Cancer Epidemiology 86 (2023) 102429

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Pre-diagnostic prescribing patterns in dyspnoea patients with as-yet-undiagnosed lung cancer: A longitudinal study of linked primary care and cancer registry data

Bethany Wickramasinghe [a,*], Cristina Renzi [a], Matthew Barclay [a], Matthew E.J. Callister [b], Meena Rafiq [a], Georgios Lyratzopoulos [a]

[a] Epidemiology of Cancer Healthcare & Outcomes (ECHO) Group, Dept. of Behavioural Science & Health, Institute of Epidemiology and Health Care (IEHC), University College London, United Kingdom
[b] Department of Respiratory Medicine, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

ARTICLE INFO

Keywords:
Lung cancer
COPD
Diagnostic window
Pre-diagnostic prescribing
Primary care

ABSTRACT

Introduction: Patients with as-yet undiagnosed lung cancer (LC) can present to primary care with non-specific symptoms such as dyspnoea, often in the context of pre-existing chronic obstructive pulmonary disease (COPD). Related medication prescriptions pre-diagnosis might represent opportunities for earlier diagnosis, but UK evidence is limited. Consequently, we explored prescribing patterns of relevant medications in patients who presented with dyspnoea in primary care and were subsequently diagnosed with LC.

Method: Linked primary care (Clinical Practice Research Datalink) and National Cancer Registry data were used to identify 5434 patients with incident LC within a year of a dyspnoea presentation in primary care between 2006 and 2016. Primary care prescriptions relevant to dyspnoea management were examined: antibiotics, inhaled medications, oral steroids, and opioid analgesics. Poisson regression models estimated monthly prescribing rates during the year pre-diagnosis. Variation by COPD status (52 % pre-existing, 36 % COPD-free, 12 % new-onset) was examined. Inflection points were identified indicating when prescribing rates changed from the background rate.

Results: 63 % of patients received 1 or more relevant prescriptions 1–12 months pre-diagnosis. Pre-existing COPD patients were most prescribed inhaled medications. COPD-free and new-onset COPD patients were most prescribed antibiotics. Most patients received 2 or more relevant prescriptions. Monthly prescribing rates of all medications increased towards time of diagnosis in all patient groups and were highest in pre-existing COPD patients. Increases in prescribing activity were observed earliest in pre-existing COPD patients 5 months pre-diagnosis for inhaled medications, antibiotics, and steroids,

Conclusion: Results indicate that a diagnostic window of appreciable length exists for potential earlier LC diagnosis in some patients. Lung cancer diagnosis may be delayed if early symptoms are misattributed to COPD or other benign conditions.

1. Introduction

Lung cancer outcomes remain poor [1]. Most lung cancers are diagnosed at advanced stage [2]. Diagnosis after GP referral is associated with earlier stage diagnosis and better survival [3]. According to National Institute for Health and Care Excellence (NICE) recommendations, patients with "red flag" symptoms such as haemoptysis should be referred via urgent "two-week-wait" pathways for specialist diagnostic assessment. However, approximately half of lung cancer patients present with non-specific (non-alarm) symptoms [4], often experiencing longer pathways to diagnosis [5]. Cough and dyspnoea can represent signs of underlying lung malignancy [6]. However, cough is common in the general population [7], and both cough and dyspnoea can mimic Chronic Obstructive Pulmonary Disease (COPD) [8]. Consequently, only 28 % of lung cancers are currently diagnosed via urgent "two-week-wait" GP referral pathways, and 21 % following a non-urgent GP referral [9]. Improvements in the diagnostic process are needed for these patient groups.

* Corresponding author.
E-mail address: bethany.wickramasinghe.19@ucl.ac.uk (B. Wickramasinghe).

https://doi.org/10.1016/j.canep.2023.102429
Received 29 March 2023; Received in revised form 10 July 2023; Accepted 13 July 2023
Available online 19 July 2023
1877-7821/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

The term "diagnostic (time) window" describes the earliest point in time before diagnosis when a change is observed in a relevant clinical event type [10]. Diagnostic windows can only be estimated at the population level as opposed to individual patients. Intervention during the diagnostic window could possibly reduce time to diagnosis, though this potential is predicated on the availability and use of diagnostic tests. Studies show that some patients present with symptoms of as-yet-undiagnosed cancer months before their diagnosis, indicating opportunities for earlier diagnosis from 6 to 24 months pre-diagnosis [11–17].

Examining patient medication history is a promising approach to achieving earlier diagnosis. When cancer is not suspected, medication is often prescribed, sometimes expectantly. Many patients with symptoms of as-yet-undiagnosed-lung cancer are prescribed medicines before their diagnosis [18], including inhaled medication used in COPD, oral antibiotics, or opioids [14,19]. Published research has not considered symptomatic presentation or UK data. We therefore aimed to examine pre-diagnostic prescribing patterns among patients who presented with dyspnoea and were subsequently diagnosed with lung cancer. We selected dyspnoea as a relevant respiratory symptom which is not cancer-specific but often requires appropriate clinical management including prescription medication, independently of whether the patient is further investigated. Unlike cough, dyspnoea is not as self-limiting or easily managed with over-the-counter medication. We aimed to understand whether prescribing patterns could define diagnostic windows for earlier cancer diagnosis, and explore variability between clinically relevant patient groups.

2. Methods

We investigated prescribing patterns for patients with dyspnoea recorded in primary care between 1/1/2006 and 31/12/2015 who received a lung cancer diagnosis up to a year after a dyspnoea presentation (Fig. 1).

2.1. Data sources and aggregation

Patient level primary care data from the UK Clinical Practice Research Datalink (CPRD) GOLD (March 2019 database build) was deterministically linked to UK cancer registry data by NHS number, sex, date of birth, and postcode [20,21]. During the study period, CPRD covered between 5 % and 10 % of all UK practices [20]. Coded information on consultations, diagnoses, prescriptions, and referrals are available for patients included in CPRD practices. The UK Cancer Registry is a national register of all UK cancer patients, including information on the patient, their diagnosis, tumour, and cancer-treatment events.

2.2. Cohort selection

Patients actively registered with a CPRD practice during the study period who were over 40 years old were eligible for inclusion. Patients with a dyspnoea presentation recorded in CPRD within the study period, with a new lung cancer diagnosis (ICD-10 code C34) recorded within 12 months of a dyspnoea presentation, and still alive at diagnosis were identified. Patients with a lung cancer diagnosis recorded within a year of registering at their GP practice were excluded to ensure at least one year of primary care records pre-cancer diagnosis were available. Prescriptions recorded up to 12 months before a lung cancer diagnosis that followed or accompanied a dyspnoea presentation were identified, with duplicate prescriptions of the same medication on the same day removed. Medications relevant to dyspnoea management were retained and then classified (Fig. 2).

Fig. 1. Defining the study population.

2.3. Study variables

Linked demographic and socioeconomic information (determined using The Index of Multiple Deprivation (IMD) quintile of patient neighbourhood of residence) for all patients were extracted on age, sex, and socioeconomic status of a patients' registered GP practice.

2.4. COPD status

COPD is common among lung cancer patients, as both conditions are strongly related to smoking [22]. COPD and lung cancer share symptoms including dyspnoea [23]. Patients were therefore characterised by COPD status ("COPD-free" during the 6 years pre-cancer diagnosis, "pre-existing COPD" records in primary care longer than 12 months and up to 6 years before lung cancer diagnosis, "new-onset COPD" [24] where COPD records in primary care occurred 12 months before lung cancer diagnosis only.) (Appendix A1).

2.5. Medication classification

Medications were classified into one of four categories based on their relevance to dyspnoea management and prior literature [18,25]: 1) antibiotics, 2) oral steroids, 3) inhaled respiratory medications comprising bronchodilators and/or steroids, 4) opioids. Relevant BNF indications guided a priori definitions to best reflect clinical management of dyspnoea (Appendix A2).

2.6. Statistical analysis

We examined the prescribing frequency of each medication group of interest per patient group and per month pre-diagnosis (created by splitting the 365 days pre-diagnosis into 12 equal periods of 30.42 days each). Consistent with prior literature, the last month (30.42 days) pre-cancer diagnosis was excluded as it likely reflects the final stage of the diagnostic process for possible cancer [13,14,19,26–28]. Poisson regression models adjusted for age and sex estimated monthly prescribing rates and incidence rate ratios (IRRs) of each medication and patient group up to a year pre-diagnosis. IRRs were calculated using the prescribing rate at 12 months pre-diagnosis as baseline.

For each patient group, we estimated inflection points at which the prescribing rate of each medication group increased above baseline. Poisson models described prescribing rates over the 12 months pre-diagnosis. Ten such models were sequentially fitted, corresponding to each potential inflection point occurring at any month pre-diagnosis (excluding months 1 and 12 due to collinearity). Each model included the month-on-month baseline trend, the post-inflection deviation from the baseline trend, and adjustment for patient age and sex. Robust standard errors clustered per patient were used. As 4 medication groups and 3 patient groups were investigated, 4 sets of 10 Poisson models were fitted for each patient groups. Each model included data across the whole 10-month pre-diagnostic period per patient group. The inflection point from the best fitting model (with the largest log likelihood) was taken as the best point estimate of the start of the diagnostic window for each patient-medication stratum. Bootstrapping provided confidence intervals around each inflection point (Appendix A3).

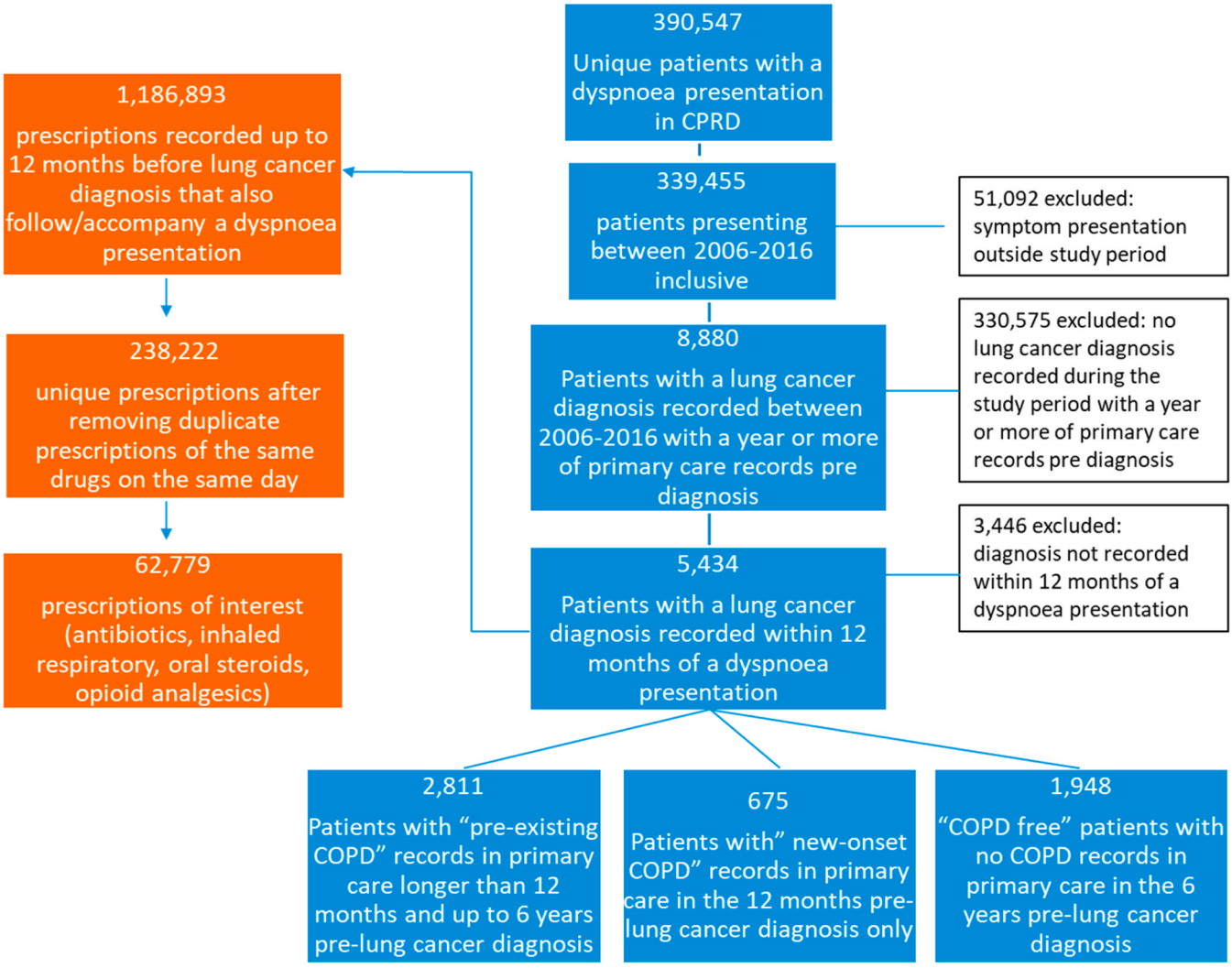

Fig. 2. Cohort selection: inclusion criteria combinations and related exclusions.

3. Results

3.1. Patient characteristics

5434 patients (55 % male) met our inclusion criteria of having an incident lung cancer diagnosis within a year of presenting to primary care with dyspnoea. Median age at diagnosis was 73 years in male (IQR: 66,79) and 72 in female patients (IQR: 65,79). 2811 patients (52 %) were classified as having "pre-existing" COPD, 1948 COPD-free (36 %), and 675 "new onset" COPD (12 %) in the 12 months pre-lung cancer diagnosis (Table 1).

3.2. Prescribing activity

3445 (63 %) patients received at least one prescription of a relevant medication in the 12 months pre-diagnosis. 728 (37 %) COPD-free patients received at least one prescription of interest during this time compared to 397 (59 %) new-onset COPD and 2320 (83 %) pre-existing COPD patients. The most commonly prescribed medication among COPD-free and new onset-COPD patients was antibiotics (17 %, N = 333 % and 36 %, N = 246 respectively), and among COPD patients was inhaled medications (71 %, N = 1986). Of the 3445 (63 %) patients who had at least one prescription, 3100 (57 %) received 2 or more prescriptions of any of the 4 classes of medications of interest (Table 2).

Table 1
Patient characteristics.

	All patients		Women		Men	
	N	%*	N	%*	N	%*
Total	5434		2419	44.52	3015	55.48
Age						
40–60	131	2.41	72	2.98	59	1.96
61–70	560	10.31	268	11.08	292	9.68
71–80	1624	29.89	724	29.93	900	29.85
80+	3119	57.40	1355	56.01	1764	58.51
Median (IQR)	73 (65–70)		72 (65–79)		73 (66–79)	
COPD status						
Pre-existing COPD	2811	51.73	1270	52.50	1541	51.11
New onset COPD	675	12.42	289	11.95	386	12.80
COPD Free	1948	35.85	860	35.55	1088	36.09
Deprivation Index Quintile						
1	960	17.67	410	7.55	550	10.12
2	1021	18.79	435	8.01	586	10.78
3	1102	20.28	475	8.74	627	11.54
4	1125	20.70	514	9.46	611	11.24
5	1225	22.54	585	10.77	640	11.78
Unknown	1	0.02	0	0.00	1	0.02

*Column %s displayed

Table 2
Descriptives.

	Prescriptions during the 12 months preceding lung cancer diagnosis							
	All patients		COPD Status					
			COPD-free		Pre-existing COPD		New onset COPD	
	N	%*	N	%*	N	%*	N	%*
Total	5434		1948		2811		675	
Any prescription of interest								
0	1989	36.60	1220	62.63	491	17.47	278	41.19
1	345	6.35	210	10.78	92	3.27	43	6.37
2 +	3100	57.05	518	26.59	2228	79.26	354	52.44
mean	20		10		21		10	
Antibiotics								
0	2996	55.13	1615	82.91	952	33.87	429	63.56
1	178	3.28	73	3.75	71	2.53	34	5.04
2 +	2260	41.59	260	13.35	1788	63.61	212	31.41
mean	7		4		8		4	
Oral steroids								
0	4424	81.41	1855	95.23	1969	70.05	600	88.89
1	19	0.35	8	0.41	7	0.25	4	0.59
2 +	991	18.24	85	4.36	835	29.70	71	10.52
mean	8		10		8		3	
Inhaled respiratory								
0	2978	54.80	1718	88.19	825	29.35	435	64.44
1	109	2.01	36	1.85	44	1.57	29	4.30
2 +	2347	43.19	194	9.96	1942	69.09	211	31.26
mean	25		12		26		12	
Opioid analgesics								
0	3964	72.95	1710	87.78	1691	60.16	537	79.56
1	68	1.25	33	1.69	26	0.92	9	1.33
2 +	1402	25.80	205	10.52	1094	38.92	129	19.11
mean	15		11		16		11	

*Column %s displayed

3.3. Prescribing rates over time

Monthly prescribing rates of all medications increased during the year before cancer diagnosis in all patient groups. Antibiotic, steroid, and inhaled medication prescribing rates were consistently highest amongst pre-existing COPD patients. Larger increases in prescribing activity were observed in new-onset COPD and COPD-free patients. For example, antibiotic prescribing in new-onset COPD and COPD-free patients increased 13-fold and 11-fold respectively from baselines of approximately 50 and 57 prescriptions per 1000 patients respectively at 12 months pre-diagnosis, to 661 and 614 prescriptions per 1000 people respectively at 1 month pre-diagnosis (new-onset COPD IRR 13.25, 95 % CI: 7.83–22.38, $p < 0.001$; COPD-free IRR 10.94, 95 %CI 7.38–16.23, $p < 0.001$). In contrast, pre-existing COPD patients received 235–554 prescriptions per 1000 people between 12 and 1 months pre-diagnosis (IRR 2.37, 95 %CI:2.12–2.64, $p < 0.001$). Similarly, inhaled medication prescribing in new-onset COPD and COPD-free patients increased 11-fold and 4-fold respectively from baselines of approximately 87 and 190 prescriptions per 1000 patients respectively at 12 months pre-diagnosis, to 972 and 813 prescriptions per 1000 patients respectively at 1 month pre-diagnosis (new-onset COPD IRR 11.25, 95 %CI: 7.47–16.94, $p < 0.001$; COPD-free IRR 4.32, 95 %CI 3.26–5.72, $p < 0.001$). In contrast, pre-existing COPD patients received approximately 736 – 1003 prescriptions per 1000 patients between 12 and 1 months pre-diagnosis (IRR 1.37, 95 %CI:1.28–1.47, $p < 0.001$) (Fig. 3).

3.4. Diagnostic windows

Among all patients, inflection points were observed in the year pre-diagnosis for each medication group. Considering individual patient groups, there was evidence of an inflection point for all four medication groups for pre-existing COPD and COPD-free patients. In new-onset COPD patients, there was evidence of an inflection for antibiotic and opioid prescribing ($P < 0.001$, Appendix 5). Confidence intervals around inflection points for new-onset COPD patients were generally wide. The earliest increase in prescribing activity with greatest certainty (indicated by small confidence intervals) was observed for inhaled medications in pre-existing COPD patients (5 months pre-diagnosis, 95 % CI: 6, 5 months pre-diagnosis), antibiotics in pre-existing COPD patients (5 months pre-diagnosis, 95 % CI: 5, 3 months pre-diagnosis), antibiotics in COPD-free patients (5 months pre-diagnosis, 95 % CI: 6, 4 months pre-diagnosis), and steroids in pre-existing COPD patients (5 months pre-diagnosis, 95 % CI: 6, 3 months pre-diagnosis). The earliest increase in opioid prescribing was observed for new-onset COPD patients (4 months pre-diagnosis) but with wide uncertainty (95 % CI: 5, 1 months pre-diagnosis). 95 % confidence intervals around inflection points identified for each patient group overlapped for each medication group (Appendix A5, Fig. 3).

4. Discussion

4.1. Summary

Antibiotic, oral steroid, inhaler, and opioid prescribing increased during the year preceding lung cancer diagnosis in patients presenting with dyspnoea. Prescribing rates were highest in pre-existing COPD patients, but larger relative increases were observed in new-onset COPD and COPD-free patients. Increased prescribing activity commenced as early as 5 months pre-diagnosis, defining the start of a diagnostic window wherein the potential for a timelier diagnosis would exist in principle.

4.2. Strengths, limitations, and comparison with previous literature

To our knowledge this is the first UK study to examine prescribing for dyspnoea patients in the year pre-lung cancer diagnosis. Prescriptions information had high levels of completeness [20,29–31], and the UK cancer registry provided high validity cancer diagnosis data. [21,32].

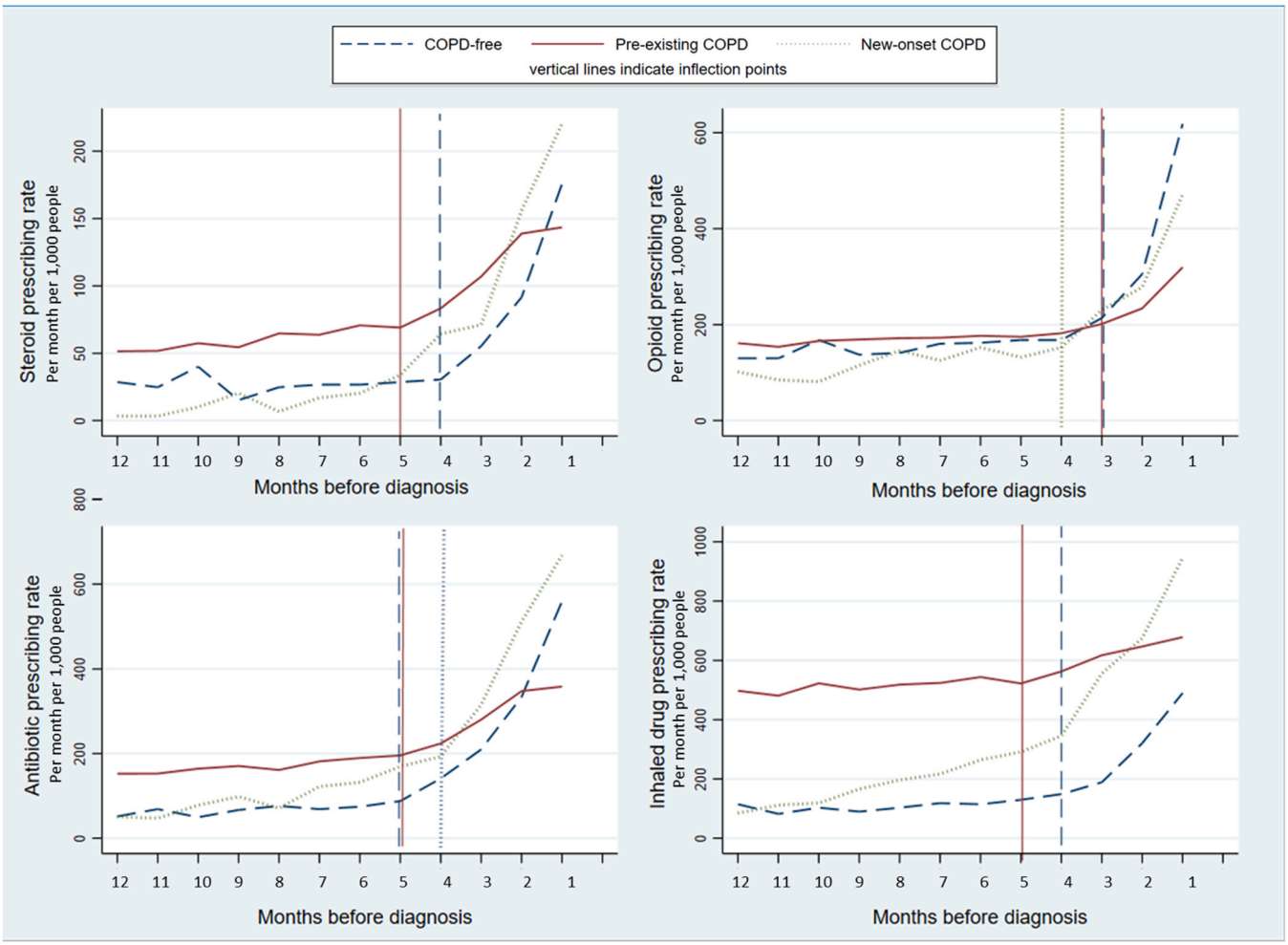

Fig. 3. Prescribing rates during the year pre lung cancer diagnosis.

General antibiotic utilisation rates in UK primary care practices changed little during the study period. Any resulting biases from such secular changes (relating to antibiotic prescriptions) are unlikely to be large [33]. CPRD is representative of the UK population [34], and documents high accuracy for identifying COPD patients [29] supporting the external validity of our findings. The possibility that symptoms may not have been recorded in CPRD's structured fields is therefore minimal and unlikely to have introduced bias into the cohort [35,36].

By examining prescriptions relevant (but not exclusive) to dyspnoea management, and up to a year before lung cancer diagnosis, we captured key aspects of clinical management after dyspnoea presentation. Our methods could be used to examine patterns of other pre-diagnostic activities and in patients with other cancers.

The medicines included in our study are available almost exclusively through prescription and have clear clinical indications. However it cannot be assumed that these would be the only medications prescribed to manage dyspnoea, or that dyspnoea was their sole indication. Concordant with our findings, previous studies indicate that antibiotics, opioids, and medications used for COPD management are prescribed to patients preceding lung cancer diagnosis [13,19,25], although these studies did not consider symptom presentation.

Poisson modelling allowed inflection point estimation without data from cancer-free controls, and bootstrapping provided 95 % confidence intervals around inflection points. Similar approaches have been used in diagnostic window case-only studies [10,37,38]. Although our case-only method did not control for trends in population prescribing rates, we anticipate such changes to be subtle and unlikely responsible for the clear inflection points and substantial pre-diagnostic prescribing increases observed pre-diagnosis.

Inflection points identified in our data (5–3 months pre-diagnosis) concur with the observed prescribing rates and rate ratios, indicating that earlier inflection points would be unlikely. Previous studies have explored pre-diagnostic prescribing up to a year pre-diagnosis and identified possible diagnostic windows within this period [13,14,19]. Guldbrandt et al. report similar prescribing patterns between lung cancer cases and controls 24–12 months pre-cancer diagnosis, subsequently using a 12-month study period pre-diagnosis in their investigations. Pottergard et al. suggest that increases in new prescriptions up to 6 months pre-cancer diagnosis likely reflect management of as-yet-undiagnosed cancer, suggesting this is a sufficient period to identify such associations [18]. Although our analysis is not restricted to new prescriptions, as most COPD patients (comprising 52 % of our sample) receive regular medication, the observed timing of inflection in prescribing activity falls within that proposed by Pottegard et al. Increased prescribing is observed from 6 months pre-lung cancer diagnosis in the literature compared to 5–3 months pre-lung cancer diagnosis in our study. Diagnostic delays of 3 months or longer have been shown to negatively impact cancer outcomes in observational and modelling studies [39–42]. This evidence indicates that our observed diagnostic window lengths are of appreciable length and likely to represent opportunities for earlier diagnosis in some patients, although it is not possible to identify the exact clinical scenarios relating to such opportunities.

Definition of COPD status required a look-back period of 6-years pre-

index date [24], but this was not a prerequisite in the initial inclusion criteria. Some patients in the final cohort may not have had 6 years of continuous date pre-index date available, resulting in possible undercount of true COPD status. Nonetheless this effect is likely small as the observed frequency of pre-existing COPD (52 %) in our cohort conforms to expectations [43].

We did not control for other diseases characterised by dyspnoea including heart disease or anxiety disorder. However unlike COPD, these are not associated with increased risk of lung cancer [44]. Our results could have been affected by smoking status [45], but its effects are largely represented by the inclusion of COPD status.

Stratifying by COPD status generated a small new-onset COPD group, resulting in imprecise estimates for this group. Exploration of additional management data, including pre-diagnostic X-ray or lung function tests, could be combined with prescribing activity to better define possible diagnostic windows [19,37].

4.3. Research implications

Diagnostic windows could represent lung cancer symptoms being misattributed to the diagnosis of common non-neoplastic conditions. Among COPD patients, lung cancer symptoms may be misattributed to COPD exacerbations, which are typically managed with administration of short-course oral steroids, intensification of maintenance inhaled therapy, and/or antibiotic prescriptions. GPs and patients often attribute presenting symptoms to pre-existing chronic disease, especially where chronic conditions and cancer share common symptoms that offer an 'alternative explanation' as in COPD and lung cancer [46–49]. Lung cancer patients without COPD may receive an initial COPD diagnosis or other working non-neoplastic diagnosis when the underlying dyspnoea cause was lung cancer. Patients often attribute non-specific symptoms such as dyspnoea to benign conditions [50,51], and GPs often interpret these symptoms as manifestations of non-neoplastic illnesses [52].

The findings indicate possible opportunities to improve the diagnostic process, and integrate safe prescribing practices (aiming to prevent harmful side-effects) into safety-netting approaches (which aim to improve the diagnostic process) [53]. These may include alerts for GPs to consider alternative diagnoses or follow-up approaches following repeated prescribing decisions of the same medication or medication class. "Safe prescribing" has been described as prescribing "….a medicine appropriate to the patient's condition.within the limits created by the uncertainty that attends therapeutic decisions" [54]. We posit that diagnostic (as opposed to therapeutic) decisions could also form part of its remit. Explicit UK guidance on safe prescribing in the context of safety-netting for possible cancer could be developed.

Research into safety-netting and follow-up approaches in the context of COPD and dyspnoea presentations in primary care could elucidate related clinical implications such as, timely reviews of COPD management (particularly after an acute exacerbation or recent diagnosis), and greater use of chest imaging [55]. However, it is difficult to identify exact circumstances and clinical scenarios that will document missed diagnostic opportunities in our data. Zhou and colleagues have approached this challenge by estimating the number of abnormal tests that occur during the first half of the diagnostic window for bladder and renal cancers [37]. This approach helps to quantify the proportion of patients that could potentially benefit from improved clinical evaluation. However, when diagnostic windows are defined by change in prescribing activity (as opposed to test abnormalities) such inferences are not possible for individual patients.

Prescribing activity and opportunities for earlier lung cancer diagnosis identified in our study should therefore be considered together with additional research into patient and clinical factors surrounding symptom presentation and medication prescription. For example, medication reviews or further diagnostic investigation may be appropriate in the context of continuous or intensifying symptoms [56], and/or repeated patient help-seeking [57]. This is particularly relevant for patients with pre-existing COPD who have an increased baseline risk of developing lung cancer [58–60].

Future studies examining additional symptoms treatable by medication could illuminate similar opportunities in different cancers.

5. Conclusion

Pre-diagnostic prescribing patterns indicate that opportunities likely exist for earlier lung cancer diagnosis. These relate particularly to COPD patients whose symptoms may be misattributed to their underlying chronic disease. Further research can be guided by these findings, potentially exploring guidance for GPs or pharmacists on safe-prescribing in the context of safety-netting for possible cancer, or the development of information resources for patients with a recent prescription when symptoms persist or re-occur.

CRediT authorship contribution statement

Bethany Wickramasinghe: Conceptualisation, Methodology, Software, Validation, Formal analysis, Writing – original draft, Visualisation. **Cristina Renzi**: Supervision, Methodology, Writing – review & editing. **Matthew Barclay**: Methodology. **Matthew EJ Callister**: Writing – review & editing. **Meena Rafiq**: Conceptualisation, Writing – review & editing. **Georgios Lyratzopoulos**: Supervision, Methodology, Writing – review & editing.

Declaration of Competing Interest

None.

Acknowledgement

This work was supported by the Medical Research Council (grant number MR/N013867/1). Additionally, Georgios Lyratzopoulos acknowledges support by Cancer Research UK Advanced Clinician Scientist Fellowship [18081/A18180] and Cristina Renzi by Cancer Research UK-Early Detection and Diagnosis Committee (grant number EDDCPJT \100018). This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. The study was approved by the MHRA (UK) Independent Scientific Advisory Committee, protocol number 18_299RMnA5, under Section 251 (NHS Social Care Act 2006).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2023.102429.

References

[1] Statistics, Of.N., *Cancer survival in England: national estimates for*. 2019: London.
[2] F.M. Walter, et al., Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study, Br. J. Cancer 112 (1) (2015) S6–S13.
[3] L. Elliss-Brookes, et al., Routes to diagnosis for cancer – determining the patient journey using multiple routine data sets, Br. J. Cancer 107 (8) (2012) 1220–1226.
[4] A.S. Forster, C. Renzi, G. Lyratzopoulos, Diagnosing cancer in patients with 'non-alarm' symptoms: Learning from diagnostic care innovations in Denmark, Cancer Epidemiol. 54 (2018) 101–103.
[5] G. Lyratzopoulos, et al., Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England, Lancet Oncol. 13 (4) (2012) 353–365.
[6] W. Hamilton, D. Sharp, Diagnosis of lung cancer in primary care: a structured review, Fam. Pract. 21 (6) (2004) 605–611.
[7] G. Moth, F. Olesen, P. Vedsted, Reasons for encounter and disease patterns in Danish primary care: changes over 16 years, Scand. J. Prim. Health care 30 (2) (2012) 70–75.

[8] L.M. Guldbrandt, et al., The role of general practice in routes to diagnosis of lung cancer in Denmark: a population-based study of general practice involvement, diagnostic activity and diagnostic intervals, BMC Health Serv. Res. 15 (1) (2015) 1–10.

[9] UK, N.C.I.Na.C.R. *Routes to diagnosis of cancer by stage, 2012-2013* 2016.

[10] B. White, et al., Risk of cancer following primary care presentation with fatigue: a population-based cohort study of a quarter of a million patients, Br. J. Cancer 126 (11) (2022) 1627–1636.

[11] P.L. Hansen, P. Hjertholm, P. Vedsted, Increased diagnostic activity in general practice during the year preceding colorectal cancer diagnosis, Int. J. Cancer 137 (3) (2015) 615–624.

[12] L.M. Guldbrandt, et al., General practice consultations, diagnostic investigations, and prescriptions in the year preceding a lung cancer diagnosis, Cancer Med. 6 (1) (2017) 79–88.

[13] A. Pottegård, J. Hallas, New use of prescription drugs prior to a cancer diagnosis, Pharmacoepidemiol. Drug Saf. 26 (2) (2017) 223–227.

[14] Hansen, Hjertholm, Vedsted, Increased diagnostic activity in general practice during the year preceding colorectal cancer diagnosis, Int. J. Cancer 137 (3) (2015) 615–624.

[15] K. Christensen, et al., Use of general practice, diagnostic investigations and hospital services before and after cancer diagnosis - a population-based nationwide registry study of 127,000 incident adult cancer patients, BMC Health Serv. Res 12 (2012) 224.

[16] C. Nygaard, et al., Health care use before a diagnosis of primary intracranial tumor: a Danish nationwide register study, Clin. Epidemiol. 10 (2018) 809.

[17] S. Price, et al., Examining methodology to identify patterns of consulting in primary care for different groups of patients before a diagnosis of cancer: an exemplar applied to oesophagogastric cancer, Cancer Epidemiol. 82 (2023), 102310.

[18] A. Pottegård, J. Hallas, New use of prescription drugs prior to a cancer diagnosis, Pharmacoepidemiol. Drug Saf. 26 (2) (2016).

[19] L. Guldbrandt, et al., General practice consultations, diagnostic investigations, and prescriptions in the year preceding a lung cancer diagnosis, Cancer Med. 6 (1) (2017) 79–88.

[20] E. Herrett, et al., Data resource profile: clinical practice research datalink (CPRD), Int. J. Epidemiol. 44 (3) (2015) 827–836.

[21] K.E. Henson, et al., Data resource profile: National cancer registration dataset in England, Int. J. Epidemiol. 49 (1) (2020) 16. -16h.

[22] A.L. Durham, I.M. Adcock, The relationship between COPD and lung cancer, Lung Cancer (Amst., Neth.) 90 (2) (2015) 121–127.

[23] P.J. Barnes, I.M. Adcock, Chronic obstructive pulmonary disease and lung cancer: a lethal association, Am. Thorac. Soc. (2011).

[24] C. Maringe, et al., Reproducibility, reliability and validity of population-based administrative health data for the assessment of cancer non-related comorbidities, PloS One 12 (3) (2017), e0172814.

[25] French, et al., Identification of Patient Prescribing Predicting Cancer Diagnosis Using Boosted Decision Trees, Springer,, Cham, 2019.

[26] J. Watson, et al., Predictive value of inflammatory markers for cancer diagnosis in primary care: a prospective cohort study using electronic health records, Br. J. Cancer 120 (11) (2019) 1045–1051.

[27] J. Sheringham, et al., Comparing primary and secondary health-care use between diagnostic routes before a colorectal cancer diagnosis: cohort study using linked data, Br. J. Cancer 111 (8) (2014) 1490–1499.

[28] C. Renzi, et al., Do colorectal cancer patients diagnosed as an emergency differ from non-emergency patients in their consultation patterns and symptoms? A longitudinal data-linkage study in England, Br. J. Cancer 115 (7) (2016) 866–875.

[29] J.K. Quint, et al., Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD), BMJ Open 4 (7) (2014), e005540.

[30] T. Williams, et al., Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource, Ther. Adv. Drug Saf. 3 (2) (2012) 89–99.

[31] R. Boggon, et al., Cancer recording and mortality in the General Practice Research Database and linked cancer registries, Pharmacoepidemiol. Drug Saf. 22 (2) (2013) 168–175.

[32] K.E. Henson, et al., Cohort profile: prescriptions dispensed in the community linked to the national cancer registry in England, BMJ Open 8 (7) (2018), e020980.

[33] M.C. Gulliford, et al., *Patterns of antibiotic prescribing in UK primary care from 2002 to 2017*, in *Safety of reducing antibiotic prescribing in primary care: a mixed-methods study*, NIHR J. Libr. (2021).

[34] J. Campbell, et al., Is the CPRD GOLD population comparable to the UK population?, 111 RIVER ST, HOBOKEN 07030-5774. Pharmacoepidemiology and Drug Safety Wiley-Blackwell,, NJ USA, 2013.

[35] E. Herrett, et al., Validation and validity of diagnoses in the General Practice Research Database: a systematic review, Br. J. Clin. Pharmacol. 69 (1) (2010) 4–14.

[36] E.I. Benchimol, et al., The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement, PLoS Med. 12 (10) (2015), e1001885.

[37] Y. Zhou, et al., Identifying opportunities for timely diagnosis through patterns of primary care tests in patients with bladder and renal cancer: a longitudinal linked data study, Br. J. Gen. Pract. (2021).

[38] M. Moullet, et al., Pre-diagnostic clinical features and blood tests in patients with colorectal cancer: a retrospective linked-data study, Br. J. Gen. Pract. 72 (721) (2022) e556–e563.

[39] M.P. Kennedy, et al., Lung cancer stage-shift following a symptom awareness campaign, Thorax 73 (12) (2018) 1128–1136.

[40] C.-F.J. Yang, et al., Impact of timing of lobectomy on survival for clinical stage IA lung squamous cell carcinoma, Chest 152 (6) (2017) 1239–1250.

[41] Branch, H.S.I., *Healthcare Safety Investigation Branch*. Missed detection of lung cancer on chest X-rays of patients being seen in primary care. Oct 2021.

[42] A. Sud, et al., Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study, Lancet Oncol. 21 (8) (2020) 1035–1044.

[43] R.P. Young, et al., COPD prevalence is increased in lung cancer, independent of age, sex and smoking history, Eur. Respir. J. 34 (2) (2009) 380–386.

[44] A. Durham, I. Adcock, The relationship between COPD and lung cancer, Lung Cancer 90 (2) (2015) 121–127.

[45] A. Verma, et al., Are pharmacists reducing COPD'S impact through smoking cessation and assessing inhaled steroid use? Respir. Med. 106 (2) (2012) 230–234.

[46] C. Renzi, et al., Comorbid chronic diseases and cancer diagnosis: disease-specific effects and underlying mechanisms, Nat. Rev. Clin. Oncol. 16 (12) (2019) 746–761.

[47] G. Black, et al., Patients' experiences of cancer diagnosis as a result of an emergency presentation: a qualitative study, PloS One 10 (8) (2015), e0135027.

[48] D. Brandenbarg, et al., Possible missed opportunities for diagnosing colorectal cancer in Dutch primary care: a multimethods approach, Br. J. Gen. Pract. 68 (666) (2018) e54–e62.

[49] A. Kaushal, et al., The role of chronic conditions in influencing symptom attribution and anticipated help-seeking for potential lung cancer symptoms: a vignette-based study, Bjgp Open 4 (4) (2020).

[50] L.F. Jensen, et al., Symptom attributions in patients with colorectal cancer, BMC Fam. Pract. 16 (1) (2015) 1–10.

[51] K.L. Whitaker, et al., Attributions of cancer 'alarm'symptoms in a community sample, PloS One 9 (12) (2014), e114028.

[52] R. Wagland, et al., Facilitating early diagnosis of lung cancer amongst primary care patients: The views of GPs, Eur. J. Cancer care 26 (3) (2017), e12704.

[53] (NICE), N.I.f.C.E., NICE guidelines [NG12]: Suspected cancer: recognition and referral 2015. 2019.

[54] J. Aronson, Balanced prescribing, Br. J. Clin. Pharmacol. 62 (6) (2006) 629.

[55] S.H. Bradley, et al., Sensitivity of chest X-ray for detecting lung cancer in people presenting with symptoms: a systematic review, Br. J. Gen. Pract. 69 (689) (2019) e827–e835.

[56] M. de la Poza Abad, et al., Prescription strategies in acute uncomplicated respiratory infections: a randomized clinical trial, JAMA Intern. Med. 176 (1) (2016) 21–29.

[57] S. Scott, et al., The model of pathways to treatment: conceptualization and integration with existing theory, Br. J. Health Psychol. 18 (1) (2013) 45–65.

[58] G. Caramori, et al., Mechanisms involved in lung cancer development in COPD, Int. J. Biochem. Cell Biol. 43 (7) (2011) 1030–1044.

[59] Y. Sekine, et al., Early detection of COPD is important for lung cancer surveillance, Eur. Respir. J. 39 (5) (2012) 1230–1240.

[60] J.P. de-Torres, et al., Identification of COPD patients at high risk for lung cancer mortality using the COPD-LUCSS-DLCO, Chest 149 (4) (2016) 936–942.