    | 1265 (9.7)        |
| Intermediate risk    | 8086 (28.3)            | 12020 (40.7)          | 5772 (33.7)                 | 1108 (20.7)    | 2351 (8.9)   | 29337 (27.4)      |
| High risk            | 3701 (13.0)            | 3761 (12.7)           | 6462 (37.7)                 | 2437 (45.6)    | 8677 (32.9)  | 25038 (23.4)      |
| Regionally metastatic| 430 (1.6)              | 380 (1.3)             | 905 (5.3)                   | 830 (15.9)     | 4455 (16.9)  | 7040 (6.6)        |
| Distant metastases   | 237 (0.8)              | 148 (0.5)             | 280 (1.6)                   | 643 (12.0)     | 10289 (39.0) | 11597 (10.8)      |
| Missing data         | 1429 (5.0)             | 976 (3.3)             | 178 (1.0)                   | 47 (0.9)       | 131 (0.5)    | 2761 (2.6)        |

GnRH: Gonadotropin Releasing Hormone

*aBased on a modification of the guidelines of the National Comprehensive Cancer Network (1): Low risk (T1–2, Gleason score 2–6 and PSA < 10 ng/ml); intermediate risk (T1–2, Gleason score 7 and/or PSA 10 to < 20 ng/ml); High risk (T3 and/or Gleason score 8–10 and/or PSA 20 to < 50 ng/ml); Regionally metastatic disease (T4 and/or N1 and/or PSA 50 to < 100 ng/ml in the absence of distant metastases (M0 or Mx)); distant metastases (M1 and/or PSA = 100 ng/ml and above).

*bFor men diagnosed as of 2008.

Figure 3. Flow chart of data collection for conservative treatment in PCBaSeTraject.

NPCR: National Prostate Cancer Register, CTWW: watchful waiting, CTAS: active surveillance, CTUNS: Unspecified conservative treatment, SAMS: Study on Active Monitoring in Sweden.
Information on curative treatment was collected from the NPCR, the NPCR Follow-up studies, the National Patient Registry, and RetroRad to define radical prostatectomy and radiotherapy. The majority of primary radical prostatectomies and radiotherapies registered in NPCR were verified by data in other registers (Figure 4). A total of 679 men registered with curative treatment in NPCR, but with no corresponding treatment in other registers, and who had received ADT according to the Prescribed Drug Registry within 9 months of date of diagnosis, were considered to be treated with primary ADT.

To collect information on deferred curative radiotherapy following a period of conservative treatment or as adjuvant/salvage therapy following radical prostatectomy, we used the NPCR Follow-up study and information from the Patient Registry (Figure 2). Since 1987, the National Patient Registry has collected information regarding inpatient care. Each record contains medical information on surgical procedures, hospital department, and discharge diagnoses coded according to ICD-9 or ICD-10. A common classification of surgical procedures has been used in Sweden since 1997.

To collect information on deferred curative radiotherapy following a period of conservative treatment or as adjuvant/salvage therapy following radical prostatectomy, we used information from the NPCR, the NPCR Follow-up study, RetroRad and the National Patient Registry.
(Figure 2). In 2008, the NPCR created a specific form to collect information on radiotherapy (RTForm) (Appendix A1, available as Supplementary data at IJE online). There is little information regarding radiotherapy in the National Patient Registry, although this information has gradually become more detailed in recent years. To overcome this lack of information, mainly for the time period before 2008, a retrospective data collection was performed (RetroRad). Radiotherapy data were retrieved from the verification/oncology information systems and local databases of radiotherapy departments in Sweden, including information on type of radiotherapy, treatment dates, total dose and fractionation. RetroRad captures information from the early 1990s until 2008–12, depending on the availability of databases at each centre.

Information about primary ADT was collected from the NPCR, the NPCR Follow-up study, the National Patient Registry and the Prescribed Drug Registry (Figure 2). First, we assessed whether a prescription had been filled for an anti-androgen or a GnRH agonist within 3 months after date of diagnosis. If this was not the case, the treatment strategy was defined as watchful waiting (Figure 5). Hence, ADT used as adjuvant or neoadjuvant in combination with curative treatment was ignored. To distinguish neoadjuvant and adjuvant ADT from use of ADT due to disease progression, we retrieved information on ADT from the Prescribed Drug Registry and compared with information for ADT on the RTForm and RPForm in the NPCR. ADT given before curative treatment was considered as neoadjuvant if delivered less than 18 months prior to that treatment. If ADT was initiated more than 18 months prior to curative treatment, it was considered to be primary ADT. With respect to adjuvant ADT for men who did not have information on the RTForm or RPForm in the NPCR, use of ADT without a discontinuation of at least 9 months during the first 3 years after curative treatment was considered to be adjuvant. For men receiving curative treatment with no information from the RTForm or RPForm, dates were retrieved from RetroRAD or the Patient Registry. Furthermore, a distinction was required between anti-androgen monotherapy and flare protection. Anti-androgens initiated less than 3 months before subsequent GnRH agonists were considered to be flare protection, whereas other time frames for anti-androgen

Figure 5. Flow chart of data collection for androgen deprivation therapy in PCBaSeTraject.

NPCR: National Prostate Cancer Register, RP: radical prostatectomy RT: curative radiotherapy, ADT: androgen deprivation therapy, AA: anti-androgen monotherapy, GnRH: GnRH agonists.
prescriptions were considered as indicators of anti-androgen monotherapy. Additional treatment information was obtained from the National Patient Registry, the Prescribed Drug Registry and the RetroRad (Figure 2).

Follow-up in PCBaSe for data from the Prescribed Drug Registry, the National Patient Registry and the Cause of Death Registry are annually updated. All data management was conducted with SAS 9.3 (SAS Institute, Cary, NC), and statistical modelling was performed with R 2.13.2 (R Foundation for Statistical Computing, Vienna). The Research Ethics Board at Umeå University Hospital approved the study.

**What has it found?**

We found that the time to treatment changes was dependent on type of primary treatment and subsequent treatments (Figure 6). For example, men treated with primary radical prostatectomy were more likely to receive adjuvant or salvage radiotherapy than men who underwent deferred prostatectomy after an initial period of active surveillance. There was also a difference in timing and proportion of men who received androgen deprivation therapy due to disease progression after primary or secondary radiotherapy, as ADT was introduced earlier and to a larger proportion of men who had received primary

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**Figure 6.** Time to treatment changes based on different primary and subsequent treatments for men with prostate cancer as registered in PCBaSeTraject.

PCa: prostate cancer, AA: anti-androgen monotherapy, RT: curative radiotherapy, RP: radical prostatectomy.
radiotherapy. One-third of the men who were registered as active surveillance had converted to curative treatment 6 years after diagnosis, and most of these men had undergone radical prostatectomy (24%) or radiotherapy (12%) (results not shown). The proportion of men who died of Pca was higher among those who received GnRH agonists as primary treatment, compared with men who received GnRH as second-line treatment. Overall, 17% of men received two subsequent treatments and 2% received three treatments (Table 2).

Table 2. Treatment trajectories in PCaSeTraject

| Men with one treatment | n   | (%) |
|------------------------|-----|-----|
| CTAS                   | 6609| (6.2)|
| CTWW                   | 8280| (7.7)|
| CTUNS                  | 3667| (3.4)|
| RT                     | 23 252| (21.7)|
| CurRT                  | 14 525| (13.6)|
| AA                     | 3534| (3.3)|
| GnRH                   | 26 405| (24.7)|

| Men with two treatments | n   | (%) |
|-------------------------|-----|-----|
| CTAS → RP               | 1584| (1.5)|
| CTAS → RT               | 824| (0.8)|
| CTAS → AA               | 271| (0.3)|
| CTAS → GnRH             | 186| (0.2)|
| CTWW → AA               | 1274| (1.2)|
| CTWW → GnRH             | 2402| (2.2)|
| CTUNS → RP              | 674| (0.6)|
| CTUNS → RT              | 523| (0.5)|
| CTUNS → AA              | 495| (0.5)|
| CTUNS → GnRH            | 746| (0.7)|
| RP → RT                 | 3829| (3.6)|
| RP → AA                 | 720| (0.7)|
| RP → GnRH               | 429| (0.4)|
| CurRT → AA              | 1063| (1.0)|
| CurRT → GnRH            | 1098| (1.0)|
| AA → GnRH               | 1812| (1.7)|

| Men with three treatments | n   | (%) |
|---------------------------|-----|-----|
| Starting in CT            | 916| (0.9)|
| Starting in RP            | 1077| (1.0)|
| Starting in RT            | 443| (0.4)|

| Men with four treatments | n   | (%) |
|--------------------------|-----|-----|
| Starting in CT           | 72| (0.1)|
| Starting in RP           | 204| (0.2)|

| Men with five treatments | n   | (%) |
|-------------------------|-----|-----|
| Starting in CT          | 6| (0.0)|

CT, conservative treatment; CTWW, watchful waiting; CTAS, active surveillance; CTUNS, unspecified conservative treatment; RP, radical prostatectomy; RT, curative radiotherapy; AA, anti-androgen monotherapy; GnRH, gonadotropin-releasing hormone agonist.

different registers. One limitation of PCaSeTraject is the lack of information on indications for additional treatment. Continuous registration of PSA levels would be a useful way to assess disease progression and efforts to obtain such data are under way. Finally, it is worth noting that due to the later start date of the Prescribed Drug Registry (1 July 2005), PCaSeTraject requires use of left-truncation in all time-to-event analysis.

Can I get hold of the data? Where can I find out more?
The steering groups of the NPCR and PCaSe welcome external collaborations. For more information please see [www.npcr.se/in-english], where registration forms,

What are the main strengths and weaknesses?
PCaSeTraject contains comprehensive data on the treatment trajectory for men with PCa. Our results demonstrate that both clinical knowledge and ‘register know how’ are necessary to correctly perform analysis and interpret data from such register-based studies. PCaSeTraject showed high concordance of treatment classification between the additional data from PCaSeTraject have already allowed us to investigate the association between types and duration of ADT and risk of cardiovascular disease (CVD) in greater detail than was previously possible. We found an increased risk of CVD, in particular within the first year of ADT, which was strongest for men with a previous history of CVD.

In another study, we investigated long-term complications for men who were curatively treated with radiotherapy or radical prostatectomy. We specifically evaluated urinary incontinence, lower urinary tract symptoms and gastrointestinal symptoms up to 12 years after treatment. It was found that these complications mostly occurred within the first 3 years after radical prostatectomy, whereas complications after radiotherapy were more frequent at a later date after treatment.

An overview of all publications based on PCaSe Sweden can be found at [www.npcr.se/forskning].
manuals and annual reports from the NPCR are found as well as a full list of publications from PCBaSe.

Supplementary Data

Supplementary data are available at IJE online.

PCBaSe$^{\text{Traject}}$: UPDATE IN A NUTSHELL

- PCBaSe Sweden 2.0 was updated to include more information on the prostate cancer treatment trajectory: PCBaSe$^{\text{Traject}}$.
- Prostate cancer has become a chronic disease in a large proportion of afflicted men, so that many men with prostate cancer receive multiple subsequent treatments and their treatment trajectory often spans decades. To better delineate the pattern of care and outcomes, data collection has been enhanced in the National Prostate Cancer Register (NPCR) of Sweden and the Prostate Cancer data Base Sweden (PCBaSe), resulting in PCBaSe$^{\text{Traject}}$.
- This includes a precise delineation of the treatment trajectory for men with PCa who were alive on 1 January 2006 ($n = 106922$). Following primary treatment, a subsequent treatment was initiated in 17932 (17%) of these men and 2436 (2%) men received three subsequent PCa treatments.
- In addition to linkages to several health care registries and demographic databases, PCBaSe$^{\text{Traject}}$ also includes data on radiotherapy (RetroRad) from oncology information systems and local databases at radiotherapy departments for treatments performed before 2008.
- For more new collaborative projects and enquiries about data sharing, please contact [npcr@npcr.se].

Figure 7. Time to initiation of GnRH agonists and time to PCa death since time of GnRH agonists initiation for men with prostate cancer, as registered in PCBaSe$^{\text{Traject}}$.
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