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Association between use of urgent suspected cancer referral and mortality and stage at diagnosis:

a 5-year national cohort study

Abstract

Background
There 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
National cohort study of 1.4 million patients diagnosed with cancer in England between 2011 and 2015.

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] = 0.95 to 0.97), with similar patterns for individual cancers: colorectal (HR = 0.95; CI = 0.93 to 0.97); lung (HR = 0.95; CI = 0.94 to 0.97); breast (HR = 0.96; CI = 0.93 to 0.99); and prostate (HR = 0.88; CI = 0.85 to 0.91). Similarly, 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.

INTRODUCTION

Late diagnosis contributes to relatively worse cancer survival rates in the UK,[1,2] with longer diagnostic intervals associated with higher mortality.[3,4] Although most of those with cancer present symptomatically to primary care,[5,6] diagnosis of cancer is not straightforward.[7,8] Patient-, doctor-, and system-related factors can all contribute to longer cancer diagnostic intervals.[9–13] Concerns about potential diagnostic delays led to the implementation of urgent suspected cancer referral pathways,[14,15] 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,[16,17] whereas longer diagnostic intervals are associated with more advanced cancers at diagnosis.[18] The NICE suspected cancer referral guidelines were updated in June 2015,[19] lowering the risk threshold for referral. Referrals have been increasing by approximately 10% year on year, with >2 million referrals in England in 2018. As a result, more patients are being diagnosed with cancer following GP referrals, with significant reductions in those diagnosed via emergency routes.[20] There is significant variation between practices in their use of urgent suspected cancer referrals,[21–23] which has been a cause for concern.[24] 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.[25]

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).[26] Previously published evidence that higher practice use of urgent referral is associated with lower cancer patient mortality[27] 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.[14,23,28] 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.[27]

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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How this fits in

There is considerable variation in use of urgent referral for suspected cancer between general practices. This study shows a significant association between higher practice use of urgent referral for suspected cancer and lower cancer patient mortality (2011–2015), for all cancers combined and for the most common types of cancer (colorectal, lung, breast, and prostate). A significant proportion of this reduction in mortality is likely due to earlier stage at diagnosis for all cancers, except colorectal. This study supports the observed increased use of urgent referral for suspected cancer in primary care following the updated National Institute for Health and Care Excellence guidelines.

2011 and 2015 in England from PHE's National Cancer Registration and Analysis Service (NCRAS).[29] Demographic data included sex, deprivation, age at diagnosis, and vital status. For each tumour, data included diagnosis date, cancer type, stage at diagnosis, mortality, and the associated GP practice code.

These tumours were linked to GP practice metrics on urgent referrals for suspected cancer, derived from the English national Cancer Waiting Times (CWT) database.[30] These metrics were based on patients with a date of first hospital appointment or treatment recorded in financial years April 2011 to March 2016, relating to approximately 6.9 million urgent referrals for suspected cancer from >9000 English general practices. Those with missing practice-level referral metrics were analysed separately.

Three practice-level referral metrics[26] were used:

- practice referral ratio (RR) — indirectly standardised number of urgent referrals for suspected cancer, standardised according to the general practice's registered list, and age–sex distributions (mean value 1);
- practice detection rate (DR) — proportion of CWT-recorded cancers resulting from an urgent referral for suspected cancer (that is, the sensitivity of the selection of patients for urgent referral in the general practice); and,
- practice conversion rate (CR) — proportion of urgent referrals for suspected cancer that result in a diagnosis of cancer (that is, the positive predictive value [PPV] for cancer among the patients selected for urgent referral).

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,[27,31] 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[32,33] 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

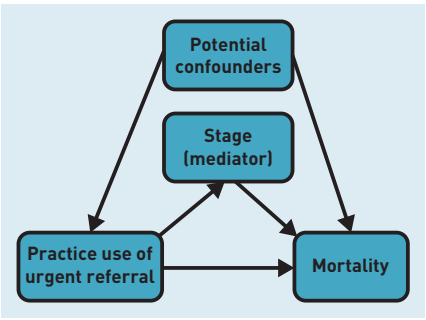
Of 1 469 160 new cancer registrations between 2011 and 2015 (Figure 2), 57 registrations were excluded because of a negative duration of follow-up (that is, they were reported as having died before their cancer was registered). During follow-up 660 606 deaths occurred (45.0%) (for the increase in urgent 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

Figure 1. Possible associations between practice use of urgent referral and mortality, in the presence of a mediator (stage).



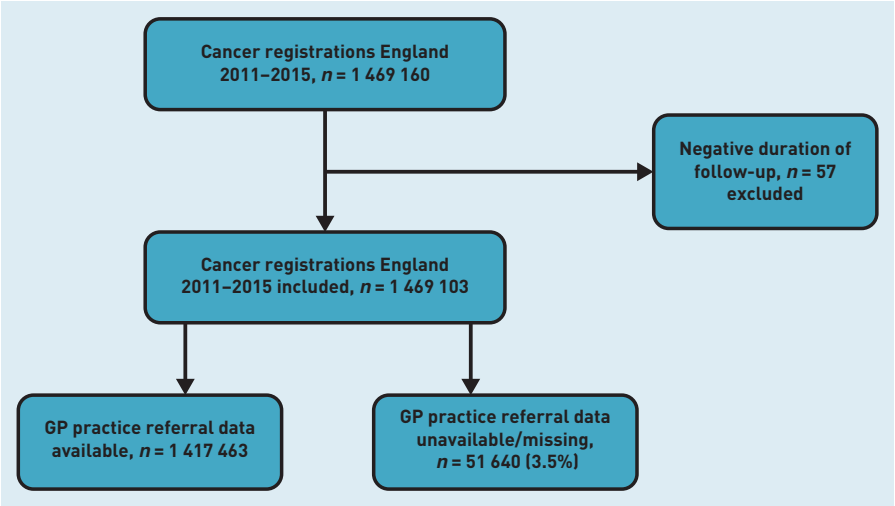


Figure 2. Flow diagram of study population with inclusions and exclusions.

(*n* = 173 293; 11.8%), lung (*n* = 186 018; 12.7%), breast (*n* = 221 695; 15.1%), and prostate (*n* = 196 745; 13.4%), together accounting for 52.9% of the cohort. One-third (32.9%) of the cohort had missing stage data, with variation by cancer type. Separate analysis was done of the 51 640 (3.5%) cancer registrations with missing 5-year GP referral data (see Supplementary Table S1 for details). Analysis of the cohort showed that approximately 1% of cancer patients changed practice within 4 months of referral, and approximately 2.5% changed practice within 4 months of diagnosis.

Distributions of referral metrics

Table 2 reports values for the three practice referral metrics. For all cancers combined, RR medians varied from 0.67 to 1.36, DR medians from 0.38 to 0.56, and CR medians from 0.06 to 0.13. Practices in the highest referral ratio quintile utilised the urgent referral pathway approximately twice as much as those in the lowest quintile.

Mortality and stage analysis

All cancers. Table 3 shows 5-year all-cause mortality, odds of late- versus early-stage cancer at diagnosis, and mortality taking stage into account, in relation to quintiles of practice referral metrics.

Higher RR and DR quintiles were both significantly associated (*P*<0.001) with lower hazard of death for all cancer patients (Table 3a), with four and five percentage point reductions in mortality, respectively. Moving from lowest to highest quintiles for RR and DR showed a consistent significant trend in the association with lower mortality. CR was not significantly associated with mortality (*P* = 0.872).

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*-values of <0.001, 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.

Table 1. Characteristics of the study cohort

	Colorectal		Lung		Breast		Prostate		Other		Total	
Variable	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Year of diagnosis												
2011	34 781	20.1	35 849	19.3	41 937	18.9	36 768	18.7	131 811	19.1	281 146	19.1
2012	35 241	20.3	37 250	20.0	43 038	19.4	38 082	19.4	135 742	19.6	289 353	19.7
2013	34 269	19.8	37 410	20.1	44 770	20.2	41 355	21.0	140 997	20.4	298 801	20.3
2014	34 279	19.8	37 868	20.4	46 166	20.8	40 231	20.4	141 297	20.4	299 841	20.4
2015	34 723	20.0	37 641	20.2	45 784	20.7	40 309	20.5	141 505	20.5	299 962	20.4
Male	96 306	55.6	100 512	54.0	0	0.0	196 745	100.0	356 394	51.6	749 957	51.0
Female	76 987	44.4	85 506	46.0	221 695	100.0	0	0.0	334 958	48.4	719 146	49.0
Age band in years at diagnosis												
0–9	17	0.0	11	0.0	0	0.0	6	0.0	5092	0.7	5126	0.3
10–19	382	0.2	20	0.0	15	0.0	0	0.0	4736	0.7	5153	0.4
20–29	955	0.6	168	0.1	1070	0.5	6	0.0	15 357	2.2	17 556	1.2
30–39	2475	1.4	603	0.3	8082	3.6	35	0.0	25 238	3.7	36 433	2.5
40–49	6533	3.8	4017	2.2	33 845	15.3	2108	1.1	50 157	7.3	96 660	6.6
50–59	18 881	10.9	17 466	9.4	47 260	21.3	20 139	10.2	92 720	13.4	196 466	13.4
60–69	41 841	24.1	49 054	26.4	56 719	25.6	66 511	33.8	160 391	23.2	374 516	25.5
70–79	52 402	30.2	63 508	34.1	39 089	17.6	70 260	35.7	178 541	25.8	403 800	27.5
80–89	41 661	24.0	43 782	23.5	28 181	12.7	32 241	16.4	131 084	19.0	276 949	18.9
≥90	8146	4.7	7389	4.0	7434	3.4	5439	2.8	28 036	4.1	56 444	3.8
Ethnicity												
White	151 041	87.2	162 955	87.6	185 967	83.9	163 013	82.9	588 007	85.1	1 250 983	85.2
Mixed	436	0.3	395	0.2	973	0.4	648	0.3	2542	0.4	4994	0.3
Asian	2634	1.5	2226	1.2	5788	2.6	2831	1.4	16 146	2.3	29 625	2.0
Black	2090	1.2	1499	0.8	3700	1.7	5493	2.8	9681	1.4	22 463	1.5
Chinese	374	0.2	333	0.2	580	0.3	232	0.1	1459	0.2	2978	0.2
Other	1445	0.8	1316	0.7	2312	1.0	1448	0.7	6788	1.0	13 309	0.9
Unknown	15 273	8.8	17 294	9.3	22 375	10.1	23 080	11.7	66 729	9.7	144 751	9.9
Deprivation quintile												
1 — Least deprived	39 133	22.6	27 661	14.9	52 523	23.7	50 180	25.5	147 216	21.3	316 713	21.6
2	39 222	22.6	33 855	18.2	50 806	22.9	47 269	24.0	151 352	21.9	322 504	22.0
3	36 421	21.0	37 795	20.3	46 244	20.9	40 889	20.8	143 742	20.8	305 091	20.8
4	32 209	18.6	41 363	22.2	40 004	18.0	32 820	16.7	132 040	19.1	278 436	19.0
5 — Most deprived	26 308	15.2	45 344	24.4	32 118	14.5	25 587	13.0	117 002	16.9	246 359	16.8
Stage at diagnosis												
I	23 543	13.6	24 724	13.3	82 528	37.2	52 736	26.8	133 428	19.3	316 959	21.6
II	35 968	20.8	13 127	7.1	73 156	33.0	34 749	17.7	55 482	8.0	212 482	14.5
III	39 418	22.7	34 234	18.4	17 429	7.9	31 140	15.8	59 427	8.6	181 648	12.4
IV	36 214	20.9	87 066	46.8	11 119	5.0	31 960	16.2	108 842	15.7	275 201	18.7
Not known	38 150	22.0	26 867	14.4	37 463	16.9	46 160	23.5	334 173	48.3	482 813	32.9
2WW referral group												
2WW	55 641	32.1	55 806	30.0	98 517	44.4	88 507	45.0	219 732	31.8	518 203	35.3
Not a 2WW	76 961	44.4	75 999	40.9	87 754	39.6	60 232	30.6	244 595	35.4	545 541	37.1
Tumour not in CWT database	40 691	23.5	54 213	29.1	35 424	16.0	48 006	24.4	227 025	32.8	405 359	27.6
Total	173 293	11.8	186 018	12.7	221 695	15.1	196 745	13.4	691 352	47.1	1 469 103	

2WW = two-week wait. CWT = Cancer Waiting Times.

Missing GP referral data

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

Table 2. Quintiles of practice referral metrics (RR/DR/CR) for all cancers combined and specific cancer type

Practice referral indices		Total (all cancers combined)			Colorectal			Lung			Breast			Prostate		
	Quintiles	*N*	%	Median	*N*	%	Median	*N*	%	Median	*N*	%	Median	*N*	%	Median
RR quintiles	Q1	283 567	19.3	0.67	33 500	19.3	0.60	35 748	19.2	0.52	43 006	19.4	0.61	38 062	19.3	0.59
	Q2	283 510	19.3	0.86	33 529	19.3	0.82	35 790	19.2	0.77	42 924	19.4	0.86	38 037	19.3	0.83
	Q3	283 408	19.3	1.00	33 476	19.3	0.99	35 708	19.2	0.98	42 965	19.4	1.02	38 042	19.3	1.00
	Q4	283 580	19.3	1.14	33 505	19.3	1.16	35 755	19.2	1.25	42 955	19.4	1.18	38 057	19.3	1.18
	Q5	283 398	19.3	1.36	33 479	19.3	1.45	35 736	19.2	1.81	42 961	19.4	1.44	38 035	19.3	1.49
	Missing	51 640	3.5		5804	3.3		7281	3.9		6881	3.1		6512	3.3	
DR quintiles	Q1	283 796	19.3	0.38	33 786	19.5	0.20	36 576	19.7	0.17	43 096	19.4	0.34	38 220	19.4	0.39
	Q2	283 615	19.3	0.44	36 006	20.8	0.31	34 949	18.8	0.32	43 866	19.8	0.42	38 112	19.4	0.52
	Q3	283 702	19.3	0.48	34 597	20.0	0.38	35 821	19.3	0.40	42 038	19.0	0.48	37 774	19.2	0.59
	Q4	283 559	19.3	0.51	30 019	17.3	0.43	35 669	19.2	0.47	43 041	19.4	0.54	38 620	19.6	0.67
	Q5	282 791	19.3	0.56	33 058	19.1	0.52	35 697	19.2	0.57	42 762	19.3	0.63	37 443	19.0	0.76
	Missing	51 640	3.5		5827	3.4		7306	3.9		6892	3.1		6576	3.3	
CR quintiles	Q1	283 585	19.3	0.06	33 614	19.4	0.02	35 777	19.2	0.09	43 128	19.5	0.06	38 101	19.4	0.06
	Q2	283 585	19.3	0.08	33 416	19.3	0.04	35 797	19.2	0.17	43 178	19.5	0.08	37 993	19.3	0.09
	Q3	283 308	19.3	0.09	33 518	19.3	0.05	35 669	19.2	0.22	42 669	19.3	0.09	38 800	19.7	0.11
	Q4	283 657	19.3	0.10	33 520	19.3	0.06	36 086	19.4	0.27	42 871	19.3	0.11	37 334	19.0	0.14
	Q5	283 328	19.3	0.13	33 476	19.3	0.08	35 382	19.0	0.33	42 965	19.4	0.15	38 003	19.3	0.18
	Missing	51 640	3.5		5749	3.3		7307	3.9		6884	3.1		6514	3.3	

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

(a) 5-year HR-based (adjusted for age, sex, socioeconomic status)

Standardised RR quintiles	HR	L CI	U CI	DR quintiles	HR	L CI	U CI	CR quintiles	HR	L CI	U CI
1	1.00	1	1.00	1	1.00						
2	0.98	0.98	0.99	2	0.98	0.97	0.98	2	1.02	1.02	1.03
3	0.97	0.96	0.98	3	0.97	0.96	0.98	3	1.02	1.01	1.03
4	0.97	0.96	0.98	4	0.96	0.95	0.97	4	1.00	1.00	1.01
5	0.96	0.96	0.97	5	0.95	0.94	0.95	5	1.01	1.01	1.02
χ^2 (one df)	106.4			χ^2 (one df)	187.9			χ^2 (one df)	0.03		
P for trend	<0.001			*P* for trend	<0.001			*P* for trend	0.872		

(b) Odds of stage III/IV versus I/II cancer at diagnosis (adjusted for age, sex, socioeconomic status)

Standardised RR quintiles	OR	L CI	U CI	DR quintiles	OR	L CI	U CI	CR quintiles	OR	L CI	U CI
1	1.00	1	1.00	1	1.00						
2	0.99	0.98	1.00	2	0.97	0.96	0.98	2	0.99	0.98	1.01
3	0.97	0.96	0.98	3	0.98	0.96	0.99	3	0.98	0.97	0.99
4	0.97	0.95	0.98	4	0.97	0.96	0.99	4	0.97	0.96	0.98
5	0.97	0.95	0.98	5	0.96	0.94	0.97	5	0.98	0.97	1.00
χ^2 (one df)	38			χ^2 (one df)	26.1			χ^2 (one df)	14.7		
P for trend	<0.001			*P* for trend	<0.001			*P* for trend	<0.001		

(c) 5-year HR (adjusted for age, sex, socioeconomic status) and adjusted for stage

Standardised RR quintiles	HR	L CI	U CI	DR quintiles	HR	L CI	U CI	CR quintiles	HR	L CI	U CI
1	1.00	1	1.00	1	1.00						
2	0.99	0.98	1.00	2	0.99	0.98	1.00	2	1.04	1.03	1.05
3	0.99	0.98	1.00	3	0.98	0.98	0.99	3	1.05	1.04	1.06
4	0.98	0.98	0.99	4	0.97	0.97	0.98	4	1.04	1.03	1.05
5	0.98	0.97	0.98	5	0.97	0.96	0.97	5	1.05	1.04	1.06
χ^2 (one df)	31.9			χ^2 (one df)	96.7			χ^2 (one df)	100.9		
P for trend	<0.001			*P* for trend	<0.001			*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.[34,35]

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,[16,36] 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 breast[42,43] 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 level[33] and for both 1-year and 5-year mortality, suggesting robust results. However, as in any observational study, the possibility of confounding remains.[38,49]

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-mix[50] 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

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

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

[a]No statistically significant trend over quintiles. CR = conversion ratio. DR = detection ratio. RR = referral ratio.

of suspected cancer referral pathways and lower patient mortality for all cancers,[27] previously found for a single-year (2009) cohort study.[23] 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.[52]

In a study using data from 2012 on referral and cancer stage,[53] 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.

As noted, there have been studies investigating the reliability of these routinely collected practice measures[28,50,51] and around practice and GP characteristics associated with their use.[47,54]

Higher practice CRs were associated with higher mortality when stage was taken into account for all cancers, suggesting worse outcomes. This could be due to a high threshold for referral by some GPs, with research showing an association between CRs and individual GP decision making.[55]

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[31] that are important to consider.[56]

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.[57,58] 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,[39] from 25% to 20%.[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[41,46] 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,[55] practice,[47] and wider healthcare organisation levels.[56]

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[59] and pose diagnostic challenges.[25] Further development and implementation of evidence-based clinical decision tools,[34,60] including addressing issues around clinician cognitive error[61,62] and the potential of future novel biomarkers[60,63] 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.[19] 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,[34] especially given finite staff and resources,[64] and the risks of overdiagnosis.[64,65] 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,[60,63] 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 Carolynn 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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