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# Prescription rates for commonly used drugs before and after a prostate cancer diagnosis

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## Abstract

**Purpose** To investigate differences in prescription rates of commonly used drugs among prostate cancer patients and cancer-free comparisons and between patients diagnosed with localized and non-localized disease.

**Methods** We conducted a register-based study including all men aged 50–85 years diagnosed with prostate cancer in Denmark from 1998 to 2015 and an age-matched cancer-free comparison cohort. We calculated the number of new and total prescriptions from three years before to three years after the date of diagnosis of the case for selected drug classes divided by the number of person-months and stratified by stage at diagnosis.

**Results** We included 54,286 prostate cancer patients and 249,645 matched comparisons. 30,712 patients were diagnosed with localized disease and 12,884 with non-localized disease. The rates of new prescriptions increased considerably among patients within the year before the diagnosis. Hereafter the rates varied between drug classes. For most drug classes, total prescription rates for patients and comparisons increased similarly in the study period. Total prescription rates varied between men with localized and non-localized disease for all drug classes apart from statins.

**Conclusion** Our findings indicate that a large proportion of prostate cancer cases are likely diagnosed during medical work-up for other reasons than prostate cancer. Increased rates occur within the last year before diagnosis and future studies on the interaction between drug use and prostate cancer should at least include a one year pre-diagnostic lag-time. Post-diagnostic prescription rates demonstrated an increased use of drugs most likely associated with the consequences of the disease.

**Keywords** Prostate cancer · Prescription rate · Drug use · Surveillance bias · Lag-time

## Background

Prostate cancer is the most common cancer among elderly men, and therefore a substantial number of prostate cancer patients will have concomitant morbidity at the time of diagnosis [1–3]. Some morbidities might be identified during cancer work-up or cancer might be detected during work-up for other diseases. However, changes in the pattern of drug use close to the time of prostate cancer diagnosis could, if not taken into account, potentially lead to bias in epidemiological studies. Information on rates of new and total prescriptions may help when choosing lag-time periods in the design process of pharmacoepidemiological studies and when evaluating the level of bias in the interpretation of the derived estimates.

A previous Danish study showed that the rate of new prescriptions increased up to 6 months before a cancer diagnosis and that the number of prescriptions of preselected

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drugs gradually increased among men with a subsequent prostate cancer diagnosis [4]. This study clearly illustrated differences in the rates of new prescriptions before a prostate cancer diagnosis but lack important details regarding the stage of disease at the time of diagnosis which are crucial for prostate cancer, where patients with localized versus non-localized disease may differ significantly in many aspects. We further lack information on prescription rates after prostate cancer diagnosis and patterns of total prescription rates.

In this study, we present nationwide data of both new and total prescription rates of selected drug classes among prostate cancer patients and an age-matched comparison cohort three years before and three years after a prostate cancer diagnosis. The primary aim is to improve the general knowledge of prescription patterns among prostate cancer patients, to facilitate the design and interpretation of future pharmacoepidemiological studies of prostate cancer.

## Materials and methods

We conducted a nationwide study of prescription rates of selected drug classes among prostate cancer patients and an age-matched comparison cohort three years before and three years after a prostate cancer diagnosis. We selected six classes of drugs commonly used among elderly men that are not directly related to any urological symptoms, including analgesics, antidepressants, antidiabetics, beta-blockers, NSAIDs, and statins.

### Data sources

We used information from Danish nationwide demographic and health registries. The Danish Civil Registration System administers individual information on the unique personal identification number, including date of birth, and continuously updated information on vital status, place of residence, and migration [5]. The personal identification number enables unambiguous linkage at an individual level between Danish registries. The Danish Cancer Registry holds almost complete and accurate information on incident cancer cases in Denmark, including information on clinical stage recorded as "localized", "regional", "distant", or "unknown" until 2003 and according to the tumor node metastasis (TNM) system from 2004 onwards [6]. The Danish National Prescription Registry contains information on all drug prescriptions dispensed at Danish pharmacies since 1 January 1995 [7]. Data include the type and quantity of drugs dispensed and the date of dispensing. Drugs are categorized according to the anatomical therapeutic chemical (ATC) classification system, a hierarchical classification system developed by the World Health Organization.

### Study population

From the Cancer Registry, we identified all prostate cancer cases (International Classification of Diseases, 10th Revision (ICD-10): C61.9) from 1998 to 2015 among Danish men aged 50–85 years. Men with a previous cancer diagnosis (except non-melanoma skin cancer) were excluded. We categorized prostate cancer patients as having localized, non-localized, or unknown clinical stage at diagnosis based on information from the Danish Cancer Registry (see Appendix Table 2 for stage algorithm).

For each prostate cancer patient, we randomly selected up to five male population controls, matched on date of birth that were alive and cancer-free at the time of diagnosis (index date) of the corresponding prostate cancer patient. All men were followed from three years before to three years after the index date, or to the date of death or migration, whichever came first. Information on vital status and migration was obtained from the Civil Registration System and information on previous cancer diagnoses from the Cancer Registry.

### Study drugs

From the Prescription Registry, we obtained information for all men in the study population on filled prescriptions for analgesics, antidepressants, antidiabetics, beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), and statins within three years before to three years after the index date (ATC codes listed in Appendix Table 3). New prescriptions were defined as a prescription within a specific drug class, filled by a man with no previous prescription within the same drug class for the preceding two years. Total prescriptions were defined as any prescription within the same drug class in the study period.

### Statistical analyses

We performed descriptive analyses of characteristics among all prostate cancer patients and the comparison cohort and prostate cancer patients stratified by stage at the time of diagnosis. The number of either new or total prescriptions was calculated from three years before to three years after the index date for each drug class divided by the number of person-months, i.e., for each one-month interval during the six years of follow-up we counted the number of prescriptions (new or total) and divided it with the number of person-months in that interval to estimate the rate. The prescription rates before and after the index date were reported as the prescription rate per 100 person-months with 95% confidence intervals for all prostate cancer patients and the

comparison cohort and patients stratified by localized and advanced disease compared to their own matched comparisons, respectively.

## Results

### Characteristics of the study population

We included 54,286 prostate cancer patients and 249,645 matched comparisons. Among the prostate cancer patients, 30,712 were identified with localized disease at diagnosis and 12,884 were identified with non-localized disease at diagnosis. It was not possible to gain information on stage of disease at diagnosis for 10,690 patients (20%) and they were thus excluded from the stratified analyses. Overall, the median age was close to 70 years, however, men with localized disease were younger at diagnosis (68.8 years, IQR, 63.7–74.1) compared to men with non-localized disease (72.4 years, IQR, 66.2–78.1) (Table 1). The percentage of men with localized disease increased throughout the study period.

### Rates of new prescriptions

Figure 1 shows the plots of the new prescription rates among all prostate cancer patients and the comparison cohort. For all drug classes, new prescriptions were similar for patients and comparisons in the period until 12 months before the index date. Within 12 months before the index date, the new prescription rate increased considerably among prostate cancer patients but not in the comparison cohort. Following the time of diagnosis, the rate varied between the selected drug classes. For antidiabetics, beta-blockers, and statins, the new prescription rate among prostate cancer patients decreased shortly after diagnosis to the same level as the comparisons, whereas analgesics and NSAIDs remained slightly elevated throughout the observation period. The new prescription rate of antidepressants remained considerably elevated among prostate cancer patients the first three years after a diagnosis.

Similar trends in new prescriptions were seen in analyses stratified by stage of disease (Fig. 2). However, for analgesics, antidepressants, and NSAIDs, the peak in new prescriptions close to the time of diagnosis was most pronounced among prostate cancer patients with non-localized disease. Moreover, for antidepressants, the new prescription rate remained considerably elevated up to three years after diagnosis among patients with non-localized prostate cancer compared with the comparison cohort, whereas only a small increase in new prescriptions was seen in the analyses of patients with localized prostate cancer.

### Rates of total prescriptions

The total prescription rates showed very different patterns between the selected drug classes (Fig. 3). Except for NSAIDs and statins, the total prescription rate before the index date was lower among men with prostate cancer than among men in the comparison cohort. Shortly before the index date, the total prescription rates increased for analgesics and NSAIDs and stayed significantly elevated throughout the remaining study period. The total prescription rate for antidepressants was lower among prostate cancer patients but increased to the same level as the comparison cohort after diagnosis. For the other drug classes, the total prescription rates among prostate cancer patients and comparisons increased similarly throughout the study period. The total

**Table 1** Descriptive characteristics 54,286 Danish prostate cancer patients diagnosed from 1998 to 2015 and 248,645 age-matched comparisons, stratified by stage at diagnosis

| | Comparison cohort *n* (%) | All prostate cancer *n* (%) | Localized disease *n* (%) | Non-localized disease *n* (%) | Missing *n* (%) |
|---|---|---|---|---|---|
| Number of men | 249,645 | 54,286 | 30,712 | 12,884 | 10,690 |
| Median age in years (IQR) | 70.42 (64.97–76.20) | 70.22 (64.79–76.05) | 68.80 (63.74–74.12) | 72.35 (66.23–78.12) | 72.65 (66.91–78.05) |
| Age group, year (%) | | | | | |
| < 65 | 62,685 (25.1) | 14,052 (25.9) | 9,416 (30.7) | 2,681 (20.8) | 1,954 (18.3) |
| 65–70 | 57,155 (22.9) | 12,483 (23.0) | 7,892 (25.7) | 2,479 (19.2) | 2,112 (19.8) |
| 70–75 | 55,426 (22.2) | 11,943 (22.0) | 6,768 (22.0) | 2,764 (21.5) | 2,411 (22.6) |
| > 75 | 74,379 (29.8) | 15,809 (29.1) | 6,636 (21.6) | 4,960 (38.5) | 4,213 (39.4) |
| Year of diagnosis (%) | | | | | |
| 1998–2003 | 52,095 (20.9) | 10,881 (20.0) | 4,296 (14.0) | 3,467 (26.9) | 3,118 (29.2) |
| 2004–2007 | 58,751 (23.5) | 12,580 (23.2) | 7,261 (23.6) | 3,188 (24.7) | 2,131 (19.9) |
| 2008–2011 | 70,631 (28.3) | 15,501 (28.6) | 9,852 (32.1) | 3,162 (24.5) | 2,487 (23.3) |
| 2012–2015 | 68,168 (27.3) | 15,324 (28.2) | 9,303 (30.3) | 3,067 (23.8) | 2,954 (27.6) |

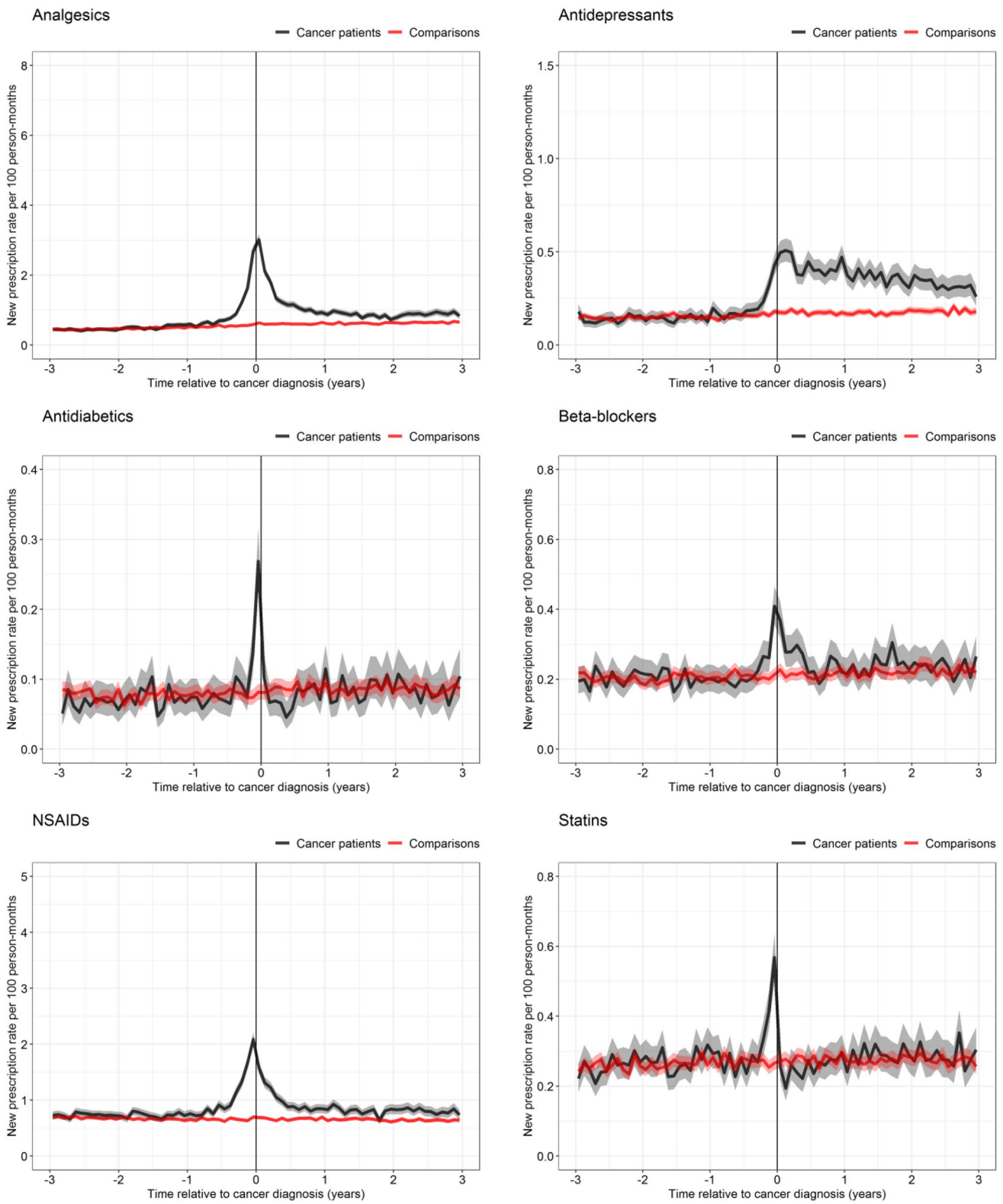


**Fig. 1** Rates of new prescriptions for selected drug classes among 54,286 Danish prostate cancer patients diagnosed from 1998 to 2015 and 248,645 age-matched comparisons. Note different Y-axis

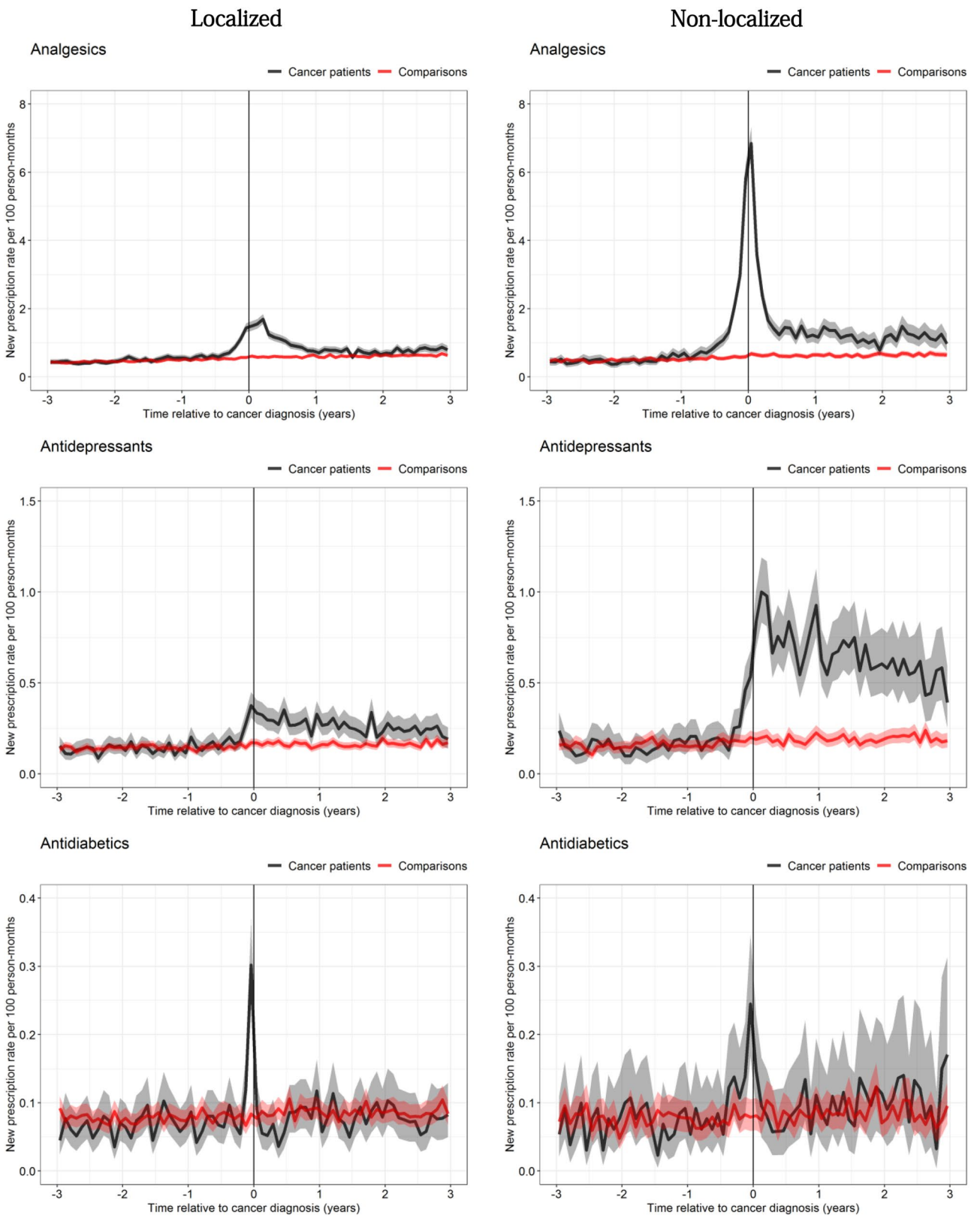


**Fig. 2** Rates of new prescriptions among Danish prostate cancer patients diagnosed from 1998 to 2015 stratified by stage of diseases at the time of diagnosis and their age-matched comparisons. Rate of new prescriptions among 54,286 Danish prostate cancer patients diagnosed from 1998 to 2015 and 248,645 matched comparisons. Note different Y-axis between drug classes

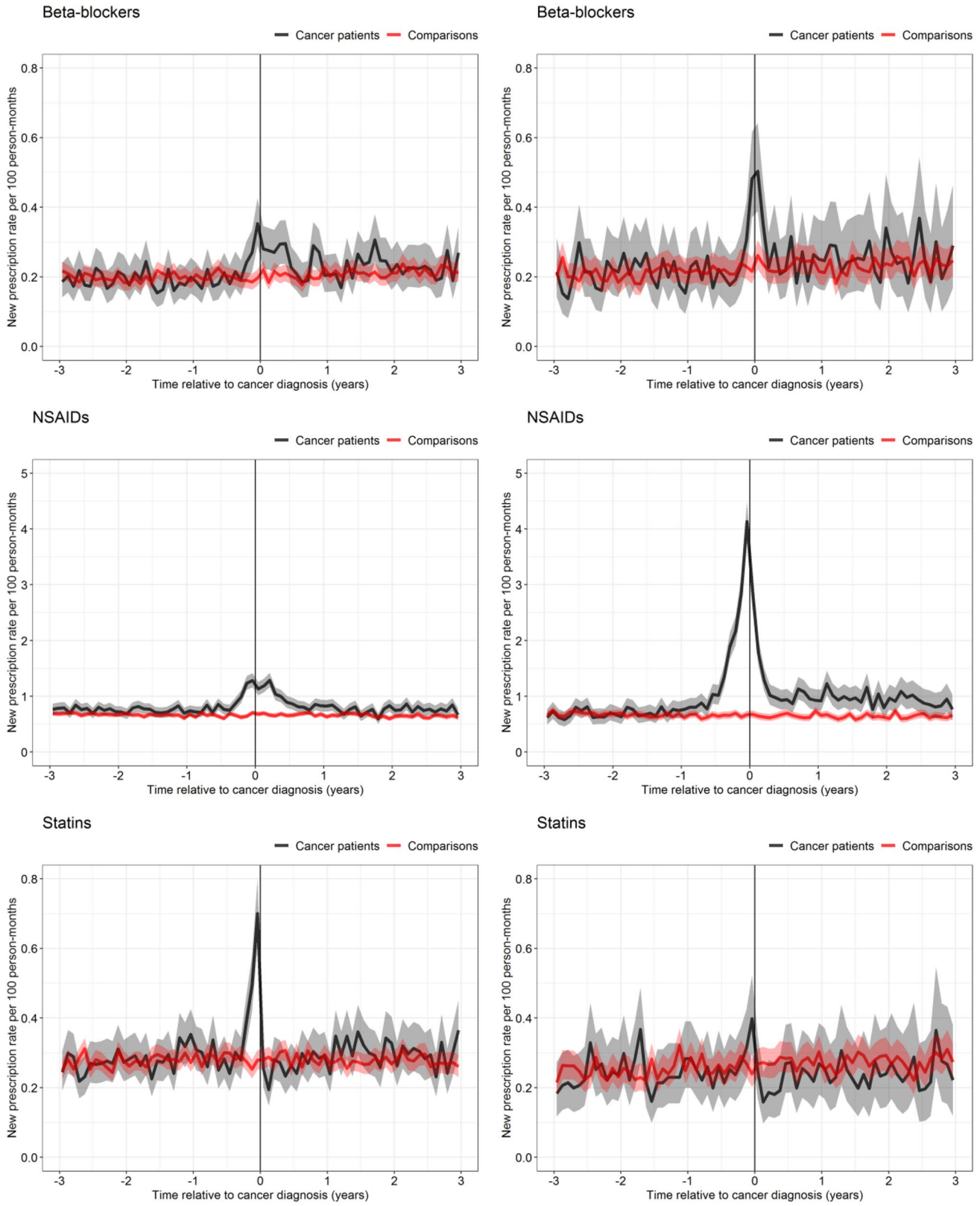


**Fig. 2** (continued)

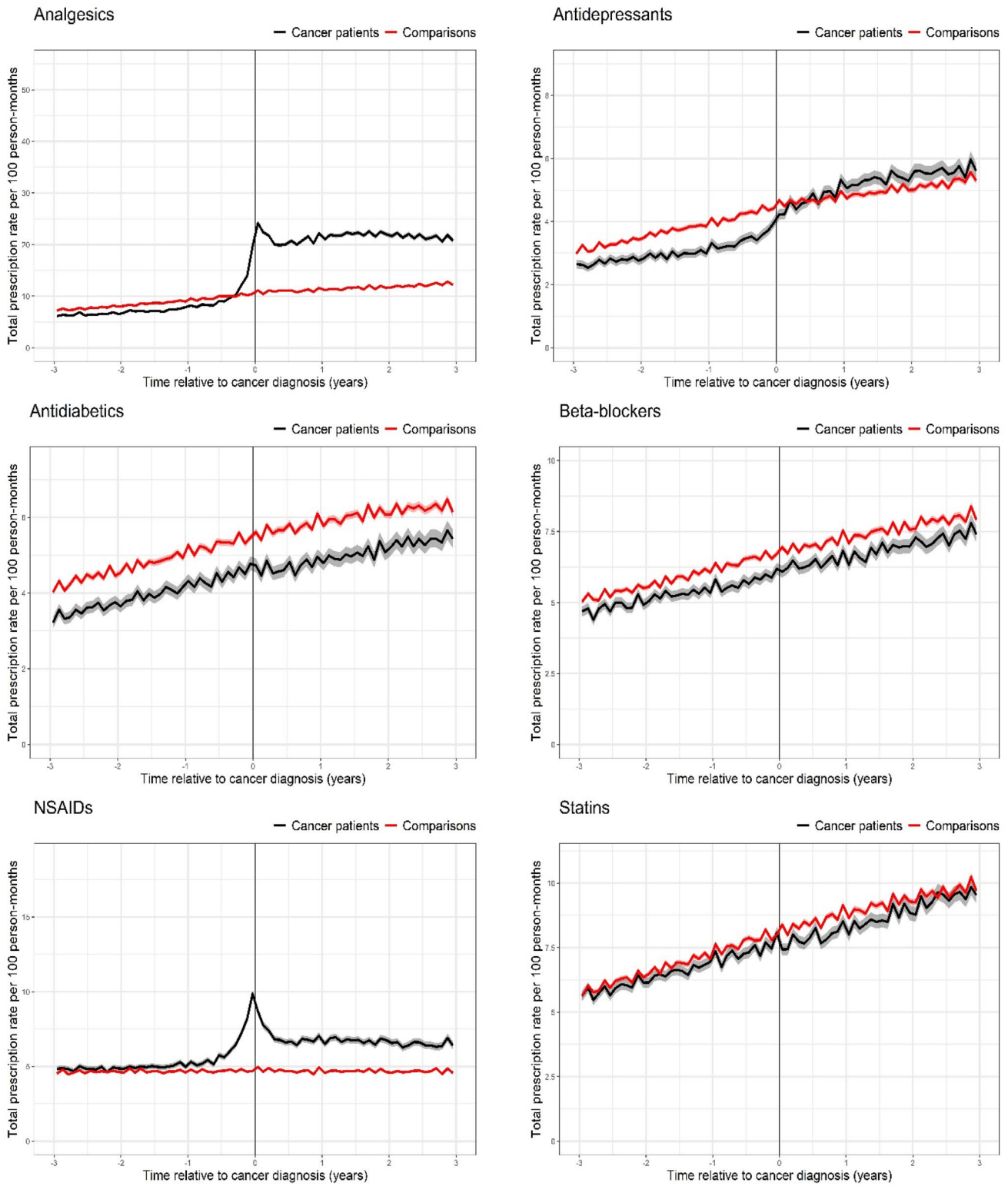


**Fig. 3** Total prescription rates among 54,286 Danish prostate cancer patients diagnosed from 1998 to 2015 and 248,645 age-matched comparisons. Note different Y-axis

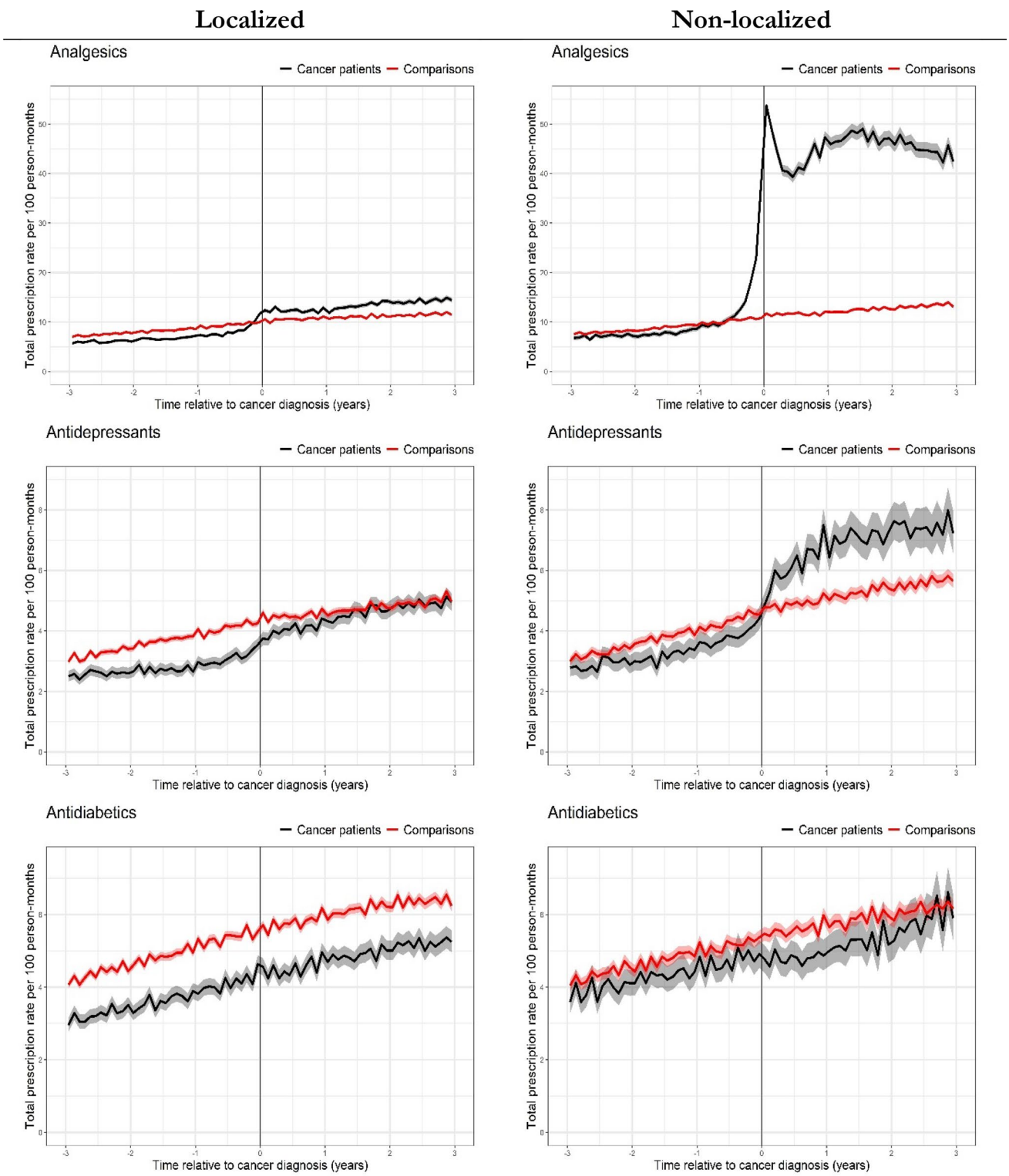


**Fig. 4** Rates of total prescriptions among Danish prostate cancer patients diagnosed from 1998 to 2015 stratified by stage of diseases at the time of diagnosis and their age-matched comparisons. Note different Y-axis between drug classes

prescription rate for beta-blocking agents, antidiabetics, and statins was not affected by a prostate cancer diagnosis.

The total prescription rates varied between men with localized and non-localized disease for all drug classes apart from statins (Fig. 4). For analgesics, the total prescription

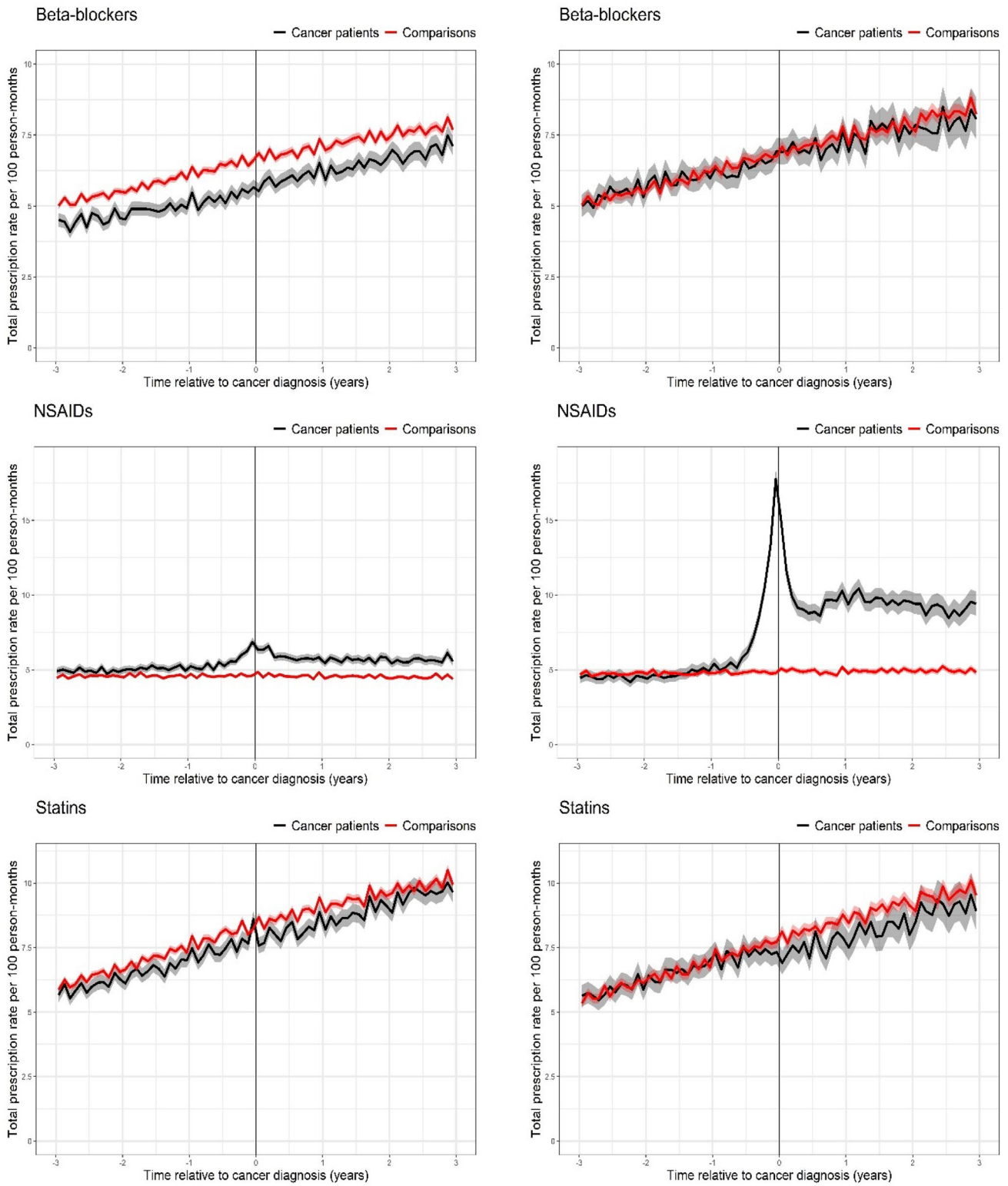


**Fig. 4** (continued)

rate among men with non-localized disease increased to 53.8 prescriptions per 100 person-months (95% CI 52.5–55.1) compared to 12.4 prescriptions per 100 person-months (95% CI 12.0–12.8) for men with localized disease in the first

month after diagnosis. The increased rate for men with non-localized disease was sustained three years after diagnosis. Regarding antidepressants, men with localized disease had a lower prescription rate up to one year after diagnosis, from where the rate aligned with that of the comparison cohort. For men with non-localized disease, the prescription rate of antidepressants was lower before diagnosis but increased and exceeded that of the comparisons shortly after diagnosis. Men with localized disease had a lower total prescription rate for beta-blocking agents than their comparisons both before and after diagnosis, whereas the rate did not differ between men with non-localized disease and their comparisons. The total prescription rate of antidiabetics was lower among men with localized and non-localized disease compared to their matched comparisons both before and after diagnosis, most pronounced among men with localized disease. The total prescription rate of NSAIDs increased before diagnosis for both localized and non-localized disease, and remained elevated throughout the three years, most noticeably among patients with non-localized disease.

## Discussion

Our analyses of new prescription rates among men with and without prostate cancer showed that incorporation of a lag-time period of one year before the diagnosis is adequate to avoid surveillance and protopathic bias in future pharmacoepidemiological studies investigating associations between commonly used drugs and prostate cancer risk and outcomes. Although a previous Danish study found that 6 months would be an appropriate lag-time period for most drug classes, our findings indicate, that the prescription rates start raising around 6 months and a lag-time of one year may therefore minimize the risk of surveillance biases [4]. Adding stratification by the stage of cancer at the time of diagnosis did not reveal any need for prolonging the lag-time period beyond one year based on clinical information. Our analyses of total prescription rates illustrated variations in patterns of drug use between the selected drug classes. For most drug classes, the prescription rate more than one year before diagnosis was lower among men with prostate cancer compared to the matched comparison cohort. After diagnosis, the total prescription rate increased among men with prostate cancer for analgesics, antidepressants, and NSAIDs which most likely can be explained by factors related to the cancer disease or diagnostic work-up. The lower total prescription rates before diagnosis among prostate cancer patients were to a large extent carried by patients with localized disease, whereas patients with a non-localized disease carried a major part of the increased prescription rate after diagnosis.

The rapid increase in new prescriptions within the year up to diagnosis could indicate widespread use of PSA-testing in men seeking their general practitioner for reasons other than prostate cancer, and diagnoses in this setting likely reflect the consequence of surveillance, especially among prostate cancer patients with localized disease. However, the increased rate of analgesics before a diagnosis is highly increased among patients with non-localized disease indicating that parts of these patients have presented with symptomatic disease. After diagnosis, the new prescription rate decreased to about the same level as among the comparisons, however, one drug class deviated from the overall trend. The use of antidepressants remained elevated at least three years after diagnosis. This finding aligns with previous results demonstrating an increased use of antidepressants among men undergoing diagnostic work-up and being diagnosed with prostate cancer [8–11].

Our findings regarding total prescription rates may indicate that men with prostate cancer, in general, are healthier than the background population, which we also have experienced in a previous study among men treated with radical prostatectomy [12]. Although systematic screening for prostate cancer has never been implemented in Denmark, better general health in this group of patients might be caused by more frequent testing in general practice among men with high socioeconomic position who are less likely to have concomitant morbidity compared to men with lower socioeconomic position [13–15]. After diagnosis, the total prescription rates either increased or stayed stabile for most drug classes. A decrease in the rate of total prescriptions could indicate discontinuation of drugs, but we did not observe any indication for this phenomenon.

Our study included more than 50,000 prostate cancer patients and almost 250,000 men in the comparison cohort. Due to the Danish civil registration system, we had complete follow-up of all included men and complete prescription history [16, 17]. A major strength is the possibility to stratify the analyses by the stage at the time of diagnosis. Prostate cancer patients with localized disease differ significantly from those with non-localized disease in many aspects and it is therefore important to gain knowledge on both patient groups. An important limitation of our study is the lack of information on indications for the prescriptions that prevents us from drawing any conclusion on the specific disease burden in the study populations. Almost 20% of the prostate cancer cases lack information on stage at time of diagnosis, which may affect the distribution of stage, but not the findings in the stratified analyses, since they are only compared to their own matched comparisons. We did not include information on treatment, which obviously can affect the prescription patterns after diagnosis. This might, however, in parts be reflected in the analyses stratified by stage at time of diagnosis. Recurrence

and progression may, as around diagnosis, affect the prescription patterns as well, but in the present study we focused on patterns around diagnosis and therefore only excluded by death and migration. Due to differences between cancer types, our findings among prostate cancer patients may not be comparable to other groups of cancer patients.

Based on our findings, we can conclude that a one-year lag-time period before a prostate cancer diagnosis is adequate to avoid effects of surveillance and protopathic bias, also among men with non-localized disease. We further observed that prostate cancer patients, in general, have lower prescription rates before diagnosis compared to the general population, which may indicate a general better health. In addition, we observed differences in the prescription rates between prostate cancer patients with localized and non-localized diseases indicating the importance of this including information on cancer stage in future pharmacoepidemiological studies of prostate cancer.

## Appendix

See Tables 2 and 3.

**Table 2** Definition of clinical stage

| Clinical stage | Clinical variable |
|---|---|
| Localized: classification until 2003 | Localized |
| Localized: TNM-codes | T1-4,x, and N0 and M0 |
| | T1-2 and N0,x and M0,x |
| Non-localized: classification until 2003 | Regional, metastatic |
| Non-localized: TNM-codes | T1-4,x and N1-3 and M0,x |
| | T1-4,x, and N0-3,x, and M1 |
| | T3-4 and Nx and Mx |

**Table 3** List of included drug classes

| ATC | Name of the drug class | Used drug names |
|---|---|---|
| C10AA | HMG CoA reductase inhibitors | Statins |
| M01A | Anti-inflammatory and antirheumatic products, non-steroids | NSAIDs |
| A10B | Blood glucose lowering drugs, excl. insulin | Antidiabetics |
| N06A | Antidepressants | Antidepressants |
| C07 | Beta blocking agents | Beta-blockers |
| N02 | Analgesics including salicylic acids | Analgesics |

**Author contributions** Study idea and design: SBL, CD, KB, AP, MAR, SF, AKDH. Statistical analyses: CD, AKDH. Writing manuscript: SBL, CS, KB, AKDH. Interpretation and critical review of the manuscript: SBL, CD, CS, SF, AP, MAR, KB, AKDH. All authors had read and approved the final version of the manuscript.

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**Data availability** Access to data can be obtained by request to the corresponding authors and the Danish data protection authorities.

**Code availability** The code can be obtained by request to the corresponding author.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** Not needed for register-based studies.

**Consent to participate** NA

**Consent for publication** All authors have approved the final version of the manuscript before submission.

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