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Pre-diagnostic prescription patterns in bladder and renal cancer: a longitudinal linked data study

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Abstract

Background

Understanding pre-diagnostic prescribing activity could reveal windows during which more timely cancer investigation and detection may occur.

Aim

To examine prescription patterns for common urological clinical features prior to renal and bladder cancer diagnoses.

Design and setting

We performed a retrospective cohort study using electronic primary care and cancer registry data on patients with bladder and renal cancer diagnosed between April 2012–December 2015 in England.

Method

We analysed primary care prescriptions up to 2 years pre-diagnosis for five groups of clinical features (irritative urological symptoms, obstructive symptoms, urinary tract infections, genital infections, atrophic vaginitis). Poisson regressions estimating the inflection point, from which the rate of prescriptions increased from baseline, were used to identify the start of diagnostic windows during which cancer could be detected.

Results

48,094 prescriptions for 5,322 patients were analysed. Inflection points for an increase in UTI prescriptions were identified 9 months pre-diagnosis for renal (CI:5.3–12.7) and bladder (CI:7.4–10.6) cancers. For bladder cancer, the change in UTI antibiotic prescription rates occurred four months earlier in women (11 months, CI:9.7–12.3) than men (7 months, CI:5.4–8.6). No inflection points were identified, and so no diagnostic windows could be defined, for other clinical features.

Conclusion

Prescription rates for UTIs increased 9 months before bladder and renal cancer diagnosis, indicating that there is potential to expedite diagnosis of these cancers in patients presenting with features of UTI. The greatest opportunity for more timely diagnosis may be in women with bladder cancer, who experienced the earliest increase in UTI prescription rate.

How this fits in

Previous studies have demonstrated that prescription rates for certain medications increase many months before the diagnosis of some cancers. Determining whether prescribing for common urological clinical features increases in patients with renal and bladder cancer could help us identify opportunities for more timely diagnosis. We found that prescription rates for UTI medications increased 9 months before bladder and renal cancer diagnosis, with an even earlier increase occurring before bladder cancer diagnosis in women (11 months). This indicates that there is a window of opportunity in which investigation and referral could lead to earlier cancer detection in some patients presenting to their GP with features of UTI.

Introduction

In the UK, around 13,000 and 10,000 people are diagnosed with renal and bladder cancer respectively each year.[1 2] The majority are diagnosed after they present with urological symptoms in general practice and are subsequently referred for specialist investigation.[3] Patients with bladder and renal cancer frequently present to primary care multiple times before diagnosis and studies have identified the presence of potential missed opportunities for timely detection.[4-6]

Clinical activities, such as primary care consultation rates and routine tests, can increase in patients many months prior to cancer diagnosis. These periods, particularly if prolonged, may represent 'windows' in which cancer can be detected earlier in some patients.[7] Understanding when and how clinical activities change during this period can help us determine the potential for more timely diagnosis.

Studies on colorectal cancer, Hodgkin lymphoma, lung cancer and all cancers have demonstrated increased rates of prescriptions pre-diagnosis, both in terms of certain specific medications and when all prescriptions were examined collectively.[8-12] We have previously examined pre-diagnostic primary care blood tests and secondary care imaging test patterns in bladder and renal cancer patients but are not aware of any studies exploring prescription patterns prior to the diagnoses of these malignancies.[13 14]

In this study, we examined patterns of relevant primary care prescriptions for urological symptoms and conditions in the 24 months before renal and bladder cancer diagnoses. We focused on medications used to treat symptoms (e.g. urgency, or irritative urological symptoms) or conditions (e.g. urinary tract infections) which may be a manifestation or concomitant feature of urological cancer. We aimed to identify 'inflection points'; time points from which changes in the rate of prescribing occurred, in order to define diagnostic windows during which opportunities to detect cancer earlier might exist.

Methods

Study design

We performed a retrospective cohort study using linked data from the Clinical Practice Research Datalink (CPRD) GOLD and Cancer Registry data, consisting of 5,322 patients with bladder, renal and upper tract urothelial cancer (UTUC) who were diagnosed between April 2012 and December 2015 in England. UTUC cancer was distinguished from the other two cancers as UTUC arises mostly from the renal pelvis, but presents more similarly to bladder cancer. Its distinction is to allow more reliable interpretation of the findings of the bladder and renal cancer cohorts, as the overall number of UTUC cases was small (N=209, 3.9%).

The cohort was a subset derived from a linked dataset containing patients with 11 common cancers identified from cancer diagnosis codes within CPRD. Patients were aged 25 years and over, with a first diagnosis of these cancers. The preparation of this cohort has been described previously.[13]

Prescription categories

We identified prescriptions recorded in CPRD in the 24 months pre-diagnosis, given that such changes have previously been noted as early as 18 months prior to cancer diagnosis.[7] We included prescriptions used to treat symptoms that might be related to renal and bladder cancer, or to conditions that might mimic these cancers. These include irritative (such as dysuria, urinary frequency and urgency) and obstructive urinary symptoms (such as hesitancy, poor stream, urinary retention). We also included prescriptions used to treat urinary tract infections (UTIs), genitourinary infections, and atrophic vaginitis, as there is a significant overlap between the symptom profiles of these conditions and those of renal and bladder cancer.

We defined medication categories in line with British National Formulary (BNF) treatment categories for five groups of clinical features (Table 1). Two general practitioners (GPs) (GF and YZ) reviewed all lists of medication to ensure relevance (Supplementary Material 1).

Table 1. Medication categories and rationale for inclusion.

Clinical feature examined	**Rationale**		**Medication category in BNF, and examples**	**Prescription dimension studied**	
	A*	**B^**		**Rate of prescription**	**Rate of 'first ever' prescription**
Irritative symptoms	X		**Anti-muscarinics**: oxybutynin hydrochloride, immediate release tolterodine tartrate, or darifenacin	X	X
Obstructive symptoms	X		**Alpha-blockers** (eg. Tamsulosin, doxazosin, alfuzosin) **Beta-agonists** **Alpha-reductase** (eg. Finasteride)	X	X
UTI		X	**Antibiotics** listed in BNF as a treatment for urinary tract infection or pyelonephritis. Examples: nitrofurantoin, trimethoprim. **Alkalysing agent**s used in the treatment of cystitis.	X	
Genital infections		X	**Antifungals** and **antibacterial** topical treatments	X	

Atrophic vaginitis		X	**Topical oestrogens**	X	X

BNF = British National Formulary.

**Symptoms related to bladder and renal cancer, or to conditions that might mimic these cancers*

^Conditions with symptoms which overlap with those of bladder and/or renal cancer

Analysis

We performed a descriptive analysis summarising: a) frequency and rate of prescription by clinical features, and b) frequency of 'first ever' prescriptions of three clinical features (irritative symptoms, obstructive symptoms and atrophic vaginitis) by examining historical prescription records (Table 1). The latter features often have a more gradual presentation and chronic history of progression, such as in urinary incontinence, benign prostatic disease or atrophic vaginitis. Therefore, an entirely new prescription type could signify the onset of a new symptom. As in previous studies, we excluded prescriptions issued in the month before diagnosis from our analyses, due to the likelihood that these patients would have already entered the final stage of the diagnostic process for cancer.[13]

Next, we constructed a series of multi-level Poisson regression models, adjusting for age, to identify the most likely month (28-day period, resulting in 26 such 'periods' over two years) when cohort-level rates of prescriptions increased above baseline. The models were based on the concept of Joinpoint regression which examined for discontinuity in trends.[15 16] This approach has been used in our previous studies examining pre-diagnostic pattern of health care events.[13 14 17] Each model included a variable to account for the background rate, which increased from 0 at 2 years pre-diagnosis to 24 in the period before diagnosis. Separate "inflection month" variables captured any deviation from the background trend, with separate models for each possible month of inflection. This inflection variable was held at 0 for all months prior to the inflection month for that model and then increased by one each month up to diagnosis. The model with the largest log likelihood was considered the best-fitting model, and the corresponding month for its included inflection point noted. Confidence intervals for this month were then estimated via bootstrapping. We discounted inflection points where confidence intervals spanned either the diagnosis date or the study start date (two years pre-diagnosis). A detailed explanation of the method has been published.[18]

We considered bladder, renal cancer and UTUC separately in the analysis because they can present differently and therefore associated prescriptions may differ. Inflection points were estimated for all combined prescriptions for each clinical feature (e.g. antibiotics and alkalysing agents collectively for UTI) and medication category (i.e. antibiotics and alkalysing agents separately), as grouped in Table 1. Given prior evidence on the potential sex inequality and contribution of UTI in the timeliness of bladder cancer diagnosis[4-6 19 20], we described rates of prescriptions separately for men and women, and performed a further analysis examining the inflection point for UTI prescriptions by sex.

All analyses were performed in STATA/IC 16.1. Graphs were drawn using R and the *ggplot* package.

Results

We included 5,322 patients with linked CPRD and Cancer Registry data. 48,094 prescriptions up to 2 years pre-diagnosis from 3,398 (64%) bladder, 1,715 (32%) renal cancer and 209 (4%) UTUC patients were examined (Table 2).

Prescription for different clinical features

Between 60-63% of all prescriptions were for the five examined clinical features (i.e. relevant prescriptions). The average number of relevant prescriptions 2 years pre-diagnosis were 5 and 6 for women and men respectively. In patients with bladder and renal cancer, most prescriptions in women were for UTI (61% and 52% for bladder and renal cancer respectively), and for obstructive symptoms in men (65% and 68% for bladder and renal cancer respectively).

First ever prescriptions

32% of women and 44% of men had a first ever prescription for at least one of the three studied "chronic" features (irritative symptoms, obstructive symptoms and atrophic vaginitis), in the 2 years pre-diagnosis. A large proportion of women (40%) and men (46%) with bladder cancer received a first ever prescription for irritative and obstructive symptoms respectively in the two years before diagnosis. This pattern was not seen for renal cancer, with 8% and 32% of women and men receiving first ever prescriptions for irritative and obstructive symptoms pre-diagnosis.

Table 2: Background characteristics of patients by cancer site and sex

	Bladder cancer N=3398		**Renal cancer N=1715**		**Upper UTUC N=209**		**Overall N=5322**	
	female	**male**	**female**	**male**	**female**	**male**	**female**	**male**
	N=941	**N=2457**	**N=649**	**N=1066**	**N=88**	**N=121**	**N=1678**	**N=3644**
Age group *								
<35	4 (0.4%)	7 (0.3%)	7 (1.1%)	10 (0.9%)	0 (0%)	0 (0%)	11 (0.7%)	17 (0.5%)
35-44	22 (2.3%)	37 (1.5%)	34 (5.2%)	39 (3.7%)	1 (1.1%)	2 (1.7%)	57 (3.4%)	78 (2.1%)
45-54	59 (6.3%)	130 (5.3%)	76 (11.7%)	151 (14.2%)	3 (3.4%)	15 (12.4%)	138 (8.2%)	296 (8.1%)
55-64	135 (14.3%)	367 (14.9%)	127 (19.6%)	240 (22.5%)	17 (19.3%)	18 (14.9%)	279 (16.6%)	625 (17.2%)
65-74	281 (29.9%)	801 (32.6%)	189 (29.1%)	326 (30.6%)	30 (34.1%)	44 (36.4%)	500 (29.8%)	1171 (32.1%)
75-84	298 (31.7%)	810 (33.0%)	137 (21.1%)	225 (21.1%)	27 (30.7%)	29 (24.0%)	462 (27.5%)	1064 (29.2%)
85+	142 (15.1%)	305 (12.4%)	79 (12.2%)	75 (7.0%)	10 (11.4%)	13 (10.7%)	231 (13.8%)	393 (10.8%)
Number of prescriptions up to 2 years pre-diagnosis	33,421		12,881		1,792		48,094	
Total ^	7,136 (21.4%)	26,285 (78.6%)	3,471 (26.9%)	9,410 (73.1%)	716 (40.0%)	1,076 (60.0%)	11,323 (23.5%)	36,771 (76.5%)
Per patient	7.8	10.7	5.3	8.8	3.4	8.9	6.7	10.1

Number of relevant prescriptions (by clinical feature)	20,704		7759		1126		29,265	
Total by cancer/sex [+]	5,377 (75.4%)	15,327 (58.3%)	2,422 (69.8%)	5,337 (56.7%)	491 (68.6%)	635 (59.0%)	7,966 (70.4%)	21,299 (57.9%)
Prescription per patient	5.7	6.2	3.7	5.0	5.6	5.2	4.7	5.8
Irritative symptoms	1,117 (20.8%)	1,148 (7.5%)	474 (19.6%)	484 (5.1%)	185 (37.7%)	33 (5.2%)	1,776 (22.3%)	1,665 (7.8%)
Obstructive symptoms	658 (12.2%)	9,991 (65.2%)	575 (23.7%)	3,635 (68.1%)	40 (8.1%)	417 (65.7%)	1,273 (16.0%)	14,043 (65.9%)
UTI	3,261 (60.6%)	4,080 (26.6%)	1,251 (51.7%)	1,176 (22.0%)	241 (21.4%)	180 (28.3%)	4,753 (59.7%)	5,436 (25.5%)
Atrophic vaginitis	116 (2.2%)	0 (-)	41 (1.7%)	0 (-)	7 (0.6%)	0 (-)	164 (2.1%)	0 (-)
Genital infections	225 (4.2%)	108 (0.7%)	81 (3.3%)	42 (0.9%)	18 (3.7%)	5 (0.8%)	324 (4.1%)	155 (0.7%)
First prescription*								
For at least one of the three features below	440 (46.8%)	1224 (49.8%)	68 (10.5%)	356 (33.4%)	25 (28.4%)	36 (29.8%)	533 (31.8%)	1616 (44.3%)
Irritative symptoms	375 (39.9%)	464 (18.9%)	52 (8%)	108 (10.1%)	15 (17%)	18 (14.9%)	442 (26.3%)	590 (16.2%)
Obstructive symptoms	85 (9%)	1132 (46.1%)	24 (3.7%)	336 (31.5%)	15 (17%)	24 (19.8%)	124 (7.3%)	1492 (40.9%)
Atrophic vaginitis	155 (16.5%)	0 (-)	12 (1.8%)	0 (-)	5 (5.7%)	0 (-)	172 (10.3%)	0 (-)

^ percentages represent the proportion of total prescriptions for each cancer attributed to male and female patients.
[+] percentages represent the proportion of total relevant prescriptions for each cancer attributed to male and female patients
** percentages represent the proportion of patients in this category with a corresponding prescription*

Rates of prescriptions before diagnosis

Across all three cancer types, there was an increase in the rate of prescriptions for UTIs in both sexes in the year before diagnosis (Figure 1). In patients with bladder cancer, there was a slight increase in the rate of prescriptions for irritative and obstructive symptoms, as well as for genital infections and atrophic vaginitis in women in this year. In patients with renal cancer, there was an increase in prescription rate for obstructive symptoms, particularly in men.

Inflection point estimates

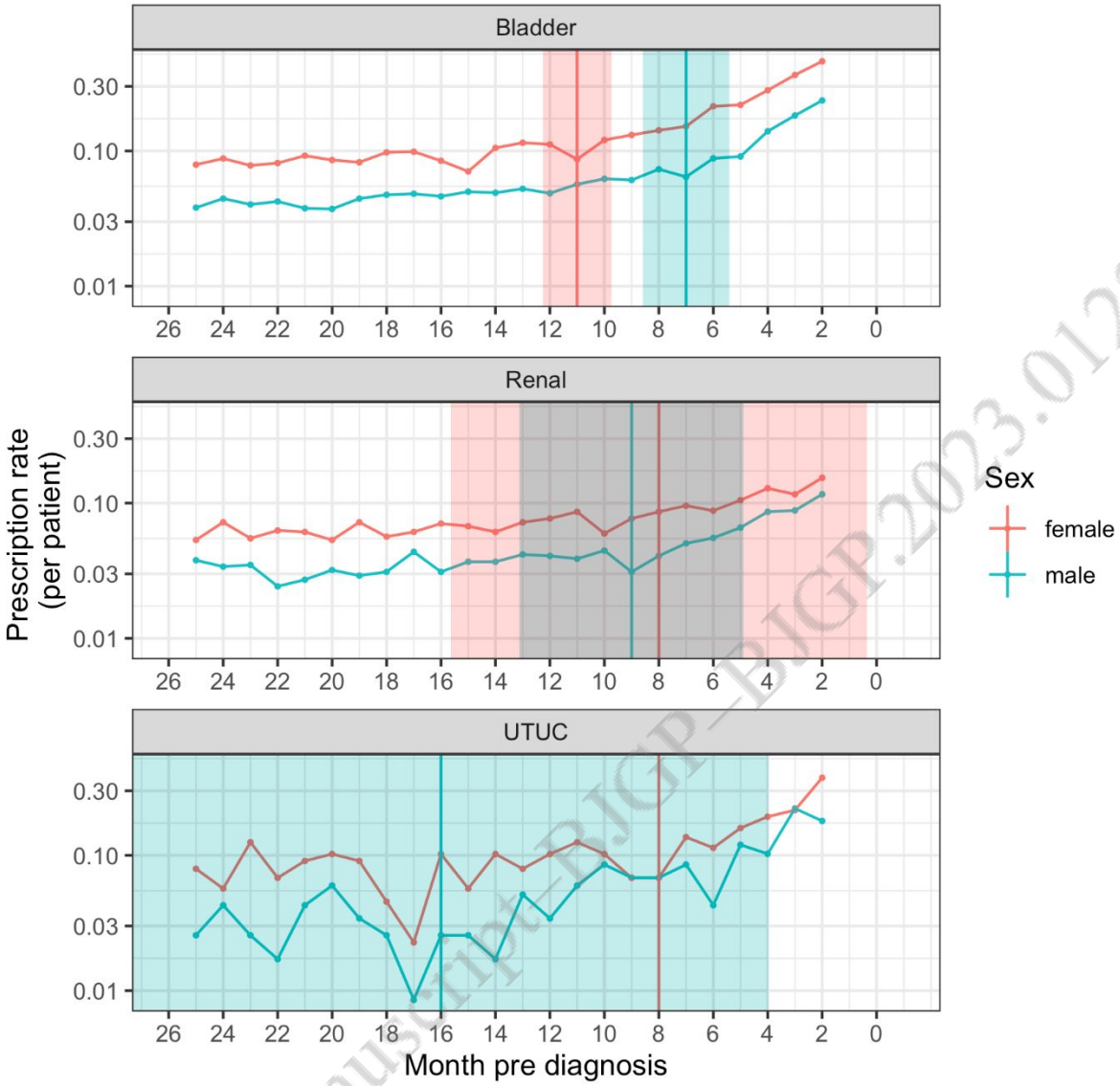
Inflection points were identified for UTI prescriptions in bladder and renal cancer, indicating an increase in rate of prescriptions above baseline at 9 months for bladder (CI 7.4–10.6) and renal cancer (CI 5.3–12.7) (Figure 1). Inflection points were identified for alpha-blockers in bladder cancer, and anti-muscarinics, antibiotics and topical anti-fungals in UTUC (Supplementary Material 2). However, confidence intervals for these estimates were wide and crossed the 24-months pre-diagnosis point so no pre-diagnostic windows could be defined.

Figure 1: Rate of prescriptions before diagnosis by cancer site, clinical feature and sex

**red line denotes the presence of an estimated inflection point with the intervals representing the confidence interval around the estimate (both sexes combined).*

When examining UTI antibiotic prescriptions by sex, for bladder cancer, women had an earlier inflection point at 11 months (CI 9.7–12.3) compared to 7 months (CI 5.4–8.6) for men (Figure 2). In patients with renal cancer, there was a smaller difference in the inflection point estimates, with men (9 months, CI 4.9–13.1) having an earlier infection point than women (8 months, 0.4–15.6).

Figure 2: Antibiotics prescription rates by sex for each cancer site



** Red line and red shaded area denote inflection point and confidence intervals for women, blue line and blue shaded area denote inflection point and confidence intervals for men. Grey shaded area denote overlapping confidence interval for men and women with renal cancer.*

Rate of first-ever prescriptions

When examining 'first-ever' prescriptions for conditions that might be more chronic, there was an increase in the number of alpha-blockers prescribed in male patients with bladder and renal cancer pre-diagnosis but no pre-diagnostic window could be defined (Supplementary Material 3).

Discussion

Summary

Our study found evidence for an increase in the rate of prescriptions for UTIs from baseline 9 months before diagnosis of renal and bladder cancer. An earlier infection point for UTI antibiotic prescriptions was noted in women than in men (11 vs 7 months) prior to bladder cancer diagnosis. No pre-diagnostic windows could be defined using prescriptions for other clinical features. Our findings demonstrate that some patients are receiving increasing numbers of prescriptions for apparent UTI, which may indicate underlying cancer, many months prior to cancer diagnosis. This indicates that opportunities exist to perform cancer investigations and initiate referrals earlier within the diagnostic window to expedite diagnoses for some patients.

Strengths and limitations

This study uses a large, routinely collected, representative dataset from primary care and the cancer registry. Important strengths are that the quality of prescription data in CPRD is high, as prescriptions are not subject to manual coding, and that we used cancer registry data (which reports high levels of case ascertainment and diagnosis date accuracy) to confirm study participants and cancer diagnosis dates for linked cases (around half of the cohort).

Although we only included patients with confirmed cancer, the use of 2 years of data allowed estimation of inflection points relative to a baseline trend without data from non-cancer controls. Bootstrapping allowed estimation of 95% CIs, which are more informative than point estimates alone. This direct maximum likelihood method is less prone to bias than similar methods when examining changes in rates of clinical events.[18] For the purposes of this study, having controls would have added little other than to account for general trends in prescribing in the primary care population over time. We used data from patients diagnosed up to December 2015. Prescribing practices may have changed since, particularly during the COVID pandemic period and further research would be needed to examine the impact of this on inflection points. However, as we grouped prescriptions by clinical feature, changes in the types of medication prescribed by GPs (e.g. if one antibiotic becomes more widely used than another) would not affect our results.

A Limitation of this study is that we were not able to determine the exact indication for each prescription or whether the medications were taken by patients. However, the aim was to examine trends in prescribing rather than reasons for prescriptions or medication concordance.

Comparison with existing literature

A recent systematic review identified 28 studies exploring different aspects of clinical activity in primary care prior to cancer diagnosis.[7] Four studies examined prescription patterns, two of which focussed on colorectal cancer, one on lung cancer and one on all cancers. Our findings provide evidence that prescription rates also increase prior to bladder and renal cancer diagnosis but that these changes only appear to occur for some medication types, notably antibiotics for UTI. The period pre-diagnosis over which significantly increased prescription rates were detected in previous studies ranged from 6 up to 18 months. This is comparable to our findings where changes were noted at 9 months for UTI prescriptions.

Our finding that prescriptions for UTI antibiotics increase in the year before diagnosis is in line with current evidence indicating that opportunities to expedite diagnosis in patients with UTIs exist. In particular, the rate of increase of UTI antibiotic prescriptions started earlier in women than men with bladder cancer, suggesting that the propensity to improve diagnostic timeliness is greater in women. This further substantiates current evidence which indicate that women with bladder cancer experienced longer diagnostic intervals than men,[19 21-23] and that they were more likely to receive multiple courses of antibiotics for UTIs before cancer diagnosis.[24]

Implications for research and practice

The findings that prescribing for UTIs increases in the year prior to bladder and kidney cancer diagnosis provides evidence that there is an opportunity to improve diagnostic timeliness in some patients with UTI presentations, more so in women than men.

The sex inequality with respect to prescription patterns for UTI antibiotics was most notable for bladder cancer, with prescription rates increasing earlier in women than men by four months. This difference is less for renal cancer, with men having an earlier increase in UTI antibiotic prescriptions (by one month) than women. Our findings substantiate evidence that the sex inequality seen in diagnostic timeliness mainly relate to bladder cancer. This may represent a genuine increase in the frequency of UTI episodes pre-diagnosis (as indicated by the increase in UTI prescriptions), and/or in the symptomatic presentation of bladder cancer mimicking UTI symptoms. The relatively high percentages of female bladder cancer patients in our study who were given a first-ever prescription for irritative symptoms, and obstructive symptoms in men, suggests that besides UTI, bladder cancer may present with other symptoms, and differently in men and women.

It is likely that women with bladder cancer are being prescribed more courses of antibiotics than men before diagnosis. Although some cases may represent genuine concomitant UTI and bladder cancer, the increased use of UTI antibiotics may explain some of the observed delay in referral found in women in other studies.[6 20 25]

Lastly, the observed sex inequality in prescribing pattern in our study can be related to clinicians' perception that many urological symptoms in women may be due to UTIs (given their commonality in women), clinicians' higher threshold for referring women due to their known lower risk of bladder cancer than men, and preference to use antibiotics as a 'trial of treatment' for some symptoms. Furthermore, current referral guidelines from the National Institute for Health and Care Excellence (NICE) for suspected cancer in patients recommends clinicians to consider a routine specialist referral in patients with recurrent or persistent UTIs.[26] The lack of definitive number of UTI episodes, and firm recommended action by the guidelines, may further contribute to inconsistent clinical practice.[27]

Besides UTI prescriptions, there is a slight increase in first ever prescriptions of alpha-blockers in male bladder and renal cancer patients (Supplementary Figure 3), suggesting that men might be presenting more with obstructive or lower urinary tract symptoms in the year before diagnosis. Further research confirming the concordance between prescriptions and clinical codes could shed light on the true indication of these prescriptions.

It is possible that changes in prescription patterns, such as increase in frequency of antibiotics for UTI symptoms, could act as an alert for GPs to consider bladder, renal and UTUC malignancies in individual patients. Further research is needed to determine the predictive value of such changes alone and alongside other predictors of undiagnosed cancer. Future research should examine the predictive value of increases in UTI antibiotic prescriptions and the value of different risk stratifying strategies for improving management of UTIs in patients at risk of urological cancer.

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Ethical approval:

A research protocol (17_107R) was submitted to and approved by the CPRD Independent Scientific Advisory Committee before the study was conducted. This study is a secondary analysis of anonymised patient data.

Competing interest:

All authors have no competing interests.

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