Age-related and socio-economic inequalities in timeliness of referral and start of treatment in colorectal cancer. A population-based analysis

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ABSTRACT

Background: Poorer colorectal cancer survival in the United Kingdom than in similar countries may be partly due to delays in the care pathway. To address this, cancer waiting time targets were established. We investigated if socio-demographic inequalities exist in meeting cancer waiting times for colorectal cancer.

Methods: We identified primary colorectal cancers (ICD10 C18-C20; n=35,142) diagnosed 2001-2010 in the Northern & Yorkshire Cancer Registry area. Using multivariable logistic regression, we calculated likelihood of referral and treatment within target by age-group and deprivation quintile.

Results: 48% of patients were referred to hospital within target (≤14 days from GP referral to first hospital appointment); 52% started treatment within 31 days of diagnosis; and 44% started treatment within 62 days of GP referral. Individuals aged 60-69, 70-79 and 80+ were significantly more likely to attend a first hospital appointment within 14 days than those <60 years (adjusted OR=1.23 [1.12, 1.34]; 1.19 [1.09, 1.29]; 1.30 [1.18, 1.42] respectively). Older age was significantly associated with reduced likelihood of starting treatment within 31 days of diagnosis and 62 days of referral. Deprivation was not related to referral within target, but was associated with lower likelihood of starting treatment within 31 days of diagnosis or 62 days of referral (most vs least:0.82 [0.74-0.91]).

Conclusions: Older colorectal cancer patients were less likely to experience referral delays but more likely to experience treatment delays. More deprived patients were more likely to experience treatment delays. Investigation of patient pathways, treatment decision-making and treatment planning would improve understanding of these inequalities.

Keywords: colorectal cancer, inequalities, registry, population-based, delays, referral, treatment

What is already known about this subject?

- Pronounced socio-demographic inequalities in receipt of colorectal cancer treatment have been demonstrated in many healthcare settings, including the UK.
- It is unclear whether similar inequalities exist in timeliness of referral or start of treatment.

What this study adds

- In this large population-based study, older colorectal cancer patients were significantly less likely to experience referral delays but more likely to experience treatment delays.
- The most deprived patients were significantly more likely to experience treatment delays.
- Timeliness and equity are key features of high quality healthcare. Implementation of strategies to reduce these inequalities could reduce psychological distress and improve patient experiences of cancer care.

INTRODUCTION

Survival from many cancers is lower for patients in the UK than in similar countries.[1] For example, 5-year age-standardised net survival in the UK for patients diagnosed in 2010-2014 was 58.9% for colon cancer and 62.1% for rectal cancer, lower than in Norway, Ireland, Denmark, New Zealand, Canada and Australia, where rates of 65-71% were reported.[2] This pattern has been evident for colorectal (and other) cancers diagnosed since the late 1970s. While UK survival rates have increased in recent years, improvements have also been seen elsewhere,[3] so the survival gap has not narrowed.[4]

Evidence suggests that this survival gap is due, at least in part, to later stage diagnosis alongside inequalities in access to optimal treatment.[5,6] Both diagnosis and treatment can be subject to delays. Indeed delays can exist across the entire cancer care "pathway" from the first symptom noted by the individual through diagnosis to treatment initiation.[7,8] These delays can be attributed to both patient behaviour and limitations in the healthcare provider or system.[8]

The NHS Cancer Plan for England, published in 2000, recognised the possibility of healthcare provider or system delays in cancer and established, for the first time, cancer waiting time targets.[9] A target of 14 days between urgent referral (usually from a GP) with symptoms suggesting cancer and first assessment by a specialist was established in 2000. For those subsequently diagnosed with cancer, treatment should start within 62 days of referral. Since 2005, there has also been a target of 31 days between the date of the decision-to-treat and start of treatment.

Equity and timeliness are key features of high-quality healthcare.[10] Despite this, persistent and pronounced socio-demographic inequalities in colorectal cancer treatment receipt have been reported. Population-based studies show that older patients and those of lower socio-economic status are less likely to receive cancer-directed, or guideline recommended, treatment (see, for example, [11-14]).

It is less clear whether similar inequalities exist in relation to the cancer waiting time targets or, more generally, in timeliness of referral, diagnosis or start of treatment. In the only UK study, of lung cancer, older patients (aged 80+) were 20% less likely to start treatment within 31 days than younger patients (<60).[15] North American colorectal cancer studies have reported that older patients have longer times between referral and diagnosis or first treatment.[16,17] As regards socio-economic

status, in Denmark, among a mixed group of cancer patients, those with higher household incomes experienced shorter healthcare system delays[18] while modestly-sized, non population-based, studies in Germany, Jordan and Spain have reported socio-economic patterning in treatment delays for colorectal cancer patients.[19-21] Evidence from the UK is lacking.

We undertook a large, population-based, study to investigate age and socio-economic inequalities in whether the cancer waiting time targets are met for colorectal cancer in England.

METHODS

Setting & Data sources

Data were abstracted on primary colorectal cancers (ICD10 C18-C20) diagnosed 2001-2010 from the Northern and Yorkshire Cancer Registry (NYCRIS), which covers a population of 6.8 million resident in the North East and most of the Yorkshire and the Humber regions. Cancer notification is mandatory; hospitals report cases directly to NYCRIS and this is supplemented by manual data collection. The area comprises some densely population urban centres and large rural expanses. Cancer care is almost entirely provided in NHS hospitals. At the time of the study, the area had three cancer networks, each with several cancer units and a cancer centre providing integrated services. The Bowel Cancer Screening Programme, offering home-based faecal occult blood tests, commenced in 2006.

Data were available on age at diagnosis, deprivation category of area of residence at diagnosis (a proxy for socioeconomic status (SES) measured using the rank of the income domain of the Index of Multiple Deprivation (IMD))[22], sex, diagnosis date, tumour site, stage and cancer-directed treatments (surgery, radiotherapy, chemotherapy) received by 31/12/2011. Where available, information was extracted on dates of referral to hospital by general practitioner (GP), first hospital appointment and first cancer-directed treatment. Each record was linked to NHS Hospital Episode Statistics (HES) data to provide information on comorbidities. Cancers registered from death certificates only were excluded (n=644) as were those with no HES link (n=8,950), leaving 35,142 patients in the dataset.

The study was approved by the NRES Committee East of England REC on 13/12/2011 (reference 11/EE/0537) and performed in accordance with the Declaration of Helsinki.

Outcome variables

Three binary outcome variables were created representing whether the interval (i) between referral and first hospital appointment was ≤14 days (henceforth "referral interval"); (ii) between diagnosis and first treatment was ≤31 days ("diagnosis-treatment interval"); and (iii) between referral and first treatment was ≤62 days ("referral-treatment interval"). Cases with implausible intervals (e.g. treatment date before referral date) were excluded. The referral interval was created for patients for whom dates of GP referral and first hospital appointment (surrogate for date of first assessment by a specialist) were recorded (n=19,798). The diagnosis-treatment interval was created for patients for whom dates of cancer diagnosis (surrogate for the date of the decision-to-treat) and first cancer-directed treatment were recorded (n=29,445). The referral-treatment interval was created for patients for whom dates of GP referral and first cancer-directed treatment were recorded (n=17,622). Where dates were not recorded for patients, we assumed they did not apply (e.g. the patient was not referred by a GP).

Explanatory variables

The two main explanatory variables were age (categorised as <60, 60-69, 70-79 and 80+ years) and deprivation category (grouped into fifths, based on the national distribution, with the lowest fifth ("1") representing least deprived areas and "5" representing most deprived). IMD2007 was used for patients diagnosed 2001-2006 and IMD2010 for those diagnosed 2007 onwards.

To explore whether timeliness had changed over time, year of diagnosis was grouped: 2001-2005/2006-2010. Cancer stage, assigned using TNM, was categorised as I, II, III, IV, unstaged or staged post-treatment. Cancer site was grouped as colon or rectum. Comorbidities influence treatment decisions and prognosis in colorectal cancer.[23,24] NYCRIS provided a weighted comorbidity score based on the Charlson comorbidity index (CCM),[25] using the number of relevant in-patient admissions (excluding metastatic cancer) recorded in HES in the 3-18 months before the cancer diagnosis (Supplementary table S1). This score was categorised based on the observed distribution: none/1-2/3+ comorbidities. Patients were categorised by the first cancer-directed treatment they received (cancer-directed surgery/radiotherapy/ chemotherapy).

Statistical analyses

For each interval (referral; diagnosis-treatment; and referral-treatment), the number and percentage of cases referred and treated within target was calculated overall and by age-group, deprivation category, and for the other variables. Logistic regression models were used to estimate the odds of referral or treatment within target by age-group and deprivation category with and

without adjustment for other variables. The three outcomes were modelled separately. We considered variables that were significant in univariate analyses for inclusion in multivariable models. We took care to avoid multicollinearity and also eliminated variables that caused poor model fit. Cancer site and type of first treatment are strongly correlated; we therefore adjusted the referral interval model for site (as this is more pertinent to diagnosis) and the diagnosis-treatment and referral-treatment interval models for first treatment. A variable categorising referral interval (≤14/>14 days) was considered for inclusion in the referral-treatment model. Likelihood ratio tests were used to determine the overall statistical significance of each variable in the final models. Final models had adequate fit.

RESULTS

Table 1 shows socio-demographic and clinical characteristics of the 35,142 cases. 19,798 (56%) were referred by a GP to hospital and were included in the referral interval analysis; 29,445 (84%) received cancer-directed treatment and were included in diagnosis-treatment interval analysis; and 17,622 (50%) were referred by a GP and had cancer-directed treatment and were included in the referral-treatment interval analysis. Sixteen percent of the colorectal cancers were aged ≤60 at diagnosis, 24% were 60-69, 34% were 70-79 and 25% were 80+. Slightly less than one fifth were resident in the least deprived areas, 57% were male, 61% had colon cancer, 35% had stage I or II disease and 13% had comorbidities. In general, compared to this full dataset, the cases included in the referral interval, diagnosis-treatment interval and referral-treatment interval analyses were slightly younger and more often earlier stage, but the distribution across deprivation categories was similar.

Referral interval

Overall, 48% of cases referred to hospital by a GP had their first hospital appointment within 14 days. The median referral interval was 16 days (interquartile range (IQR) 9-37 days)(Supplementary table S2).

Likelihood of attending a first hospital appointment within 14 days of GP referral is shown in Table 2. In adjusted analysis individuals aged 60-69, 70-79 and 80+ were significantly more likely to attend a first hospital appointment within 14 days than those aged <60 years (OR [95% CI]=1.23 [1.12, 1.34]; 1.19 [1.09, 1.29]; 1.30 [1.18, 1.42] respectively). No significant association between timely first hospital appointment and deprivation was found, although the likelihood of timely referral was (non-significantly) 5% lower in those resident in the most, compared to the least, deprived fifth.

Other factors significantly associated with being more likely to have timely referral were: having rectal cancer and having disease that was more advanced than stage I.

Diagnosis-treatment interval

Fifty-two percent of cases started treatment within 31 days of cancer diagnosis. The median diagnosis-treatment interval was 30 days (IQR 5-49 days) (Supplementary table S2).

Older age was significantly associated with reduced likelihood of starting treatment within 31 days of diagnosis (Table 3); after adjustment those aged 60-69, 70-79, and 80+ had reduced odds compared to those aged <60 (0.74 [0.68, 0.80]; 0.68 [0.63, 0.73]; and 0.77 [0.71, 0.84] respectively). Deprivation was significantly associated with reduced likelihood of starting treatment within target. Those resident in deprivation categories 4 and 5 were 9% less likely to receive timely treatment than those resident in deprivation category 1. Other variables significantly associated with being less likely to start treatment within 31 days of diagnosis were being male and having chemotherapy and/or radiotherapy as the first treatment. More advanced disease was significantly associated with starting treatment within 31 days.

Referral-treatment interval

Overall, 44% of cases referred by a GP started treatment within 62 days of referral. The median referral-treatment interval was 61 days (IQR 49-105 days) (Supplementary table S2).

In multivariable analyses, compared to those aged <60, the two oldest age groups had 10% and 12% lower odds, respectively, of starting treatment within 62 days (Table 4). Likelihood of starting treatment within target decreased with increasing deprivation and was 0.82 [0.75-0.91] for those in the most, compared to the least, deprived category. Other factors significantly associated with not starting treatment within 62 days of GP referral were: a referral interval of ≤14 days, receiving radiotherapy and/or chemotherapy as the first treatment and more advanced stage disease.

DISCUSSION

During 2001-2010, only 48% of colorectal cancer patients referred by a GP attended a first hospital appointment within the national target of 14 days, 52% started treatment within 31 days of diagnosis and 44% waited ≤62 days between GP referral and start of treatment. Older age was

significantly positively associated with having a first hospital appointment within target, but negatively associated with starting treatment within 31 days of diagnosis or 62 days of GP referral. Greater deprivation was significantly associated with being less likely to start treatment within 31 days of diagnosis and 62 days of GP referral; the effect was more pronounced for the referral-treatment interval and remained after adjustment for having a first hospital appointment within 14 days of GP referral.

Strengths & Limitations

To our knowledge, this is the first UK population-based study of inequalities in timeliness of colorectal cancer diagnosis and treatment. Although the data source (NYCRIS) has a high level of completeness,[14] it covers only the north of England, potentially limiting generalisibility. Nationally, in 2006-2008, 65% of colorectal cancers were diagnosed through a route originating from a GP referral; the remainder were emergency presentations (26%), screen-detected (2%), identified as having cancer only at the time of death (1%) or had an unknown route (6%).[26] In our analysis, 56% (19,798/35,142) of cases had GP referral and first cancer-directed treatment dates, suggesting that some cases which originated at the GP may be missing from our analyses, perhaps because referral dates were not recorded either in medical records or by the Registry. Since our focus was comparisons *within* the group of patients referred by GPs, this is unlikely to impact internal validity. Eighty-four percent (29,445/35,142) of the study population were included in the diagnosis-treatment interval analysis, broadly consistent with the proportion of colorectal cancers reported as having cancer-directed treatment in other European population-based series.[12] Although we accounted for comorbidity, the Charlson index as applied to HES data captures information only on conditions requiring an in-patient stay, meaning we probably underestimated comorbidity. Socio-economic status was assessed using an area-based measure so may be subject to some misclassification.

GPs can refer patients with suspected cancer symptoms as urgent or non-urgent (standard) and the 14 day target technically applies only to urgent referrals. A weakness of the data is that we were unable to distinguish between urgent and non-urgent referrals. In addition, we did not have access to data after 2010. It is important to determine whether socio-demographic variations remain, especially given that the national operational standards for timely referral and treatment are frequently missed.[27]

The 31 day target refers to the time from decision-to-treat. NYCRIS does not record this date, so we used date of diagnosis as a proxy. These two dates may differ for some patients, meaning it is likely we have slightly overestimated the length of the diagnosis-treatment interval. Whether this difference will be differential by socio-demographic factors is unclear. In addition, no information was available on any cancer-directed treatments other than surgery, chemotherapy or radiotherapy.

Interpretation of findings

The "waiting time paradox", where people who are more obviously unwell are referred more quickly but have worse outcomes, is well recognised in cancer.[28] Older cancer patients more often have multiple comorbidities.[29] Thus, one explanation for the relationship between older age and more rapid referral is that patients who have multiple health problems (and seem sicker) are more likely to be urgently referred. However, we adjusted for comorbidities, albeit imperfectly, so it seems unlikely that this is the full explanation. Older patients may be more likely to present with "alarm symptoms" (e.g. rectal bleeding). New onset alarm symptoms are more predictive of cancer in older people.[30] Because of this, and because colorectal cancer incidence increases with age, GPs' index of suspicion of cancer may be higher in older than younger patients hence stimulating urgent referral of older patients. "Direct to test" services - where younger, fit, patients go straight from the GP to colonoscopy, while older patients (especially the oldest old) wait for an initial specialist appointment, then may have a less invasive test (such as CTC or barium enema) before cancer diagnosis- are also likely to result in a shorter interval from referral to cancer diagnosis in younger patients.

There was a modest (albeit non-significant) association between greater deprivation and lower likelihood of being seen at hospital within 14 days of GP referral, consistent with UK lung cancer findings.[15] In general, lower socio-economic status is associated with suboptimal healthcare use, perhaps due to more limited health literacy translating into difficulty navigating healthcare systems.[31] Research on barriers to medical help-seeking around cancer shows people of lower socio-economic status are less confident talking to the GP about symptoms.[32] raising the possibility that higher socio-economic status patients are better able to articulate symptoms and problems stimulating urgent referral.

The diagnosis-treatment interval is the window within which treatment decisions are made and patients readied for treatment. Assessing patient suitability for treatment may take longer in older patients particularly if geriatric assessments or referral to other specialities (e.g. cardiology) are

needed; this information is not generally recorded by cancer registries. Limitations in physical functioning and/or nutritional status, such as sarcopenia, malnourishment and iron-deficiency anaemia, are more common in older colorectal cancer patients.[33,34] Patients may need interventions to address these before undergoing surgery. This could delay start of treatment and explain the observed negative association between increasing age and likelihood of starting treatment within 31 days.

The observed association between greater deprivation and lower likelihood of starting treatment within 31 days of diagnosis, or 62 days of referral, is consistent with associations between delayed treatment and lower education and general (vs private) health insurance in Spain[21] and Germany,[19] respectively. Colorectal cancer patients with lower socio-economic status more often have comorbid conditions[29] which may lengthen treatment planning. We adjusted for comorbidities, but residual confounding is possible.

The increasing emphasis on patient-centred care in the NHS has led to more shared and informed decision-making. Past work shows that lack of comprehension by patients (as a result of poor health literacy) of risks and benefits of elective surgery can lead to decision conflict.[35] We might, therefore, speculate that, as a result of limited health literacy, colorectal cancer patients from more deprived areas may struggle with treatment decision making and this could lead to delays; however, we are not aware of any empirical data supporting this.

Implications

Although evidence is inconsistent on whether more rapid referral influences stage at diagnosis and more rapid start of treatment influences survival (at least when relatively short time windows are considered),[36-37] timeliness and equity are key elements of high quality healthcare.[10] Moreover, the time waiting for a hospital appointment to investigate suspected cancer or for treatment to start in those with a confirmed diagnosis is associated with considerable patient anxiety and distress.[38,39] Therefore, given that the NHS has set cancer waiting time targets, the system should seek to provide all patients with a definitive diagnosis and to start treatment in a timely manner.

The question then arises of how to achieve this. Some encouraging findings have been reported for patient navigation programmes, which are intended to promote access to timely cancer diagnosis and treatment.[40] This raises the possibility that allocating some patients (perhaps those who are older, more deprived, or have inadequate health literacy) a designated navigator, from within the

hospital care team, could help shorten the time to treatment and reduce or eliminate some of the disparities observed here.

However, there may be disadvantages of rapid diagnosis or treatment commencement; Canadian studies show that colorectal cancer patients who waited longer for diagnosis or treatment more often received higher quality care.[41,42] While we were unable to measure clinical aspects of quality of care, these findings indicate that relationships between timeliness, utilization and care quality are complex.

The findings here – both in terms of the proportions of patients first seen at hospital or treated within target, and the socio-demographic patterning - raise many questions. Research is needed to quantify: how many, and which, patients need additional time to make treatment decisions; how often more time is needed for treatment planning (e.g. for complex patients) or prehabilitation; and how often failures to meet targets are due to lack of capacity, lack of equipment or delays reporting test results. Recent qualitative research in Northern England among upper GI cancer patients diagnosed through the two-week wait pathway found that they often have complex diagnostic journeys visiting multiple hospital and primary care sites and may wait considerable time for results of tests and investigations.[43] Further research is needed to shed light on patient pathways, treatment decision-making and treatment planning overall and for different patient subgroups. This would help better understand inequalities like those reported here, why the system fails to meet the national operating standards[27] and what changes are needed if these standards are to be met.

The 2000 NHS Cancer Plan stated that *"Where patients wait longer, this should be because of the needs of the diagnostic process or their personal choice, not because of built-in delays in the system of care"*.[9] Addressing the socio-demographic inequalities observed here in relation to timely referral and start of treatment for colorectal cancer may require changes in care pathways.

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Data Availability Statement

The data used in the study are not owner by the authors. They were released by the data controller to the authors solely for the purpose of the research study and the authors do not have permission to share them with others. Public Health England is the current data controller and data for the same population may be requested through PHE's Office of Data Release.

Contributors

LH: undertook the data analyses and co-wrote the paper; **LS**: advised on the data analysis and co-wrote the paper; **JA, IM, LF, MH**, and **MW**: contributed to the study design, supervision and interpretation of data and commented critically on manuscript drafts.

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Table 1. Demographic and clinical characteristics of colorectal cancers diagnosed 2001-2010, and included in the analyses

	Overall (n=35,142)	Referral interval analysis[1] (n=19,798)	Diagnosis-treatment interval analysis[2] (n=29,445)	Referral-treatment interval analysis[3] (n=17,622)
	%	%	%	%
Age				
<60 years	16.2	16.6	18.4	18.1
60-69 years	24.4	26.6	26.9	28.6
70-79 years	34.2	35.3	35.2	35.9
80+ years	25.2	21.5	19.5	17.5
Deprivation category				
1 (least deprived)	17.6	18.1	18.5	18.8
2	19.3	19.6	19.8	19.8
3	18.7	19.2	18.8	19.2
4	20.8	20.4	20.4	20.2
5 (most deprived)	23.6	22.7	22.5	22.0
Sex				
Female	42.7	41.6	41.4	40.9
Male	57.3	58.4	58.6	59.1
Site				
Colon	61.3	53.2	60.5	52.6
Rectal	38.7	46.8	39.5	47.4
First treatment				
Surgery	65.2	64.9	77.7	73.4
Chemotherapy	7.0	8.0	8.3	9.1
Radiotherapy	7.3	9.6	8.7	10.8
Chemo/radiotherapy	4.4	6.0	5.3	6.7
No cancer-directed treatment[5]	16.1	11.5	-	-
Period of diagnosis				
2001-2005	56.9	56.0	57.5	55.7
2006-2010	43.1	44.0	42.5	44.3
Stage				
I	10.7	12.2	12.5	13.5
II	24.5	25.3	28.9	28.2
III	22.4	22.4	26.4	25.2
IV	22.6	20.9	17.5	16.9
Unstaged	14.1	11.4	8.0	7.3
Staged post-treatment	5.7	7.9	6.8	8.9
Comorbidities				
None	86.5	89.6	88.2	90.6
1-2	11.0	8.8	9.8	8.1
3+	2.5	1.6	2.0	1.4

[1] interval between GP referral and first hospital appointment; includes cases for whom date of GP referral and date of first hospital appointment were available

[2] interval between diagnosis and first cancer-directed treatment; includes cases for whom date of diagnosis and date of first cancer-directed treatment were available
[3] interval between GP referral and first cancer-directed treatment; includes cases for whom date of GP referral and date of first cancer-directed treatment were available
[4] first chemotherapy and radiotherapy received on the same day
[5] no cancer-directed surgery or chemotherapy or radiotherapy

Table 2. Referral interval[1] by socio-demographic and clinical characteristics

			Univariable			Multivariable		
	N	**%**	***OR***	***95% CI***	***p***	***OR[3]***	***95% CI***	***p***
All cases	**9461**	**47.8**						
Age					**<0.001**			**<0.001**
<60 years	1459	44.4	1.00	-		1.00	-	
60-69 years	2570	48.8	1.19	1.09, 1.30	<0.001	1.23	1.12, 1.34	<0.001
70-79 years	3323	47.5	1.33	1.04, 1.23	0.003	1.19	1.09, 1.29	<0.001
80+ years	2109	49.7	1.24	1.13, 1.35	<0.001	1.30	1.18, 1.42	<0.001
Deprivation category					**0.292**			**0.126**
1 (least deprived)	1713	47.8	1.00			1.00		
2	1879	48.5	1.03	0.94, 1.13	0.549	1.02	0.93, 1.12	0.637
3	1827	48.0	1.01	0.92, 1.11	0.842	0.99	0.91, 1.09	0.895
4	1931	47.8	1.00	0.91, 1.09	0.983	0.98	0.90, 1.08	0.715
5 (most deprived)	2111	46.9	0.97	0.88, 1.05	0.438	0.95	0.87, 1.03	0.214
Sex					**0.508**			
Female	3910	47.5	1.00					
Male	5551	48.0	1.02	0.96, 1.08	0.508			
Site					**<0.001**			**<0.001**
Colon	4791	45.5	1.00			1.00		
Rectal	4670	50.4	1.22	1.15, 1.29	<0.001	1.22	1.15, 1.30	<0.001
Period of diagnosis					**<0.001**			
2001-2005	5422	48.9	1.00					
2006-2010	4039	46.3	0.90	0.85, 0.95	<0.001			
Stage					**<0.001**			**<0.001**
I	990	41.1	1.00			1.00		
II	2263	45.3	1.18	1.07, 1.30	0.001	1.23	1.11, 1.36	<0.001
III	2073	46.7	1.25	1.13, 1.39	<0.001	1.29	1.17, 1.43	<0.001
IV	2196	53.0	1.61	1.46, 1.78	<0.001	1.67	1.51, 1.85	<0.001
Unstaged	1131	50.2	1.44	1.28, 1.62	<0.001	1.40	1.24, 1.57	<0.001
Staged post -treatment	808	51.9	1.55	1.36, 1.76	<0.001	1.46	1.28, 1.66	<0.001
Comorbidities					**0.764**			
None	8500	47.9	1.00					
1-2	806	46.1	0.93	0.84, 1.03	0.156			
3+	155	49.8	1.08	0.86, 1.35	0.501			

Figures are numbers and percentages of cases with first hospital appointment ≤14 days from GP referral, univariable and multivariable odds ratios (OR), 95% confidence intervals (CI) and p values[2]

[1] interval between GP referral and first hospital appointment; includes 19,798 cases for whom date of GP referral and date of first hospital appointment were available

[2] P values in bold are from likelihood ratio tests of the contribution of the variable to the model. Unbolded P values are from a test of whether the OR is different from 1

[3] ORs are mutually adjusted; the inclusion of period of diagnosis resulted in poor model fit, so it was not included in the multivariable model

Table 3. Diagnosis-treatment interval[1] by socio-demographic and clinical characteristics

			Univariable			Multivariable		
	N	**%**	***OR***	***95% CI***	***p***	***OR[3]***	***95% CI***	***p***
All cases	**15222**	**51.7**						
Age					**<0.001**			**<0.001**
<60 years	2881	53.3	1.00			1.00		
60-69 years	3905	49.2	0.85	0.79, 0.91	<0.001	0.74	0.68, 0.80	<0.001
70-79 years	5174	50.0	0.88	0.82, 0.94	<0.001	0.68	0.63, 0.73	<0.001
80+ years	3262	56.7	1.15	1.07, 1.24	<0.001	0.77	0.71, 0.84	<0.001
Deprivation category					**<0.001**			**0.013**
1 (least deprived)	2888	53.0	1.00			1.00		
2	3063	52.7	0.99	0.92, 1.06	0.714	0.97	0.89, 1.05	0.453
3	2885	52.0	0.96	0.89, 1.04	0.308	0.96	0.88, 1.04	0.301
4	3071	51.1	0.93	0.86, 0.99	0.041	0.91	0.84, 0.99	0.027
5 (most deprived)	3315	50.1	0.89	0.83, 0.95	0.001	0.91	0.84, 0.98	0.019
Sex					**<0.001**			**<0.001**
Female	6738	55.3	1.00			1.00		
Male	8484	49.2	0.78	0.75, 0.82	<0.001	0.88	0.84, 0.93	<0.001
First treatment					**<0.001**			**<0.001**
Surgery	14245	62.2	1.00			1.00		
Chemotherapy	583	23.8	0.19	0.17, 0.21	<0.001	0.11	0.10, 0.13	<0.001
Radiotherapy	245	9.6	0.06	0.06, 0.07	<0.001	0.05	0.04, 0.06	<0.001
Chemo/radiotherapy[4]	149	9.6	0.06	0.05, 0.08	<0.001	0.05	0.04, 0.06	<0.001
Period of diagnosis					**<0.001**			
2001-2005	9114	53.8	1.00					
2006-2010	6108	48.9	0.82	0.78, 0.86	<0.001			
Stage					**<0.001**			**<0.001**
I	1883	51.1	1.00			1.00		
II	4894	57.5	1.29	1.20, 1.40	<0.001	1.31	1.21, 1.42	<0.001
III	4498	57.9	1.32	1.22, 1.43	<0.001	1.40	1.29, 1.52	<0.001
IV	2499	48.6	0.91	0.83, 0.99	0.023	2.31	2.09, 2.57	<0.001
Unstaged	1246	52.9	1.08	0.97, 1.19	0.165	2.69	2.38, 3.05	<0.001
Staged post -treatment	202	10.2	0.11	0.09, 0.13	<0.001	1.62	1.32, 1.98	<0.001
Comorbidities					**0.020**			
None	13385	51.5	1.00					
1-2	1508	52.2	1.03	0.95, 1.11	0.472			
3+	329	56.5	1.22	1.04, 1.44	0.017			

Figures are numbers and percentages of cases who started treatment ≤31 days of date of diagnosis, univariable and multivariable odds ratios (OR), 95% confidence intervals (CI) and p values[2]

[1] interval between diagnosis and first cancer-directed treatment; includes 29,445 cases for whom date of diagnosis and date of first cancer-directed treatment were available

[2] P values in bold are from likelihood ratio tests of the contribution of the variable to the model. Unbolded P values are from a test of whether the OR is different from 1

[3] ORs are mutually adjusted; the inclusion of period of diagnosis and comorbidities resulted in poor model fit, so these variables were not included in the multivariable model

[4] Chemotherapy and radiotherapy received on the same day

Table 4. Referral-treatment interval[1] by socio-demographic and clinical characteristics

			Univariable			Multivariable		
	N	**%**	***OR***	***95% CI***	***p***	***OR[3]***	***95% CI***	***p***
All cases	**7690**	**43.6**						
Age					**0.454**			**<0.001**
<60 years	1364	42.7	1.00			1.00		
60-69 years	2305	45.8	1.14	1.04, 1.24	0.005	1.05	0.95, 1.16	0.308
70-79 years	2681	42.4	0.99	0.91, 1.08	0.835	0.90	0.81, 0.99	0.027
80+ years	1340	43.6	1.04	0.94, 1.15	0.466	0.88	0.79, 0.99	0.027
Deprivation category					**<0.001**			**<0.001**
1 (least deprived)	1513	45.7	1.00			1.00		
2	1601	46.0	1.01	0.92, 1.11	0.806	1.01	0.91, 1.12	0.849
3	1511	44.6	0.96	0.87, 1.05	0.379	0.95	0.85, 1.06	0.362
4	1497	42.1	0.86	0.78, 0.95	0.003	0.85	0.77, 0.95	0.004
5 (most deprived)	1568	40.4	0.81	0.73, 0.88	<0.001	0.82	0.74, 0.91	<0.001
Sex					**0.080**			
Female	3200	44.4	1.00					
Male	4490	43.1	0.95	0.89, 1.01	0.080			
Referral interval					**<0.001**			**<0.001**
≤14 days	5182	63.3	1.00			1.00		
>14 days	2385	25.7	0.20	0.19, 0.21	<0.001	0.17	0.16, 0.19	<0.001
First treatment					**<0.001**			**<0.001**
Surgery	6032	46.6	1.00			1.00		
Chemotherapy	625	39.2	0.74	0.66, 0.82	<0.001	0.35	0.30, 0.40	<0.001
Radiotherapy	625	32.9	0.56	0.51, 0.62	<0.001	0.21	0.18, 0.24	<0.001
Chemo/radiotherapy[4]	408	34.3	0.60	0.53, 0.68	<0.001	0.18	0.15, 0.22	<0.001
Period of diagnosis					**<0.001**			
2001-2005	3402	34.7	1.00					
2006-2010	4288	54.9	2.30	2.16, 2.44	<0.001			
Stage					**0.002**			**<0.001**
I	953	40.1	1.00			1.00		
II	2168	43.6	1.15	1.04, 1.27	0.006	1.10	0.98, 1.22	0.101
III	1957	44.2	1.18	1.07, 1.30	0.001	1.15	1.03, 1.29	0.014
IV	1357	45.5	1.25	1.12, 1.39	<0.001	1.80	1.57, 2.07	<0.001
Unstaged	516	40.0	0.99	0.87, 1.14	0.933	1.56	1.33, 1.82	<0.001
Staged post -treatment	739	47.1	1.33	1.17, 1.51	<0.001	4.89	4.07, 5.88	<0.001
Comorbidities					**0.585**			
None	6971	43.7	1.00					
1-2	604	42.4	0.95	0.85, 1.06	0.345			
3+	115	48.3	1.21	0.93, 1.56	0.153			

Figures are numbers and percentages of cases who started treatment ≤62 days of GP referral, univariable and multivariable odds ratios (OR), 95% confidence intervals (CI) and p values[2]

[1] interval between diagnosis and first cancer-directed treatment; includes 17,622 cases for whom date of diagnosis and date of first cancer-directed treatment were available

[2] P values in bold are from likelihood ratio tests of the contribution of the variable to the model. Unbolded P values are from a test of whether the OR is different from 1
[3] ORs are mutually adjusted; the inclusion of period of diagnosis resulted in poor model fit, so it was not included in the multivariable model
[4] Chemotherapy and radiotherapy received on the same day