Supplemental Online Content

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eTable 1. HR and 95% CI for Worsening Hypertension Using Different Definitions of Events in PCa Exposure Cohort and GnRH Exposure Cohort: Crude Model

eTable 2. Number of Events in PCa Cohort and GnRH Cohort

eFigure 1. Patient Inclusion and Exclusion Flowchart

eFigure 2. Schematic Diagram for the Selection Process of Exposed Men and Nonexposed Men in NDR Registrations

eFigure 3. Blood Pressure Levels Change Over Time by PCa Status in PCa Exposure Cohort

eFigure 4. Blood Pressure Levels Change Over Time by PCa Status in GnRH Exposure Cohorts

This supplemental material has been provided by the authors to give readers additional information about their work.
eTable 1. HR and 95% CI for Worsening Hypertension Using Different Definitions of Events in PCa Exposure Cohort and GnRH Exposure Cohort: Crude Model

| Exposure                                      | BP rose to 140/80 (<= 65-year-old) or 130/80 mmHg (>65-year-old) | SBP increased 10mmHg | DBP increased 5mmHg | Number of Anti-hypertension changes | Dosage of anti-hypertension changes |
|-----------------------------------------------|-----------------------------------------------------------------|----------------------|---------------------|------------------------------------|------------------------------------|
|                                               | HR (95% CI)                                                     | HR (95% CI)          | HR (95% CI)          | HR (95% CI)                        | HR (95% CI)                        |
| **PCa exposure cohort**                       |                                                                  |                      |                     |                                    |                                    |
| **Using GnRH agonists**                       |                                                                  |                      |                     |                                    |                                    |
| No PCa                                        | Ref.                                                            | Ref.                 | Ref.                | Ref.                               | Ref.                               |
| PCa without GnRH                              | 0.89 (0.83-0.95)                                                | 0.92 (0.88-0.97)     | 0.87 (0.83-0.92)     | 0.98 (0.93-1.03)                   | 0.99 (0.95-1.04)                   |
| PCa with GnRH                                 | 0.68 (0.60-0.77)                                                | 0.80 (0.72-0.87)     | 0.76 (0.70-0.83)     | 0.94 (0.85-1.03)                   | 0.98 (0.90-1.07)                   |
| **PCa diagnosis**                             |                                                                  |                      |                     |                                    |                                    |
| No                                            | Ref.                                                            | Ref.                 | Ref.                | Ref.                               | Ref.                               |
| Yes                                           | 0.83 (0.78-0.89)                                                | 0.89 (0.85-0.93)     | 0.85 (0.81-0.88)     | 0.97 (0.92-1.02)                   | 1.00 (0.95-1.04)                   |
| **PCa risk category**                         |                                                                  |                      |                     |                                    |                                    |
| No PCa                                        | Ref.                                                            | Ref.                 | Ref.                | Ref.                               | Ref.                               |
| Low-risk                                      | 1.08 (0.95-1.22)                                                | 0.96 (0.88-1.04)     | 0.91 (0.83-0.99)     | 1.00 (0.91-1.10)                   | 0.99 (0.91-1.08)                   |
| Intermediate-risk                             | 0.85 (0.76-0.95)                                                | 0.88 (0.82-0.95)     | 0.86 (0.80-0.93)     | 1.05 (0.97-1.13)                   | 1.06 (0.98-1.13)                   |
| High-risk                                     | 0.77 (0.68-0.86)                                                | 0.83 (0.77-0.91)     | 0.78 (0.72-0.85)     | 0.95 (0.87-1.04)                   | 1.00 (0.92-1.08)                   |
| Regional metastasises                         | 0.65 (0.50-0.85)                                                | 0.90 (0.76-1.06)     | 0.76 (0.64-0.90)     | 0.81 (0.67-0.98)                   | 0.86 (0.72-1.02)                   |
| Distance metastasises                         | 0.64 (0.52-0.78)                                                | 0.89 (0.78-1.02)     | 0.86 (0.75-0.98)     | 0.76 (0.64-0.89)                   | 0.78 (0.67-0.91)                   |
| Missing data                                  | 0.88 (0.64-1.22)                                                | 1.01 (0.81-1.26)     | 0.97 (0.78-1.20)     | 0.98 (0.77-1.25)                   | 1.09 (0.88-1.35)                   |
| **GnRH exposure cohort**                      |                                                                  |                      |                     |                                    |                                    |
| **Using GnRH agonists**                       |                                                                  |                      |                     |                                    |                                    |
| PCa without GnRH                              | Ref.                                                            | Ref.                 | Ref.                | Ref.                               | Ref.                               |
| PCa with GnRH                                 | 0.69 (0.57-0.84)                                                | 0.93 (0.82-1.07)     | 0.98 (0.86-1.11)     | 1.04 (0.90-1.19)                   | 1.04 (0.90-1.19)                   |
| **PCa risk category**                         |                                                                  |                      |                     |                                    |                                    |

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| Low-risk | Ref. | Ref. | Ref. | Ref. | Ref. |
| --- | --- | --- | --- | --- | --- |
| **Exposure** | BP rose to 140/80 (<= 65-year-old) or 130/80 mmHg (>65-year-old) | SBP increased 10mmHg | DBP increased 5mmHg | Number of Anti-hypertension changes | Dosage of anti-hypertension changes |
| **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| Intermediate-risk | 0.97 (0.83-1.14) | 0.98 (0.88-1.09) | 1.01 (0.91-1.12) | 1.04 (0.93-1.16) | 1.04 (0.93-1.16) |
| High-risk | 0.89 (0.74-1.07) | 0.84 (0.73-0.96) | 1.03 (0.90-1.17) | 1.04 (0.90-1.19) | 1.04 (0.90-1.19) |
| Regional metastasises | 0.82 (0.49-1.38) | 0.64 (0.45-0.92) | 0.64 (0.45-0.92) | 1.16 (0.85-1.60) | 1.16 (0.85-1.60) |
| Distance metastasises | 0.85 (0.48-1.52) | 0.49 (0.30-0.80) | 0.85 (0.57-1.25) | 0.75 (0.48-1.18) | 0.75 (0.48-1.18) |
| Missing data | 0.87 (0.56-1.35) | 0.90 (0.68-1.19) | 0.84 (0.63-1.12) | 1.16 (0.87-1.54) | 1.16 (0.87-1.54) |

a. We excluded those men with missing data on SBP and DBP.
b. We excluded those men with missing data on SBP.
c. Those men with missing data on DBP were excluded.
d. Those men with missing data on antihypertensive drugs were excluded.

**Abbreviations:** HR= Hazard ratio; 95% CI= 95% confidence interval; PCa= prostate cancer; GnRH= Gonadotropin-releasing hormone agonists; CVD= cardiovascular diseases; BP=blood pressure; SBP= systolic blood pressure; DBP= diastolic blood pressure.
eTable 2. Number of Events in PCa Cohort and GnRH Cohort

|                               | PCa cohort          |             | GnRH cohort         |             |
|-------------------------------|---------------------|-------------|---------------------|-------------|
|                               | men with PCa on/not on GnRH No.=5,714 | PCa-free men No.=28,445 | men with PCa on GnRH No.=692 | men with PCa no on GnRH No.=3,460 |
| No. (%)                       | No. (%)             | No. (%)     | No. (%)             | No. (%)     |
|                               | 1,263 (22.1)        | 4,967 (17.5)| 386 (55.8)          | 2,087 (60.3)|
| Yes                           | 4,451 (77.9)        | 23,478 (82.5)| 306 (44.2)          | 1,373 (39.7)|
| Total number of patients in the subset | 5,714 (100.0)        | 28,445 (100.0) | 692 (100.0)            | 3,460 (100.0)|
| 10% increase in CVD risk      |                     |             |                     |             |
| No                            | 1,263 (22.1)        | 4,967 (17.5)| 386 (55.8)          | 2,087 (60.3)|
| Yes                           | 4,451 (77.9)        | 23,478 (82.5)| 306 (44.2)          | 1,373 (39.7)|
| Total number of patients in the subset | 5,714 (100.0)        | 28,445 (100.0) | 692 (100.0)            | 3,460 (100.0)|
| 5% increase in CVD risk       |                     |             |                     |             |
| No                            | 1,060 (51.7)        | 4,733 (45.5)| 205 (63.9)          | 638 (49.3)  |
| Yes                           | 989 (48.3)          | 5,678 (54.5)| 116 (36.1)          | 656 (50.7)  |
| Total number of patients in the subset | 2,049 (100.0)        | 10,411 (100.0) | 321 (100.0)            | 1,294 (100.0)|
| BP rose by 140 or 130/80mmHg or higher |                     |             |                     |             |
| No                            | 1,060 (51.7)        | 4,733 (45.5)| 205 (63.9)          | 638 (49.3)  |
| Yes                           | 989 (48.3)          | 5,678 (54.5)| 116 (36.1)          | 656 (50.7)  |
| Total number of patients in the subset | 2,049 (100.0)        | 10,411 (100.0) | 321 (100.0)            | 1,294 (100.0)|
| SBP increased 10mmHg          |                     |             |                     |             |
| No                            | 3,300 (58.8)        | 14,952 (53.7)| 423 (62.9)          | 1,897 (56.3)|
| Yes                           | 2,314 (41.2)        | 12,878 (46.3)| 250 (37.1)          | 1,475 (43.7)|
| Total number of patients in the subset | 5,614 (100.0)        | 27,830 (100.0) | 673 (100.0)            | 3,372 (100.0)|
| DBP increased 5mmHg           |                     |             |                     |             |
| No                            | 3,279 (58.5)        | 14,427 (51.9)| 400 (59.7)          | 1,816 (53.9)|
| Yes                           | 2,326 (41.5)        | 13,370 (48.1)| 270 (40.3)          | 1,556 (46.1)|
| Total number of patients in the subset | 5,605 (100.0)        | 27,797 (100.0) | 670 (100.0)            | 3,372 (100.0)|
| Number of antihypertension drugs change |                     |             |                     |             |
| No                            | 3,710 (64.9)        | 17,839 (61.7)| 498 (72.0)          | 2,278 (65.8)|
| Yes                           | 2,004 (35.1)        | 11,060 (38.3)| 194 (28.0)          | 1,182 (34.2)|
| Total number of patients in the subset | 5,714 (100.0)        | 28,899 (100.0) | 692 (100.0)            | 3,460 (100.0)|
| Dosage of antihypertension drugs change |                     |             |                     |             |
| No                            | 3,351 (58.7)        | 16,066 (56.5)| 451 (65.2)          | 2,104 (60.8)|
| Yes                           | 2,362 (41.3)        | 12,379 (43.5)| 241 (34.8)          | 1,356 (39.2)|
| Total number of patients in the subset | 5,713 (100.0)        | 28,445 (100.0) | 692 (100.0)            | 3,460 (100.0)|

Abbreviations: PCa=prostate cancer; GnRH=Gonadotropin-releasing hormone agonists; CVD=cardiovascular diseases; BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure.
eFigure 1. Patient Inclusion and Exclusion Flowchart

NDR in PCBaSe4.1
2,941,720 registrations
231,334 men

Exclude T1DM
235,270 registrations
27,118 men

Exclude registrations prior to 1/1 2006
146,670 registrations
2,223 men

Exclude men in PCBaSe4.1 that are neither registered in NPCR nor randomly selected as non-cases men
843,445 registrations
52,483 men

T2DM registered in NDR from 1/1 2006
1,716,335 registrations
149,510 men

Exclude men with four or fewer registrations in NDR
96,486 registrations
40,118 men

Eligible to study
1,520,047 registrations
101,843 men

Exclude men 1) diagnosed with PCa at baseline in PCa exposure cohort, and 2) men used GnRH at baseline in GnRH exposure cohort
99,802 registrations
7,485 men

Study of exposure change
PCa vs. No PCa (PCa exposure cohort)
5,714 cases
28,445 non-cases

Study of exposure change
PCa with GnRH vs. PCa (GnRH exposure cohort)
692 cases
3,460 non-cases
eFigure 2. This figure illustrated the study design and patient selection process. We included men diagnosed with type 2 diabetes mellitus (T2DM), according to the National Diabetes Registry (NDR), amongst men included in Prostate Cancer data Base Sweden (PCBaSe) 4.1 in 2006-2016 and created two cohorts – “Prostate cancer (PCa) + Gonadotropin-releasing hormone agonists (GnRH) exposure cohort” and “GnRH exposure cohort”. 5,714 men with PCa and 28,445 PCa-free men were included in the PCa+ exposure cohort. The GnRH exposure cohort contained 692 men with PCa who started GnRH after PCa diagnosis and 3,460 men with PCa not using GnRH as non-cases.

Abbreviations: PCa=prostate cancer; GnRH= Gonadotropin-releasing hormone agonists; NDR= the National Diabetes Register; PCBaSe = Prostate Cancer data Base Sweden.
eFigure 2. Schematic Diagram for the Selection Process of Exposed Men and Nonexposed Men in NDR Registrations

Abbreviations: NDR = the National Diabetes Register

Non-exposed men were matched to exposed men based on 1) average duration between NDR visits before the start of follow-up, and 2) number of NDR visits.
In eFigure 3, we found that blood pressure levels in men with PCa with GnRH were lower than men without GnRH over time (eFigure 3).

**Abbreviations:** PCa= prostate cancer; GnRH= Gonadotropin-releasing hormone agonists; BP=blood pressure; SBP= systolic blood pressure; DBP= diastolic blood pressure.
The SBP and DBP in these men were always lower than for men with PCa without GnRH over time (eFigure 4).

Abbreviations: PCa = prostate cancer; GnRH = Gonadotropin-releasing hormone agonists; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure.