Association between use of urgent suspected cancer referral and mortality and stage at diagnosis: a 5-year national cohort study

INTRODUCTION

Late diagnosis contributes to relatively worse cancer survival rates in the UK, with longer diagnostic intervals associated with higher mortality. Although most of those with cancer present symptomatically to primary care, diagnosis of cancer is not straightforward. Patient-, doctor-, and system-related factors can all contribute to longer cancer diagnostic intervals. Concerns about potential diagnostic delays led to the implementation of urgent suspected cancer referral pathways, based on referral criteria defined by the National Institute for Health and Care Excellence (NICE). These pathways enable rapid access to a specialist opinion or diagnostic test (2-week wait [2WW] in England) for patients with specified symptoms. Evidence shows time to diagnosis and start of treatment is shorter for patients referred urgently, whereas longer diagnostic intervals are associated with more advanced cancers at diagnosis. The NICE suspected cancer referral guidelines were updated in June 2015, lowering the risk threshold for referral. Referrals have been increasing by approximately 10% year on year, with more patients being diagnosed with cancer following GP referrals, with significant reductions in those diagnosed via emergency routes. There is significant variation between practices in their use of urgent suspected cancer referrals, which has been a cause for concern. Use of urgent referrals varies by cancer site, with referral less likely for cancers characterised by non-specific presenting symptoms and patients belonging to low-cancer-incidence demographic groups.

From financial year 2009/2010 a set of yearly suspected cancer referral metrics for every practice in England became available, produced by Public Health England (PHE). Previously published evidence that higher practice use of urgent referral is associated with lower cancer patient mortality was based on a single year (2009) cohort. A more detailed analysis has been called for to understand variation in use of urgent referral pathways. This includes whether the association with cancer patient mortality can be replicated over a longer time period, is consistent across the main cancer types (colorectal, lung, breast, and prostate) — which make up approximately half of all cancer cases, and the association with stage at diagnosis.

METHOD

In this study, cancer registration data were extracted for all patients diagnosed with cancer (ICD-10 codes C00–C97, excluding non-melanoma skin cancer [C44]) between


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Abstract

BackgroundThere is considerable variation between GP practices in England in their use of urgent referral pathways for suspected cancer.

Aim
To determine the association between practice use of urgent referral and cancer stage at diagnosis and cancer patient mortality, for all cancers and the most common types of cancer (colorectal, lung, breast, and prostate).

Design and setting

Method
The cohort was stratified according to quintiles of urgent referral metrics. Cox proportional hazards regression was used to quantify risk of death, and logistic regression to calculate odds of late-stage (III/IV) versus early-stage (I/II) cancers in relation to referral quintiles and cancer type.

Results
Cancer patients from the highest referring practices had a lower hazard of death (hazard ratio [HR] = 0.96; 95% confidence interval [CI] = 0.93 to 0.97); breast (HR = 0.96; CI = 0.93 to 0.99); and lung (HR = 0.95; CI = 0.94 to 0.97) cancers. There were lower odds of late-stage diagnosis for colorectal (HR = 0.95; CI = 0.93 to 0.97) and prostate (HR = 0.88; CI = 0.85 to 0.91). Similarity, for cancer patients from these practices, there were lower odds of late-stage diagnosis for individual cancer types, except for colorectal cancer.

Conclusion
Higher practice use of referrals for suspected cancer is associated with lower mortality for the four most common types of cancer. A significant proportion of the observed mortality reduction is likely due to earlier stage at diagnosis, except for colorectal cancer. This adds to evidence supporting the lowering of referral thresholds and consequent increased use of urgent referral for suspected cancer.

Keywords
cancer; early diagnosis; general practice; primary care; referral and consultation.
Five-year aggregated practice referral metrics were used for all cancers, and metrics were separately calculated for each of the four most common types of cancer (colorectal, lung, breast, and prostate). Similar methods were used to those previously reported, with referral metrics data analysed as categorical variables by converting rates into quintiles (that is, five groups of equal population).

Cox proportional hazards regression was used to quantify the hazard of death from any cause in relation to referral metric quintiles, including for the four main cancer types. All analyses were adjusted for the age, sex, and socioeconomic status of the individual patients. The main analysis used a 5-year time window of follow-up from diagnosis to death, ending at the earliest of 5 years or the study end date in 2017.

Logistic regression was used to calculate the odds of late-stage (III/IV) versus early-stage (I/II) cancer at diagnosis in relation to referral quintiles. A further Cox proportional hazards regression was undertaken, in which stage at diagnosis (I to IV and missing) was taken into account. This was used to determine how much of the observed changes in mortality could potentially be related to stage at diagnosis (see Figure 1, with stage as a potential mediator between referral and mortality).

Stratified and sensitivity analyses were pursued to assess the consistency and internal validity of the findings, including a shared frailty random effects model to accommodate the multilevel structure of data where groups of patients with cancer belong to the same general practice list. All analyses were carried out with Stata 13 and 14.

RESULTS

Of 1,469,160 new cancer registrations between 2011 and 2015 (Figure 2), 57 registrations were excluded because of a negative duration of follow-up (that is, they were reported as having died before their cancer was registered). During follow-up, 660,606 deaths occurred (45.0%) for the increase in urgent referrals for suspected cancer from 2009/2010 to 2016/2017, and the impact on detection and conversion rates in England, see Supplementary Figure S1).

Cohort characteristics

Table 1 reports demographic and tumour-related characteristics of the 1,469,103 cancer registrations included. The four most common types of cancer were identified. They were: colorectal...
Higher practice referral (RR/DR/CR) quintiles were all significantly associated with lower odds of late-stage versus early-stage cancer at diagnosis \((P<0.001)\) (Table 3b). For the highest compared with lowest quintiles of RR and DR this equates to a two or three percentage point decrease in late-stage cancers at diagnosis.

After adjustment for stage at diagnosis, hazard ratios for the highest quintiles of RR and DR were attenuated (Table 3c compared with Table 3a), suggesting approximately half of the relative reductions in mortality for higher use of referral are potentially due to reductions in late-stage cancers at diagnosis. When stage was taken into account, higher CR quintiles were associated with a larger hazard of death \((HR = 1.05; CI = 1.04 to 1.06)\) for highest CR quintile.

The patterns of association were consistent for sensitivity analyses, including 1-year mortality, and from a shared frailty random effects model accounting for clustering in GP practices.

**Main cancer subtypes.** See Supplementary Tables S2 to S4 for a report of colorectal, lung, breast, and prostate cancer cohorts in relation to quintiles of their specific referral indices.

For the four most common cancer subtypes, similar significant associations were also found between higher RRs and lower hazard of death over 5 years \((P\text{-values of }<0.001, \text{ except for breast cancer }[P = 0.005])\).

Higher RRs were associated with lower odds of late- versus early-stage cancers at diagnosis (Supplementary Tables S2b to S5b) for all cancer types except for colorectal cancers.

When cancer stage was taken into account, hazard ratios for increasing RR were attenuated for all cancer types, except colorectal.

Table 4 summarises the percentage point difference from lowest to highest quintile of referral metrics (RR/DR/CR) for all cancers combined and most common types of cancer in relation to (a) 5-year mortality; (b) odds of late- versus early-stage cancers at diagnosis; and (c) 5-year mortality, taking stage into account. This demonstrates that a higher practice RR is significantly associated with lower cancer patient mortality and reduced late-stage diagnoses. This was found for all cancers and the most common types, except for late stage diagnosis for colorectal cancer. DR, and particularly CR, demonstrated less consistent associations.

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**Figure 2.** Flow diagram of study population with inclusions and exclusions.
Of the total number of cases, 51,640 (3.5%) did not have GP referral data available (see Supplementary Table 1b for characteristics). Although those cohorts with missing GP referral data were of similar age distribution to the total cohort, they had lower white population (75.4% white in the missing referral data group versus 89.9% in total cohort) and showed higher rates of social deprivation (21.3% from the most deprived quintile in the missing referral data group versus 16.8% in the overall cohort). The missing referral data group also had lower rates of cancer diagnosis following urgent referral (28.2% versus 35.3%), and higher rates of unknown stage at diagnosis (40.6% versus 32.9%) compared with the overall cohort. Of the total, 44,852 cases (86.9%) had a registered practice code but the missing referral data group also had lower rates of cancer diagnosis following urgent referral (28.2% versus 35.3%), and higher rates of unknown stage at diagnosis (40.6% versus 32.9%) compared with the overall cohort. Of the total, 44,852 cases (86.9%) had a registered practice code but the missing referral data group also had lower rates of cancer diagnosis following urgent referral (28.2% versus 35.3%), and higher rates of unknown stage at diagnosis (40.6% versus 32.9%) compared with the overall cohort. Of the total, 44,852 cases (86.9%) had a registered practice code but the missing referral data group also had lower rates of cancer diagnosis following urgent referral (28.2% versus 35.3%), and higher rates of unknown stage at diagnosis (40.6% versus 32.9%) compared with the overall cohort. 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Table 2. Quintiles of practice referral metrics (RR/DR/CR) for all cancers combined and specific cancer type

<table>
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<th>Practice referral indices</th>
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CR = conversion ratio. DR = detection ratio. RR = referral ratio.

Table 3. Analysis of mortality and stage for all cancers in relation to quintiles of referral metrics

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<th>Standardised RR quintiles</th>
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<th>U CI</th>
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χ² (one df) 106.4
P for trend <0.001

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<th>U CI</th>
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χ² (one df) 38
P for trend <0.001

CI = confidence intervals. CR = conversion ratio. df = degrees of freedom. DR = detection ratio. HR = hazard ratio. L = lower. OR = odds ratio. RR = referral ratio. U = upper.
practice did not have a full 5 years of referral data, primarily due to practice changes (for example, closure) or small list size (<1000). Cases numbering 6795 (13.2%) were without practice code, including those who were unregistered with a GP practice and those for whom NCRAS could not determine the registered practice.

Those with missing GP referral data were found to have an overall higher hazard of death over 5 years compared with those with practice referral data (HR = 1.15; CI = 1.14 to 1.17; P<0.001).

DISCUSSION
Summary
This analysis of >1.4 million patients diagnosed with cancer in England between 2011 and 2015 shows that a greater propensity to use referrals for suspected cancer was associated with lower mortality for all cancers combined and for the most common types of cancer. Significant reductions in late-stage cancers at diagnosis were found for patients from practices with higher RRs, including for the most common types of cancer, except for colorectal cancer, where there was not a significant association.

Overall, the accuracy in case selection for urgent referral (CR) was not significantly associated with mortality or stage at diagnosis. But when stage was taken into account there was an increase in mortality with the highest CR quintiles.

A large proportion (one-third to half) of the observed reduction in mortality with higher use of urgent referral is likely to be explained by earlier stage at diagnosis — except for colorectal cancer, where lead time or other confounders may play a more important role.

Cancer patients with missing GP referral data (due to their practice not having 5-years’ referral data or not having an identifiable practice) showed significantly higher mortality.

This study has demonstrated that lower mortality and a reduction in late-stage cancers at diagnosis are associated with higher referral use. This supports the hypothesis that increased primary care use of urgent suspected cancer referrals and associated diagnostic testing may reduce late-stage diagnoses and mortality of patients with cancer.36,35

Strengths and limitations
The analysis was based on the complete national population of England, using all CWT records and population-based cancer registrations for 2011–2015. This reduces biases that can arise from the waiting times paradox,16,28 where patients with short and long times to treatment are compared.37 Also, direct comparison of urgently referred and non-referred patients is subject to selection bias and confounding by indication.38,39

As effects on mortality were estimated by time to event [death], lead time may contribute to the observed effect. Lead-time research has been focused primarily on screening,40,41 and in particular breast42,43 and prostate cancers,44 with relatively little mention in early symptomatic diagnosis literature.27,45,46

The most likely causes of case-mix variation between the general practices were adjusted for.25,47,48 Similar associations were found in sensitivity analyses accounting for cancer patient clustering at a practice level43 and for both 1-year and 5-year mortality, suggesting robust results. However, as in any observational study, the possibility of confounding remains.38,47

With >4% of patients changing practice in the study cohort, this suggests that the registered GP practice referral metrics give an accurate indication of referral patterns for the majority of patients.

At a practice level, urgent referral metrics for a single year can be based on relatively small numbers of referrals and cancer cases, meaning they exhibit year-on-year random variation,28 with differences in case-mix29 and in referral selection accuracy and thresholds.51 By using 5-year aggregated metrics, year-on-year random variation is reduced (although not completely excluded) and reliability should be improved. Even for 1-year metrics, process measures such as referral rate were shown to demonstrate acceptable reliability,28 although longer time-intervals are likely required for cancer-specific referral metrics and outcome measures such as conversion and detection rates.

Outcome measures included all-cause mortality and late versus early stage at diagnosis, and then mortality analysis taking stage into account (I to IV and missing) (see Table 4a to 4c and Supplementary Tables S2 to S5 for details) to understand the potential impact of stage on observed mortality (Figure 1). Although approximately one-third of the cohort having missing stage means the subsequent mortality analysis is potentially less robust, over time stage is increasingly better recorded within cancer registration data.

Comparison with existing literature
This study confirms the association between higher overall practice utilisation
of suspected cancer referral pathways and lower patient mortality for all cancers, previously found for a single-year (2009) cohort study. It is also consistent with a previous study that showed an association between lower levels of referral from English general practices for gastroscopy (2006–2008) and worse patient outcomes for oesophageal-gastric cancers. In a study using data from 2012 on referral and cancer stage, higher use of urgent referral of patients with suspected cancer was associated with a smaller proportion of patients having advanced cancer. To the authors’ knowledge, this study for the first time included mortality, stage at diagnosis, and the impact of stage on mortality for all cancers and the most common types of cancer.

Table 4. Percentage point difference between lowest (Q1) to highest (Q5) quintiles of referral metrics for all cancers and the most common types of cancer

<table>
<thead>
<tr>
<th></th>
<th>Percentage point difference</th>
<th>RR</th>
<th>DR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 5-year mortality between Q1 to Q5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancers combined</td>
<td>-4%</td>
<td>-5%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>-3%</td>
<td>-2%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>-6%</td>
<td>-2%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>-4%</td>
<td>3%</td>
<td>-2%</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>-12%</td>
<td>-4%</td>
<td>-10%</td>
<td></td>
</tr>
<tr>
<td>(b) Odds of late- versus early-stage cancers at diagnosis between Q1 to Q5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancers combined</td>
<td>-3%</td>
<td>-4%</td>
<td>-2%</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>-1%</td>
<td>3%</td>
<td>-3%</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>-8%</td>
<td>2%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>-5%</td>
<td>14%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>-9%</td>
<td>8%</td>
<td>-9%</td>
<td></td>
</tr>
<tr>
<td>(c) 5-year mortality between Q1 to Q5 taking stage into account</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancers combined</td>
<td>-2%</td>
<td>-3%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>-6%</td>
<td>-2%</td>
<td>-2%</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>-3%</td>
<td>-2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>0%</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>-8%</td>
<td>-4%</td>
<td>-4%</td>
<td></td>
</tr>
</tbody>
</table>

*No statistically significant trend over quintiles. CR = conversion ratio. DR = detection ratio. RR = referral ratio.

Although this study focused on primary care and GP referrals for suspected cancer, there is clearly potential variation once patients are referred, including in the clinical practice of individual specialists, treatments offered, and in the wider healthcare system that are important to consider.

Implications for research and practice

The significant reduction in mortality between lower and higher use of urgent referral of between four and five percentage points approaches the magnitude of known and important differences between England and comparable countries. The number of referrals did increase over the period of the study and have continued to do so, with an associated increase in the number of cancer patients diagnosed following GP referral and a decrease in the proportion of cancer patients diagnosed via emergency routes, in whom there are worse outcomes, from 25% to 20%.

Further investigations are warranted into the different scale of impact on mortality and stage at diagnosis for other specific cancer-site referral pathways, including the effect of lead time in symptomatic diagnosis — which is under-researched — and other potential mediators. In particular, there is a need to understand reasons for the observed lack of mortality reduction when stage is taken into account for colorectal cancer patients. This could include the impact of colorectal screening programmes, or, more recently, the use of Faecal Immunochemical Testing (FIT) in both screening and symptomatic presentation. Further work is needed to understand the factors associated with variation in referral including at individual GP, and wider healthcare organisation levels.

Although this study focuses on symptomatic urgent referral pathways for all cancers combined and the four most common cancer types, cancers characterised by lower-risk non-specific presenting symptoms (for example, multiple myeloma or pancreas) are likely to have multiple GP consultations prior to referral and pose diagnostic challenges. Further development and implementation of evidence-based clinical decision tools including addressing issues around clinician cognitive error and the potential of future novel biomarkers are needed to aid earlier cancer detection — especially for difficult-to-diagnose cancer types.
This research adds to evidence supporting the policy of lowering referral thresholds from primary care and subsequent increased use of suspected cancer referral pathways. Recommendations supporting higher 2WW referral rates need to be tempered by an understanding of the healthcare system. Also, the health economic implications need to be further explored, especially given finite staff and resources, and the risks of overdiagnosis. With referrals in England (and other countries) increasing year on year, additional risk assessment and triage testing in primary care before referral for certain cancers, such as colorectal, may be indicated.

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Ethical approval
Ethics committee approval is not required for research based on routine data. Approval according to section 251 of the NHS Act 2006 applies to cancer registration and cancer intelligence in PHE.

Provenance
Freely submitted; externally peer reviewed.

Competing interests
Henrik Møller has an honorary contract with National Cancer Registration and Analysis Service (NCRAS) PHE, and Carolyn Gildea is employed by NCRAS PHE. There are no other relationships or activities that could appear to have influenced the submitted work.

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