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# Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England

Georgios Lyratzopoulos, Richard D Neal, Josephine M Barbiere, Gregory P Rubin, Gary A Abel

## Summary

**Background** Information from patient surveys can help to identify patient groups and cancers with the greatest potential for improvement in the experience and timeliness of cancer diagnosis. We aimed to examine variation in the number of pre-referral consultations with a general practitioner between patients with different cancers and sociodemographic characteristics.

**Methods** We analysed data from 41 299 patients with 24 different cancers who took part in the 2010 National Cancer Patient Experience Survey in England. We examined variation in the number of general practitioner consultations with cancer symptoms before hospital referral to diagnose cancer. Logistic regression was used to identify independent predictors of three or more pre-referral consultations, adjusting for cancer type, age, sex, deprivation quintile, and ethnic group.

**Findings** We identified wide variation between cancer types in the proportion of patients who had visited their general practitioner three or more times before hospital referral (7.4% [625 of 8408] for breast cancer and 10.1% [113 of 1124] for melanoma; 41.3% [193 of 467] for pancreatic cancer and 50.6% [939 of 1854] for multiple myeloma). In multivariable analysis, with patients with rectal cancer as the reference group, those with subsequent diagnosis of multiple myeloma (odds ratio [OR] 3.42, 95% CI 3.01–3.90), pancreatic cancer (2.35, 1.91–2.88), stomach cancer (1.96, 1.65–2.34), and lung cancer (1.68, 1.48–1.90) were more likely to have had three or more pre-referral consultations; conversely patients with subsequent diagnosis of breast cancer (0.19, 0.17–0.22), melanoma (0.34, 0.27–0.43), testicular cancer (0.47, 0.33–0.67), and endometrial cancer (0.59, 0.49–0.71) were more likely to have been referred to hospital after only one or two consultations. The probability of three or more pre-referral consultations was greater in young patients (OR for patients aged 16–24 years vs 65–74 years 2.12, 95% CI 1.63–2.75;  $p < 0.0001$ ), those from ethnic minorities (OR for Asian vs white 1.73, 1.45–2.08;  $p < 0.0001$ ; OR for black vs white 1.83, 1.51–2.23;  $p < 0.0001$ ), and women (OR for women vs men 1.28, 1.21–1.36;  $p < 0.0001$ ). We identified strong evidence of interactions between cancer type and age group and sex ( $p < 0.0001$  for both), and between age and ethnicity ( $p = 0.0013$ ). The model including these interactions showed a particularly strong sex effect for bladder cancer (OR for women vs men 2.31, 95% CI 1.98–2.69) and no apparent ethnic group differences in young patients aged 16–24 years, whilst the only cancers without an apparent age gradient were testicular cancer and mesothelioma.

**Interpretation** Our findings could help to prioritise and stratify early diagnosis initiatives and research, focusing on patients with cancers and sociodemographic characteristics with the largest potential for improvement.

**Funding** None.

## Introduction

Major policy initiatives in several countries aim to reduce the time between symptom onset and diagnosis of cancer (often called early diagnosis initiatives).<sup>1</sup> These initiatives result from the belief that improvements in the timeliness of diagnosis will lead to detection of cancer at an earlier disease stage, in turn leading to improved survival.<sup>2</sup> However, emerging evidence for determinants of early diagnosis is limited and complex.<sup>3–7</sup> Greater and faster improvements in cancer survival than are currently possible could be achievable if variation in the processes and timeliness of cancer diagnosis were better elucidated, helping to focus (and stratify) research and policy initiatives where there is the greatest potential for improvement.<sup>8,9</sup>

Most patients are diagnosed with cancer after having first visited their general practitioner (family doctor) with symptoms of the disease.<sup>10</sup> The number of such visits before hospital referral is a measure of the quality of patient experience. Patients express a strong preference for avoiding the inconvenience and stress of reconsulting on several occasions with cancer symptoms before diagnostic (and then management) processes are started.<sup>11–13</sup> In view of the well-recognised challenges in defining and measuring time intervals for diagnosis of cancer,<sup>14,15</sup> analysis of variation in the number of pre-referral consultations can usefully complement information that can be derived from measuring time intervals.

The number of pre-referral consultations is easier to define and measure than are time intervals (which can be more difficult to define conceptually and, in the context of patient surveys, recall accurately<sup>16</sup>). As a measure, it is also relevant to the efficiency of the health-care system and provides a direct link to the diagnostic process and interactions occurring during consultation with a general practitioner that can be targeted by subsequent quality improvement interventions and research.

For all these reasons the number of pre-referral primary care consultations of patients with cancer has great

potential for use in the context of clinical audit and quality improvement efforts as indicated by a national safety review,<sup>14</sup> and the inclusion of this measure in national audit initiatives<sup>17</sup> and patient experience surveys. Such surveys are increasingly used to help assess the quality of health care alongside clinical outcomes.<sup>18–20</sup> In England, surveys of the experience of patients with cancer were done in 2000, 2004, and 2010, and the UK Government has defined patient experience as one of the five domains of health-care quality.<sup>21–23</sup>

We analysed data from the 2010 National Cancer Patient Experience Survey in England, for the number of times patients with cancer had visited their general practitioner for symptoms relating to their cancer before they were referred to hospital. We aimed to identify variation in the number of consultations for patients with different cancers and sociodemographic characteristics.

## Methods

### Participants and procedures

We accessed data from the 2010 National Cancer Patient Experience Survey in England through the UK Data Archive.<sup>22</sup> This survey was sent to patients who were treated for cancer in English National Health Service (NHS) hospitals during the first quarter of 2010. It was commissioned by the UK Department of Health, and undertaken by Quality Health (Chesterfield, UK), a specialised patient survey provider. All survey questions were subject to previous cognitive interview testing on samples of patients with different types of cancer in different English regions. On the basis of hospital administration records, patients were included in the survey if they had International Classification of Diseases (ICD)-10 codes C00 to C99 in the first diagnosis field of their care record, excluding C44 (non-melanoma skin cancer).

Patients were sent the survey by post, with two reminders for non-respondents, excluding patients known to have died at the time of invitation. We analysed information on survey question 1, regarding the number of times a patient had visited their general practitioner with symptoms caused by their cancer before hospital referral: “Before you were told that you needed to go to hospital about cancer, how many times did you see your general practitioner about the health problem caused by cancer?” Patients who replied that they had not visited their general practitioner with cancer symptoms before diagnosis were excluded from further analysis (this group includes patients who first presented with a medical or surgical emergency leading to urgent hospital admission, or whose cancer was diagnosed through participation in NHS cancer screening programmes, or incidentally as part of an unrelated hospital appointment or admission). Information was therefore analysed from patients who responded that they had visited their general practitioner “once”, “twice”, “three or four times”, and “more than five times” before they were referred to hospital.

We defined 24 cancer types based on ICD-10 codes, and restricted further analysis to patients with these cancers. These were all cancers included in the 2000 survey (breast, lung, prostate, ovarian, non-Hodgkin lymphoma, colon, and rectal cancer—analysed as colorectal by the 2000 survey); and 17 rarer cancers (oesophageal, stomach, pancreatic, bladder, renal, endometrial, cervical, laryngeal, melanoma, mesothelioma, thyroid, vulval, testicular, brain, Hodgkin’s lymphoma, multiple myeloma, and leukaemia, table 1). Information was available for patients’ age, sex, ethnic group, and deprivation score (Index of Multiple Deprivation 2007 score of lower super output area of residence). Ethnic group information was based on participants’ responses to survey question 74, using the 2001 Census Office for National Statistics ethnicity classification. Deprivation quintile groups were defined by applying national (England) quintile-defining points (8·257, 13·525, 20·741, and 33·511). Institutional review board or ethics approval were not needed.

### Statistical analysis

Patient experience measures included in the survey are reported publicly and fed back to NHS hospitals and multidisciplinary cancer teams using a binary categorisation for more or less positive patient experience.<sup>22</sup> According to this categorisation, having visited a general practitioner three or more times with symptoms of cancer before hospital referral is regarded as a less positive experience of care compared with having visited a general practitioner once or twice. We therefore used this binary categorisation for the purposes of the main analysis and sensitivity analysis. STATA version 11.2 was used for all analyses.

For the main effects analysis, we described the proportion of patients who had visited their general practitioner three or more times before hospital referral by cancer type and sociodemographic group, and calculated the respective unadjusted odds ratios (ORs). Subsequently, we used multivariable logistic regression models to predict the ORs of visiting a general practitioner three or more times before hospital referral, adjusting for cancer type and patient characteristics (age, sex, deprivation, and ethnic group). Standard errors were calculated with a robust estimator to account for possible non-independence of findings, and significance was tested with joint Wald tests for categorical variables. Rectal cancer was used as the reference category for cancer type, because it is common in both sexes. By adjusting for sex in this model, the effect size for a specific cancer is interpreted as the effect associated with that cancer compared with rectal cancer patients of the same sex. For example, the OR for lung cancer compares either a man with lung cancer with a man with rectal cancer, or a woman with lung cancer with a woman with rectal cancer. For single sex cancers (eg, testicular) the OR relates to the comparison with a patient of the same sex with rectal cancer.

We examined interactions between each sociodemographic variable and cancer type. We sequentially added to the main model described above interaction terms for cancer by age, sex, ethnic group, and deprivation. We also investigated an interaction between ethnicity and age, to examine whether the effect associated with being a patient from an ethnic minority might differ by age. To maximise power, age and deprivation were treated as continuous and ethnicity as a two category (white or non-white) variable for the interaction terms only. We tested

significance of interaction effects with a joint Wald test retaining only those terms that were significant.

Because significant interactions were identified, we used a two-step analytical strategy, first using a simple model including main effect variables (age, sex, ethnic group, deprivation, and cancer) without interactions; and subsequently using a full model including both main effect and (significant) interaction variables, which was built on the simple initial model. The rationale for this approach is that the simple model provides a high level (although somewhat inexact) summary of the average variation by patient characteristic and cancer type. This model serves as an initial step in understanding the more complex associations examined in more detail by the full model. The findings of the simple model should therefore not be interpreted in isolation. Information provided by the two models helps to partition overall variation associated with a group of patients into that generated by compositional or contextual factors and that which is specific to a disease process (ie, cancer type). For example, the ORs obtained for women by the simple model provide information about the average effect of sex on number of pre-referral consultations because of compositional (having to do with the patient group itself) or contextual (having to do with the health-care system) factors. Whereas the ORs obtained by the full model show how outcomes for women differ from the average sex effect for different cancers.

Ordered logistic regression was considered for all analyses, but not used because of strong evidence that the proportional odds assumption was violated ( $p < 0.0001$ ). Therefore, we explored the degree to which associations between the outcome and exposure variables differed with different binary cutoff points defining more or less positive experience of care by using alternative binary outcome definitions and repeating the main analysis. More specifically, binary outcomes focusing on either the least positive experience category (ie, having visited a general practitioner more than five times vs any other category) or the most positive experience category (ie, having visited a general practitioner once vs any other category) were used. Additionally, we did a series of sensitivity analyses comprising stratification of models by sex, restriction of the model to cancers occurring in both sexes (and also excluding breast cancer), inclusion of random effects for hospital of treatment or primary care organisation (Primary Care Trust), and inclusion of fixed effect variables for NHS region or time since treatment initiation (used as a surrogate for recall accuracy).

We compared the distributions of cancers in survey participants with population-based incidence data for the 24 cancers. Further, we compared the crude (unadjusted) patterns of variation in number of pre-referral consultations with those reported by the National Audit of Cancer Diagnosis in Primary Care.<sup>17</sup> This clinical audit project collected data for different aspects of the diagnosis of cancer in primary care for 18 879 patients registered with 14% (1170 of 8387) of all practices in England. It used information from practice records obtained by a family or primary health-care professional (eg, practice nurse), and was done between April, 2009, and April, 2010.

### **Role of the funding source**

The Cancer Patient Experience Survey 2010 was sponsored by the Department of Health and was undertaken by Quality Health. Data were accessed via the UK Data Archive (deposited by the Department of Health). Our study is a secondary analysis of these data and as such these organisations had no involvement in study design, analysis, and interpretation, nor in the decision to submit the report for publication. The project was not supported by any external funding or sponsorship. GL, JMB, and GAA had access to the raw data. GL had full access to all of the data and the final responsibility to submit for publication.

### **Results**

101 773 patients aged at least 16 years who were treated for their cancer either as inpatients or day cases in one of 158 NHS hospital trusts in England were invited to participate. Of those patients, 67 713 (67%) completed the survey.<sup>24</sup> 43 792 participants had one of the 24 studied cancers, had visited their general practitioner at least once before hospital referral for cancer, and provided a valid response to the question of how many times they had visited their general practitioner before hospital referral. Further analysis was restricted to the 41 299 (94%) patients who had complete ethnic group and deprivation information (table 2). Of these patients, 9671 (23%) reported that they had visited their general practitioner with cancer symptoms three or more times before hospital referral.

In univariable analysis, we identified strong evidence of large variation between different cancers in the proportion of patients who had visited their general practitioner three or more times before hospital referral (table 2). This proportion was lowest for patients with breast cancer and melanoma and highest for patients with multiple myeloma and pancreatic cancer (table 2). Multivariable analysis (table 2, figure 1) with rectal cancer as the reference category produced concordant findings. The relative ORs for each cancer can be regarded as proxy measures of the difficulty of suspecting its diagnosis, adjusted for patient characteristics, with high ORs indicating cancers that are hard to diagnose, and low ORs indicating those that might be easier to diagnose. However, we caution against a strict interpretation of these results as ranks. The data do not allow us to differentiate the difficulty of diagnosing some individual cancer types (eg, laryngeal vs renal cancer) and the relative position of cancers should be used as a guide only.

In univariable analysis, variation by age in the proportion of patients with three or more pre-referral consultations was complex. Multivariable analysis, however, showed a simpler relation with strong evidence that younger patients had greater odds of having had three or more pre-referral consultations than older patients (table 2, figure 2). Stepwise multivariable analysis suggested that the complex univariable age group differences were mainly attributable to confounding by cancer type (data not shown).

Compared with white patients, patients from any other ethnic group were more likely to have visited their general practitioner three or more times before hospital referral (table 2, figure 2). Comparing the findings of

univariable and multivariable analysis shows that ethnic differences are largely not confounded by cancer type or other sociodemographic characteristics. Although in univariable analysis women were less likely than men to visit their general practitioner three or more times before hospital referral, the opposite was true in multivariable analysis (table 2, figure 2). The discordance between univariable and multivariable findings is mostly attributable to confounding effects of sex differences by cancer type (particularly breast cancer). By contrast with what we identified for age, ethnic group, and sex, variation between patients in different deprivation quintiles was both limited and inconsistent in direction (table 2, figure 2).

We identified no evidence of interaction between cancer type and either ethnic group or deprivation ( $p=0.12$  and  $p=0.076$ , respectively). However, we noted strong evidence of interactions between cancer type and age group and, cancer type and sex, and between ethnic group and age (table 3). In general, for any age group comparisons, younger patients were more likely to have had three or more pre-referral consultations than were older patients for any cancer other than testicular and mesothelioma. (figure 3). Similarly, women were more likely than men to have had three or more pre-referral consultations for most of the 18 cancers occurring in both sexes, except for breast cancer, stomach cancer, and melanoma (figure 4), although none of these latter three comparisons were statistically significant. We noted a particularly strong sex effect for bladder cancer (OR for women vs men 2.31, 95% CI 1.98–2.69; figure 4). Finally, the interaction between ethnic group and age shows a strong pattern of increasing frequency of three or more pre-referral consultations with increasing age of ethnic minority patients (figure 5), although we identified no appreciable ethnic differences for patients aged 16–24 years.

In view of these interactions, we provide more detailed information on variation by cancer in figure 6, which shows the combined effect of cancer and age group, by sex. Because most patients with Hodgkin's lymphoma are young, the typical patient with that cancer has the highest odds of visiting their general practitioner three or more times compared with the typical patient with any other cancer. Information included in figure 1 (and table 2) relating to the simple model (without interactions) should be interpreted in conjunction with information in figure 6 and table 3. Further, we profile variation by age group and sex for the 13 most numerous cancer types (with >1000 patients in the analysis sample) in the appendix pp 1–7. Interaction model outputs are shown in table 3.

Different binary outcome definitions of the number of general practitioner consultations before hospital referral produced much the same findings for either sociodemographic or cancer type patterns (appendix pp 8–9). Further sensitivity analyses produced highly concordant findings with those of the main model and interaction model (appendix pp 10–22). Specifically, inclusion of a variable for time from initial treatment (used as a surrogate for accuracy of patient recall) showed no evidence of confounding by potential recall bias (appendix pp 10–11). Restricting the model to patients with cancers occurring in either sex (ie, excluding reproductive organ cancers and breast cancer) produced identical ORs for sex and similar ORs for the respective cancers (appendix pp 12–15). Stratification of the simple (main effects only) model by cancer produced much the same results as expected from the full (interactions inclusive) model with regard to variation between men and women by cancer—eg, higher ORs for women with bladder cancer compared with men with bladder cancer (appendix pp 16–18). Inclusion of a variable for NHS region showed no confounding by regional variation (appendix pp 19–20). Lastly, inclusion of a random effect for either hospital of treatment or primary care organisation produced similar findings, showing no evidence for clustering at the respective levels (appendix pp 21–22).

Comparisons with incidence statistics for different cancers showed patterns of over-representation and under-representation in the study population versus the general population for several cancers (appendix pp 23–24). Comparison of our data with those for the number of pre-referral consultations reported by the National Audit of Cancer Diagnosis in Primary Care showed concordant patterns of variation by cancer site (Spearman's rank correlation coefficient  $r=0.899$ ,  $p<0.0001$ , figure 7, appendix pp 25–26).

## Discussion

With data from a national survey of patient experience we identified large variation in the number of times patients visit their general practitioner before hospital referral for suspected cancer. Patients with multiple myeloma, pancreatic cancer, stomach cancer, lung cancer, Hodgkin's lymphoma, colon cancer, and ovarian cancer were substantially more likely to have visited their general practitioner three or more times before hospital referral than were patients with rectal cancer. Younger patients, women, and those belonging to ethnic minority groups were also more likely to have had three or more consultations before they were referred to hospital than were older patients, men, and white patients, respectively. We identified notable interactions between cancer type and age, cancer type and sex, and between age and ethnicity.

A major strength of the study is its large sample size, which enabled the profiling of several rarer cancers and small age or ethnic groups. The survey also has a response rate (67%) that compares favourably with other national patient surveys with typical response rates below 40%.<sup>18,20</sup> The importance of the number of consultations with a general practitioner before hospital referral in patients with subsequent diagnosis of cancer is increasingly being appreciated.<sup>14,17</sup> Data for the number of consultations before hospital referral described by the National Audit of Diagnosis of Cancer in Primary Care show patterns of variation that are in agreement with those recorded with National Cancer Patient Experience Survey data.<sup>17</sup> These two sources have notably different methods of sampling and outcome ascertainment (eg, national vs sub-national coverage of self-selected practices; and data extraction by a general practitioner or other primary health-care professional based

on patient records in the audit project). In view of these substantive differences, this comparison supports the validity of the patient-reported data used in our study.

Direct comparison with previous patient survey data is difficult because earlier national cancer surveys in England did not include a question about the number of general practitioner consultations before hospital referral and only focused on six cancers. Additionally, previous surveys predated major cancer policy developments in the English NHS.<sup>1,25</sup> Nevertheless, analysis of the national cancer patient survey done in 2000 identified variation in patient-reported time interval measures between symptom onset and diagnosis in patients with different cancers and sociodemographic characteristics.<sup>26,27</sup> In the same survey, patients with breast cancer reported the shortest time from symptom onset to diagnosis, which is in line the findings of our study.<sup>26</sup> Relatively short diagnostic intervals for breast cancer have been reported with UK General Practice Research Database data.<sup>28</sup> In the 2000 National Cancer Patient Survey<sup>20</sup> women, young, and non-white patients reported longer intervals between symptom awareness and diagnosis, which likewise agrees with the sociodemographic differences we identified.

The large sample size of the survey allowed for a detailed examination of ethnic group differences—nevertheless, as is usually the case when exploring ethnic differences in health care, the potential for lack of power and heterogeneity within ethnic groups needs to be borne in mind when interpreting the findings. Although the frequency of three or more pre-referral consultations was higher in ethnic minority groups than for white patients, this was primarily driven by patients in the middle and older age groups. This might indicate particular problems about doctor–patient communication with older patients from ethnic minority groups, who might have limited health literacy skills and resources.

Compared with age, sex, and ethnic group differences, those relating to deprivation were small and inconsistent in their direction. This finding is reassuring, indicating that in a system with comprehensive coverage such as the NHS equal care outcomes can be obtained in patients with different socioeconomic status. However, deprivation gradients might have been either overestimated or underestimated because of non-response survey patterns or lack of power. Further, our findings might under-estimate the true size of socioeconomic differences in the frequency of pre-referral consultations because of measure attributes (ecological index). Less well-educated patients and those with limited literacy might have a higher probability of a greater number of pre-referral consultations. Inclusion of a question on educational attainment (an individual measure of socioeconomic status) in future surveys will be useful to help explore such potential differences, and to help further elucidate the nature and size of socioeconomic variation. Examination of time trends in the number of pre-referral consultations was not possible because of the cross-sectional nature of the survey. However, repeatable surveys of patients with cancer including such a question could support monitoring of this aspect of experience of cancer diagnosis in the future.

Our study was descriptive and observational, not hypothesis testing. A limitation of the study is that, for patients who reported more than one pre-referral consultation, information about the time period during which these consultations took place was not available. Also, we could not differentiate between repeat consultations because of inability to suspect the diagnosis of cancer, and those that might occur during a short time period to follow up clinically appropriate investigations (eg, blood tests). Therefore the number of pre-referral consultations is not a perfect surrogate marker of diagnostic quality at the level of an individual patient. However, even if part of the recorded variation relates to clinically appropriate management decisions, this explanation is unlikely to account for the very large effects noted for groups of patients with different cancers and characteristics.

Another limitation of the study is that we could not take into account variation at the level of general practice because this information was not available. Some of the reported differences between patients with different cancers or characteristics could be attributable to their concentration in general practices whose patients with cancer overall see their doctors more times than average before hospital referral. Research into other aspects of patient experience of primary care indicated that for Asian patients, concentration in practices with worse than average scores accounts for about half the respective ethnic differences in patient experience.<sup>29</sup> At least in part, however, ethnic differences in the number of pre-referral consultations can indicate differences in the quality of patient–doctor communication because of language barriers or sociocultural norms. Research into this issue, including qualitative studies, should be a priority to identify how the diagnostic process for patients with cancer from ethnic minority groups can be improved (eg, by making translation services more widely available, or by developing translated and culturally aware patient information resources—particularly for middle-aged and elderly patients). Inclusion of questions about the participants' native language or English language fluency in future surveys could substantiate analysis that will explore this notion, specifically in view of the strong age-gradients in ethnic differences.

We could not examine the correlation between number of pre-referral consultations and time interval measures (symptomatic presentation to diagnosis). This issue should be addressed by further research, alongside exploration of the potential independent effect of this measure on cancer survival. However, we emphasise the value of the number of pre-referral consultations as a measure of both patient experience and auditable quality improvement efforts, independent of its association with time interval measures or survival outcomes.

Although all questions included in the survey were subject to cognitive interview testing,<sup>13</sup> appreciation of the meaning of the question examined in this study might have differed between patients with different characteristics (particularly age or ethnicity). Patient survey report questions (eg, whether an event has or has not happened, as opposed to whether a patient was or was not satisfied with their care experience) have the least potential for sociodemographic differences in appreciation.<sup>30</sup> Differential understanding of the question is unlikely to account



for a major part of the large recorded ethnic differences, or the differences between patients with different cancers.

Consideration of the external validity of our findings is important with regard to potential bias arising from the nature of the survey—ie, by design it's a survey of survivors, excluding patients with short survival.<sup>26,27</sup> Patients with cancers requiring more frequent contact with hospital services (eg, patients with haematological tumours) were over-represented in the study sample (appendix pp 23–24). Despite the relatively high (for a patient survey) response rate, the proportion of non-responders is likely to vary between patients with different cancers and characteristics. In brief, when discussing the external validity of the survey sample we need to consider attrition attributable to poor short-term survival, ineligibility for inclusion in the survey (eg, if no active treatment or follow-up occurred in an NHS hospital during the recruitment period of the survey), non-response (which might be differential between patients of different economic, educational, linguistic competency, and morbidity status), and ineligibility for answering the specific survey question (ie, diagnosis of cancer without previous symptomatic presentation to a general practitioner).

Although non-response patterns might imply an increased potential for non-response bias, they do not necessarily result in such bias. The presence, size, and direction of non-response bias are notoriously difficult to study, but considering the following principles is useful: first, the higher the response rate, the lower the potential for non-response bias.<sup>31</sup> The Cancer Patient Experience Survey 2010 has a response rate (67%) that is substantially higher than other large national patient surveys, such as the US HCAPHS survey (response rate 36%) or the English General Practice Patient Survey (response rate 38%).<sup>18,32</sup> Second, although non-response patterns might bias crude (unadjusted) analysis, after appropriate adjustment for case-mix, the effect of such bias (in surveys with an appropriately defined sampling frame) is small.<sup>33,34</sup> Third, as applicable to all epidemiological research, the size of the recorded associations is important. In our study, the relatively high response rate, the multivariable analysis used, and the large size of the recorded associations mean that our findings are unlikely to result from non-response bias alone. The concordance of crude patterns of variation recorded in the patient survey compared with health-care professional ascertained number of pre-referral consultations based on patient records also supports the validity of patient-reported data (figure 7, appendix pp 25–26).

The readiness of general practitioners to suspect cancer diagnosis varies greatly between different cancers. We believe that this finding results from differences in the nature and characteristics of symptoms for different cancers. Notably, patients with the higher probability of having visited their general practitioner only once or twice before hospital referral tend to have cancers that either have known and well-understood cardinal signs and symptoms (eg, pigmented lesion in melanoma), or relate to organs that can be easily inspected or palpated (eg, breast, testicular, and thyroid cancer). Our findings also provide some indirect evidence of success in achieving professional awareness of cancer symptoms and signs for some common cancers, such as breast cancer, melanoma, and testicular cancer.

In general women and younger patients were more likely to have had three or more general practitioner consultations before hospital referral, than were men and older patients, respectively. The strength of these associations showed little variation with cancer type with a few notable exceptions. Younger patients with testicular cancer were more likely to have been referred to hospital after only one or two consultations—possibly indicative of keen awareness in general practitioners of the steep age gradients in the incidence of this cancer, with a peak in early adulthood. Sex differences in frequency of pre-referral consultations were greatest for bladder cancer, which could result from the greater potential for misattribution of bladder cancer symptoms in women to benign urinary tract pathology (eg, cystitis) or benign gynaecological presentations. Women with bladder cancer are known to have higher probability of more advanced stage at diagnosis,<sup>35</sup> and substantially shorter 1-year relative survival (64% vs 77% in men).<sup>36</sup> This strong pattern of cancer survival variation by sex is unique to bladder cancer.

Our findings might be particularly applicable to tax-funded health-care systems with a strong primary-care gatekeeper function (eg, the NHS) but also have implications for the diagnosis of cancer in community settings in general. Most patients with cancer are diagnosed after presenting with symptoms to either generalists or specialists working out of hospital (eg, in health-care centres, or private rooms or surgeries). About three-quarters of all cancer patients in England are diagnosed after an elective (ie, non-emergency) symptomatic presentation.<sup>10</sup> Acknowledging differences in cancer incidence between different patient groups,<sup>37</sup> we strongly encourage research to understand better cancer signs and symptoms in women, young, and ethnic minority patients (panel). Our findings can also help to prioritise policy initiatives and further research focused on patients with cancers associated with a non-specific symptom signature and greater number of pre-referral consultations (eg, patients with pancreatic, stomach, lung, and colon cancers). This problem is complex and requires interventions at different levels.<sup>38</sup> Therefore such research and policy should explore and assess physician-level educational interventions, further development of point-of-care decision aids, risk calculators and diagnostic tests, and system redesign to enable more appropriate and timely use of specialist diagnostic tests (eg, imaging or endoscopy).<sup>39</sup>

#### **Contributors**

The study was conceived by GL, extending concepts explored in previous work by RDN and GPR. GL, RDN, and GPR helped identify relevant published work. GL and RDN were responsible for selection and operational definitions of the profiled cancers. GL and GAA developed the statistical methods, with input from all other authors, and GAA designed the approach to interaction analysis and produced the figures. JMB, GAA, and GL analysed data. All authors interpreted findings and identified issues for discussion. GL drafted the report, which was reviewed and modified with input from all authors over a number of versions. All authors saw and approved the final version. GL and GAA are guarantors.

#### **Conflicts of interest**

We declare that we have no conflicts of interest.

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<b>Cancer</b>	<b>ICD-10 codes</b>	<b>ICD-10 code description</b>
<b>Oesophageal</b>	C15	Malignant neoplasm of oesophagus
<b>Stomach</b>	C16	Malignant neoplasm of stomach
<b>Colon</b>	C18	Malignant neoplasm of colon (C18)
<b>Rectal</b>	C19-20	Malignant neoplasm of recto-sigmoid junction (C19), and of rectum (C20)
<b>Pancreatic</b>	C25	Malignant neoplasm of pancreas
<b>Laryngeal</b>	C32	Malignant neoplasm of larynx
<b>Lung</b>	C34	Malignant neoplasm of bronchus and lung
<b>Melanoma</b>	C43	Malignant melanoma of skin
<b>Mesothelioma</b>	C45	Mesothelioma
<b>Breast</b>	C50	Malignant neoplasm of breast
<b>Vulval</b>	C51	Malignant neoplasm of vulva
<b>Cervical</b>	C53	Malignant neoplasm of cervix uteri
<b>Endometrial</b>	C54-C55	Malignant neoplasm of corpus uteri (C54), malignant neoplasm of uterus, unspecified (C55)
<b>Ovarian</b>	C56	Malignant neoplasm of ovary
<b>Prostate</b>	C61	Malignant neoplasm of prostate
<b>Testicular</b>	C62	Malignant neoplasm of testis
<b>Renal</b>	C64	Malignant neoplasm of kidney, except renal pelvis
<b>Bladder</b>	C67	Malignant neoplasm of bladder
<b>Brain</b>	C71	Malignant neoplasm of brain
<b>Thyroid</b>	C73	Malignant neoplasm of thyroid gland
<b>Hodgkin's lymphoma</b>	C81	Hodgkin's lymphoma
<b>Non-Hodgkin's Lymphoma (NHL)</b>	C82, C83, C85	Follicular [nodular] non-Hodgkin's lymphoma (C82), diffuse non-Hodgkin's lymphoma (C83), other and unspecified types of non-Hodgkin's lymphoma (C85)
<b>Multiple myeloma</b>	C90	Multiple myeloma and malignant plasma cell neoplasms
<b>Leukaemia</b>	C91-C95	Lymphoid leukaemia (C91), myeloid leukaemia (C92), monocytic leukaemia (C93), other leukaemias of specified cell type (C94), other leukaemias of unspecified cell type (C95)

**Table 1: International Classification of Diseases (ICD)-10 codes used to define different cancers**

**Table 2. Odds ratios and 95% confidence intervals of seeing a general practitioner three or more times before hospital referral, by sex, age, ethnicity, deprivation, and cancer type (n=41,299)†**

Patient characteristics	Patients with three or more pre-referral consultations				Crude odds ratios				Adjusted odds ratios**				
	N <sup>††</sup>	n	%	p	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	
Men	20,233	5,057	25.0%	<0.0001	Reference				Reference				
Women	21,066	4,614	21.9%		0.84	0.80	0.88	<0.0001	1.28	1.21	1.36	<0.0001	
16-24	282	119	42.2%	<0.0001	2.36	1.86	3.00	<0.0001	2.12	1.63	2.75	<0.0001	
25-34	730	208	28.5%		1.29	1.09	1.52		1.82	1.51	2.20		
35-44	2,501	489	19.6%		0.79	0.71	0.88		1.46	1.30	1.65		
45-54	5,532	1,254	22.7%		0.95	0.88	1.02		1.45	1.33	1.57		
55-64	10,352	2,734	26.4%		1.16	1.09	1.23		1.24	1.16	1.32		
65-74	12,702	2,999	23.6%		Reference				Reference				
75-84	7,830	1,624	20.7%		0.85	0.79	0.91		0.87	0.81	0.93		
85+	1,370	244	17.8%		0.70	0.61	0.81		0.79	0.68	0.91		
White	39,799	9,154	23.0%	<0.0001	Reference			<0.0001	Reference			<0.0001	
Mixed	171	64	37.4%		2.00	1.47	2.73		1.81	1.30	2.53		
Asian	635	213	33.5%		1.69	1.43	2.00		1.73	1.45	2.08		
Black	564	200	35.5%		1.84	1.55	2.19		1.83	1.51	2.23		
Chinese	87	27	31.0%		1.51	0.96	2.37		1.32	0.80	2.15		
Other	43	13	30.2%		1.45	0.76	2.78		1.69	0.79	3.62		
Affluent	9,526	2,141	22.5%		<0.0001	Reference				<0.0001	Reference		
Deprivation group 2	9,480	2,216	23.4%	1.05		0.98	1.13	1.05	0.98		1.13		
Deprivation group 3	8,869	1,985	22.4%	0.99		0.93	1.07	0.98	0.91		1.05		
Deprivation group 4	7,529	1,788	23.7%	1.07		1.00	1.15	1.03	0.95		1.11		
Most deprived	5,895	1,541	26.1%	1.22		1.13	1.32	1.13	1.04		1.22		
Multiple myeloma	1,854	939	50.6%	<0.0001	3.43	3.02	3.90	<0.0001	3.42	3.01	3.90	<0.0001	
Pancreatic	467	193	41.3%		2.36	1.92	2.89		2.35	1.91	2.88		
Stomach	748	269	36.0%		1.88	1.58	2.24		1.96	1.65	2.34		
Lung	2,362	795	33.7%		1.70	1.50	1.92		1.68	1.48	1.90		
HL	462	195	42.2%		2.44	1.99	3.00		1.67	1.34	2.08		
Colon	3,289	1,044	31.7%		1.56	1.38	1.75		1.58	1.41	1.78		
Ovarian	1,390	504	36.3%		1.90	1.65	2.19		1.56	1.34	1.81		
Brain	218	80	36.7%		1.94	1.45	2.59		1.55	1.16	2.08		
NHL	2,914	937	32.2%		1.59	1.41	1.79		1.50	1.33	1.69		

Patient characteristics	Patients with three or more pre-referral consultations				Crude odds ratios			Adjusted odds ratios**				
	N <sup>††</sup>	n	%	p	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
	Mesothelioma	275	77	28.0%		1.30	0.98	1.72		1.43	1.08	1.90
Rectal	2,611	601	23.0%		Reference				Reference			
Renal	564	168	29.8%		1.42	1.16	1.74		1.38	1.12	1.69	
Laryngeal	279	79	28.3%		1.32	1.00	1.74		1.34	1.02	1.77	
Oesophageal	1,099	274	24.9%		1.11	0.94	1.31		1.15	0.98	1.36	
Leukaemia	1,686	465	27.6%		1.27	1.11	1.47		1.15	0.99	1.32	
Prostate	4,059	912	22.5%		0.97	0.86	1.09		1.10	0.98	1.24	
Vulval	171	46	26.9%		1.23	0.87	1.75		1.05	0.74	1.50	
Cervical	287	86	30.0%		1.43	1.09	1.87		0.95	0.72	1.25	
Bladder	5,209	931	17.9%		0.73	0.65	0.82		0.83	0.74	0.93	
Thyroid	399	92	23.1%		1.00	0.78	1.29		0.71	0.55	0.92	
Endometrial	1,149	202	17.6%		0.71	0.60	0.85		0.59	0.49	0.71	
Testicular	275	44	16.0%		0.64	0.46	0.89		0.47	0.33	0.67	
Melanoma	1,124	113	10.1%		0.37	0.30	0.46		0.34	0.27	0.43	
Breast	8,408	625	7.4%		0.27	0.24	0.30		0.19	0.17	0.22	

OR=odds ratio. NHL=non-Hodgkin lymphoma. \*This model does not allow for effect modification of age and sex by cancer, nor for interaction of age by ethnic group, which have been shown to be important. It shows the average effects but should be interpreted in the context of subsequent interaction analysis (table 4, figures 3–6). †The analysis sample excludes 673 participants who indicated that they had visited their general practitioner before hospital referral at least once in response to question 1, but indicated this not to be the case in response to another survey question (question 2, answer category “6”). ‡From joint Wald tests for categorical variables. These tests assess the overall significance of differences across age, sex, deprivation, ethnic group and cancer type categories, as applicable (ie, they test the null hypothesis that there is no variation across categories). §Multivariable analysis, adjusting for cancer type and patient characteristics. By adjusting for sex in this model, the effect size for a given cancer is interpreted as the effect associated with that cancer compared to rectal cancer patients of the same sex. For example, the OR for lung cancer compares either a man with lung cancer with a man with rectal cancer, or a woman with lung cancer with a woman with rectal cancer. For single sex cancers (eg, testicular cancer) the OR relates to the comparison with a rectal cancer patient of the same sex.

**Table 2: ORs and 95% CIs of visiting a family doctor three or more times before hospital referral, by sex, age, ethnicity, deprivation, and cancer type\***

**Table 3. Odds ratios and 95% confidence intervals of seeing a general practitioner three or more times before hospital referral obtained from multivariate logistic regression adjusted for age, sex, deprivation, ethnicity, cancer type and interactions between cancer type and gender, cancer type and age, and ethnicity and age<sup>†</sup> (n=41,299)**

Patient characteristics	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
<i>Main Effects</i>				
Men	Reference			
Women	1.19	0.98	1.43	0.075
16-24	2.93	1.76	4.88	
25-34	2.23	1.53	3.27	
35-44	1.66	1.27	2.17	
45-54	1.49	1.25	1.77	<0.0001
55-64	1.24	1.12	1.37	
65-74	Reference			
75-84	0.88	0.79	0.98	
85+	0.80	0.65	1.00	
White	Reference			
Mixed	2.23	1.56	3.19	
Asian	2.07	1.69	2.55	<0.0001
Black	2.06	1.67	2.53	
Chinese	1.59	0.96	2.64	
Other	2.14	0.98	4.65	
Affluent	Reference			
Deprivation group 2	1.05	0.98	1.13	
Deprivation group 3	0.98	0.91	1.05	0.010
Deprivation group 4	1.02	0.95	1.10	
Most deprived	1.12	1.03	1.21	
Multiple myeloma	3.32	2.79	3.95	
Pancreatic	2.35	1.76	3.13	
Stomach	2.15	1.73	2.67	
Lung	1.62	1.37	1.93	
Hodgkin's lymphoma	1.55	1.03	2.32	
Colon	1.60	1.36	1.87	
Ovary	1.71	1.41	2.09	
Brain	1.28	0.74	2.20	
Non-Hodgkin's lymphoma	1.59	1.35	1.88	
Mesothelioma	1.45	1.05	1.99	
Rectal	Reference			
Renal	1.27	0.96	1.69	<0.0001
Laryngeal	1.17	0.81	1.69	
Oesophageal	1.10	0.89	1.36	
Leukaemia	1.20	0.98	1.46	
Prostate	1.08	0.94	1.25	
Vulvar	1.10	0.75	1.62	
Cervical cancer	0.85	0.52	1.37	
Bladder	0.68	0.59	0.79	
Thyroid	0.87	0.53	1.45	
Endometrial	0.61	0.49	0.77	
Testicular	0.92	0.41	2.05	
Melanoma	0.44	0.32	0.60	
Breast	0.47	0.19	1.12	
<i>Interaction age (continuous) by cancer type (per change in age group)</i>				
Multiple myeloma	0.92	0.82	1.04	
Pancreatic	0.91	0.75	1.12	
Stomach	0.98	0.84	1.14	
Lung	0.90	0.80	1.01	
Hodgkin's lymphoma	1.04	0.90	1.19	<0.0001
Colon	0.93	0.84	1.02	
Ovary	1.08	0.95	1.22	
Brain	0.92	0.75	1.14	

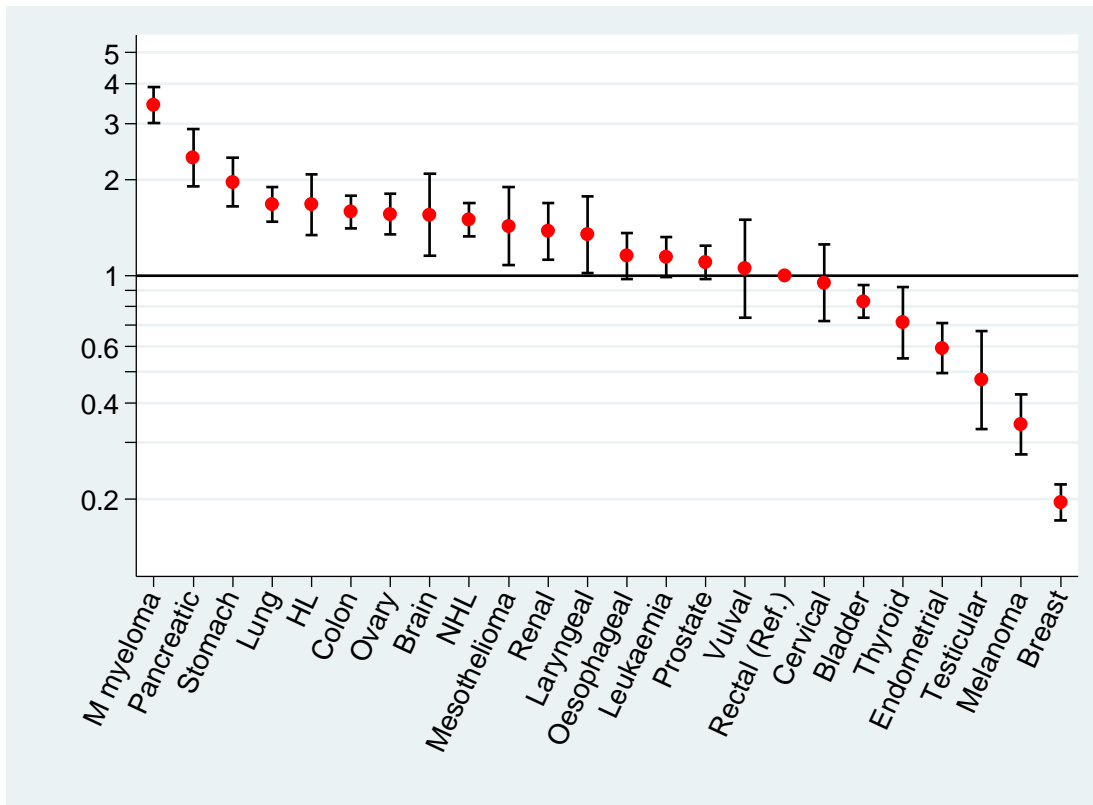
Patient characteristics	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
Non-Hodgkin's lymphoma	0.99	0.89	1.09	
Mesothelioma	1.22	0.88	1.69	
Rectal	Reference			
Renal	1.07	0.91	1.27	
Laryngeal	0.84	0.62	1.13	
Oesophageal	1.03	0.89	1.20	
Leukaemia	1.13	1.02	1.26	
Prostate	1.08	0.96	1.21	
Vulvar	1.01	0.78	1.31	
Cervical	0.95	0.79	1.16	
Bladder	0.93	0.84	1.04	
Thyroid	1.09	0.93	1.28	
Endometrial	0.97	0.82	1.15	
Testicular	1.30	1.00	1.68	
Melanoma	1.13	0.97	1.32	
Breast	1.13	1.02	1.25	
<i>Interaction gender by cancer type</i>				
Multiple myeloma	1.02	0.79	1.34	
Pancreatic	0.94	0.62	1.43	
Stomach	0.68	0.46	1.00	
Lung	1.00	0.77	1.29	
Hodgkin's lymphoma	1.19	0.78	1.82	
Colon	0.96	0.76	1.23	
Ovary	N/A			
Brain	0.98	0.53	1.79	
Non-Hodgkin's lymphoma	0.86	0.68	1.10	
Mesothelioma	1.14	0.56	2.32	
Rectal	Reference			
Renal	1.37	0.90	2.08	<0.0001
Laryngeal	1.17	0.57	2.38	
Oesophageal	1.20	0.84	1.70	
Leukaemia	1.16	0.87	1.55	
Prostate	N/A			
Vulvar	N/A			
Cervical	N/A			
Bladder	1.95	1.53	2.48	
Thyroid	0.94	0.53	1.67	
Endometrial	N/A			
Testicular	N/A			
Melanoma	0.76	0.50	1.18	
Breast	0.51	0.21	1.24	
<i>Interaction age (continuous) by ethnicity (per change in age group)</i>				
White	Reference			
Non-white	1.14	1.05	1.24	0.0013

N/A: Not applicable.

†In order to maximise power, age was treated as a continuous variable and ethnicity as a two category (White/non-White) variable for the interaction terms only.

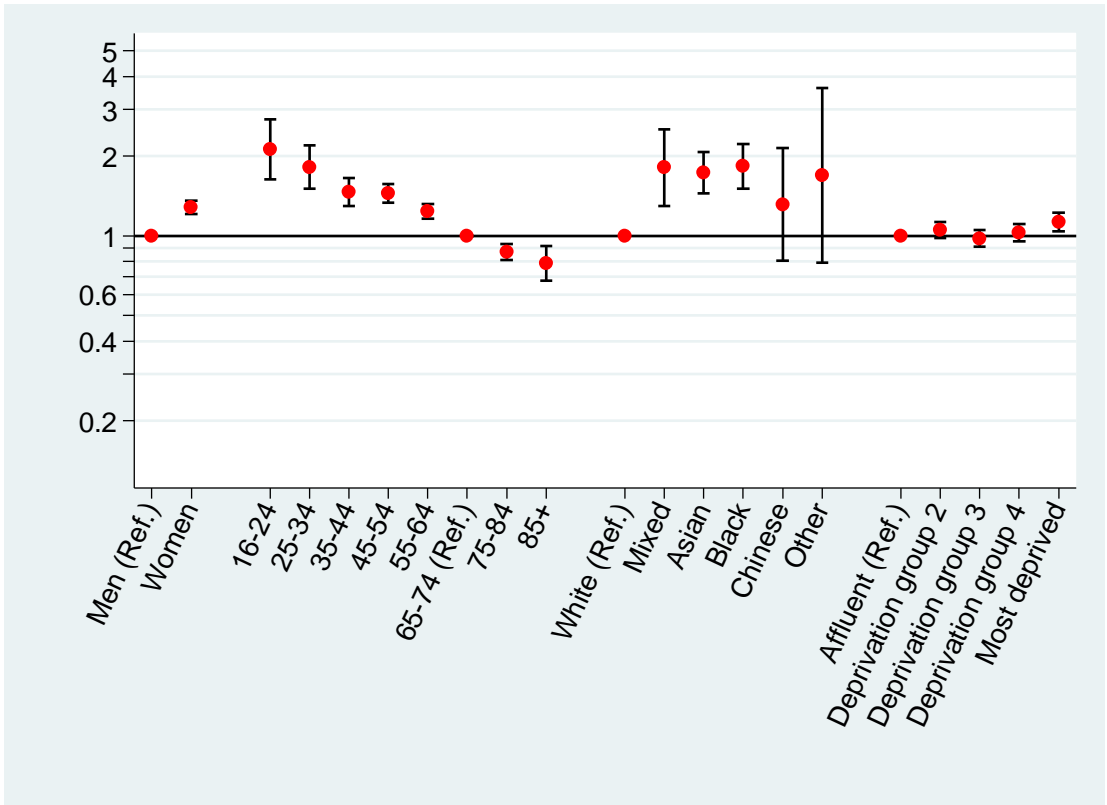
\*From joint Wald tests for categorical variables.





**Figure 1: Odds ratios and 95% CIs for three or more general practitioner consultations before hospital referral, by cancer type**

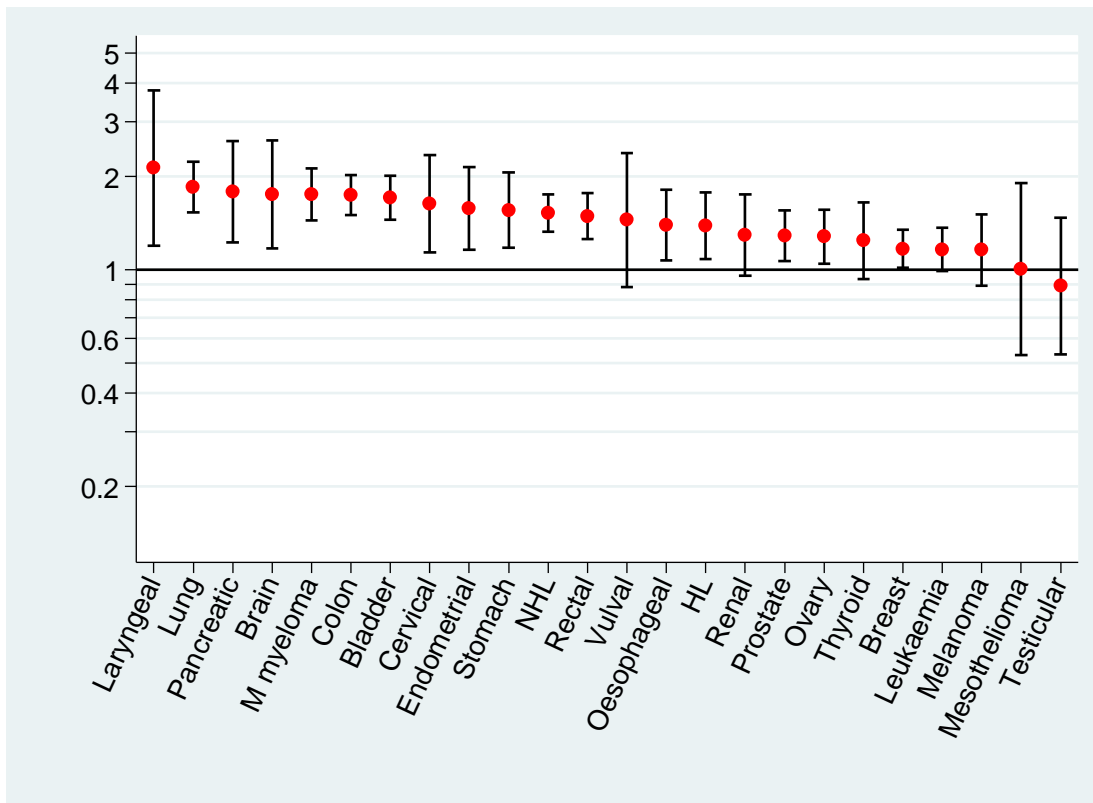
The information in this figure is derived from the main effects model (table 2). This model does not allow for effect modification of age and sex by cancer, nor for interaction of age by ethnic group, which have been shown to be important. It shows the average effects but should be interpreted in the context of interaction analysis (table 3, figures 3–6). HL=Hodgkin’s lymphoma. NHL=non-Hodgkin lymphoma. Ref=reference.



**Figure 2: Odds ratios and 95% CIs for three or more general practitioner consultations before hospital referral, by patient characteristics**

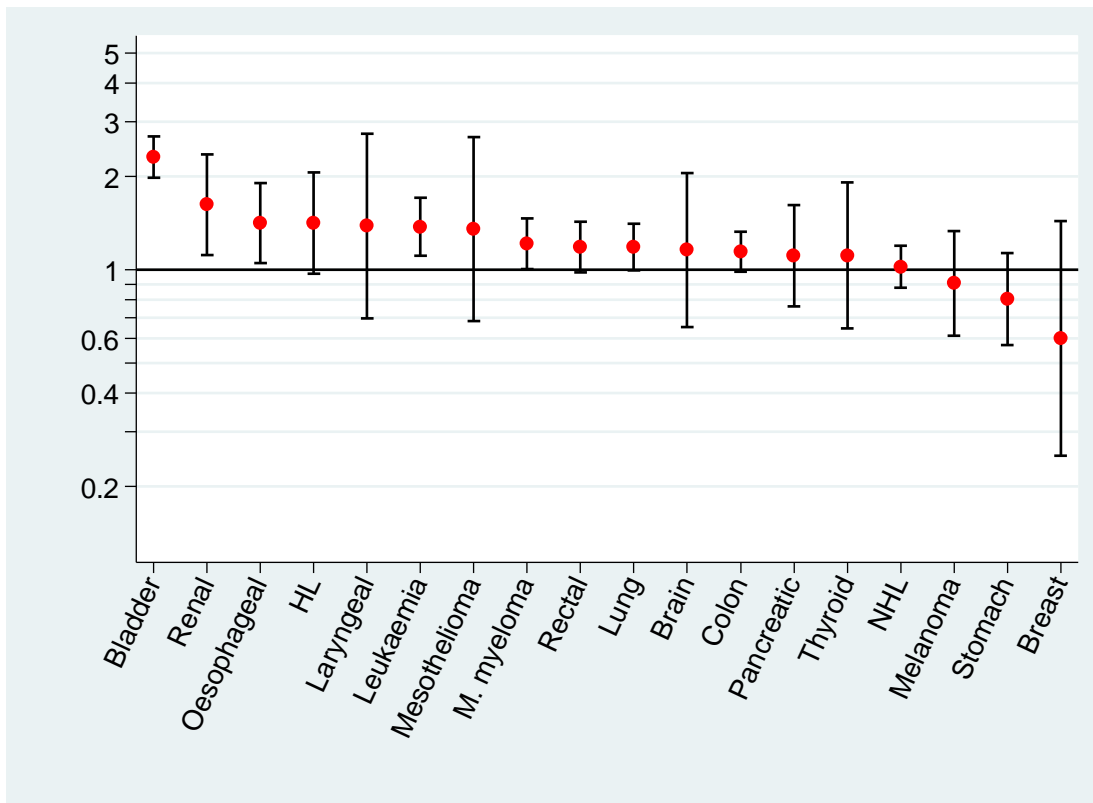
The information in this figure is derived from the main effects model (table 2). This model does not allow for effect modification of age and sex by cancer, nor for interaction of age by ethnic group, which have been shown to be important. It shows the average effects but should be interpreted in the context of interaction analysis (table 3, figures 3–6).

Ref=reference.

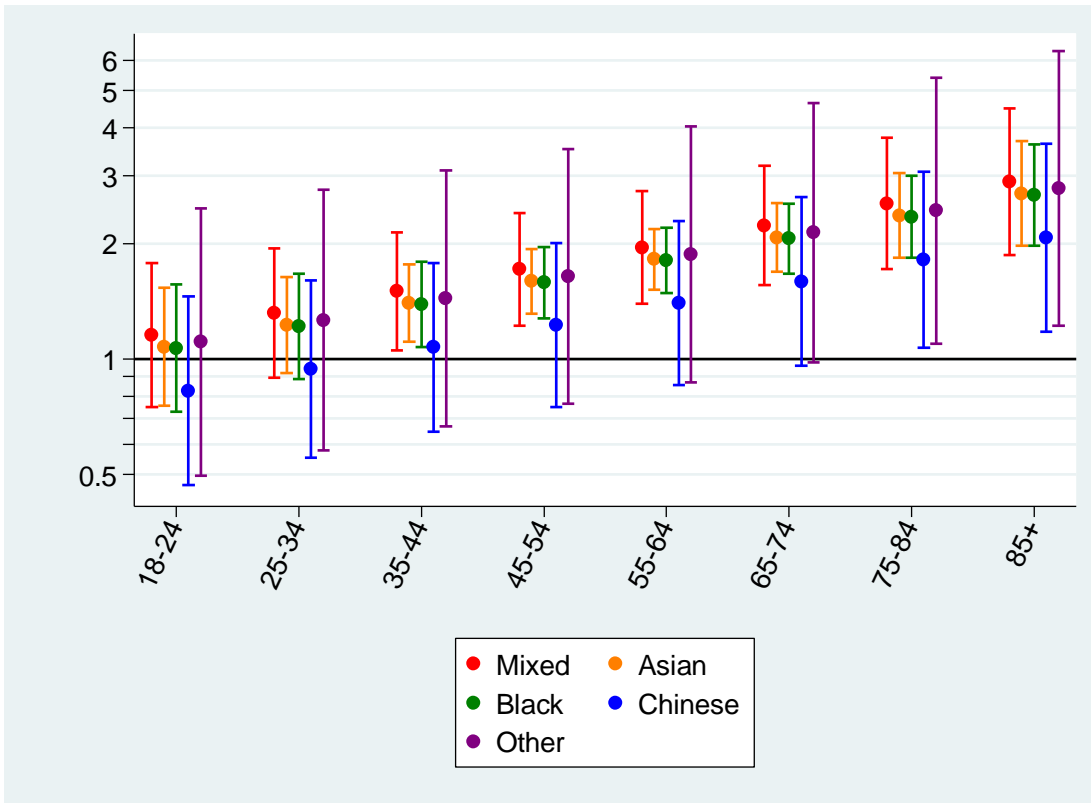


**Figure 3: Effect of age for patients aged 45–54 years vs 65–74 years (reference), by cancer type\***

HL=Hodgkin’s lymphoma. NHL=non-Hodgkin lymphoma. For simplicity, information presented in this graph relates to patients from the white ethnic group. \*Adjusted odds ratios and 95% CIs of three or more general practitioner consultations before hospital referral from a model including main effects and significant interactions (table 3).

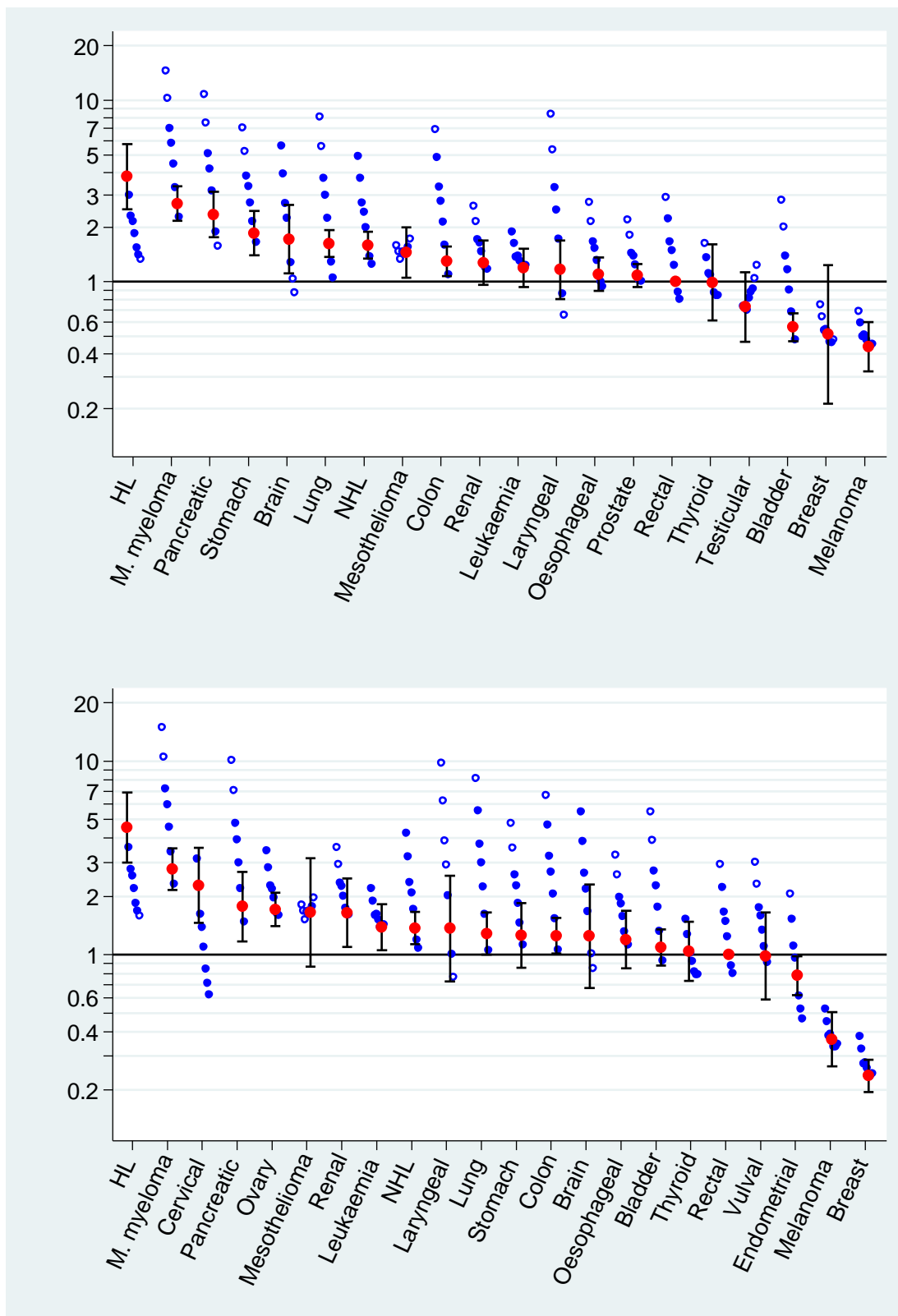


**Figure 4: Effect of sex shown for women vs men (reference), by cancer type\***  
 HL=Hodgkin's lymphoma. NHL=non-Hodgkin lymphoma. \*Adjusted odds ratios and 95% CIs for three or more general practitioner consultations before hospital referral from a model including main effects and significant interactions (table 3).

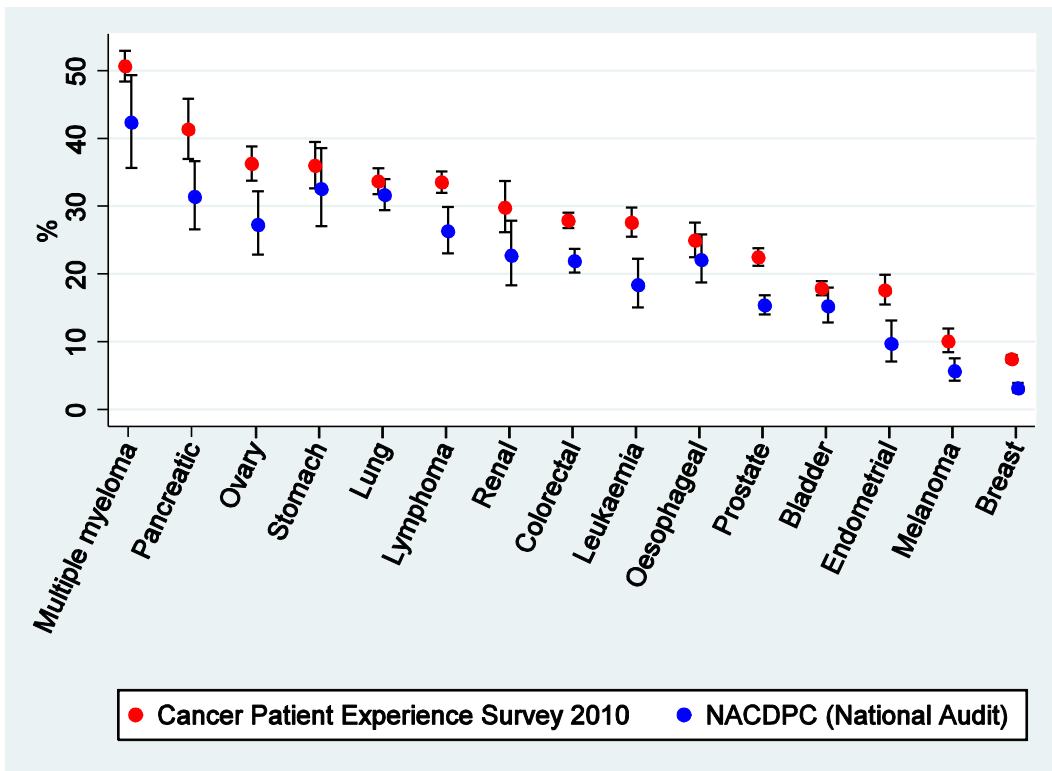


**Figure 5: Effect of ethnic group varying by age (reference white)\***

\*The interaction term was modelled for white/non-white categories, so the change of effect by age is the same for all minority ethnic groups, but the baseline is different.



**Figure 6: Variation by cancer, for the combined effect of cancer and age group** (A) men. (B) women. Each dot represents one of eight age groups (16–24 years, to ≥85 years). The red dot indicates the modal age group according to population based incidence statistics. 95% CIs are only depicted for the modal age group. Some cells (ie, combinations of cancer, age group, sex strata) have fewer than five patients: those subgroups are depicted with empty dots. They should be considered an extrapolation of the model and interpreted with caution. HL=Hodgkin's lymphoma. NHL=non-Hodgkin lymphoma.



**Figure 7: Comparison of unadjusted proportion of patients with three or more general practitioner consultations before hospital referral between the NHS Cancer Patient Survey 2010 and the National Audit of Cancer Diagnosis in Primary Care (NACDPC)**  
 See also appendix pp 25–26.

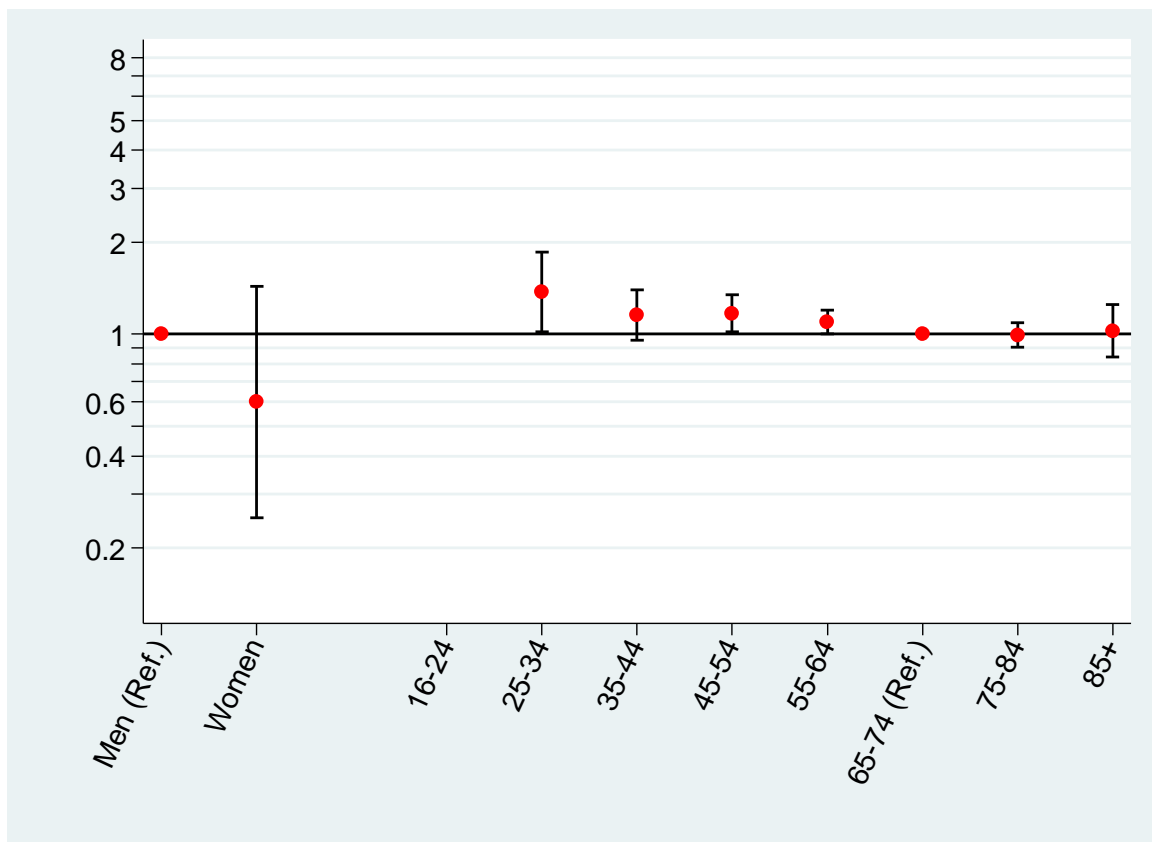
## Web appendix

### Appendix 1

#### Variation by age group and sex (where applicable) for patients with one of the 13 studied cancers with the largest sample size (>1,000 patients)

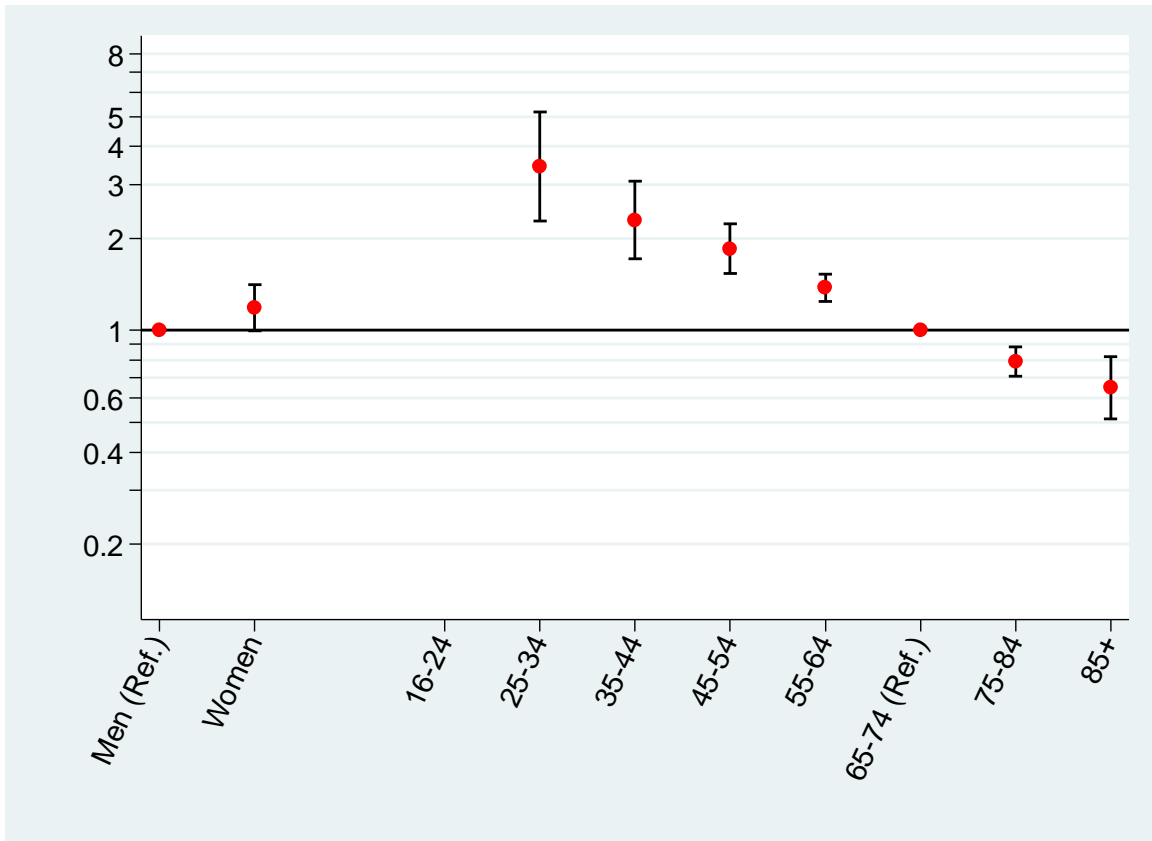
- The following figures are based on the outputs of the ‘full’ (main effects plus significant interactions) model – see Table 3 of main paper.
- Data are illustrated for 13 cancers (breast, lung, colon, rectal, prostate, ovarian, endometrial, melanoma, oesophageal, bladder, Non-Hodgkin Lymphoma, multiple myeloma and leukaemia) with a sample size >1,000 patients.
- Patterns of variation presented in the subsequent figures should be considered in the context of information presented in Tables 2 and 3 and Figures 1-6 of the main paper. Effects for ethnic groups and deprivation are not displayed because of no evidence of effect modification by cancer type (joint test for interaction terms  $p=0.12$  and  $p=0.076$  respectively).
- No effect is plotted for age groups within each cancer with fewer than five cases (including zero counts).

#### Breast cancer

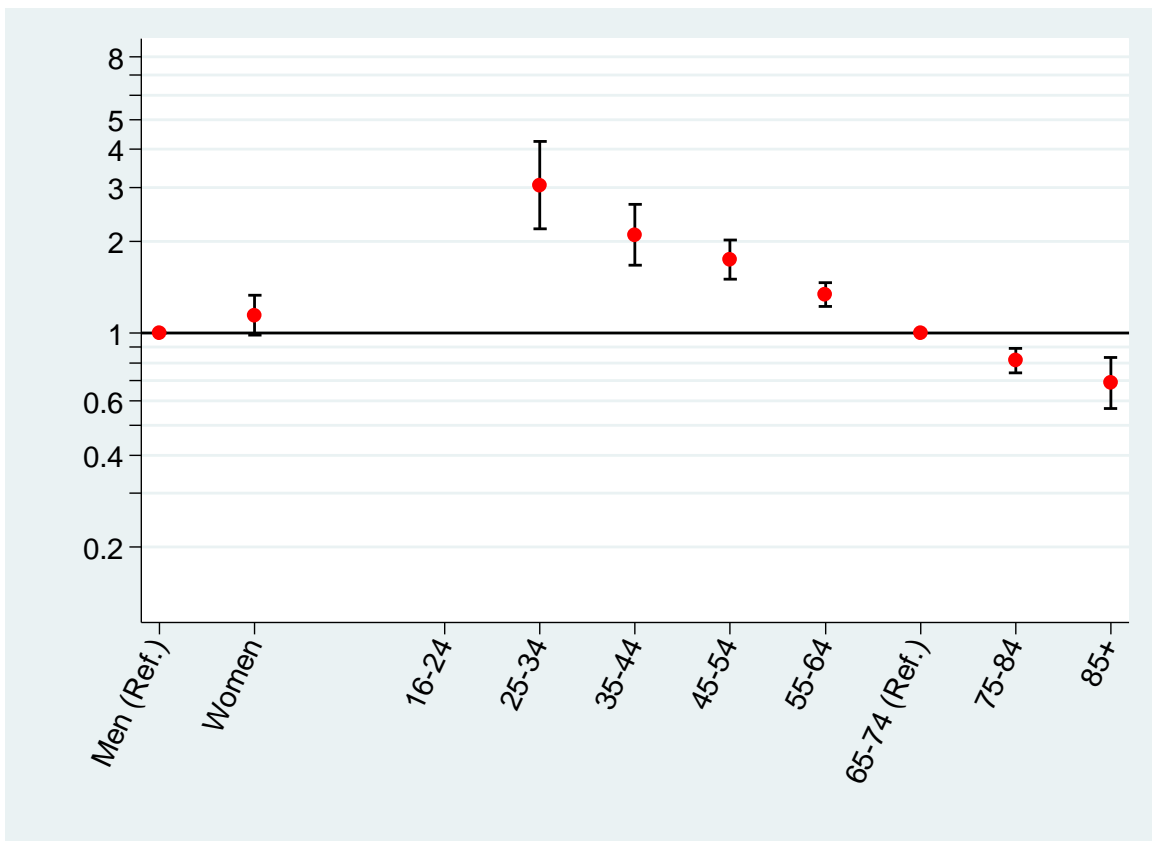




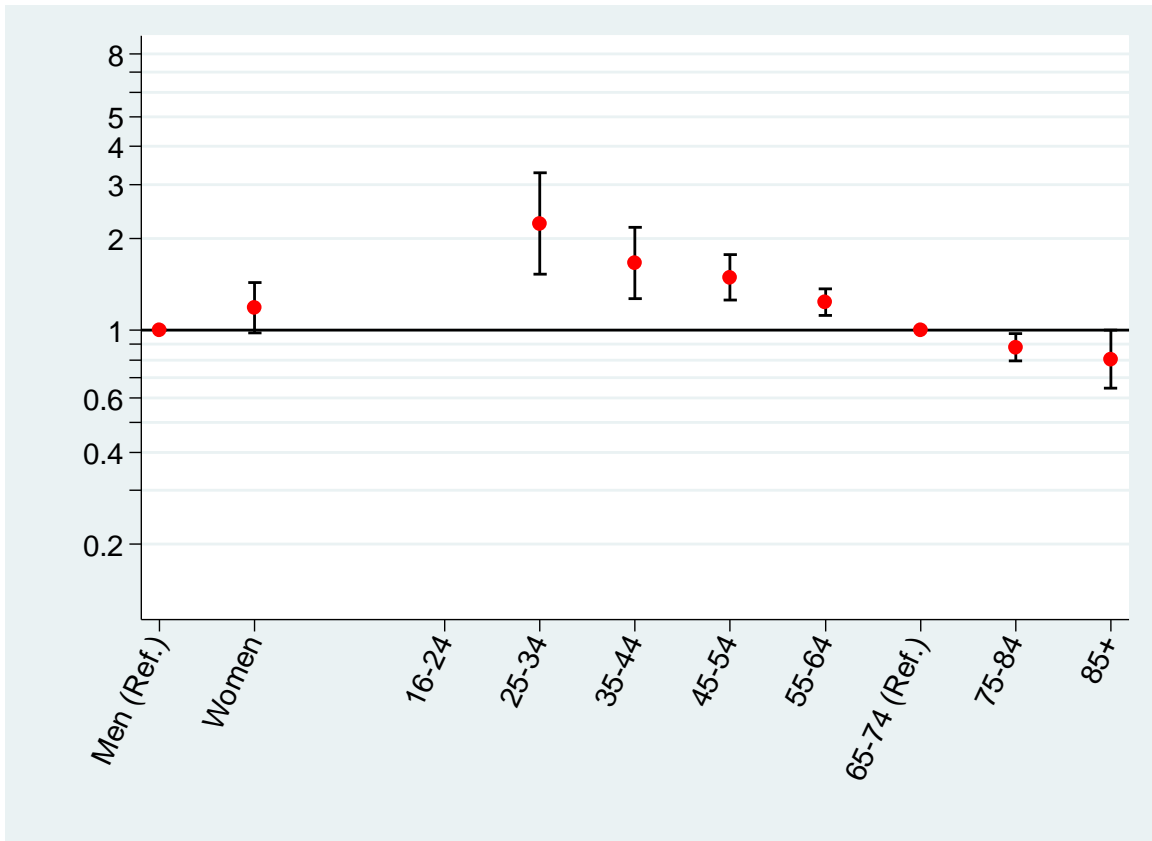
### Lung cancer



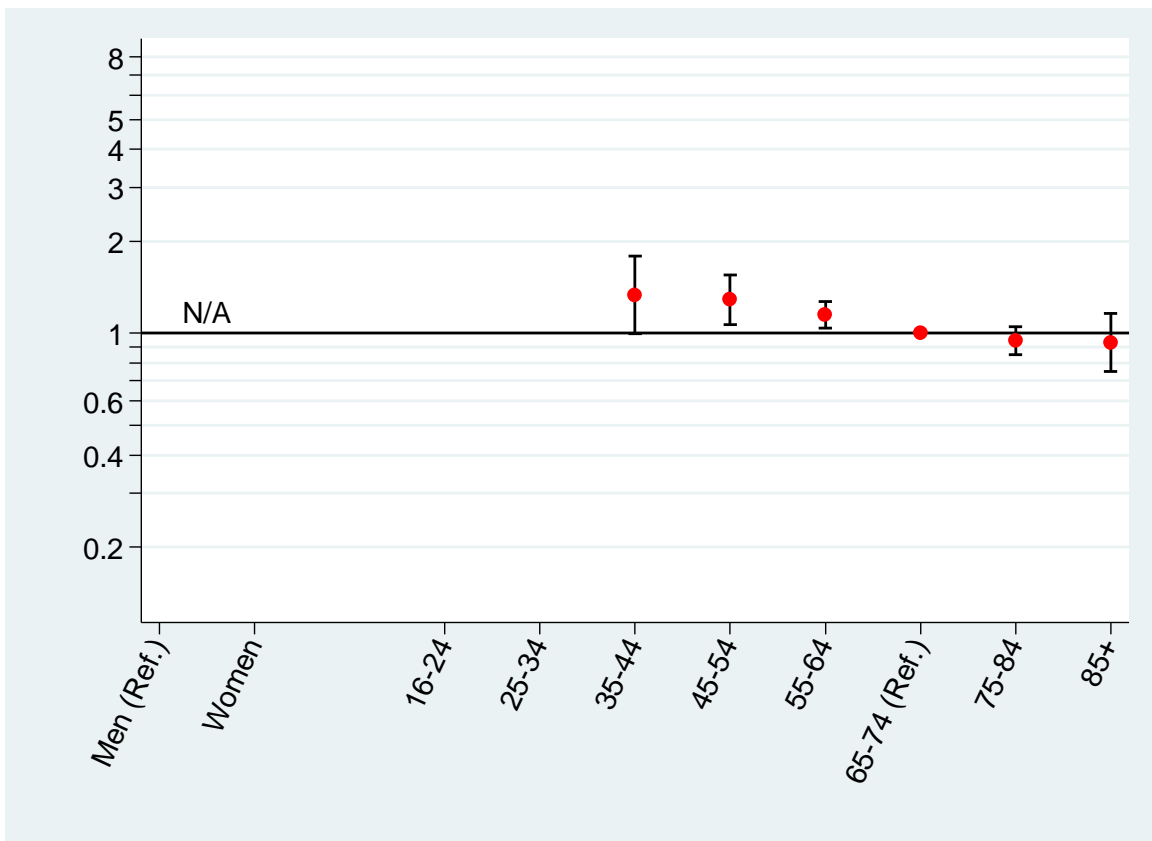
### Colon cancer



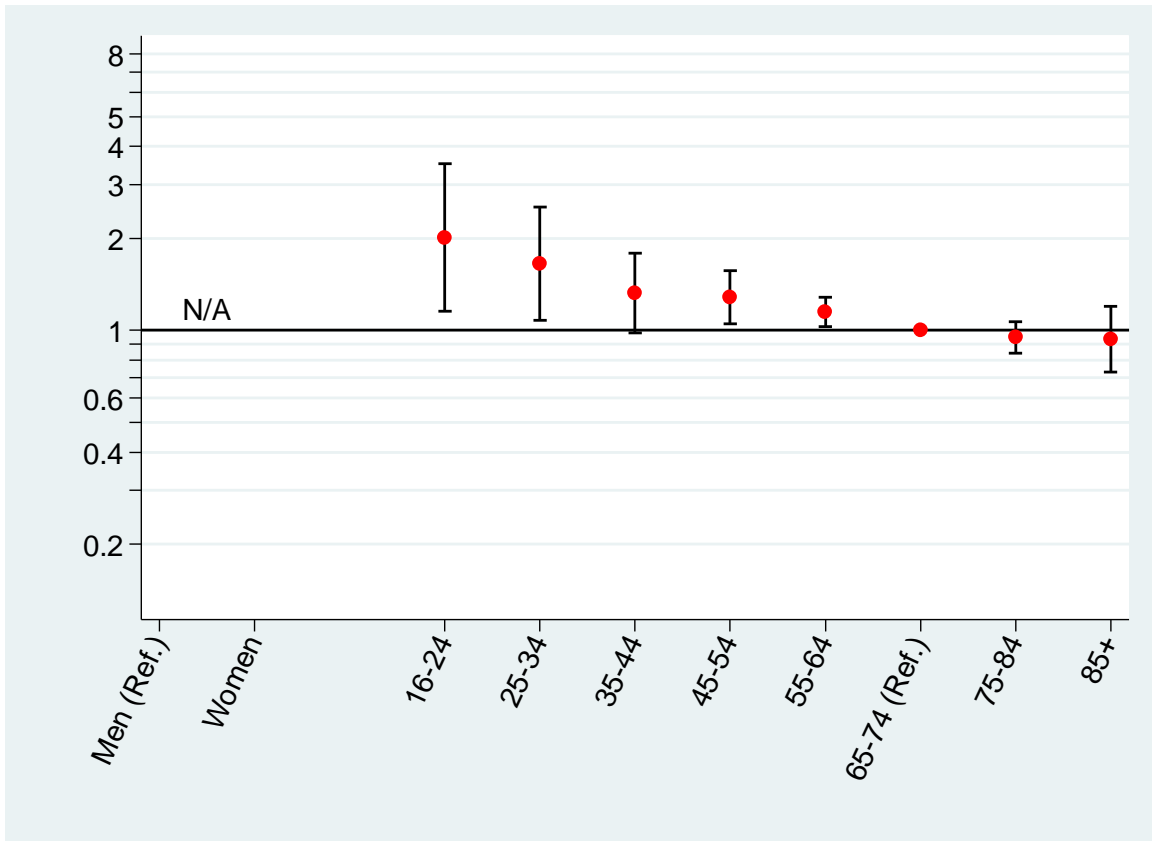
### Rectal cancer



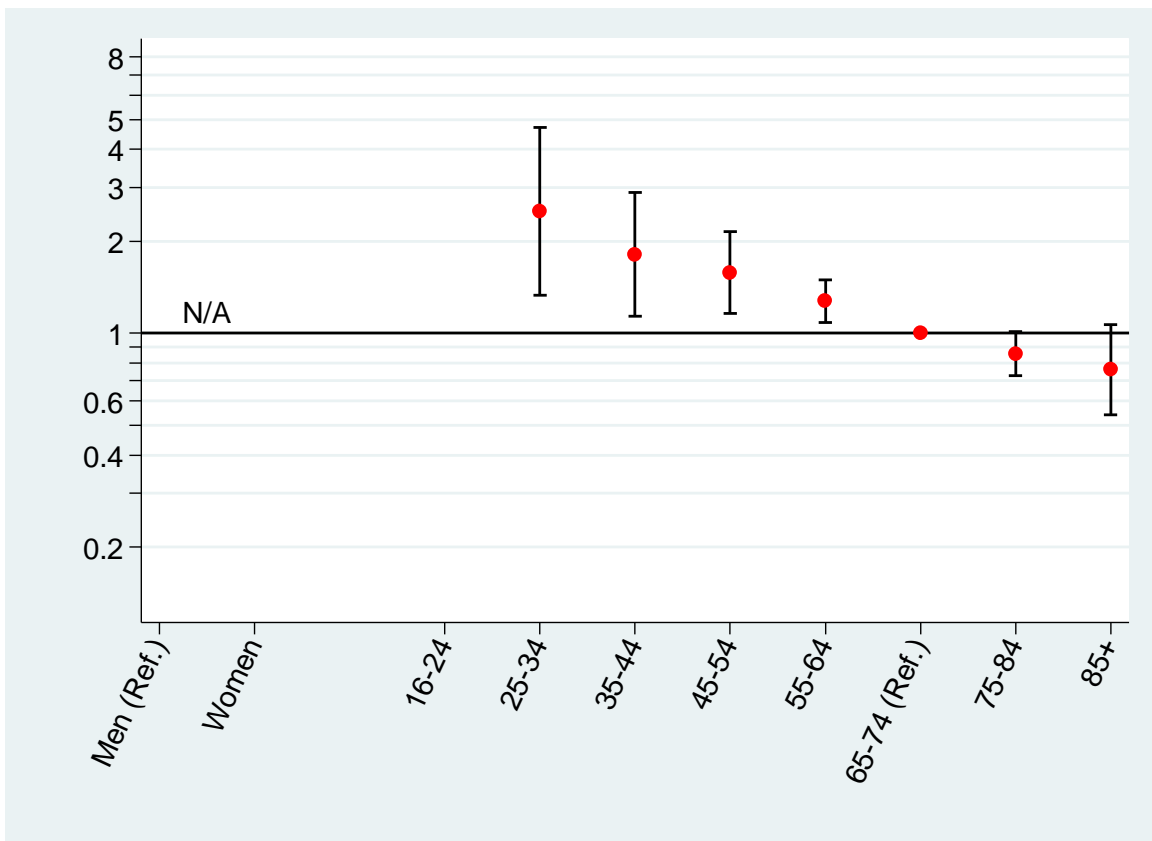
### Prostate cancer



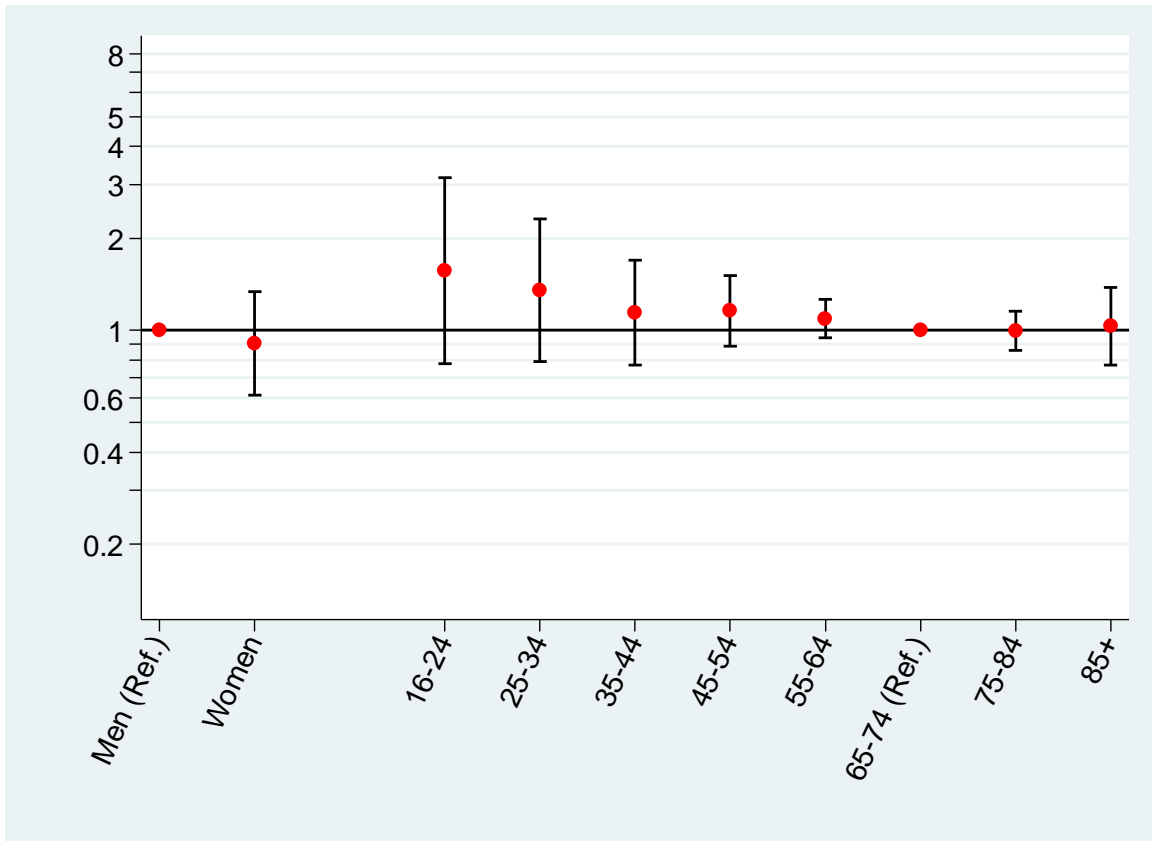
### Ovarian cancer



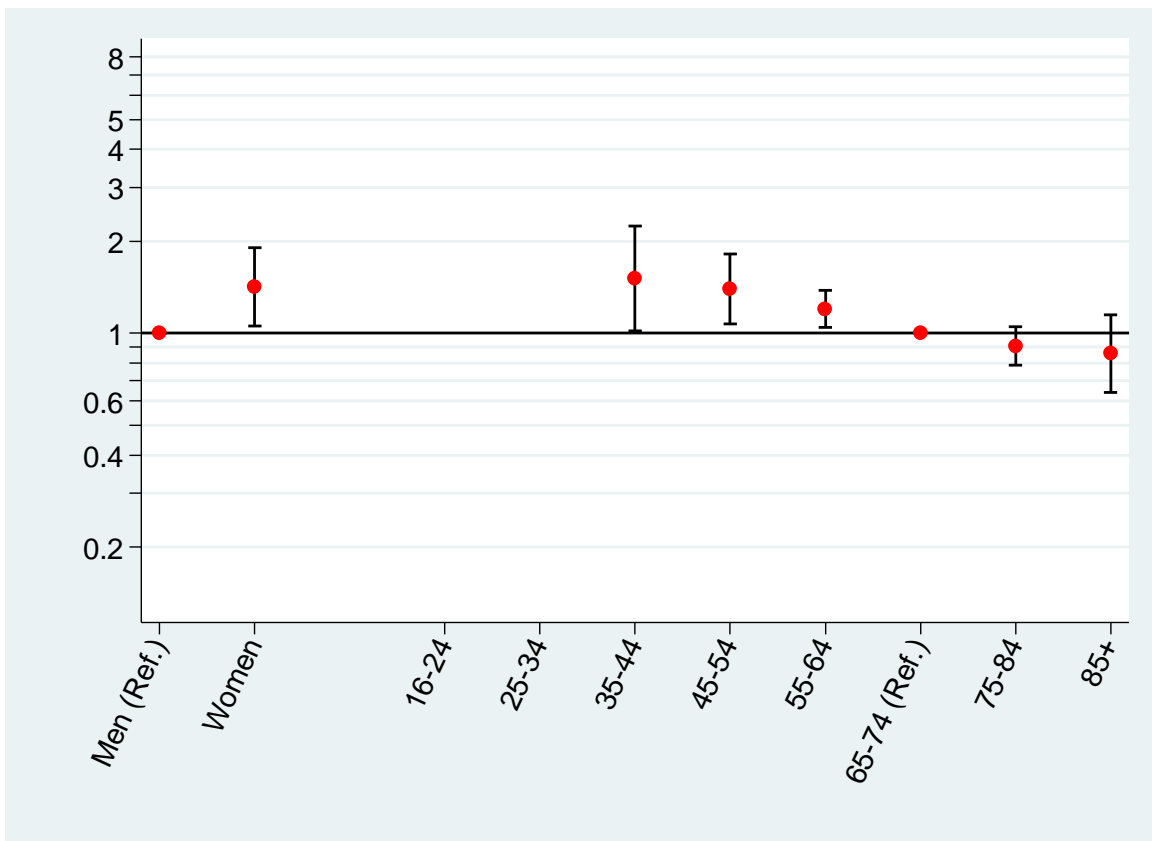
### Endometrial cancer



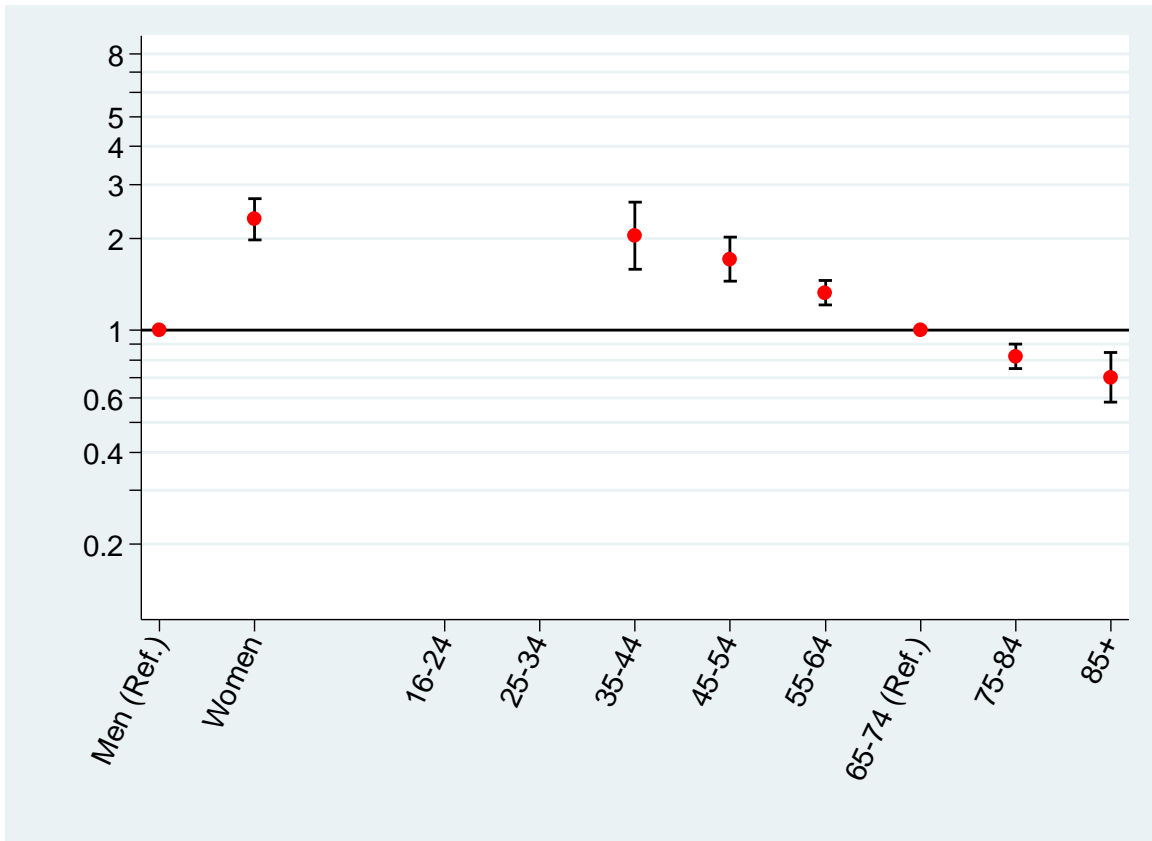
### Melanoma



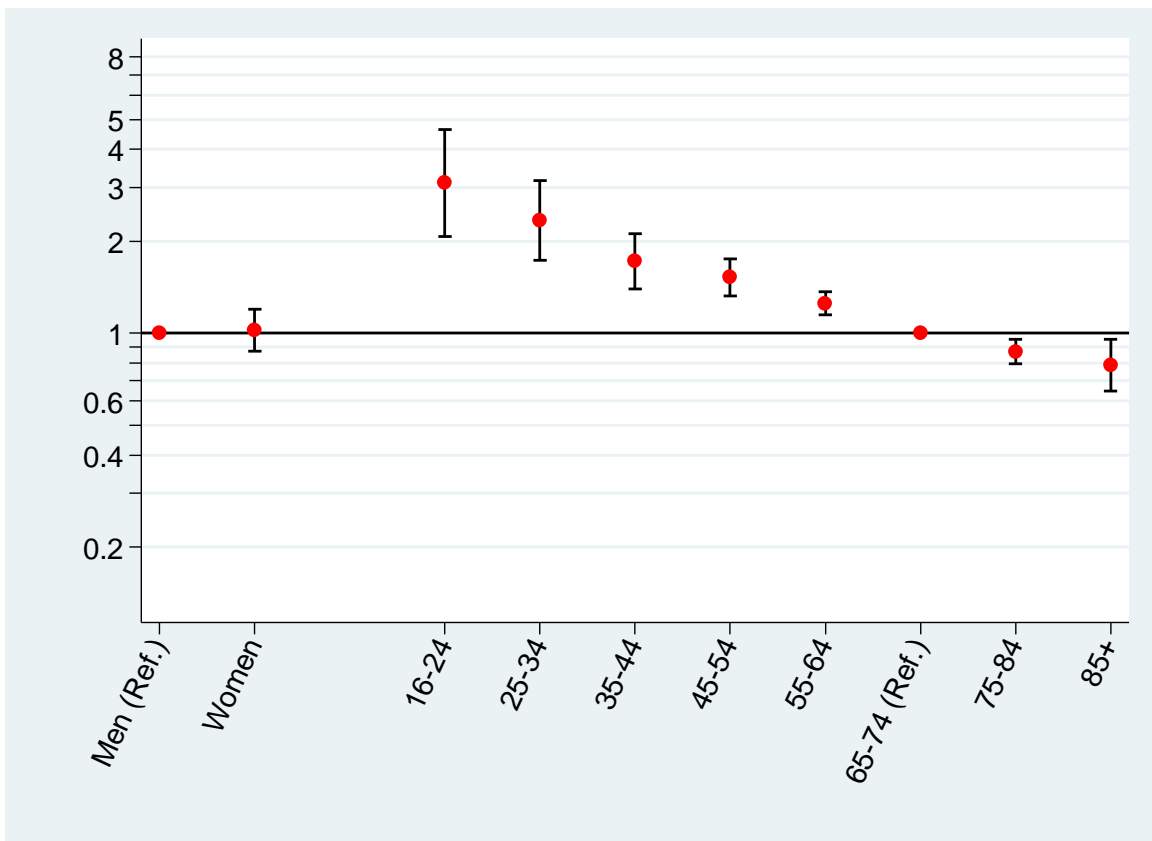
### Oesophageal



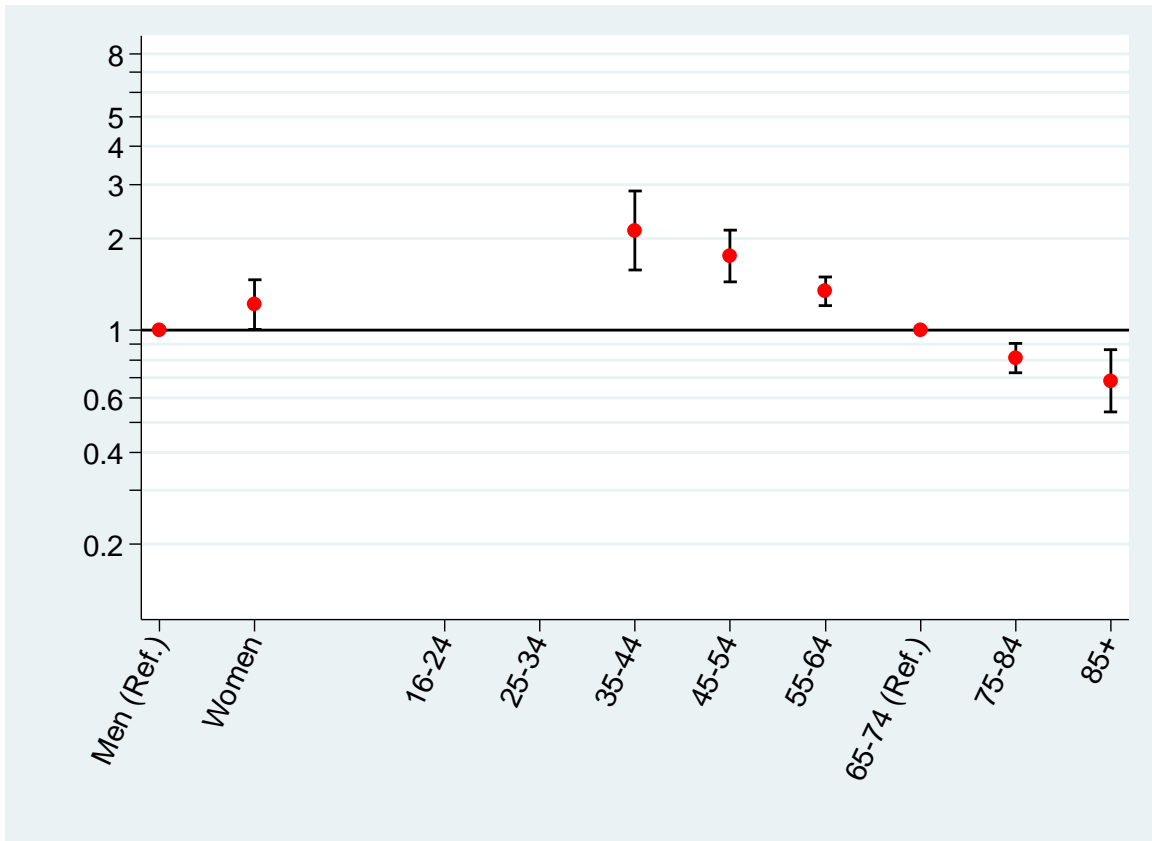
### Bladder cancer



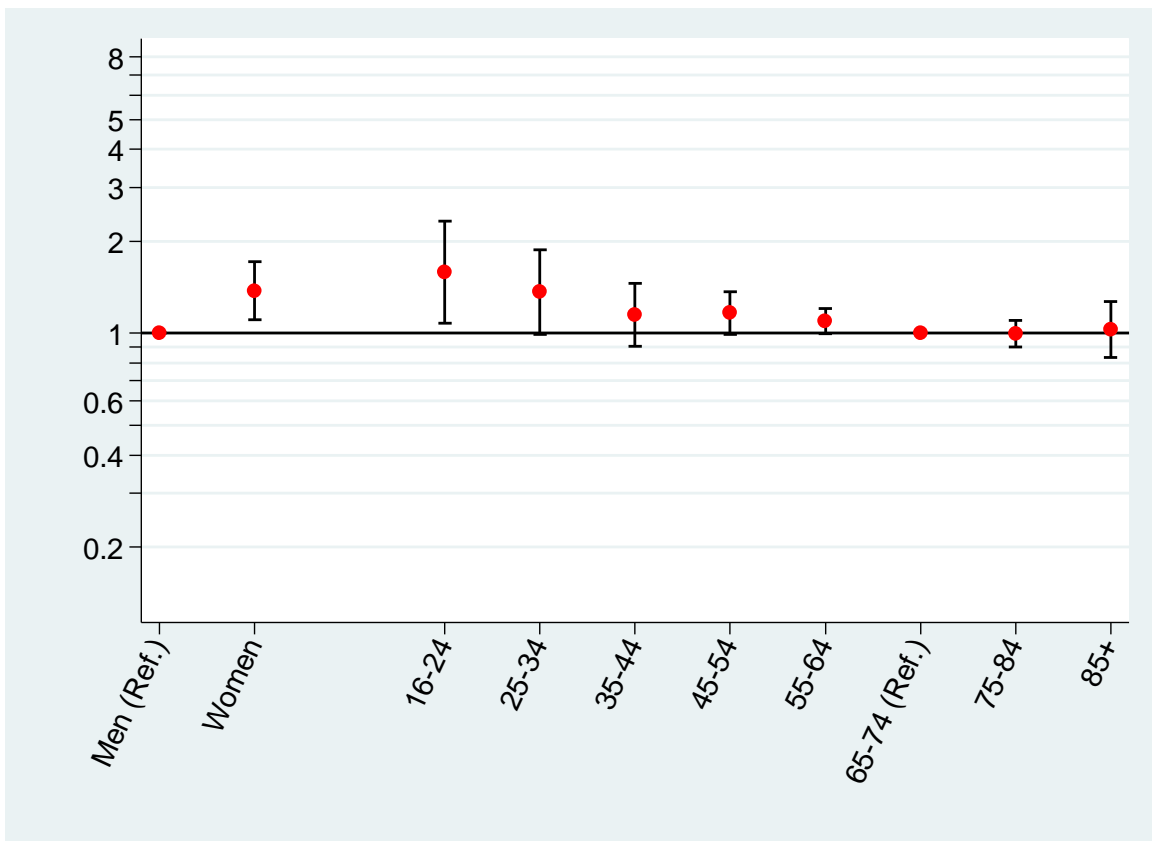
### Non-Hodgkin lymphoma



### Multiple myeloma



### Leukaemia



## Appendix 2

### Sensitivity analysis using alternative definitions of binary outcome for less / more positive experience regarding the number of general practitioner consultations before hospital referral (n=41,299 for all three models)

This analysis examines the sensitivity of the main analysis model (left) to the definition of the outcome measure. The additional two models repeat the main effects model but defining the outcome as i) having seen a general practitioner ‘five or more’ times vs. any other category (middle); or ii) having seen a general practitioner ‘twice’, ‘three-four’ or ‘five or more’ times vs. ‘once’ (right). Although some odds ratios change substantially depending on definition, the overall pattern of variation is consistent across the three models. Ordered logistic regression was considered but not used because of strong evidence that the proportional odds assumption was violated (p<0.0001) – see main paper, Methods.

Patient characteristics	Main analysis (odds ratio of having seen GP three or more times vs. ‘once’ or ‘twice’)			Sensitivity analysis focusing on the least positive category (having seen GP ‘five or more’ times vs. ‘once’, ‘twice’ or ‘three-four’ times)			Sensitivity analysis focusing on the most positive category (having seen GP ‘twice’, ‘three-four’ or ‘five or more’ times vs. ‘once’)		
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval
Men	Reference			Reference			Reference		
Women	1.28	1.21	1.36	1.45	1.32	1.58	1.22	1.15	1.28
16-24	2.12	1.63	2.75	1.79	1.25	2.55	1.71	1.32	2.22
25-34	1.82	1.51	2.20	1.80	1.37	2.35	1.87	1.58	2.22
35-44	1.46	1.30	1.65	1.41	1.17	1.69	1.55	1.40	1.72
45-54	1.45	1.33	1.57	1.44	1.27	1.62	1.35	1.26	1.45
55-64	1.24	1.16	1.32	1.24	1.13	1.36	1.19	1.13	1.26
65-74	Reference			Reference			Reference		
75-84	0.87	0.81	0.93	0.78	0.70	0.87	0.92	0.86	0.97
85+	0.79	0.68	0.91	0.77	0.60	0.98	0.80	0.71	0.90
White	Reference			Reference			Reference		
Mixed	1.81	1.30	2.53	1.74	1.11	2.73	1.54	1.11	2.14
Asian	1.73	1.45	2.08	1.76	1.38	2.25	1.56	1.31	1.85
Black	1.83	1.51	2.23	1.88	1.46	2.42	2.06	1.70	2.49
Chinese	1.32	0.80	2.15	0.99	0.48	2.06	0.97	0.60	1.55
Other	1.69	0.79	3.62	2.83	1.18	6.78	1.29	0.63	2.61
Affluent	Reference			Reference			Reference		
Deprivation group 2	1.05	0.98	1.13	1.14	1.02	1.27	1.02	0.96	1.08
Deprivation group 3	0.98	0.91	1.05	0.97	0.86	1.08	0.97	0.91	1.03
Deprivation group 4	1.03	0.95	1.11	1.09	0.97	1.23	1.00	0.94	1.07
Most deprived	1.13	1.04	1.22	1.21	1.07	1.37	1.00	0.93	1.07
Multiple myeloma	3.42	3.01	3.90	3.91	3.22	4.75	2.90	2.55	3.29

Patient characteristics	Main analysis (odds ratio of having seen GP three or more times vs. 'once' or 'twice')			Sensitivity analysis focusing on the least positive category (having seen GP 'five or more' times vs. 'once', 'twice' or 'three-four' times)			Sensitivity analysis focusing on the most positive category (having seen GP 'twice', 'three-four' or 'five or more' times vs. 'once')		
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval
Pancreatic	2.35	1.91	2.88	2.98	2.23	3.98	2.16	1.76	2.66
Stomach	1.96	1.65	2.34	2.47	1.90	3.21	1.76	1.49	2.08
Lung	1.68	1.48	1.90	2.02	1.66	2.47	1.74	1.55	1.95
Hodgkin's lymphoma	1.67	1.34	2.08	2.43	1.78	3.30	1.79	1.43	2.23
Colon	1.58	1.41	1.78	1.85	1.53	2.24	1.53	1.38	1.70
Ovarian	1.56	1.34	1.81	1.75	1.40	2.20	1.32	1.15	1.51
Brain	1.55	1.16	2.08	2.54	1.74	3.72	1.14	0.86	1.51
Non-Hodgkin lymphoma	1.50	1.33	1.69	1.65	1.36	2.01	1.36	1.22	1.52
Mesothelioma	1.43	1.08	1.90	1.16	0.70	1.92	1.76	1.37	2.26
Rectal	Reference			Reference			Reference		
Renal	1.38	1.12	1.69	1.92	1.42	2.59	1.47	1.22	1.77
Laryngeal	1.34	1.02	1.77	1.36	0.86	2.14	1.46	1.14	1.88
Oesophageal	1.15	0.98	1.36	1.03	0.77	1.38	1.17	1.02	1.35
Leukaemia	1.15	0.99	1.32	1.50	1.20	1.88	1.06	0.94	1.20
Prostate	1.10	0.98	1.24	1.36	1.11	1.67	1.39	1.25	1.54
Vulval	1.05	0.74	1.50	1.47	0.89	2.45	0.78	0.57	1.06
Cervical	0.95	0.72	1.25	1.68	1.17	2.43	0.75	0.58	0.96
Bladder	0.83	0.74	0.93	0.99	0.81	1.21	0.83	0.76	0.92
Thyroid	0.71	0.55	0.92	0.78	0.51	1.18	0.74	0.60	0.92
Endometrial	0.59	0.49	0.71	0.68	0.50	0.92	0.56	0.48	0.65
Testicular	0.47	0.33	0.67	0.35	0.17	0.74	0.60	0.45	0.78
Melanoma	0.34	0.27	0.43	0.33	0.22	0.50	0.42	0.36	0.49
Breast	0.19	0.17	0.22	0.22	0.18	0.28	0.19	0.17	0.21

GP: General Practitioner.



### Appendix 3

#### Sensitivity analysis adjusting for accuracy of patient recall (time since initiation of cancer treatment used as a surrogate marker for accuracy of recall)

This analysis examines whether there is any confounding by possible recall bias in our study. Whilst there is a tendency for patients whose treatment started over a year ago to have had higher frequency of the outcome of interest, this does not appear to confound any of the associations with cancer type or socio-demographic characteristics. It should be noted that this tendency may reflect recall bias or secular (over time) changes in clinical practice and service delivery.

Patient characteristics	Main analysis (n=41,299)				Sensitivity analysis including adjustment for time since treatment initiation (n=40,617)**			
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
Men	Reference				Reference			
Women	1.28	1.21	1.36	<0.0001	1.28	1.21	1.36	<0.0001
16-24	2.12	1.63	2.75		2.20	1.69	2.86	
25-34	1.82	1.51	2.20		1.86	1.54	2.25	
35-44	1.46	1.30	1.65		1.48	1.31	1.67	
45-54	1.45	1.33	1.57	<0.0001	1.46	1.35	1.59	<0.0001
55-64	1.24	1.16	1.32		1.25	1.17	1.33	
65-74	Reference				Reference			
75-84	0.87	0.81	0.93		0.88	0.82	0.94	
85+	0.79	0.68	0.91		0.81	0.69	0.94	
White	Reference				Reference			
Mixed	1.81	1.30	2.53		1.82	1.29	2.56	
Asian	1.73	1.45	2.08	<0.0001	1.84	1.53	2.21	<0.0001
Black	1.83	1.51	2.23		1.81	1.48	2.21	
Chinese	1.32	0.80	2.15		1.31	0.80	2.14	
Other	1.69	0.79	3.62		1.51	0.69	3.32	
Affluent	Reference				Reference			
Deprivation group 2	1.05	0.98	1.13		1.05	0.98	1.13	
Deprivation group 3	0.98	0.91	1.05	0.0064	0.97	0.91	1.05	0.0033
Deprivation group 4	1.03	0.95	1.11		1.03	0.95	1.11	
Most deprived	1.13	1.04	1.22		1.14	1.05	1.23	
Multiple myeloma	3.42	3.01	3.90		3.16	2.77	3.62	
Pancreatic	2.35	1.91	2.88	<0.0001	2.39	1.94	2.94	<0.0001
Stomach	1.96	1.65	2.34		2.01	1.69	2.41	
Lung	1.68	1.48	1.90		1.70	1.49	1.93	

Patient characteristics	Main analysis (n=41,299)				Sensitivity analysis including adjustment for time since treatment initiation (n=40,617)**			
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
Hodgkin's lymphoma	1.67	1.34	2.08		1.64	1.32	2.05	
Colon	1.58	1.41	1.78		1.60	1.42	1.81	
Ovarian	1.56	1.34	1.81		1.52	1.31	1.76	
Brain	1.55	1.16	2.08		1.50	1.12	2.02	
Non-Hodgkin lymphoma	1.50	1.33	1.69		1.46	1.29	1.65	
Mesothelioma	1.43	1.08	1.90		1.45	1.09	1.93	
Rectal	Reference				Reference			
Renal	1.38	1.12	1.69		1.35	1.10	1.66	
Laryngeal	1.34	1.02	1.77		1.35	1.03	1.78	
Oesophageal	1.15	0.98	1.36		1.18	1.00	1.40	
Leukaemia	1.15	0.99	1.32		1.07	0.93	1.24	
Prostate	1.10	0.98	1.24		1.09	0.96	1.23	
Vulval	1.05	0.74	1.50		1.08	0.76	1.54	
Cervical	0.95	0.72	1.25		0.96	0.73	1.26	
Bladder	0.83	0.74	0.93		0.79	0.70	0.89	
Thyroid	0.71	0.55	0.92		0.70	0.54	0.91	
Endometrial	0.59	0.49	0.71		0.61	0.51	0.74	
Testicular	0.47	0.33	0.67		0.48	0.34	0.69	
Melanoma	0.34	0.27	0.43		0.35	0.28	0.43	
Breast	0.19	0.17	0.22		0.19	0.16	0.21	
Treatment started < 1 year ago					Reference			
Treatment started between 1-5 years ago		Not applicable			1.20	1.13	1.27	<0.0001
Treatment started > 5 years ago					1.20	1.09	1.32	

\* From joint Wald tests for categorical variables.

\*\* This model uses information from responses to survey question 71 "How long is it since you were first treated for this cancer?" (response categories "Less than a year ago", "1 to 5 years", "More than 5 years" and "Don't know / Can't remember") to define the respective variable.

Appendix 4

Table Appendix 4-1. Sensitivity analysis by repeating the analysis excluding patients with ‘single gender’ cancers and breast cancer

Patient characteristics	Main analysis – model includes patients with any of 24 cancers, including both ‘either gender’ and ‘single gender’ cancers (n=41,299)				Sensitivity analysis –model restricted to patients with any of 17 ‘either gender’ cancers (i.e. excluding reproductive organ and breast cancer)** (n=25,560)			
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	P*
Men	Reference				Reference			
Women	1.28	1.21	1.36	<0.0001	1.28	1.21	1.36	<0.0001
16-24	2.12	1.63	2.75		2.28	1.72	3.02	
25-34	1.82	1.51	2.20		2.08	1.65	2.62	
35-44	1.46	1.30	1.65		1.80	1.54	2.10	
45-54	1.45	1.33	1.57	<0.0001	1.50	1.35	1.66	<0.0001
55-64	1.24	1.16	1.32		1.29	1.20	1.39	
65-74	Reference				Reference			
75-84	0.87	0.81	0.93		0.87	0.81	0.95	
85+	0.79	0.68	0.91		0.78	0.66	0.92	
White	Reference				Reference			
Mixed	1.81	1.30	2.53		1.66	1.11	2.50	
Asian	1.73	1.45	2.08	<0.0001	1.64	1.29	2.08	<0.0001
Black	1.83	1.51	2.23		1.80	1.37	2.35	
Chinese	1.32	0.80	2.15		1.17	0.66	2.08	
Other	1.69	0.79	3.62		1.60	0.56	4.55	
Affluent	Reference				Reference			
Deprivation group 2	1.05	0.98	1.13		1.06	0.97	1.15	
Deprivation group 3	0.98	0.91	1.05	0.0064	0.98	0.90	1.07	0.029
Deprivation group 4	1.03	0.95	1.11		1.04	0.95	1.13	
Most deprived	1.13	1.04	1.22		1.14	1.03	1.25	
Multiple myeloma	3.42	3.01	3.90		3.44	3.02	3.92	
Pancreatic	2.35	1.91	2.88		2.35	1.91	2.89	
Stomach	1.96	1.65	2.34		1.97	1.65	2.36	
Lung	1.68	1.48	1.90		1.68	1.48	1.91	
Hodgkin's lymphoma	1.67	1.34	2.08	<0.0001	1.57	1.25	1.96	<0.0001
Colon	1.58	1.41	1.78		1.59	1.41	1.79	
Ovarian	1.56	1.34	1.81		N/A			
Brain	1.55	1.16	2.08		1.49	1.11	2.00	
Non-Hodgkin lymphoma	1.50	1.33	1.69		1.49	1.32	1.68	

Patient characteristics	Main analysis – model includes patients with any of 24 cancers, including both ‘either gender’ and ‘single gender’ cancers (n=41,299)				Sensitivity analysis –model restricted to patients with any of 17 ‘either gender’ cancers (i.e. excluding reproductive organ and breast cancer)** (n=25,560)			
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	P*
Mesothelioma	1.43	1.08	1.90		1.44	1.09	1.91	
Rectal	Reference				Reference			
Renal	1.38	1.12	1.69		1.37	1.11	1.68	
Laryngeal	1.34	1.02	1.77		1.34	1.02	1.77	
Oesophageal	1.15	0.98	1.36		1.16	0.98	1.36	
Leukaemia	1.15	0.99	1.32		1.13	0.97	1.30	
Prostate	1.10	0.98	1.24		N/A			
Vulval	1.05	0.74	1.50		N/A			
Cervical	0.95	0.72	1.25		N/A			
Bladder	0.83	0.74	0.93		0.84	0.75	0.94	
Thyroid	0.71	0.55	0.92		0.67	0.52	0.88	
Endometrial	0.59	0.49	0.71		N/A			
Testicular	0.47	0.33	0.67		N/A			
Melanoma	0.34	0.27	0.43		0.33	0.27	0.42	
Breast	0.19	0.17	0.22		N/A			

N/A: Not applicable.

\*From joint Wald tests for categorical variables.

\*\*I.e. excluding patients with ovarian, endometrial, cervical, vulval, prostate, testicular and breast cancer.

### Comment on Table Appendix 4-1

This analysis investigates the sensitivity of the main effects model to the inclusion of cancers which occur in either only one sex (ovarian, endometrial, cervical, vulval, testicular and prostate cancer) or predominantly in one sex (breast cancer). We see little difference between the two models for applicable comparisons. In particular it can be seen that:

- The odds ratios (and respective confidence intervals) for gender are identical in either model.
- The odds ratios for the 17 relevant cancers are very similar in the two models. The minor differences in the odds ratios for 17 relevant cancers principally reflect variation by chance – because of differences in sample size and composition between the two models – for example the sample size for the main model is 41,299 whereas the that of the sensitivity analysis model (after exclusion of patients with the seven relevant cancers) is 25,560.\*

\*Regarding changes in the odds ratios for cancer: We explore the role of chance variation due to sampling differences for the cancer with the largest (although still small) difference in odds ratios (OR), which is Hodgkin's Lymphoma, with OR=1.67 / OR=1.57 in the 'main analysis' and in the restricted to 'either gender' cancer model. This cancer has relatively few patients (462) many of whom are young (specifically 37% of all Hodgkin's Lymphoma patients are aged 16-34, compared with 2% of patients in the respective age bracket for all other cancers) – see *Table Appendix 4-2* below. The difference in the odds ratios for Hodgkin's lymphoma between the two models reflects the large fraction of young patients who have been removed from the analysis when restricting to 'either gender' cancers [i.e. only 61% of 16-34 year olds included in the main analysis model (n=41,299) are included in the restricted model (n=25,560)], thus increasing imprecision. The difference in the age distribution of patients included in either model reflects the fact that 'single sex' cancers have substantially different age distribution to that of 'either gender' cancers – for example the age distribution of testicular and cervical cancer is markedly skewed to younger age groups – see below]. These considerations also apply to brain and thyroid cancer – which are the other two cancers with the 2<sup>nd</sup> and 3<sup>rd</sup> larger differences in odds ratio values (OR=1.55 / OR=1.49 and OR=0.71 / OR 0.67 in the 'main' and the 'restricted' model respectively). I.e., just like Hodgkin's lymphoma, brain and thyroid cancers also have a small sample size (219 and 399 patients respectively) and an atypically (compared to average) high proportion of young patients – see below). In conclusion differences between the odds ratios by cancer in the two models are only minor, and when they occur, they principally reflect differences in the composition and size of the population of patients included in either model.

**Table Appendix 4-2. Number and % of patients aged 16-34 by cancer type.**  
**Italics denote 'single gender' cancers and breast cancer**

<b>Cancer</b>	<b>n</b>	<b>N</b>	<b>%</b>
	<b>16-34</b>	<b>All ages</b>	<b>16-34</b>
<i>Testicular</i>	108	275	39.3%
Hodgkin's Lymphoma	170	462	36.8%
<i>Cervical</i>	54	287	18.8%
Thyroid	72	399	18.0%
Brain	35	218	16.1%
Leukaemia	126	1,686	7.5%
Melanoma	56	1,124	5.0%
Non-Hodgkin Lymphoma	81	2,914	2.8%
<i>Breast</i>	208	8,408	2.5%
<i>Ovarian</i>	18	1,390	1.3%
<i>Vulval</i>	2	171	1.2%
Colon	29	3,289	0.9%
<i>Endometrial</i>	9	1,149	0.8%
Rectal	19	2,611	0.7%
Renal	3	564	0.5%
Lung	11	2,362	0.5%
Stomach	2	748	0.3%
Multiple myeloma	3	1,854	0.2%
Bladder	5	5,209	0.1%
Oesophageal	1	1,099	0.1%
Laryngeal	0	279	0.0%
Mesothelioma	0	275	0.0%
<i>Prostate</i>	0	4,059	0.0%
Pancreatic	0	467	0.0%
All cancers	1,012	41,299	2.5%

## Appendix 5

**Table Appendix 5-1. Sensitivity analysis with regression models stratified to either sex**

Patient characteristics	Model restricted to men (n=20,233)				Model restricted to women (n=21,066)			
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
16-24	1.80	1.23	2.62		2.60	1.79	3.78	
25-34	2.03	1.49	2.77		1.73	1.36	2.20	
35-44	1.63	1.33	2.01		1.39	1.19	1.62	
45-54	1.42	1.25	1.61	<0.0001	1.46	1.30	1.64	<0.0001
55-64	1.24	1.14	1.34		1.25	1.13	1.37	
65-74	Reference				Reference			
75-84	0.90	0.82	0.99		0.83	0.74	0.93	
85+	0.80	0.65	0.99		0.74	0.59	0.93	
White	Reference				Reference			
Mixed	1.76	1.07	2.92		1.86	1.18	2.91	
Asian	1.64	1.26	2.13	<0.0001	1.84	1.43	2.37	<0.0001
Black	2.40	1.84	3.13		1.37	1.03	1.84	
Chinese	1.32	0.62	2.79		1.35	0.70	2.60	
Other	2.23	0.53	9.32		1.60	0.65	3.91	
Affluent	Reference				Reference			
Deprivation group 2	1.08	0.98	1.19		1.02	0.92	1.13	
Deprivation group 3	1.01	0.92	1.12	0.15	0.93	0.84	1.04	0.055
Deprivation group 4	1.02	0.92	1.13		1.03	0.92	1.15	
Most deprived	1.13	1.01	1.26		1.12	0.99	1.25	
Multiple myeloma	3.40	2.87	4.02		3.50	2.85	4.29	
Pancreatic	2.44	1.86	3.20		2.27	1.66	3.11	
Stomach	2.16	1.75	2.66		1.49	1.07	2.06	
Lung	1.67	1.41	1.97		1.70	1.40	2.06	
Hodgkin's lymphoma	1.55	1.14	2.10		1.80	1.31	2.49	
Colon	1.61	1.38	1.88		1.58	1.32	1.90	
Ovarian	N/A			<0.0001	1.63	1.35	1.96	<0.0001
Brain	1.57	1.07	2.30		1.51	0.96	2.40	
Non-Hodgkin lymphoma	1.62	1.38	1.90		1.39	1.15	1.67	
Mesothelioma	1.39	1.01	1.91		1.51	0.79	2.88	
Rectal	Reference				Reference			
Renal	1.22	0.93	1.58		1.67	1.21	2.32	
Laryngeal	1.31	0.96	1.78		1.44	0.78	2.68	
Oesophageal	1.09	0.89	1.33		1.29	0.97	1.73	

Patient characteristics	Model restricted to men (n=20,233)				Model restricted to women (n=21,066)			
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
Leukaemia	1.09	0.90	1.32		1.22	0.98	1.53	
Prostate	1.07	0.93	1.23		N/A			
Vulval	N/A				1.11	0.76	1.60	
Cervical	N/A				1.00	0.74	1.35	
Bladder	0.68	0.58	0.78		1.33	1.09	1.61	
Thyroid	0.78	0.48	1.26		0.72	0.52	0.98	
Endometrial	N/A				0.62	0.50	0.77	
Testicular	0.45	0.31	0.65		N/A			
Melanoma	0.40	0.30	0.55		0.30	0.22	0.41	
Breast	0.42	0.17	1.02		0.20	0.17	0.24	

N/A: Not applicable.

\*From joint Wald tests for categorical variables.

### Comment on Table Appendix 5-1

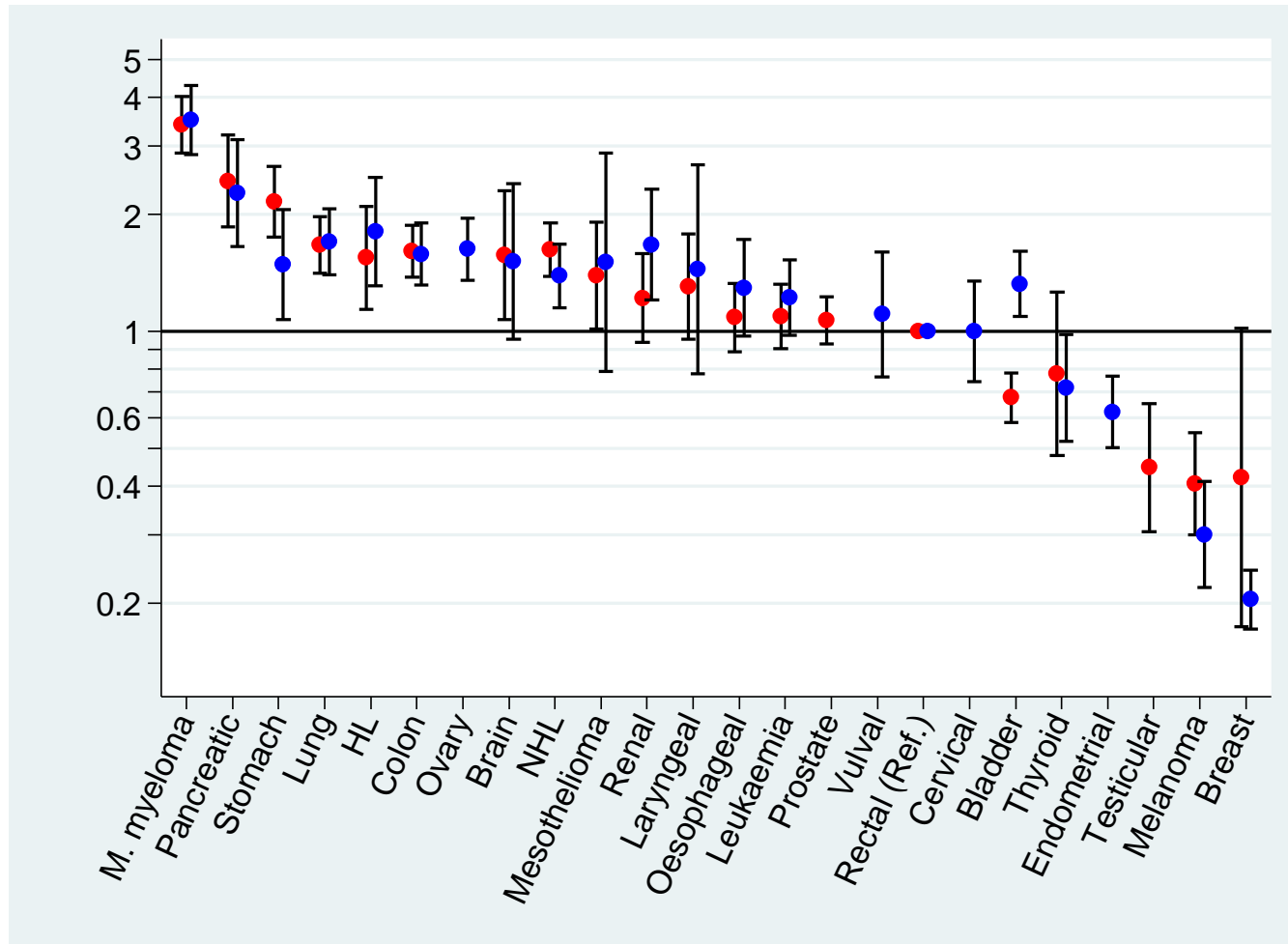
This analysis examines the effect of stratifying the main effects analysis by gender. It can be seen that:

- Subject to sampling differences, patterns of variation by socio-demographic characteristic (other than gender) are similar in either model (i.e. for patients of either sex).
- Patterns of gender variation by cancer fall into two patterns. For some cancers the odds ratios are similar for both men and women (e.g. multiple myeloma, brain and thyroid cancer). For other cancers, the odds ratios differ substantially for patients of either sex (e.g. bladder, renal, stomach cancer) – as could be expected given the interaction effects by sex observed for these cancers (see also main text, Table 3, Figure 4, and also Figures 6A-B). We also provide a graphical summary of data on gender variation by cancer presented in the above table below (Figure Appendix 5-1).

When considering differences in odds ratio by cancer between men and women, we recommend use of data from the ‘full’ model (inclusive of both main effect and interaction variables, Table 3, and Figures 3-6) because using ‘stratified’ models can lead to misinterpretation (e.g. by potentially comparing non-significant effects in men with significant ones in women and vice versa), reduces power, increases imprecision and does not allow for quantification or testing of the significance of the effect associated with sex.



**Figure Appendix 5-1. Adjusted odds ratios and 95% confidence intervals of three or more general practitioner consultations before hospital referral, for cancer type from main effects models stratified by gender (please see notes on Table Appendix 5-1 for interpretation). Men are denoted in red and women in blue dots**



M. myeloma: Multiple myeloma; HL: Hodgkin's lymphoma; NHL: Non-Hodgkin lymphoma.

## Appendix 6

### Sensitivity analysis for region (including in the analysis model a fixed effect variable for NHS Region)

This analysis investigates the degree of any regional variation in the probability of seeing a general practitioner three or more times before hospital referral for cancer; and whether it has any confounding effect. Whilst there is some weak evidence of regional variation (p=0.021) there is no indication of confounding.

Patient characteristics	Main analysis (n=41,299)				Sensitivity analysis including adjustment for NHS region (n=41,051)			
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
Men	Reference				Reference			
Women	1.28	1.21	1.36	<0.0001	1.28	1.21	1.36	<0.0001
16-24	2.12	1.63	2.75		2.11	1.63	2.74	
25-34	1.82	1.51	2.20		1.83	1.51	2.21	
35-44	1.46	1.30	1.65		1.47	1.30	1.66	
45-54	1.45	1.33	1.57	<0.0001	1.45	1.33	1.58	<0.0001
55-64	1.24	1.16	1.32		1.24	1.16	1.32	
65-74	Reference				Reference			
75-84	0.87	0.81	0.93		0.86	0.81	0.93	
85+	0.79	0.68	0.91		0.78	0.67	0.91	
White	Reference				Reference			
Mixed	1.81	1.30	2.53		1.78	1.28	2.49	
Asian	1.73	1.45	2.08	<0.0001	1.70	1.41	2.04	<0.0001
Black	1.83	1.51	2.23		1.76	1.44	2.14	
Chinese	1.32	0.80	2.15		1.29	0.79	2.12	
Other	1.69	0.79	3.62		1.63	0.76	3.49	
Affluent	Reference				Reference			
Deprivation group 2	1.05	0.98	1.13		1.06	0.99	1.14	
Deprivation group 3	0.98	0.91	1.05	0.0064	0.99	0.92	1.06	0.0015
Deprivation group 4	1.03	0.95	1.11		1.04	0.96	1.12	
Most deprived	1.13	1.04	1.22		1.16	1.07	1.26	
Multiple myeloma	3.42	3.01	3.90		3.42	3.00	3.89	
Pancreatic	2.35	1.91	2.88		2.32	1.89	2.86	
Stomach	1.96	1.65	2.34		1.97	1.65	2.35	
Lung	1.68	1.48	1.90	<0.0001	1.67	1.48	1.90	<0.0001
Hodgkin's lymphoma	1.67	1.34	2.08		1.66	1.33	2.07	
Colon	1.58	1.41	1.78		1.59	1.41	1.79	
Ovarian	1.56	1.34	1.81		1.55	1.33	1.79	

Patient characteristics	Main analysis (n=41,299)				Sensitivity analysis including adjustment for NHS region (n=41,051)			
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	p*
Brain	1.55	1.16	2.08		1.55	1.16	2.08	
Non-Hodgkin lymphoma	1.50	1.33	1.69		1.49	1.32	1.68	
Mesothelioma	1.43	1.08	1.90		1.44	1.08	1.90	
Rectal	Reference				Reference			
Renal	1.38	1.12	1.69		1.38	1.13	1.69	
Laryngeal	1.34	1.02	1.77		1.36	1.03	1.80	
Oesophageal	1.15	0.98	1.36		1.16	0.98	1.36	
Leukaemia	1.15	0.99	1.32		1.13	0.98	1.31	
Prostate	1.10	0.98	1.24		1.10	0.98	1.24	
Vulval	1.05	0.74	1.50		1.05	0.74	1.50	
Cervical	0.95	0.72	1.25		0.95	0.72	1.25	
Bladder	0.83	0.74	0.93		0.83	0.74	0.93	
Thyroid	0.71	0.55	0.92		0.72	0.56	0.93	
Endometrial	0.59	0.49	0.71		0.59	0.49	0.70	
Testicular	0.47	0.33	0.67		0.47	0.33	0.67	
Melanoma	0.34	0.27	0.43		0.34	0.28	0.43	
Breast	0.19	0.17	0.22		0.19	0.17	0.22	
West Midlands					Reference			
East Midlands					0.96	0.86	1.06	
East of England					1.05	0.95	1.16	
London					1.00	0.91	1.11	
North-East					0.86	0.76	0.97	
North--West		Not applicable			0.92	0.83	1.02	0.021
South-Central					1.02	0.91	1.15	
South-East					0.92	0.82	1.04	
South-West					0.95	0.87	1.05	
Yorkshire and Humber					0.91	0.82	1.00	

NHS: National Health Service.

\*From joint Wald tests for categorical variables.

## Appendix 7

### Sensitivity analysis by inclusion of random effect for hospital of treatment, and primary care organisation (n=41,299 for all three models)

With this analysis we investigate whether there is any evidence that any of the socio-demographic or cancer differences are caused by clustering of groups of patients within either certain hospitals or primary care organisations. Ideally we would use general practice as a random effect but such data were not available (see also main paper). Whilst there is some evidence of variation by hospital or primary care organisation (p=0.0020 for hospital random effect, and p= 0.051 for primary care organisation random effect, respectively) there is very little change in the odds ratios of the main effect variables. Furthermore the confidence intervals also change very little. These observations indicate that none of the observed associations with cancer type or socio-demographic characteristic are caused by clustering at the level of hospital or primary care organisation.

Patient characteristics	Main analysis (no random effect variable included)			Model including a random effect for hospital of treatment*			Model including a random effect for primary care organisation**		
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval
Men	Reference			Reference			Reference		
Women	1.28	1.21	1.36	1.28	1.21	1.36	1.28	1.21	1.36
16-24	2.12	1.63	2.75	2.09	1.61	2.73	2.12	1.63	2.75
25-34	1.82	1.51	2.20	1.82	1.51	2.19	1.82	1.51	2.20
35-44	1.46	1.30	1.65	1.46	1.29	1.64	1.46	1.30	1.65
45-54	1.45	1.33	1.57	1.44	1.33	1.57	1.45	1.33	1.57
55-64	1.24	1.16	1.32	1.24	1.16	1.32	1.24	1.16	1.32
65-74	Reference			Reference			Reference		
75-84	0.87	0.81	0.93	0.87	0.81	0.93	0.87	0.81	0.93
85+	0.79	0.68	0.91	0.79	0.68	0.91	0.79	0.68	0.91
White	Reference			Reference			Reference		
Mixed	1.81	1.30	2.53	1.80	1.29	2.52	1.81	1.30	2.53
Asian	1.73	1.45	2.08	1.73	1.44	2.07	1.73	1.45	2.07
Black	1.83	1.51	2.23	1.81	1.49	2.19	1.83	1.51	2.22
Chinese	1.32	0.80	2.15	1.31	0.81	2.13	1.31	0.81	2.13
Other	1.69	0.79	3.62	1.66	0.81	3.41	1.68	0.82	3.44
Affluent	Reference			Reference			Reference		
Deprivation group 2	1.05	0.98	1.13	1.06	0.99	1.14	1.05	0.98	1.13
Deprivation group 3	0.98	0.91	1.05	0.98	0.91	1.06	0.98	0.91	1.05
Deprivation group 4	1.03	0.95	1.11	1.03	0.96	1.12	1.03	0.95	1.11
Most deprived	1.13	1.04	1.22	1.14	1.05	1.23	1.13	1.04	1.23
Multiple myeloma	3.42	3.01	3.90	3.43	3.01	3.91	3.43	3.01	3.91

Patient characteristics	Main analysis (no random effect variable included)			Model including a random effect for hospital of treatment*			Model including a random effect for primary care organisation**		
	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval	Odds ratios	Lower 95% confidence interval	Upper 95% confidence interval
Pancreatic	2.35	1.91	2.88	2.34	1.90	2.88	2.35	1.91	2.89
Stomach	1.96	1.65	2.34	1.96	1.64	2.34	1.97	1.65	2.35
Lung	1.68	1.48	1.90	1.68	1.48	1.91	1.68	1.48	1.90
Hodgkin's lymphoma	1.67	1.34	2.08	1.67	1.34	2.08	1.67	1.34	2.08
Colon	1.58	1.41	1.78	1.58	1.41	1.78	1.58	1.41	1.78
Ovarian	1.56	1.34	1.81	1.55	1.34	1.80	1.56	1.34	1.81
Brain	1.55	1.16	2.08	1.57	1.16	2.10	1.56	1.16	2.09
Non-Hodgkin lymphoma	1.50	1.33	1.69	1.50	1.33	1.69	1.50	1.33	1.69
Mesothelioma	1.43	1.08	1.90	1.43	1.08	1.89	1.43	1.08	1.90
Rectal	Reference			Reference			Reference		
Renal	1.38	1.12	1.69	1.38	1.12	1.69	1.38	1.12	1.69
Laryngeal	1.34	1.02	1.77	1.36	1.03	1.79	1.35	1.02	1.79
Oesophageal	1.15	0.98	1.36	1.16	0.98	1.36	1.16	0.98	1.37
Leukaemia	1.15	0.99	1.32	1.14	0.99	1.32	1.15	0.99	1.32
Prostate	1.10	0.98	1.24	1.11	0.98	1.25	1.11	0.98	1.25
Vulval	1.05	0.74	1.50	1.04	0.73	1.49	1.05	0.74	1.50
Cervical	0.95	0.72	1.25	0.94	0.71	1.24	0.95	0.72	1.25
Bladder	0.83	0.74	0.93	0.83	0.74	0.93	0.83	0.74	0.93
Thyroid	0.71	0.55	0.92	0.71	0.55	0.92	0.71	0.55	0.92
Endometrial	0.59	0.49	0.71	0.59	0.49	0.71	0.59	0.49	0.71
Testicular	0.47	0.33	0.67	0.47	0.33	0.67	0.47	0.33	0.67
Melanoma	0.34	0.27	0.43	0.34	0.28	0.43	0.34	0.28	0.42
Breast	0.19	0.17	0.22	0.19	0.17	0.22	0.19	0.17	0.22

NHS: National Health Service

\*NHS Trust

\*\*NHS Primary Care Trust

## **Appendix 8**

### **Patterns of distribution of cancers compared with population incidence statistics**

We compared the distribution of cancers in the 67,713 survey respondents and in the 41,299 patients included in the analysis against population-based incidence statistics.<sup>1</sup> Because patterns were very similar for all survey respondents and for patients in the analysis sample,<sup>2</sup> we only report comparisons between population statistics and survey respondents (n=67,713) hereafter. It was felt appropriate to also consider 1-year relative survival.<sup>3</sup> We hypothesised that cancers with low short-term survival may be under-represented in the survey sample, and vice versa.

An inconsistent pattern of comparisons is apparent, including cancers that are under-represented, cancers that are over-represented, and cancers that appear to be appropriately represented in the survey sample (Figures A-B, below).

Two cancers with very low 1-year survival (i.e. pancreatic and lung cancer) were substantially under-represented. However, some cancers with very high 1-year survival (such as prostate cancer in men, and melanoma in both sexes) were also under-represented, possibly reflecting non-response patterns specific to those cancers or confounding by age non-response patterns.

Breast cancer and cancers requiring frequent contact with hospital services (e.g. bladder and haematological cancers) were also over-represented.

A number of cancers (including cancers with both low and average survival) appear to be neither over- nor under-represented (oesophageal, stomach and colon cancers).

We urge caution about the potential misinterpretation of these findings: The patterns are crude (unadjusted) and some of the apparent variation may be explained by non-response patterns by age, deprivation or ethnicity. Time from diagnosis and treatment initiation may also be relevant (the survey was dominated by patients whose treatment started in the last year). Lastly, it is also important to consider the pattern of hospital care (treatment or follow-up appointments) for different cancers. For example patients with bladder and haematological cancers tend to have a larger number of outpatient / day-case appointments or treatment sessions compared to the average cancer patient. The exact direction and size of these sources of variation is complex and difficult to infer.

We also urge caution against the potential over-interpretation of these patterns as indicative of ‘non-response bias’: we explain in the Discussion section of the main paper why non-response patterns are far from being a sufficient condition for non-response bias. Given the relatively high response rate, the multivariable (case-mix adjusted) analysis used, and the large size of observed associations, it is unlikely that the findings can simply reflect non-response bias.

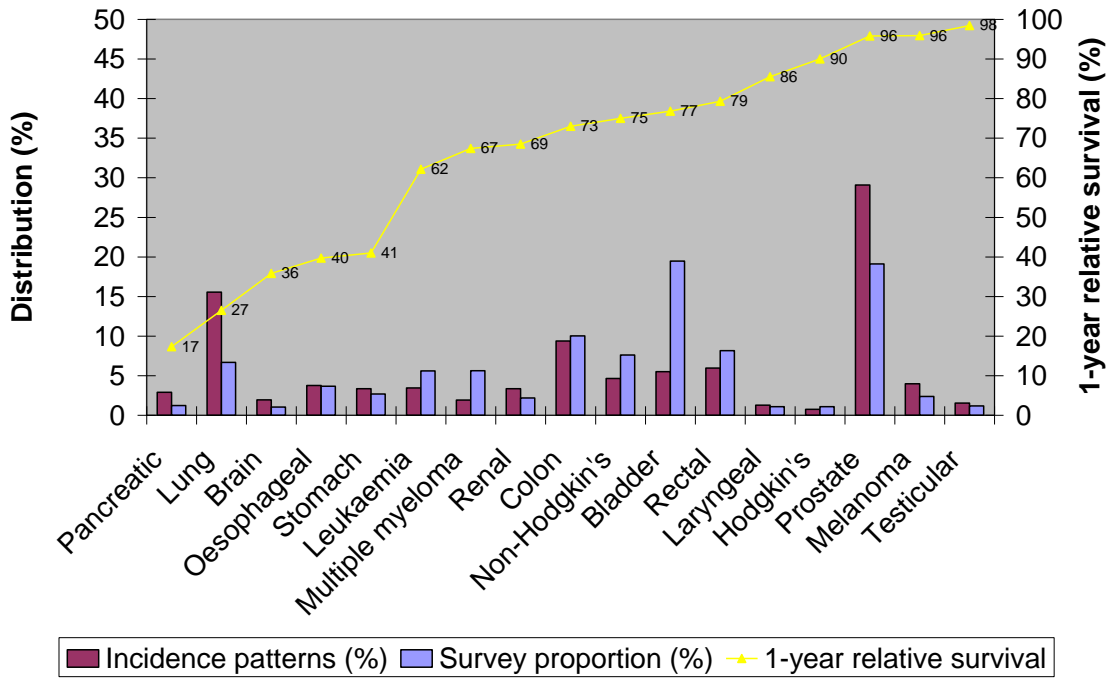
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<sup>1</sup> Office for National Statistics, Cancer Registrations in England, 2009.

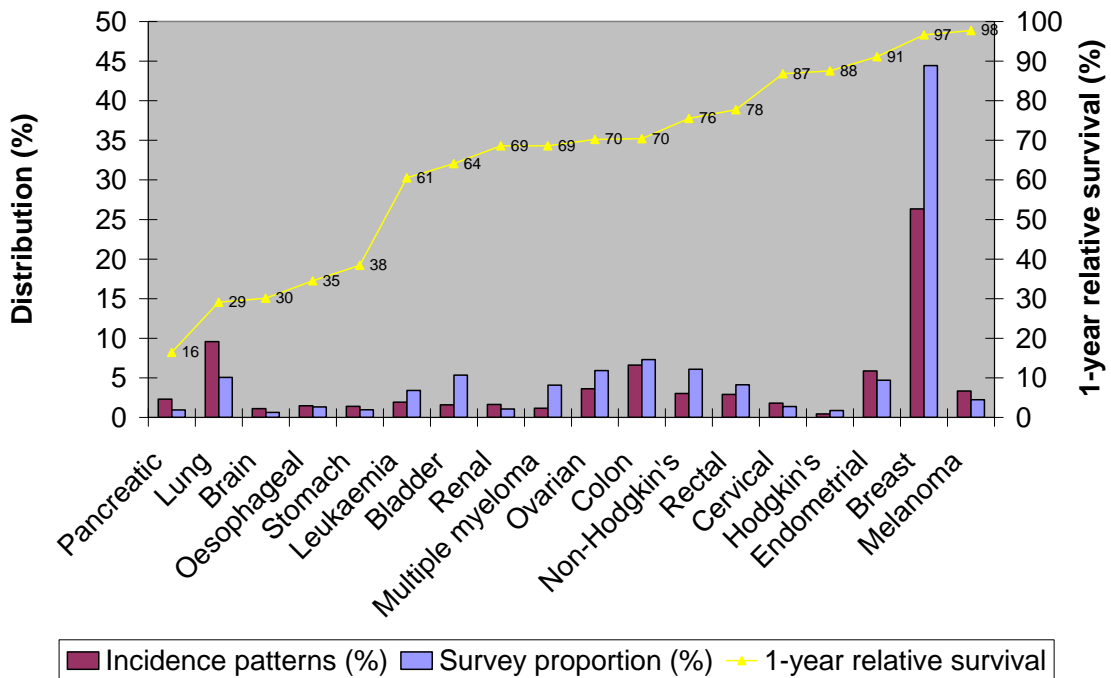
<sup>2</sup> I.e. among patients with one of the studied cancers who provided a valid answer to survey question 1, and with no missing data for ethnic group or deprivation.

<sup>3</sup> 1-year relative survival data are based on: Rachet B, Maringe C, Nur U, Quaresma M, Shah A, Woods LM, Ellis L, Walters S, Forman D, Steward J, Coleman MP. Population-based cancer survival trends in England and Wales up to 2007: an assessment of the NHS cancer plan for England. *Lancet Oncol.* 2009;10(4):351-69.

**Figure Appendix 8-A. Comparisons of incidence and sample proportions by cancer, against 1-year relative survival estimates, men**



**Figure Appendix 8-B. Comparisons of incidence and sample proportions by cancer, against 1-year relative survival estimates, women**



## Appendix 9

### Indirect comparison of unadjusted variation in number of general practitioner consultations before hospital referral observed in the Cancer Patient Experience Survey 2010 and the National Audit of Diagnosis of Cancer in Primary Care

The proportion of patients who saw their general practitioner three or more times with cancer symptoms before hospital referral in the Cancer Patient Experience Survey 2010 (column 2) and in the National Audit of Cancer Diagnosis in Primary Care (column 4),<sup>4</sup> is compared, by cancer:

**Table Appendix 9. Comparison of proportions of patients with three or more pre-referral consultations in the Cancer Patient Survey 2010 and the National Audit of Cancer Diagnosis in Primary Care\***

Cancer	Cancer Patient Experience Survey 2010 (n=41,299)				National Audit of Cancer Diagnosis in Primary Care (n=14,239)			
	n	N	%	Rank	n	N	%	Rank
Multiple myeloma	939	1,854	50.6%	1	83	196	42.3%	1
Pancreatic	193	467	41.3%	2	102	325	31.3%	4
Brain	80	218	36.7%	3	39	167	23.4%	8
Ovarian	504	1,390	36.3%	4	94	345	27.2%	6
Stomach	269	748	36.0%	5	82	252	32.6%	2
Lung	795	2,362	33.7%	6	494	1561	31.6%	3
Lymphoma	1,132	3,376	33.5%	7	166	631	26.3%	7
Cervical	86	287	30.0%	8	26	133	19.5%	13
Renal	168	564	29.8%	9	67	295	22.8%	9
Laryngeal	79	279	28.3%	10	23	107	21.5%	12
Mesothelioma	77	275	28.0%	11	20	67	29.8%	5
Colorectal	1,645	5,900	27.9%	12	467	2132	21.9%	11
Leukaemia	465	1,686	27.6%	13	81	441	18.4%	14
Vulval	46	171	26.9%	14	4	60	6.6%	19
Oesophageal	274	1,099	24.9%	15	115	521	22.1%	10
Thyroid	92	399	23.1%	16	11	99	11.2%	17
Prostate	912	4,059	22.5%	17	376	2446	15.4%	15
Bladder	931	5,209	17.9%	18	115	755	15.2%	16
Endometrial	202	1,149	17.6%	19	36	371	9.7%	18
Testicular	44	275	16.0%	20	8	139	5.7%	20
Melanoma	113	1,124	10.1%	21	43	759	5.7%	21
Breast	625	8,408	7.4%	22	76	2437	3.1%	22

\*Comparisons relate to 22 cancers because of aggregation in the audit report (which considered 'colorectal' and 'lymphoma' as single categories including colon and rectal cancers, and Hodgkin's and Non-Hodgkin lymphoma respectively). Data relating to patients diagnosed with cancer without prior general practitioner consultation with cancer symptoms, and missing data, were excluded from both datasets.

There is a high degree of concordance in patterns of (unadjusted) variation by cancer site between the two datasets:

- The Spearman's rank correlation coefficient is 0.899 ( $p < 0.0001$ ) – indicating high level of rank agreement.
- Although the pattern of variation by cancer is similar, the proportion of patients with three or more pre-referral consultations is systematically (consistently) higher in the Cancer Patient Experience Survey 2010 compared to the audit dataset. This may reflect the fact that the Cancer Patient Experience Survey encompassed an unselected sample of patients (all patients treated in an NHS hospital during the first quarter of 2010); whereas the National Audit of Cancer Diagnosis in Primary Care

<sup>4</sup> [http://www.rcgp.org.uk/pdf/National\\_Audit\\_of\\_Cancer\\_Diagnosis\\_in\\_Primary-Care.pdf](http://www.rcgp.org.uk/pdf/National_Audit_of_Cancer_Diagnosis_in_Primary-Care.pdf)



relates to patients registered with 1,170 general practices (a selected group of practices, representing 14% of all 8,387 practices in England). Other explanations include a systematic over-recall of this outcome when reported by cancer patients, or a systematic under-count in the audit dataset – e.g. because of incomplete capturing of symptoms in practice patient records.

- Please also see Figure 7 in main paper – illustrating differences in proportions and 95% confidence intervals for the 15 cancers with the largest sample size (excluding cancers with a sample size < 250 patients in the audit dataset).

## Appendix 10

### Overview of cancer patient experience survey evidence – additional references

The directly relevant publicly available report documents of the Cancer Patient Experience Survey 2010 and the National Audit of Diagnosis of Cancer in Primary Care are referenced in the main paper. We provide below a list of other papers, of indirect relevance to the study.

#### 1. Patient-reported timeliness of cancer diagnosis

- Neal RD, Allgar VL. Sociodemographic factors and delays in the diagnosis of six cancers: analysis of data from the "National Survey of NHS Patients: Cancer". *Br J Cancer*. 2005;92(11):1971-5.
- Allgar VL, Neal RD. Delays in the diagnosis of six cancers: analysis of data from the National Survey of NHS Patients: Cancer. *Br J Cancer*. 2005;92(11):1959-70.

#### 2. Cancer patient experience survey development or methodological considerations

- Madden PB, Davies EA. Reporting cancer patients' experiences of care for quality improvement: analysis of 2000 and 2004 survey results for South East England. *J Eval Clin Pract*. 2010;16(4):776-83.
- Malin JL, Ko C, Ayanian JZ, Harrington D, Nerenz DR, Kahn KL, Ganther-Urmie J, Catalano PJ, Zaslavsky AM, Wallace RB, Guadagnoli E, Arora NK, Roudier MD, Ganz PA. Understanding cancer patients' experience and outcomes: development and pilot study of the Cancer Care Outcomes Research and Surveillance patient survey. *Support Care Cancer*. 2006;14(8):837-48.

#### 3. Evaluation of care quality based on the experience of cancer patients

- Davidson R, Mills ME. Cancer patients' satisfaction with communication, information and quality of care in a UK region. *Eur J Cancer Care (Engl)*. 2005;14(1):83-90.
- Sherlaw-Johnson C, Datta P, McCarthy M. Hospital differences in patient satisfaction with care for breast, colorectal, lung and prostate cancers. *Eur J Cancer*. 2008;44(11):1559-65.
- McCarthy M, Datta P, Sherlaw-Johnson C, Coleman M, Rachet B. Is the performance of cancer services influenced more by hospital factors or by specialization? *J Public Health (Oxf)*. 2008;30(1):69-74.
- Ayanian JZ, Zaslavsky AM, Guadagnoli E, Fuchs CS, Yost KJ, Creech CM, Cress RD, O'Connor LC, West DW, Wright WE. Patients' perceptions of quality of care for colorectal cancer by race, ethnicity, and language. *J Clin Oncol*. 2005;23(27):6576-86.
- McCarthy M, Datta P, Sherlaw-Johnson C. Organizational determinants of patients' experiences of care for breast, lung and colorectal cancers. *Eur J Cancer Care (Engl)*. 2009;18(3):287-94.
- Allgar VL, Neal RD. General practitioners' management of cancer in England: secondary analysis of data from the National Survey of NHS Patients-Cancer. *Eur J Cancer Care (Engl)*. 2005;14(5):409-16.