Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional population-based study

Minjoung Monica Koo, Ruth Swann, Sean McPhail, Gary Abel, Lucy Elliss-Brookes, Greg P Rubin & Georgios Lyratzopoulos

University College London, 1–19 Torrington Place, London WC1E 6BT, UK (M M Koo PhD, S McPhail PhD, Prof G Lyratzopoulos MD); National Cancer Registration and Analysis Service, Public Health England, Wellington House, 133–155 Waterloo Road, London, SE1 8UG, UK (M M Koo, R Swann PhD, S McPhail, L Elliss-Brookes BSc, Prof G Lyratzopoulos); Cancer Research UK, Angel Building, 407 St John Street, London EC1V 4AD (R Swann); University of Exeter Medical School, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU, UK (G A Abel PhD); Institute of Health and Society, Newcastle University, Sir James Spence Institute, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP (Prof G P Rubin, FRCGP).

Author for correspondence:
Dr Minjoung Monica Koo
Email: Monica.koo.14@ucl.ac.uk
Tel: +44 (0) 203 108 3293
Address:
Epidemiology of Cancer Healthcare and Outcomes (ECHO) group
Department of Behavioural Science and Health
University College London 1–19 Torrington Place, London WC1E 6BT, UK

Abstract: 300 including funding statement
Main text: 2578
References: 34
Tables: 1
Figures: 3
Abstract

Background
Early diagnosis interventions such as symptom awareness campaigns increasingly form part of global cancer control strategies. These strategies however, will have limited value in improving cancer outcomes if the targeted symptoms represent advanced disease. Therefore, we aimed to examine associations between common presenting symptoms of cancer and stage at diagnosis.

Methods
We analysed population-level data from the English National Cancer Diagnosis Audit (2014) on 7,997 patients with one of twelve solid tumours (bladder, breast, colon, endometrial, laryngeal, lung, melanoma, oral/oropharyngeal, ovarian, prostate, rectal, and renal cancer). We considered 20 common presenting symptoms and examined their associations with stage at diagnosis (TNM IV versus I–III) using logistic regression. For each symptom, we estimated these associations when reported as a single presenting symptom and together with other symptoms.

Findings
The proportion of patients diagnosed with stage IV cancer varied substantially by presenting symptom. Three of the examined symptoms (neck lump, chest pain, back pain) were consistently associated with greater odds of stage IV, whether reported alone or with other symptoms, while the opposite was true for abnormal mole, breast lump, post-menopausal bleeding (PMB), and rectal bleeding.

For 13 symptoms, more than half were diagnosed in stages other than stage IV; for 19 of the 20 studied symptoms, more than a third of patients were diagnosed in stages other than stage IV.

Interpretation
In spite of certain presenting symptoms being more strongly associated with advanced stage at diagnosis than others, for most symptoms, large proportions of patients are diagnosed in stages other than stage IV. The findings provide support for early diagnosis interventions targeting common cancer symptoms obviating concerns that they may be simply expediting the detection of advanced stage disease.

Funding
The UK Department of Health’s Policy Research Unit in Cancer Awareness, Screening and Early Diagnosis and Cancer Research UK.
Research in context

Evidence before this study
We searched PubMed for manuscripts published between Jan 1 1980 and Jun 17 2019 using the search terms “presenting symptom” or “symptom” AND “cancer” AND “stage”, with additional hand-searching of reference lists of identified papers and relevant subject reviews. We identified 12 single cancer site studies (five on ovarian, three on colon/colorectal, one on lung, one on anal, one on pancreatic, and one on renal cancer), of which three examined associations between presenting symptoms and stage adjusting for possible confounders. Only one study (on colorectal cancer patients) considered both single presenting symptoms and symptom combinations.

Added value of this study
The findings characterise associations between common presenting symptoms and stage at diagnosis in a population-based incident cohort of patients with different cancers. For 13 of the 20 studied symptoms more than half of patients were diagnosed with cancer in stages other than stage IV, and for 19 symptoms more than third.

Implications of all the available evidence
Common presenting symptoms have variable associations with advanced stage at diagnosis, though for all symptoms large proportions of patients are diagnosed in stages other than stage IV. Early diagnosis initiatives, such as public health campaigns aimed at raising awareness of the possible symptoms of cancer and clinical practice guidelines for specialist assessment of patients with symptoms of possible cancer, have the potential to help detect early stage disease.
Introduction

Globally, cancer control strategies increasingly encompass early diagnosis of symptomatic cancer alongside primary prevention policies and screening programmes. Several countries have introduced health system interventions that aim to expedite the investigation and diagnosis of symptomatic individuals presenting in primary care, while public health education campaigns aimed at raising awareness of cancer symptoms are increasingly being used in both high and low-middle income countries.

By their nature, early diagnosis interventions focus on the presenting symptoms of cancer. If the selected symptoms predominantly represent advanced stage disease however, these initiatives may have limited value in improving cancer outcomes. Understanding associations between presenting symptoms and stage at diagnosis of cancer is therefore a critical consideration.

Current evidence regarding associations between presenting symptoms and stage at diagnosis is limited, and in the form of cancer-site specific studies. This overlooks the fact that symptoms at presentation (particularly those of non-specific nature) are shared among different types of cancer; for example abdominal pain is a common symptom of colorectal, ovarian, and renal cancer.

Furthermore, symptoms are typically examined as being either present or absent, without consideration of the possible additive or interactive effects of multiple symptoms.

Motivated by these considerations, we aimed to examine associations between common presenting symptoms of cancer and stage at diagnosis using data from a population-based cohort of incident cancer patients.
Methods

Study design and participants
We analysed cross-sectional data on patients included in the English National Cancer Diagnosis Audit (NCDA) 17. As described previously, general practitioners and other healthcare professionals in participating practices provided information on the diagnostic pathway of patients identified as having been diagnosed with a malignant neoplasm in 2014 by Public Health England’s National Cancer Registration and Analysis Service (NCRAS). The data were collated by NCRAS under regulation 2 of the Health Service (Control of Patient Information) Regulations 2002. Ethical approval for this study was obtained by the London Hampstead Research Ethics Committee (REC reference: 8/LO/0377).

A total of 439 practices submitted data (approximately 5% of all English practices) on 17,042 tumour records. The sex, age and cancer site distribution of included patients was representative of the contemporary national incident cohort. Further, participating practices were similar to non-participating practices regarding their demographic case-mix, patient experience scores, and referral rates for suspected cancer, but served slightly larger registered populations 17.

Procedures
We restricted our study population to symptomatic adult patients aged 25 years and over diagnosed with one of 12 solid tumours with a high degree (>85%) of stage completeness (in descending order): endometrial (94% complete staging), lung, rectal, breast, melanoma, prostate, colon, renal, bladder, 

Figure 1: Flow chart indicating derivation of the study population
ovarian, oral/oropharyngeal, laryngeal cancer (85% complete staging), representing 79% of incident cases of solid tumours in England in the study year (2014) \(^{18}\) (Figure 1; see appendix p3 for list of excluded cancers).

Information on stage at diagnosis was available from NCRAS as TNM stage I to IV; we defined advanced stage as TNM stage IV (see below for alternative parameterisation of stage at diagnosis).

Information on presenting symptoms (specified as symptom(s) noted at first presentation before diagnosis and referral) was provided by participating GPs from a list of 81 pre-specified symptoms (in yes/no format). We examined nineteen symptoms recorded in at least 50 patients: abnormal mole; abdominal pain; back pain; breast lump; chest infection; chest pain; change in bowel habit (CIBH); cough; dyspnoea; fatigue; haematuria; haemoptysis; hoarseness; lower abdominal pain; lower urinary tract symptoms (LUTS); neck lump; post-menopausal bleeding (PMB); rectal bleeding; and weight loss. All other symptoms were considered together in a 20\(^{th}\) “any other symptom” category (appendix p4). Therefore, patients could have a single presenting symptom, or one or more of the above symptoms, in any combination.

**Statistical analyses**

We estimated the proportion of patients diagnosed at stage IV by single/multiple symptom status for each of the 20 symptoms. As patients with different cancers often present with the same symptom \(^{16}\), we examined the cancer site case-mix of each presenting symptom (namely the percentage of patients with different cancers diagnosed following presentation with a particular symptom) to aid interpretation of our findings (see appendix p5–6 for cancer site signatures of all 20 symptoms).

Subsequently, we examined patient-level associations between symptoms and stage at diagnosis using logistic regression (stage IV versus stages I–III). Ideally we would have studied associations between every symptom combination (pairs, triplets, etc.) and stage at diagnosis as the presence of additional symptoms may affect a given symptom’s association with the outcome of interest; however, this was not feasible given sample size limitations. Instead, we modelled each presenting symptom as a pair of binary variables: one denoting its presence/absence, and the other denoting its presence when recorded with other symptoms. As we did not examine patients without symptoms, the constant was constrained to 0, fixing the baseline odds of stage IV to 1.

For each symptom, two odds ratios could be estimated from the above model for each symptom: “single” and “multiple”. The “single” odds ratio represents the association of a given symptom with stage at diagnosis when seen alone, compared to change in bowel habit (used as the reference, as the most common symptom). Further, by adding the coefficients from the first and second binary variables for each symptom, we estimated a “multiple” odds ratio for each symptom, which represents its association with stage when seen together with one or more of the other 19 symptom categories, compared to patients with multiple symptoms other than the symptom of interest. An OR value of 1 implies that stage at diagnosis is no different between patients with and without the symptom of interest among those with multiple symptoms.

We additionally adjusted for age group (parameterised as 25–49 years, 50–59 years, 60–69 years, 70–79 years, and 80+ years), sex (male, female), IMD income domain quintiles (1 – least deprived, 2, 3, 4, 5 – most deprived), ethnicity (white, non-white, and missing), and cancer site (12 sites as described above). The events per variable criterion for sample size considerations was satisfactory \(^{19}\).

We conducted a range of sensitivity analyses, as follows:
**Alternative parameterisation of advanced stage category:** We repeated the analysis by parameterising advanced stage as stage III–IV, compared to stage I–II disease.

**Extreme case scenario for missing information on stage:** Unlike with missing exposure variable data, a complete case analysis where only outcome variable data are missing (as is the case for stage at diagnosis in our study) is unbiased under the ‘missing at random’ assumption. Multiple imputation can make this assumption more reasonable if auxiliary variables absent from the analysis model are used in the imputation model, however, no such variables were available and so the multiple imputation approach would have been of no value. Instead, we performed an extreme case sensitivity analysis where all patients with missing stage were assumed to have stage IV. While this extreme scenario is unlikely to be realistic, we can be reasonably confident that the true bias in our findings will be less than that illustrated with this analysis.

**Restricting analysis to patients who had a diagnostic interval of 0–60 days:** Time to diagnosis may influence the association between presenting symptoms and stage. Therefore, we repeated the main analysis restricted to patients with a diagnostic interval (time from symptomatic presentation to diagnosis) of 0–60 days.

**Adjustment for route to diagnosis:** The association between route to cancer diagnosis (a patient’s healthcare utilisation pathway before diagnosis) and stage may additionally influence the association of interest. We therefore repeated the main analysis further adjusting for route to diagnosis among patients with complete information on diagnostic route. Specifically, we examined the following five diagnostic route categories: ‘two-week-wait’ referral (urgent referrals for suspected cancer from primary care to specialist hospital services); elective referral (routine, non-urgent referrals); emergency presentation; secondary care (both inpatient and outpatient) routes; and unknown route.

All analyses were conducted using STATA SE version 15.1 (StataCorp, College Station, TX, USA; 2017).

**Role of the funding source**
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Results
Breast lump was the most common presenting symptom, reported in 1260 patients in our study sample, and neck lump the least common (Figure 2). A third of all patients (2,685/7,997, 34% (95% CI: 33–35%)) had two or more symptoms; symptoms varied in their likelihood to be seen alone or with other symptoms.

Certain, typically localised, symptoms had relatively narrow cancer site signatures where the majority (>80%) of patients were diagnosed with the same cancer site, such as breast lump (breast cancer), abnormal mole (melanoma), post-menopausal bleeding (endometrial cancer), lower urinary tract symptoms (prostate cancer), and haemoptysis, dyspnoea, chest infection, chest pain, and cough (lung cancer). In comparison, less specific symptoms such as abdominal pain, change in bowel habit, back pain, fatigue, and weight loss had more diverse cancer site signatures (see appendix p5–6).

![Figure 2 Presenting symptoms and proportions of stage I–II and stage IV. The first bar of each pair represents symptoms recorded alone (single) while the second bar of each pair represents that symptoms recorded with other symptoms (multiple).]
The proportion of patients diagnosed at stage IV by symptom varied from 1% (1–3%) (8/584 patients with abnormal mole) to 80% (71–87%) (84/105 patients with neck lump) (Table 1). For 13 of the 20 symptoms, >50% of patients were diagnosed with non-advanced stage cancer, while for all symptoms apart from neck lump, more than a third (at least 38%) were diagnosed in stages other than stage IV.

Table 1 Observed proportions (and 95% CIs) of stage IV associated with 20 presenting symptoms (overall, as a single symptom, and as one of multiple symptoms) among cancer patients diagnosed with one of 12 cancers (n=7,997). NB symptom rows are ordered by overall % stage IV.

| Presenting symptom          | Total | Overall N (% (95% CI)) stage IV | Symptoms reported alone N (%(95% CI)) stage IV | Symptoms reported with other symptoms N (%(95% CI)) stage IV |
|-----------------------------|-------|---------------------------------|-----------------------------------------------|-----------------------------------------------------------|
| Abnormal mole               | 584   | 8 (1% (1–3%))                  | 564 7 (1% (1–3%))                              | 20 1 (5% (0.13–25%))                                      |
| Breast lump                 | 1260  | 58 (5% (4–6%))                 | 1074 36 (3% (2–5%))                            | 186 22 (12% (8–17%))                                     |
| PMB                         | 292   | 17 (6% (3–9%))                 | 229 9 (4% (2–7%))                              | 63 8 (13% (6–23%))                                      |
| Rectal bleeding             | 498   | 80 (16% (13–20%))              | 215 28 (13% (9–18%))                           | 283 52 (18% (14–23%))                                    |
| LUTS                        | 1135  | 210 (19% (16–21%))             | 805 121 (15% (13–18%))                         | 330 89 (27% (22–32%))                                    |
| Haematuria                  | 487   | 101 (21% (17–25%))             | 322 57 (18% (14–22%))                          | 165 44 (27% (20–34%))                                    |
| CIBH                        | 819   | 236 (29% (26–32%))             | 186 46 (25% (19–32%))                          | 633 190 (30% (26–34%))                                   |
| Lower abdominal pain        | 285   | 83 (29% (24–35%))              | 51 18 (35% (22–50%))                           | 234 65 (28% (22–34%))                                    |
| Any other symptom           | 2433  | 873 (36% (34–38%))             | 876 265 (30% (27–33%))                         | 1557 608 (39% (37–42%))                                  |
| Abdominal pain              | 424   | 156 (37% (32–42%))             | 89 29 (33% (23–43%))                           | 335 127 (38% (33–43%))                                   |
| Hoarseness                  | 124   | 51 (41% (32–50%))              | 68 21 (31% (20–43%))                           | 56 30 (54% (40–67%))                                     |
| Fatigue                     | 365   | 170 (47% (41–52%))             | 58 18 (31% (20–45%))                           | 307 152 (50% (44–55%))                                   |
| Weight loss                 | 584   | 287 (49% (45–53%))             | 71 27 (38% (27–50%))                           | 513 260 (51% (46–55%))                                   |
| Cough                       | 672   | 361 (54% (50–58%))             | 161 72 (45% (37–53%))                          | 511 289 (57% (52–61%))                                   |
| Haemoptysis                 | 179   | 97 (54% (47–62%))              | 59 33 (56% (42–69%))                           | 120 64 (53% (44–62%))                                    |
| Chest infection             | 317   | 176 (56% (50–61%))             | 63 34 (54% (41–67%))                           | 254 142 (56% (50–62%))                                   |
| Dyspnoea                    | 513   | 289 (56% (52–61%))             | 108 52 (48% (38–58%))                          | 405 237 (59% (54–63%))                                   |
| Back pain                   | 269   | 163 (61% (54–66%))             | 107 62 (58% (48–67%))                          | 162 101 (62% (54–70%))                                   |
| Chest pain                  | 293   | 181 (62% (56–67%))             | 83 50 (60% (49–71%))                           | 210 131 (62% (55–69%))                                   |
| Neck lump                   | 105   | 84 (80% (71–87%))              | 65 52 (80% (68–89%))                           | 40 32 (80% (64–91%))                                     |

CIBH: change in bowel habit; LUTS: lower urinary tract symptoms; PMB: post-menopausal bleeding

The pattern of variation in symptom-specific associations with stage IV when reported alone (Figure 3a) was comparable to the associations seen for symptoms when reported with other symptoms (both Chi-squared p<0.0010 appendix p7–9). Three symptoms (neck lump, chest pain, and back pain) were consistently associated with greater odds of stage IV disease while abnormal mole, breast lump, post-menopausal bleeding (PMB), or rectal bleeding were associated with lower odds of stage IV disease (appendix p10).

Adjusting for patient characteristics and cancer site made little difference to the order of symptom-specific odds of stage IV for both single and multiple symptoms (Figure 3b and appendix p7–9).
Additional sensitivity analyses examining different parameterisation of stage, stratification by diagnostic interval, and additional adjustment for route to diagnosis also provided comparable findings (see appendix p11–20).
Discussion

In our population-based cohort of cancer patients, certain presenting symptoms had stronger associations with stage IV than others but for most symptoms, large proportions of patients were diagnosed in stages other than stage IV. The relative order of symptom-specific associations were broadly comparable whether symptoms were seen alone, or with other symptoms. Adjustment for confounders including cancer site made little difference to the overall pattern of associations between symptoms and stage at diagnosis.

Regarding associations between presenting symptoms and stage at diagnosis, direct comparisons with existing literature are challenging because existing studies are cancer-site specific.

Evidence from studies examining specific cancer-sites provides an incomplete picture of associations between presenting symptoms and stage at diagnosis as individuals who present with the same symptoms may be diagnosed with cancers of different sites. In contrast, we studied the presenting symptoms of patients with a range of common and rarer cancers and examined associations adjusting for the case-mix of cancer sites in our study population. Nevertheless, among colorectal cancer patients, rectal bleeding has been associated with earlier stage at diagnosis compared to abdominal pain and change in bowel habits \(^8,10\), while among ovarian cancer patients, gastrointestinal symptoms (including abdominal pain, digestive bowel symptoms, and distension) have been more strongly associated with advanced stage cancer compared to other symptoms \(^9,14\).

Except for one study (which examined three symptoms and their combinations with stage \(^14\)), prior literature does not differentiate symptoms for when they are reported on their own or together with other symptoms. In contrast, our study characterised associations between symptoms and stage both when a symptom was reported alone, and when it was reported together with other symptoms, which allowed us to adjust for potential interactions between all possible symptom combinations.

A major strength of our study is that it examines the association between presenting symptoms and stage in a well-characterised population-based incident cohort of patients with different cancers. The NCDA represents a unique combination of information provided by general practitioners and other healthcare professionals based on clinical insight and judgement, and high-quality information on patient and tumour characteristics from the English national cancer registry \(^17,25\).

In addition to adjusting our findings by sociodemographic factors, we adjusted by cancer site. While this did not appear to alter the observed patterns of variation substantially, the associations between symptoms and stage at diagnosis may differ in a population-based incident cohort with a different distribution of cancer sites.

As is the case for other studies based on clinical audits of cancer diagnosis \(^26–28\), elicitation and recording of symptoms during the index consultation, and subsequent extraction of information from primary care records, may be incomplete and prone to bias \(^29\). Nevertheless, alternative approaches using self-reported data from individuals diagnosed with cancer are susceptible to under-representation of patients with poor prognosis \(^30\). With either method, it is possible that some of the recorded symptoms may relate to concomitant chronic illness, particularly among patients with multiple symptoms. However the observed distribution of cancer sites among patients with specific symptoms (cancer site signatures, appendix p5–6) concord with prior knowledge regarding the presenting symptoms of each cancer site. This observation provides strong indication that the
recorded information on presenting symptoms chiefly relates to the subsequently diagnosed cancer site rather than other unrelated conditions.

The study population represents around four-fifths of the incident cohort of solid tumours. Among the cancer sites included in the study, a small proportion of patients with missing stage information were excluded from analyses, variably by cancer site (see appendix p3). Sensitivity analyses which would demonstrate the effect of maximum possible bias arising from missing data (i.e. by assigning patients missing stage information to stage IV) provided comparable findings (see appendix p13).

Our findings refute concerns that early diagnosis interventions centred on common presenting symptoms of cancer would typically expedite the diagnosis of individuals with stage IV disease. Rather, they indicate that a substantial proportion of patients with these symptoms are diagnosed with non-advanced disease, associated with potentially good prognosis. This was the case even for patients with symptoms most strongly associated with advanced stage in our study, and for symptoms often considered indicative of advanced disease such as weight loss.

Further, examination of the effect of single and multiple symptoms separately indicates that the presence of multiple symptoms is a poor predictor of stage IV disease. Rather, it is the nature of the symptom that appears to be more important, than the number of reported symptoms. This is reassuring, given that public health education campaigns typically do not focus on specific symptom combinations.

Symptom awareness and appraisal by patients and doctors is an important determinant of timely presentation and investigation but the optimal design of early diagnosis interventions aimed at the earlier recognition of possible symptoms of cancer by members of the public and healthcare professionals remains unclear. Alongside considerations such as cancer site incidence, psychosocial barriers to presentation, and the predictive value of symptoms, evidence on associations between presenting symptoms and stage at diagnosis can guide the design of early diagnosis interventions. Our findings provide support for such interventions, and counter concerns that they simply expedite the detection of advanced stage disease.
References

1. WHO. Guide to cancer: early diagnosis. 2017
   http://apps.who.int/iris/bitstream/10665/254500/1/9789241511940-eng.pdf?ua=1.

2. Ott JJ, Ullrich A, Miller AB. The importance of early symptom recognition in the context of early detection and cancer survival. Eur J Cancer 2009; 45: 2743–8.

3. Abuidris DO, Elsheikh A, Ali M, et al. Breast-cancer screening with trained volunteers in a rural area of Sudan: a pilot study. Lancet Oncol 2013; 14: 363–70.

4. Thakur J, Prinja S, Jeet G, Bhatnagar N. Costing of a State-Wide Population Based Cancer Awareness and Early Detection Campaign in a 2.67 Million Population of Punjab State in Northern India. Asian Pacific J Cancer Prev 2016; 17: 791–7.

5. Kennedy MPT, Cheyne L, Darby M, et al. Lung cancer stage-shift following a symptom awareness campaign. Thorax 2018; 73: 1128–36.

6. Schliemann D, Donnelly M, Dahlui M, et al. The ‘Be Cancer Alert Campaign’: protocol to evaluate a mass media campaign to raise awareness about breast and colorectal cancer in Malaysia. BMC Cancer 2018; 18: 881.

7. Calanzani N, Nijenhuis L, Shahaj O, Weller D, Campbell C. A Systematic Review of Health System Level Initiatives Promoting the Earlier Diagnosis of Cancer Among the Adult Population in High-Income Countries. J Glob Oncol 2018; 4: 38s-38s.

8. Lurie G, Wilkens LR, Thompson PJ, Matsuno RK, Carney ME, Goodman MT. Symptom presentation in invasive ovarian carcinoma by tumor histological type and grade in a multiethnic population: A case analysis. Gynecol Oncol 2010; 119: 278–84.

9. Alexiusdottir KK, Möller PH, Snaebjornsson P, et al. Association of symptoms of colon cancer patients with tumor location and TNM tumor stage. Scand J Gastroenterol 2012; 47: 795–801.

10. Ryerson AB, Eheman C, Burton J, et al. Symptoms, Diagnoses, and Time to Key Diagnostic Procedures Among Older U.S. Women With Ovarian Cancer. Obstet Gynecol 2007; 109: 1053–61.

11. Sauter M, Keilholz G, Kranzbühler H, et al. Presenting symptoms predict local staging of anal cancer: a retrospective analysis of 86 patients. BMC Gastroenterol 2016; 16: 46.

12. Porta M, Fabregat X, Malats N, et al. Exocrine pancreatic cancer: Symptoms at presentation and their relation to tumour site and stage. Clin Transl Oncol 2005; 7: 189–97.

13. Khan A. Sultana K. Presenting signs and symptoms of ovarian cancer. JPMA - J Pakistan Med Assoc 2010; 60: 260–2.

14. Thompson MR, Asiimwe A, Flashman K, Tsavellas G. Is earlier referral and investigation of bowel cancer patients presenting with rectal bleeding associated with better survival? Color Dis 2011; 13: 1242–8.

15. Bedir O, Kiziltas S, Kostek O, Ozkanli S. The relation of presenting symptoms with staging, grading, and postoperative 3-year mortality in patients with stage I–III nonmetastatic colon cancer. Turkish J Gastroenterol 2016; 27: 239–45.

16. Koo MM, Hamilton W, Walter FM, Rubin GP, Lyrratzopoulos G. Symptom Signatures and Diagnostic Timeliness in Cancer Patients: A Review of Current Evidence. Neoplasia 2017; 20: 165–74.
Swann R, McPhail S, Witt J, et al. Diagnosing cancer in primary care: results from the National Cancer Diagnosis Audit. *Br J Gen Pract* 2018; 68: e63–72.

Office for National Statistics. Cancer registration statistics, England 2014; Table 1. 2016 https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatistics/cancerregistrationstatisticsengland.

Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; 49: 1373–9.

Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; 338: b2393.

NCIN. Cancer survival in England by stage. 2014 http://www.ncin.org.uk/view?rid=2752.

Tørring ML, Falborg AZ, Jensen H, et al. Advanced-stage cancer and time to diagnosis: An International Cancer Benchmarking Partnership (ICBP) cross-sectional study. *Eur J Cancer Care (Engl)* 2019; : e13100.

McPhail S, Johnson S, Greenberg D, Peake M, Rous B. Stage at diagnosis and early mortality from cancer in England. *Br J Cancer* 2015; 112: S108–15.

Elliss-Brookes L, McPhail S, Ives A, et al. Routes to diagnosis for cancer – determining the patient journey using multiple routine data sets. *Br J Cancer* 2012; 107: 1220–6.

Henson KE, Elliss-Brookes L, Coupland VH, et al. Data Resource Profile: National Cancer Registration Dataset in England. *Int J Epidemiol* 2019; : 1–9.

Baughan P, O’Neill B, Fletcher E. Auditing the diagnosis of cancer in primary care: the experience in Scotland. *Br J Cancer* 2009; 101 Suppl: S87-91.

Hansen RP, Vedsted P, Sokolowski I, Søndergaard J, Olesen F. Time intervals from first symptom to treatment of cancer: a cohort study of 2,212 newly diagnosed cancer patients. *BMC Health Serv Res* 2011; 11: 284.

Leiva A, Esteva M, Llobera J, et al. Time to diagnosis and stage of symptomatic colorectal cancer determined by three different sources of information: A population based retrospective study. *Cancer Epidemiol* 2017; 47: 48–55.

Verheij RA, Curcin V, Delaney BC, McGilchrist MM. Possible Sources of Bias in Primary Care Electronic Health Record Data Use and Reuse. *J Med Internet Res* 2018; 20: e185.

Abel GA, Saunders CL, Lyratzopoulos G. Post-sampling mortality and non-response patterns in the English Cancer Patient Experience Survey: Implications for epidemiological studies based on surveys of cancer patients. *Cancer Epidemiol* 2016; 41: 34–41.

Hamilton W, Walter FM, Rubin G, Neal RD. Improving early diagnosis of symptomatic cancer. *Nat Rev Clin Oncol* 2016. DOI:10.1038/nrclinonc.2016.109.

Whitaker KL, Smith CF, Winstanley K, Wardle J. What prompts help-seeking for cancer ‘alarm’ symptoms? A primary care based survey. *Br J Cancer* 2016; 114: 334–9.

Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez A. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. *Br J Cancer* 2009; 101 Suppl: S92–101.

Car LT, Papachristou N, Urch C, et al. Preventing delayed diagnosis of cancer: clinicians’ views on main problems and solutions. *J Glob Health* 2016; 6. DOI:10.7189/jogh.06.020901.
Additional information

Authors’ contributions
MMK, GPR, LEB and GL conceived the study. MMK, RS and SMc were responsible for data management. MMK conducted statistical analyses with expert advice from GAA. All authors contributed to multiple revisions and approved the final manuscript.

Declaration of interests
All authors declare no competing interests.

Acknowledgements
The National Cancer Diagnosis Audit (NCDA) received enabling support from Cancer Research UK, NHS England, and the National Cancer Registration and Analysis Service. This work was supported by a grant from the UK Department of Health [grant number no. 106/0001] as part of the programme of the Policy Research Unit in Cancer Awareness, Screening and Early Diagnosis. The Policy Research Unit in Cancer Awareness, Screening, and Early Diagnosis is a collaboration between researchers from seven institutions (Queen Mary University of London, University College London, King’s College London, London School of Hygiene and Tropical Medicine, Hull York Medical School, Durham University and Peninsula Medical School/University of Exeter). GPR is Chair, GL Associate Director, GAA Senior Investigator and MMK Junior Faculty member of the multi-institutional CanTest Collaborative, which is funded by Cancer Research UK [grant number: C8640/A23385]. GL is supported by a Cancer Research UK Clinician Advanced Scientist Fellowship [grant number: C18081/A18180]. The views expressed are those of the authors and not necessarily those of the Department of Health or Cancer Research UK.

The authors would like to thank all GPs and health professionals who participated in the NCDA, and contributing Cancer Research UK staff; the National Cancer Registration and Analysis Service, NHS England, the Royal College of General Practitioners, Macmillan Cancer Support, and Health Data Insight. Data for this audit are based on patient-level information collected by the NHS, as part of the care and support of cancer patients. The data are collated, maintained, and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England.