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The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis: a national population based modelling study

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Abstract

Background

Since a national lockdown was introduced across the UK in response to the COVID-19 pandemic, cancer screening has been suspended, routine diagnostic work deferred, and only urgent symptomatic cases prioritised for diagnostic intervention. In this study we estimate the impact of delays in diagnosis on cancer survival outcomes in four major tumour types.

Methods

The study uses linked English National Health Services (NHS) cancer registration and hospital administrative datasets for patients aged 15-84, diagnosed between 01/01/2010 and 31/12/2010 with follow-up until 31/12/2014 for breast (*n*=32,583), colorectal (*n*=24,975), and oesophageal cancer (*n*= 6,744), and for lung cancer patients (*n*= 29,305) diagnosed between 01/01/2012 and 31/12/2012 with follow-up until 31/12/2015. We use a 'routes to diagnosis' framework to estimate the impact of diagnostic delay over a 12-month period from the commencement of lockdown measures, 16/03/2020. We reallocate patients who were on screening and routine referral pathways to urgent and emergency pathways, which are associated with more advanced stage of disease at diagnosis. We consider three reallocation scenarios which reflect actual changes in the diagnostic pathway being seen in the NHS, and estimate the impact on net survival at 1, 3 and 5 years to calculate the additional deaths that can be attributed to cancer, and the total years of life lost (YLL) compared to pre-pandemic figures.

Findings

Across the three scenarios, compared to pre-pandemic figures, we estimate an 8-10% increase in the number of deaths due to breast cancer up to Year 5, corresponding to between 281 (266-295) and 344 (329-358) additional deaths. For colorectal cancer we estimate 1,445 (1,392-1,591) to 1,563 (1,534-1,592) additional deaths (a 15-17% increase); lung cancer 1,235 (1,220-1,254) to 1,372 (1,343-1,401) additional deaths (5% increase) and oesophageal cancer 330 (324-335) to 342 (336-348) additional deaths (6% increase). For these four tumour types, this corresponds to a total of 3,291 to 3,620 additional deaths across the scenarios within 5 years. The total additional years of life lost (YLL) across these cancers is estimated to be between 59,203 to 63,229 years.

Interpretation

There are expected to be substantial increases in the number of avoidable cancer deaths in the UK, predominantly related to the expected increase in diagnoses following an emergency presentation.

Urgent policy interventions are necessary, in particular the need to manage the backlog within routine diagnostic services, to mitigate the expected impact of the COVID-19 pandemic on cancer patients.

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Background

A national lockdown was introduced across the United Kingdom (UK) on 23rd March 2020, as part of the national strategy to 'flatten the curve' of the COVID-19 pandemic and reduce the potential impact on the National Health Service (NHS).[1] This has been associated with a decline in, or cessation of, most non-COVID-19 NHS services, increasing concern about the impact this will have on other patient groups requiring time-critical access to health care services. This includes cancer patients for whom timely diagnosis and the prompt initiation of treatment is vital for ensuring optimal outcomes.[2,3]

During the pandemic, multiple changes in the provision of cancer care from the point of diagnosis, including modification of treatment schedules (change in therapy, deferral or omission), have been advised by professional bodies and commissioners of services.[4-7] However, there is significant heterogeneity in the implementation of these recommendations across providers nationally and for individual patients. Such variations in the extent of treatment delay, and in changes to treatment doses and schedules (including new treatment techniques) means that at a population level it is challenging to model these variations in practice on cancer outcomes.

Instead, we focus on analysing the impact of changes in cancer diagnostic pathways and subsequent delays in diagnosis during the COVID-19 pandemic. It is already evident that routine non-urgent diagnostic work initiated by referral from both general practitioners (GPs) and secondary care teams (for radiology or endoscopic procedures,[8] for example) has been deferred across the UK. Cancer screening services have been suspended, and patients' only routes to diagnosis in recent weeks has been via urgent 'two-week wait' (2WW) suspected cancer pathway referrals initiated by the GP or through direct presentation to an emergency department.[9] Patients are eligible for these rapid access two-week wait (2WW) pathways to access diagnostic investigations, on the basis of their age, symptom profile (e.g. dysphagia), signs (e.g. breast lump) or results of investigations (e.g. iron deficiency anaemia) as specified by guidelines developed by the National Institute for Health and Care Excellence (NICE).[9]

However, since March 2020, there has been evidence of changes in health seeking behaviour with urgent 2WW cancer referrals falling by up to 80% in response to social distancing, and concerns about contracting SARS-Cov2 virus.[10] In addition, some form of social distancing is expected to continue for up to 12 months, which will impact further on health care presentations.[11,12]

Quantifying the exact impact of delays in diagnosis on stage and prognosis are complex, but a 'routes to diagnosis' approach provides a validated methodological framework for understanding their impacts. Work by Ellis-Brookes et al.[13] demonstrated that referral routes to diagnosis are

characterised by differences in both stage at presentation and survival. For example, urgent 2WW suspected cancer referrals and emergency presentations are associated with later-stage of disease at diagnosis compared to patients diagnosed through routine GP and secondary care referral routes and screening. In addition, diagnosis following initial presentation to an emergency department is consistently associated with the worst survival outcomes compared to all other routes.[13]

Given the changes in health seeking behaviour and the availability and access to diagnostic services as a result of the COVID-19 lockdown, these 'routes to diagnosis' provide a framework for estimating the impact of these changes on stage migration and excess mortality, based on patients moving to different referral routes during the pandemic.

The effect of delayed presentation on cancer patients is not immediate, and premature death as a result may occur up to 5 years later and will differ according to tumour type. In this study we consider the impact on four major tumour types: breast, colorectal, lung, and oesophagus because they differ in their predominant routes to referral (including screening), stage at presentation, and both short- and long-term prognoses according to stage. Using national population datasets of patients diagnosed and treated in the English National Health Service (NHS) we estimate the impact of delays in diagnosis that are attributed to the measures put in place to halt the COVID-19 pandemic in the UK. We estimate their effect on patient survival and the number of additional deaths expected due to these cancers, as well as the additional years of life lost.

Methods

Conceptual framework

Based on previous years' trends we assume that the incidence of each of the four tumour types will remain relatively stable year on year,[14] and that the current pandemic and subsequent lockdown will mean patients will be more likely to delay presentation. We estimate the subsequent impact on survival, by reallocating patients from screening and non-urgent routine referral pathways (from GPs and secondary care) to urgent pathways, namely 2WW referral routes and emergency presentation. Both of these urgent pathways are associated with later stage of diagnosis and enable us to estimate the impact of diagnostic delay on stage migration and survival outcome.

We justify our reallocation model on four assumed factors: 1. 2WW and emergency pathways are the only referral routes at the present time; 2. While routine diagnostic work and non-urgent referral pathways are delayed and screening suspended, some patients awaiting investigation will become symptomatic as their cancer progresses and will meet the criteria for urgent 2WW suspected cancer referrals or present as emergencies direct to secondary care; 3. For patients awaiting routine

diagnostic investigations from GP and secondary care referrals there are expected to be significant delays (>6 months) in this pathway,[12] due to the backlogs of routine work across all medical and surgical services increasing the likelihood of disease progression, which we estimate through reallocation to 2WW and emergency pathways. 4. Changes in health seeking behaviour as a result of the pandemic means that some patients will delay presentation until more prominent symptoms develop, and these patients will be more likely to present through 2WW and emergency pathways.

The starting point for our estimation is from the 16th March 2020, which is the date social distancing measures were introduced, and the impact is modelled over a 12-month period to account for the expected duration of disruption to services and patterns of referral. This-period defines our cohort of expected number of cancer diagnoses for each tumour type, but It is acknowledged that patients may present and be diagnosed beyond this period due to diagnostic delay. Our model reallocates patients based on pre-pandemic ratios. For example, if 10% of new diagnoses for a given tumour type is following an emergency department presentation, and 90% via an outpatient referral, our simulation analysis will maintain these proportions when reallocating patients from screening and routine referral pathways.

For breast cancer patients diagnosed through the screening referral pathway, we accounted for the fact that many are diagnosed with pre-invasive disease[15] or disease that is unlikely to progress even within a 12-month period. We therefore reallocated only 25% (n=2,700) of breast cancer screening patients. This reflects the proportion of screening patients with T3, T4, node positive or metastatic disease at the time of diagnosis. Reallocation was used to estimate the excess mortality compared to the pre-pandemic period.

Scenarios

We based our analysis on three sets of predictions according to possible changes in referral patterns (Figure 1) representing best/worst case scenarios:

Scenario A – We estimate survival outcomes for patients by reallocating those who are expected to be diagnosed through screening and routine referral pathways (GP or secondary care) to 2WW and emergency presentation pathways, from 16th March 2020.

Scenario B - As per scenario A, but from 16th March we simulate the impact of an 80% reduction in 2WW referrals already observed during the lockdown period, and assume that this reduction will continue (due to COVID-19-related concerns) for up to three months. Emergency presentations are assumed to continue at their usual rate. We therefore re-allocate the backlog of patients in Months 4-12 to 2WW pathways and emergency presentations.

Scenario C – As per Scenario B, but we simulate the impact of 2WW referrals continuing to be reduced beyond the first three-month period by 25% for a further three-month period, that is until Month 6 post introduction of social distancing measures. Emergency presentations are assumed to continue at the usual rate. We therefore re-allocate the backlog of patients in Months 7-12 to 2WW pathways and emergency presentations.

Population and datasets

Information on adults with non-small cell lung cancer (NSCLC, hereafter "lung cancer" ICD-10: C33, C34), cancers of the colon (ICD-10: C18) and rectum (ICD-10: C19), cancers of the oesophagus and gastro-oesophageal junction (ICD-10: C15, C16.0) and women with breast cancer (ICD-10: C50) were obtained from the National Cancer Registration Service (NCRS). The pre-pandemic cohort refers to patients diagnosed between 01/01/2010 and 31/12/2010 with follow-up until 31/12/2014 for cancers of the colon, rectum, oesophagus and breast, and to patients diagnosed between 01/01/2012 and 31/12/2012 with follow-up until 31/12/2015 for lung cancer. We restricted the analyses to patients aged 15-84 years at diagnosis and those who had a known route of diagnosis coded (91% for colorectal cancer, 93% for oesophagus, 94% for breast and 97 % for lung).

The NCRS records and updates patient and tumour characteristics for virtually all cancers (98-100%) diagnosed in England.[16] Information on referral pathway is derived from linkages of the cancer registrations with secondary care data (Hospital Episode Statistics, HES), screening records, and cancer waiting times data.[13] These linkages were performed with deterministic linkage using the NHS Number, with a linkage success of 99-100%.[16] Information on patient's comorbidity status is derived from HES diagnostic codes when patients attend hospital.[17] Levels of deprivation are determined by the quintiles of the Index of Multiple Deprivation (IMD) income domain, for the patients' residential postcodes, measured at Lower Super Output Area level.[18] This study has been undertaken in accordance with existing statutory and ethical approvals from the Confidentiality Advisory Group and Research Ethics Committee (PIAG 1-05(c)/2007 and REC 13/LO/0610).

Statistical analyses

The mode of presentation and dates of diagnosis of the pre-pandemic cohorts were randomly modified according to scenarios A-C. Patients diagnosed through screening and routine referral pathways (outpatient or inpatient), were reallocated to either emergency presentation or 2WW referral routes. For scenarios B and C, we reallocated a proportion of patients diagnosed through the

2WW pathway as these referral routes are expected to operate at 20% and 75% of their capacity as previously described.

The reallocation of patients from routine and screening pathways to the emergency presentation route was estimated at the same proportion observed in the pre-pandemic cohorts: 930 (2.9%) of 32,583 patients for breast, 4,143 (26.1%) of 15,867 patients for colon, 1,040 (11.4%) of 9,108 patients for rectum, 9,636 (32.9%) of 29,305 patients for lung, and 1,228 (18.2%) of 6,744 patients for oesophageal cancer (Table 1).

Whilst pre-pandemic patients diagnosed through emergency routes were more likely to be older and have more comorbidities; during this pandemic significant changes have been noted to the availability of diagnostic services through both routine and 2WW referral pathways, which has affected all patients. In addition, there has been evidence of changes in health seeking behaviour resulting in an 80% reduction in the volume of urgent 2WW referrals since the UK lockdown. We therefore account for the fact that new groups of patients with a different sociodemographic profile are likely to first present with cancer following an emergency admission and therefore reallocate any patient in the cohort to either the urgent 2WW referral or emergency presentation route.

To estimate the impact that the response to COVID-19 could have on cancer survival, we compared the net survival of pre-pandemic cohorts of cancer patients to that of patients diagnosed according to the postulated scenarios A to C. Of note for colorectal cancer even though the reallocation from routine to urgent pathways was undertaken separately for patients with rectal and colon cancer, the survival estimates are for the combined colorectal cancer population. We translated the differences in net survival between pre-pandemic and pandemic cohorts into the number of deaths due to cancer for each scenario. Compared to the number of deaths due to cancer in the pre-pandemic cohorts, we derived the additional number of deaths due to cancer and additional number of years of life expectancy lost. Confidence intervals were calculated using bootstrap resampling.

These estimates are obtained from multivariable excess hazard models. When analysing population-based data, the measure of interest, excess mortality due to cancer, is conventionally retrieved by removing the impact of competing risks of death, i.e. deaths from causes other than the cancer of interest.[19] These competing risks are derived from general population life tables, defined by sex, single years of age, calendar years, deprivation quintile, and Government Office Regions. All-cause mortality from general population life tables does include cancer-related mortality but each site-specific mortality represents a negligible cause of death and therefore does not impact the estimation of cancer survival.[20,21] Further details and mathematical formulas are provided in the Web-*Appendix, pages 1-3*. All statistical analyses were performed using Stata version 16.

Role of the funding source

None of the co-author funding sources had any role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication. CM, BR and AA had full access to all the data in the study, take responsibility for the integrity of the data and accuracy of the data analysis, and had final responsibility for the decision to submit to publication.

Results

We analysed data on 32,583 breast, 24,975 colorectal, 29,305 lung, and 6,744 oesophagus cancer patients (Table 1). Pre-pandemic, survival varied significantly by tumour type and referral pathway with the worst prognosis evident for oesophageal and lung cancers and with emergency presentations. These differences in survival between referral pathways correlated with higher proportions of patients diagnosed at stages III and IV, irrespective of tumour type (Table 1, *Web-Appendix page 4*). As demonstrated, 2WW referral pathways are not associated with marked differences in stage or survival compared to non-urgent referral routes.

The estimations were undertaken over a 12-month period from 16/03/2020 to 15/03/2021. Across Scenarios A-C, we estimate an absolute decline in cancer survival ranging between 1.0% (Breast, all scenarios) and 6% (Oesophagus, scenarios B and C) at 1-year, and between 4% (Lung, scenario A) and 6% (Colorectal, scenario C), 5 years after diagnosis (Table 1).

The differences in survival translate into substantial additional number of deaths due to cancer in the first five years of follow-up. Table 2 presents the estimated number of deaths due to each cancer up to 1, 3 and 5 years following diagnosis prior to the pandemic and across scenarios A to C. The number of additional deaths estimated across the scenarios are presented as cumulative estimates up to year 5 (Table 2 and Figure 2).

We estimate across scenarios A to C, compared to pre-pandemic, a 2-7% increase in the number of deaths due to breast cancer in Year 1 (corresponding to between 20 (15-25) and 63 (57-70) additional deaths), a 7-9% increase up to Year 3 (169 (159-179)-228 (218-239) additional deaths) and an 8-10% increase up to Year 5 (281 (266-295)-344 (329-358) additional deaths). For colorectal cancer, we estimate across scenarios A to C a 18-20% increase in deaths due to cancer in Year 1 (921 (894-970)-1,027 (999-1,094) additional deaths), a 16-18% increase up to Year 3 (1,301 (1,257-1,411)-1,414 (1,371-1,568) additional deaths) and a 15-17% increase up to Year 5 (1,445 (1,392-1,591)-1,563 (1,534-1,592) additional deaths). For lung cancer across scenarios A to C, we estimate a 6-8% increase in number of deaths due to cancer in Year 1 (1,102 (1,087-1,117)-1,412 (1,379-1,447) additional deaths), a 5-6% increase up to Year 3 (1,231 (1,216-1,249)-1,412 (1,381-1,442) additional

deaths), and a 5% increase up to Year 5 (1,235 (1,220-1,254) -1,372 (1,343-1,401) additional deaths). For oesophageal cancer, across scenarios A to C, we estimate a 9-10% increase in deaths due to cancer in Year 1 (339 (334-343)-377 (372-383) additional deaths), a 6-7% increase up to Year 3 (343 (337-348)-359 (354-365) additional deaths) and a 6% increase up to Year 5 (330 (324-335)-342 (336-348) additional deaths).

The plateau in additional deaths due to cancer over the 5-year period for lung and oesophageal cancer reflects relatively higher proportions of early cancer deaths at Year 1 due to more advanced stage at presentation in our scenarios. Pre-pandemic, some of these patients would have been expected to die beyond Year 1 as a result of less advanced disease at presentation compared to the pandemic scenarios.

Overall, in comparison with the pre-pandemic period, the estimated total number of additional deaths attributable to these four cancers at 5 years is between 3,291 and 3,620 deaths across the scenarios due to delays in cancer diagnosis (Table 2, Figure 2). These additional cancer deaths in the first few years after diagnosis translate into years of life expectancy lost by the entire cohort of patients. At 5 years, across scenarios A to C, the total additional years of life lost for breast cancer was estimated to range from 8,181 (7,797-8,535) to 9,261 (8,843-9,631) years, for colorectal cancer from 25,583 (24,792-27,744) to 27,735 years (27,188-28,241), for lung cancer from 20,413 (19,833-20,909) to 20,860 (20,250-21,277) years and for oesophageal cancer from 5,027 (4,861-5,213) to 5,373 (5,227-5,530) years. In total we estimate between 59,203 to 63,229 years of life expectancy lost because of additional deaths due to these four cancers in the first five years after diagnosis (Table 3).

Discussion

We find that across four major tumour types: breast, colorectal, lung and oesophageal cancer, there will be an estimated 3,291 to 3,620 avoidable deaths and an additional 59,203 to 63,229 years of life lost that are attributable to delays in cancer diagnosis alone. The increase in cancer related deaths up to 5 years from diagnosis ranged from 5% for lung cancer to 17% for colorectal cancer. These additional deaths are projected to occur as a consequence of the national COVID-19 pandemic measures reducing the number of people seeking health care as well as reducing access to and availability of diagnostic services. Our findings complement those from a recent study by Sud et al.[22] demonstrating the impact of treatment delay, predominantly surgical, on excess mortality.

Some essential diagnostic services are currently suspended (e.g. endoscopy) even through the urgent 2WW referral pathway. This is due to the perceived risk of SARS-COV2 virus exposure for patients and clinicians, and because of re-deployment of staff towards critical care to manage COVID-19 cases. This

will result in further delays, which could impact on survival, that are not included in our model. Our results also highlight the significant proportion of patients diagnosed with cancer through routine outpatient referral pathways (30-40%) and the subsequent impact of deferral and delay within these referral pathways during the pandemic. Even when routine diagnostic services are re-initiated it is anticipated that there will be significant delays in routine and 2WW pathway referrals due to backlogs currently building up across all benign and malignant medical and surgical sub-specialities.

Changes in health seeking behaviour have meant that routine referrals from GPs have reduced in volume because patients are being asked to only present if they have significant or urgent concerns.[12] In addition, it is unknown whether the increasing number of remote consultations via telephone or videoconferencing will result in a greater proportion of missed diagnoses without the ability to examine and triage the patient directly.

Conversely, increased diagnostic efficiency has potentially been introduced into the system as a result of the pandemic. For example, those patients who now report a symptom to their GP are an enriched population compared to those reporting pre-COVID and potentially more likely to have cancer. Similarly, GP selection for investigation will most likely enrich the population further. However, these impacts are likely to be small when considering concerns about the overall shortfall in numbers of new cancer diagnoses. In addition, 2WW referrals are still not operating at their usual pre-pandemic level, particularly for endoscopic intervention.

Our findings therefore reflect the urgent need for policy interventions to mitigate the predicted additional cancer deaths resulting from delays in diagnosis. Key areas to consider include public health messaging; the public's perception of their personal risk of severe illness from COVID-19 versus the risks of not seeking healthcare advice if symptomatic; provision of evidence-based information to enable health care workers to adequately risk manage patients during the pandemic with respect to the balance of risk and benefit of procedures; and to consider options and opportunities for increasing diagnostic capacity.

In the UK, the 'Stay at Home' and subsequent 'Stay Alert' public health messaging has had a marked impact on health seeking behaviour.[23] Even as lockdown measures are being relaxed, presentation to primary care services continues to be much lower than pre-pandemic levels, and it cannot be assumed that, once all restrictions have been lifted, this will return to the pre-pandemic levels in a reasonable timeframe. Any exit strategy from lockdown[24] therefore needs to include accurate and measured public health messaging that is tailored towards patients, GPs and secondary care services that puts into perspective the infection fatality risk of COVID-19 compared to other serious illnesses. Dedicated cancer awareness programmes will need to consider a range of media channels to reach their target

groups, including direct messaging from GPs to their patients to seek attention if they are experiencing new or concerning symptoms.

Increasing diagnostic capacity is complex as this necessitates effective coordination across all hospital sub-specialities and not just within specialist cancer teams. In addition, the requirement for full personal protective equipment (PPE) when performing procedures and the initiation of robust cleaning protocols between patients has reduced capacity compared to pre-pandemic levels. In the short term, diagnostic capacity can be increased through changes in working patterns: longer working hours, 7 days-a-week working. In addition, a central coordinating system for diagnostic investigations in a similar vein to 'choose and book' whereby primary care physicians are able to refer to any NHS hospital will optimise use of capacity.[25] For bowel cancer detection, surgeons are increasingly using new tools such as the faecal immunochemical test[26] to triage their patients for investigation to avoid unnecessary colonoscopy and CT imaging and therefore improving capacity in this diagnostic pathway.

The paucity of information for health care workers and patients regarding their risk of contracting COVID-19 infection from different health care interactions remains a challenge as hospitals plan towards restarting routine services. Antibody testing would increase confidence in clinicians performing procedures if 'immunity' does exist for even a short period.[27] The health care community need accurate data on the true nosocomial risk of COVID-19 depending on the type of diagnostic procedure being undertaken e.g. colonoscopy versus Computerised Tomography scan. When rapid antigen testing becomes available routinely, patients requiring investigation can receive testing on the day of the procedure and risk managed accordingly. Equally the implication of contracting COVID-19 needs to be considered, specifically what is the true risk of life-threatening illness and death to be able to counsel patients effectively.

A strength of this study is the use of linked national administrative health records of actual patients diagnosed and treated in the NHS for the four tumour types. This provides a robust template for understanding the impact of current and predicted changes in availability, access and health seeking behaviour in response to the COVID-19 pandemic on cancer survival. This method does not require any *de novo* estimation of changes in cancer outcomes but derives this from previous real-world observations.

We chose the 'routes to diagnosis' concept as our method of analysing diagnostic delay to overcome some of the challenges raised in the literature regarding the relative risk of death from diagnostic delay across tumours.[2,28,29] Inconsistencies in the evidence are primarily related to flaws in study design where the true onset of symptoms remains unclear. In addition, recent work has pointed to a 'waiting time paradox' whereby quicker diagnosis is associated with later stage of presentation; this

confounds an assessment of the impact of diagnostic delay on outcome.[30,31] It is challenging to model the extent and duration of diagnostic delay at the population level given that this is predicated on health system factors such as the access and, availability of diagnostic capacity, and patient level factors (awareness, symptoms, health seeking behaviour). Our model accounts for both and is grounded in the reality of current service levels in the English NHS by providing best/worst case estimates. We acknowledge that our approach may under- or over-estimate the impact of diagnostic delay on survival and retrospective evaluation will be necessary to further appraise this modelling approach.

Our model assumes that disruptions due to the COVID-19 pandemic will impact timely access to routine and urgent diagnostic services as well as alter health seeking behaviour for a 12-month period. This is likely given the changes in patterns of patient presentation and availability of diagnostic services observed since the lockdown. As well as the suspension of screening, the first three months has seen a significant reduction in 2WW referrals[10] as we predict in Scenario B. Scenario A conservatively considers no reduction in 2WW referrals. Given the ongoing reductions in 2WW referral volumes (estimates suggest a 40-50% reduction),[32] this is expected to continue for up to 6 months as predicted in scenario C due to the effects of pandemic lockdown measures on health care presentations. This includes, advice to minimise non-essential travel and the continued shielding of at-risk groups.[1,12] Cancer Research UK have estimated that the first 10 weeks of the UK lockdown has already resulted in 2.1 million deferred cancer screening investigations with 290,000 fewer people being referred on 2WW pathways.[32]

Following this six-month period there will be a considerable backlog of patients with potential cancers awaiting investigation whilst healthcare presentations will continue to be impacted due to social distancing measures that are expected until 2021.[11,12] Additionally NHS hospital Trusts suspended their routine diagnostic services at the start of the lockdown. This is a concern as routine referral routes account for 30-40% of cancer diagnoses and the backlog in this pathway once routine services restart will include all patients still awaiting diagnostic investigations both pre-pandemic and during the pandemic. Further competition for capacity will subsequently arise from the surge in new referrals for suspected cancers on 2WW referrals and those referred for investigation or follow-up of seemingly benign health conditions. At the same time diagnostic capacity has decreased for some procedures due the greater time taken per case since the introduction of new infection control measures. Together all these factors will increase the likelihood of patients becoming symptomatic and presenting via 2WW referral or emergency pathways. Alternatively, if and when diagnosed through routine pathways there is an increased likelihood of stage migration and associated poorer prognosis due to delays in diagnosis.

Our analysis uses a retrospective population cohort and we therefore note that the predicted survival for patients presenting via the different referral pathways, even for patients with stage IV disease, has marginally improved[33] given the evolution in treatments and processes of care. However, our analysis focuses on the differences in cancer deaths between two situations (pre-pandemic and pandemic) and not on the absolute numbers of cancer deaths. In addition, these estimates do not consider the impact of treatment delay or suboptimal treatment on survival during the pandemic.[22] The proportions of patients presenting through different referral pathways has changed over time which may also impact on our results.[34] However, we consider the likely impact on the overall results to be small given the steady trajectories of improvements we have seen over the past five years.

We did not analyse patients aged 85 years or over at diagnosis as competing events, such as deaths from other causes are predominant. Although delays in cancer diagnosis in the elderly will lead to excess short-term cancer mortality, the impact on society is likely to be less. Furthermore, given we report up-to 5-year survival, such an estimate is less reliable in over 90's.

In the screening population we recognise that not all patients diagnosed with breast cancer through this route would have progressed or developed symptomatic disease. As a result, we include only 25% of this cohort in our re-allocation. For colorectal cancer, 10% of patients are diagnosed through the screening route of which 45% are diagnosed with Stage III/IV disease (70% Stage II-IV) compared to 6% diagnosed with Stage III/IV through breast cancer screening. Over-diagnosis and over-treatment are not specific concerns associated with the bowel screening programme[35] and the suspension of the programme is likely to result in delayed presentation and stage migration if untreated.[36]

Our model also considers the English NHS as a whole and therefore assigns blanket reallocation across the country. However, there is variation across the country with respect to GP access, the burden of COVID-19 and the extent of discontinuation of critical diagnostic services within secondary care settings. In this regard we acknowledge that 2WW referrals have not fallen uniformly by 80% across all tumour types and UK regions, as per our estimations in Scenarios B and C. In addition, there will be variation in the recovery of services across regions and individual hospitals, which are not included in our estimations.

In conclusion we demonstrate that changes in health seeking behaviour and the availability of and access to essential diagnostic services resulting from national pandemic measures will result in significant additional deaths from breast, colorectal, lung and oesophageal cancer in the medium (1 year) and longer term (5 years). The study results do not consider the effect of delay on other cancer types, or the additional impact of changes in treatment pathways for these cancers which are likely to

significantly increase the expected avoidable deaths beyond what we have estimated. Urgent policy interventions are necessary to mitigate the indirect effects of the national COVID-19 pandemic on cancer patients. These should focus on increasing routine diagnostic capacity through which up to 40% of cancer patients are diagnosed, public health messaging that accurately conveys the risk of severe illness from COVID-19 versus the risks of not seeking healthcare advice if symptomatic, and the provision of evidence-based information for clinicians to adequately risk-manage patients as to the risk and benefits of procedures during the pandemic.

Research in context

Evidence before this study

In the UK, national COVID-19 pandemic measures since 16rd March 2020 have resulted in the suspension of cancer screening and deferral of routine diagnostic investigations. In addition, urgent two-week wait suspected cancer referrals initiated by General Practitioners (GPs) have fallen by up to 80% in response to social distancing. To identify studies reporting on the current or predicted impact of diagnostic delay on cancer mortality during the COVID-19 pandemic we conducted a literature search of PubMed from 01/01/2020 to 30/04/2020 in order to identify national estimates and methods of estimation. Search terms included (COVID-19 OR coronavirus OR SARS-Cov-2) AND cancer AND (diagnosis OR diagnostic) AND delay. To date, no study has attempted to model the impact of changes in health seeking behaviour and in the availability and access to diagnostic services as a result of the COVID-19 lockdown on cancer survival and the additional number of deaths expected.

Added value of this study

Our study presents the results of an innovative method that uses a 'routes to diagnosis' validated framework to estimate the impact of the delays in diagnosis that we are seeing on cancer survival and excess cancer deaths for four tumour types: breast, colorectal, lung and oesophageal cancer. Using linked national cancer registration and hospital administrative datasets, we have modelled the impact across three pragmatic scenarios that reflect actual changes in the diagnostic pathway being observed in the National Health Service (NHS).

Implications of all the available evidence

We find that across four major tumour types there will be an estimated 3,291 to 3,620 avoidable excess deaths up to 5 years from diagnosis. This equates to approximately 60,000 years of lost life for just these four tumour types that we attribute to delays in diagnosis. Our results are conservative estimates as we do not consider the impact of suboptimal or delayed cancer treatment. This data is essential for policymakers to drive changes in national lockdown and stay-at-home messaging, as well as to urgently reduce diagnostic delay, particularly for routine investigations, through outreach and accessibility programmes. This model can also be utilised by other countries in their unique healthcare settings to understand the impact of delays in diagnosis on cancer outcomes.

Author Contributions

AA, MM, EN, RS, and BR conceived and designed the study. CM and BR analysed the data. AA, BR, JS, RS, CM were involved in data interpretation. AA and CM wrote the first draft of the paper. CM produced the manuscript figures and tables. CM, JS, MM, AP, EN, RS, BR, AA were involved in reviewing and editing drafts of the paper and approving the manuscript.

Figure Legends

Figure 1. Conceptual framework for the modelling scenarios.

Notes:

1. **2WW** – Two week wait urgent suspected cancer referrals; **EP** – Emergency presentation
2. For Breast cancer note that in addition to patients on routine pathways only 25% (n= 2700) of patients diagnosed through screening (i.e. the proportion of patients with T3, T4, Node positive, or Metastatic disease) are reallocated to 2WW/EP in the pandemic scenarios (see Methods section).

Figure 2. Estimated additional numbers of deaths due to cancer for each pandemic scenario A-C, by tumour type.

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Declaration of Interest

We declare no competing interests

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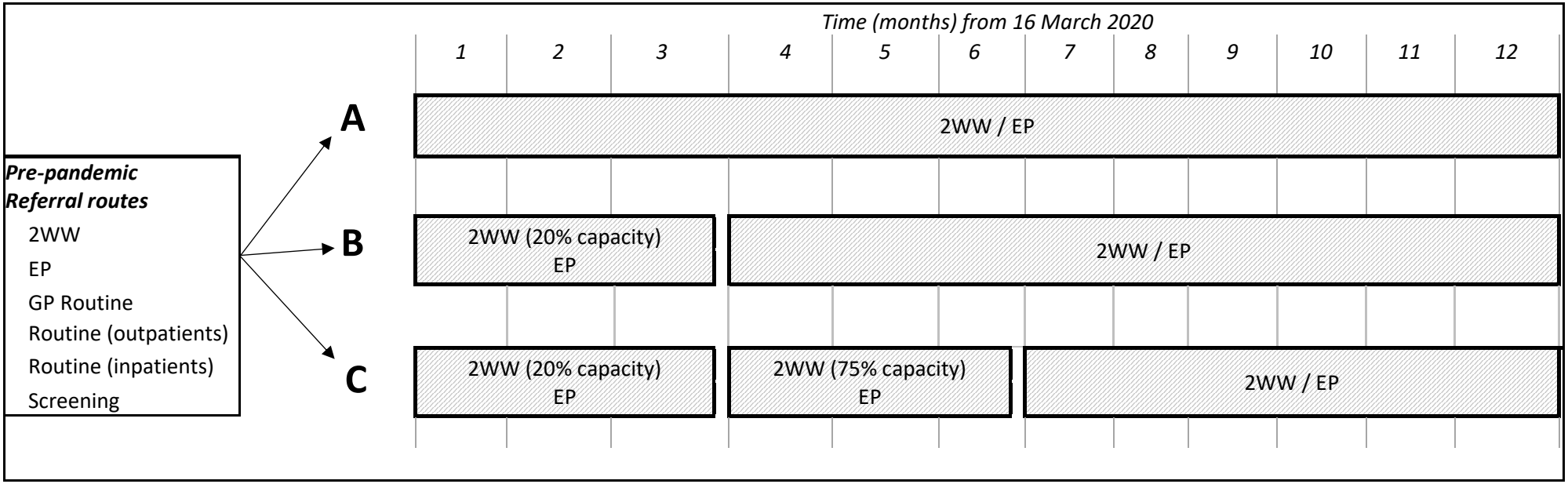
Figure 1. Conceptual framework for the modelling scenarios



Notes:

1. **2WW** – Two week wait urgent suspected cancer referrals; **EP** – Emergency presentation
2. For Breast cancer note that in addition to patients on routine pathways only 25% (n= 2700) of patients diagnosed through screening (i.e. the proportion of patients with T3, T4, Node positive, or Metastatic disease) are reallocated to 2WW/EP in the pandemic scenarios (see Methods section).

Table 1. Distribution of patients by referral pathway, and 1-, 3- and 5-year net survival (NS), pre-pandemic and by each pandemic scenario (A-C)

	Distribution of patients		**Stages III-IV**	1-year	3-year	5-year
	N	**%**	**(%)**	**NS (95% CI)**	**NS (95% CI)**	**NS (95% CI)**
Breast cancer						
Pre-pandemic						
EP	930	2.9	68.8	56.3 (53.9-58.6)	39.0 (37.0-41.0)	33.4 (31.8-35.1)
GP referral	5,136	15.8	20.0	96.3 (96.2-96.3)	90.0 (89.9-90.1)	86.2 (86.2-86.3)
Other routine	887	2.7	22.2	94.0 (93.8-94.2)	85.8 (85.5-86.1)	81.3 (81.0-81.7)
Screening	10,795	33.1	6.0	100 (100-100)	99.6 (99.6-99.6)	98.8 (98.8-98.8)
2WW	14,835	45.5	20.4	97.9 (97.9-97.9)	91.3 (91.3-91.4)	86.3 (86.2-86.3)
Overall	**32,583**	**100**		**97.0 (97.0-97.1)**	**92.2 (92.2-92.3)**	**88.8 (88.7-88.8)**
Scenario A						
EP	1,149	4.7		96.0 (95.9-96.1)	89.0 (88.9-89.1)	83.9 (83.9-84)
2WW	23,357	95.3				
Scenario B						
EP	1,225	5.0		95.9 (95.9-96)	88.8 (88.7-88.9)	83.6 (83.6-83.7)
2WW	23,286	95.0				
Scenario C						
EP	1,249	5.1		95.9 (95.8-96)	88.7 (88.6-88.8)	83.6 (83.5-83.6)
2WW	23,240	94.9				
Colorectal cancer						
Pre-pandemic	Colon / Rectum	Colon / Rectum	Colon / Rectum			
EP	4,143 / 1,040	26.1 / 11.4	77.5 / 78.6	54.8 (54.6-55.1)	40.3 (40.1-40.4)	35.1 (34.9-35.2)
GP referral	3,769 / 2,538	23.8 / 27.9	60.6 / 59.0	83.5 (83.4-83.5)	70.6 (70.5-70.7)	64.4 (64.3-64.4)
Other routine	2,063 / 1,001	13.0 / 11.0	59.9 / 62.2	83.7 (83.6-83.8)	71.3 (71.2-71.4)	65.4 (65.3-65.5)
Screening	1,922 / 1,102	12.1 / 12.1	43.8 / 45.3	97.5 (97.5-97.5)	92.9 (92.9-93.0)	89.6 (89.6-89.7)
2WW	3,970 / 3,427	25.0 / 37.6	61.1 / 61.8	85.0 (85.0-85.1)	71.2 (71.2-71.3)	64.2 (64.1-64.2)
Overall	**15,867/9,108**	**100 / 100**		**79.7 (79.7-79.8)**	**67.3 (67.2-67.3)**	**61.4 (61.4-61.5)**
Scenario A						
EP	6,166 / 1,570	38.9 / 17.2		76.0 (75.9-76.0)	61.9 (61.8-61.9)	55.3 (55.3-55.3)
2WW	9,700 / 7,538	61.1 / 82.8				
Scenario B						
EP	6,384 / 1,654	40.2 / 18.2		75.7 (75.6-75.7)	61.6 (61.6-61.7)	55.1 (55.1-55.2)
2WW	9,482 / 7,454	59.8 / 81.8				
Scenario C						
EP	6,456 / 1,678	40.7 / 18.4		75.5 (75.5-75.6)	61.5 (61.4-61.5)	55.0 (55.0-55.0)
2WW	9,410 / 7,430	59.3 / 81.6				

Lung cancer						
Pre-pandemic						
EP	9,636	32.9	88.3	15.9 (15.9-15.9)	6.6 (6.6-6.6)	4.6 (4.6-4.6)
GP referral	6,549	22.3	68.1	46.4 (46.4-46.4)	26.1 (26.1-26.1)	19.6 (19.6-19.6)
Other routine	4,003	13.7	66.5	50.3 (50.3-50.4)	29.1 (29.1-29.1)	22.0 (22.0-22.0)
2WW	9,117	31.1	76.3	48.7 (48.7-48.7)	21.9 (21.9-21.9)	13.6 (13.6-13.6)
Overall	**29,305**	**100**		**37.6 (37.6-37.6)**	**18.8 (18.8-18.8)**	**13.1 (13.1-13.1)**
Scenario A						
EP	12,802	43.7		34.1 (34.0-34.1)	15.1 (15.1-15.1)	9.6 (9.6-9.6)
2WW	16,503	56.3				
Scenario B						
EP	13,715	46.8		33.3 (33.3-33.3)	14.7 (14.7-14.7)	9.4 (9.4-9.4)
2WW	15,590	53.2				
Scenario C						
EP	13,538	46.2		33.1 (33.1-33.1)	14.6 (14.6-14.6)	9.3 (9.3-9.3)
2WW	15,767	53.8				
Oesophageal cancer						
Pre-pandemic						
EP	1,228	18.2	91.2	20.7 (20.3-21.1)	9.5 (9.4-9.7)	7.9 (7.8-8.1)
GP referral	1,410	20.9	71.7	54.8 (54.6-55.0)	27.3 (27.2-27.4)	21.2 (21.0-21.3)
Other	1,303	19.3	73.1	55.7 (55.6-55.9)	29.7 (29.6-29.9)	23.9 (23.7-24.0)
2WW	2,803	41.6	83.3	48.2 (48.1-48.3)	19.1 (19.0-19.2)	13.4 (13.3-13.5)
Overall	**6,744**	**100**		**46.0 (45.9-46.1)**	**21.1 (21.1-21.2)**	**16.1 (16.0-16.1)**
Scenario A						
EP	1,690	25.1		41.3 (41.2-41.4)	16.7 (16.7-16.8)	12.0 (12.0-12.1)
2WW	5,054	74.9				
Scenario B						
EP	1,783	26.4		39.9 (39.7-40.0)	15.8 (15.7-15.8)	11.3 (11.3-11.4)
2WW	4,961	73.6				
Scenario C						
EP	1,812	26.9		39.7 (39.6-39.8)	15.7 (15.7-15.8)	11.3 (11.2-11.3)
2WW	4,932	73.1				

Notes:

1. **NS** - Net survival; **EP** - Emergency Presentation; **2WW** - Two-week wait urgent suspected cancer referral.
2. 'Other routine' includes referrals within secondary care.

3. Net survival for colorectal cancer is for both colon and rectum tumour type combined. However, allocation of patients to 2WW and EP diagnostic routes was done separately for each tumour type.
4. For Breast cancer note that in addition to patients on routine pathways only 25% (n= 2700) of patients diagnosed through screening (i.e. the proportion of patients with T3, T4, Node positive, or Metastatic disease) are reallocated to 2WW/EP in the pandemic scenarios (see Methods section)

Table 2. Estimated cumulative number of deaths due to cancer up to Years 1, 3 and 5, pre-pandemic and for each pandemic scenario A-C (also presented as additional number of deaths)

	Number of deaths due to cancer			Additional number of deaths due to cancer					
				up-to 1 year		up-to 3 years		up-to 5 years	
	up-to 1 year (95% CI)	up-to 3 years (95% CI)	up-to 5 years (95% CI)	N (95% CI)	%*	N (95% CI)	%*	N (95% CI)	%*
Breast (N = 32,583)									
Pre-pandemic	965 (958-972)	2,495 (2,484-2,505)	3,565 (3,554-3,577)						
Scenario A	985 (977-993)	2,664 (2,651-2,676)	3,846 (3,831-3,861)	20 (15-25)	2.1	169 (159-179)	6.8	281 (266-295)	7.9
Scenario B	1,018 (1,009-1,026)	2,709 (2,696-2,722)	3,894 (3,876-3,911)	53 (47-59)	5.5	214 (202-226)	8.6	329 (313-344)	9.2
Scenario C	1,028 (1,019-1,036)	2,723 (2,709-2,737)	3,908 (3,890-3,926)	63 (57-70)	6.6	228 (218-239)	9.1	344 (329-358)	9.6
Colorectum (N = 24,975)									
Pre-pandemic	5,051 (5,004-5,099)	8,056 (8,007-8,109)	9,417 (9,367-9,470)						
Scenario A	5,986 (5,943-6,025)	9,436 (9,391-9,475)	10,980 (10,940-11,020)	935 (918-953)	18.5	1,379 (1,354-1,405)	17.1	1,563 (1,534-1,592)	16.6
Scenario B	5,972 (5,929-6,028)	9,357 (9,299-9,459)	10,862 (10,797-10,995)	921 (894-970)	18.2	1,301 (1,257-1,411)	16.1	1,445 (1,392-1,591)	15.3
Scenario C	6,078 (6,032-6,140)	9,470 (9,409-9,613)	10,972 (10,903-11,162)	1,027 (999-1,094)	20.3	1,414 (1,371-1,568)	17.6	1,555 (1,498-1,760)	16.5
Lung (N = 29,305)									
Pre-pandemic	18,443 (18,388-18,503)	24,138 (24,097-24,172)	25,934 (25,901-25,963)						
Scenario A	19,545 (19,497-19,594)	25,369 (25,339-25,398)	27,170 (27,148-27,191)	1,102 (1,087-1,117)	6.0	1,231 (1,216-1,249)	5.1	1,235 (1,220-1,254)	4.8
Scenario B	19,769 (19,721-19,817)	25,498 (25,464-25,531)	27,267 (27,240-27,297)	1,326 (1,295-1,362)	7.2	1,360 (1,331-1,389)	5.6	1,332 (1,306-1,360)	5.1
Scenario C	19,855 (19,804-19,901)	25,549 (25,519-25,582)	27,306 (27,280-27,334)	1,412 (1,379-1,447)	7.7	1,412 (1,381-1,442)	5.8	1,372 (1,343-1,401)	5.3
Oesophagus (N = 6,744)									
Pre-pandemic	3,656 (3,642-3,670)	5,359 (5,349-5,369)	5,730 (5,720-5,741)						
Scenario A	3,995 (3,978-4,012)	5,701 (5,690-5,714)	6,060 (6,049-6,073)	339 (334-343)	9.3	343 (337-348)	6.4	330 (324-335)	5.8
Scenario B	4,024 (4,006-4,041)	5,714 (5,703-5,726)	6,069 (6,058-6,081)	367 (362-373)	10.1	355 (350-361)	6.6	339 (333-345)	5.9
Scenario C	4,034 (4,017-4,050)	5,718 (5,707-5,731)	6,072 (6,061-6,084)	377 (372-383)	10.3	359 (354-365)	6.7	342 (336-348)	6.0

Notes:

1. Point estimates and 95% confidence intervals were calculated from bootstrap samples of the original data.

2. For Breast cancer note that in addition to patients on routine pathways only 25% (n= 2700) of patients diagnosed through screening (i.e. the proportion of patients with T3, T4, Node positive, or Metastatic disease) are reallocated to two-week wait urgent cancer referral (2WW) or Emergency Presentation (EP) in the pandemic scenarios (see Methods section).

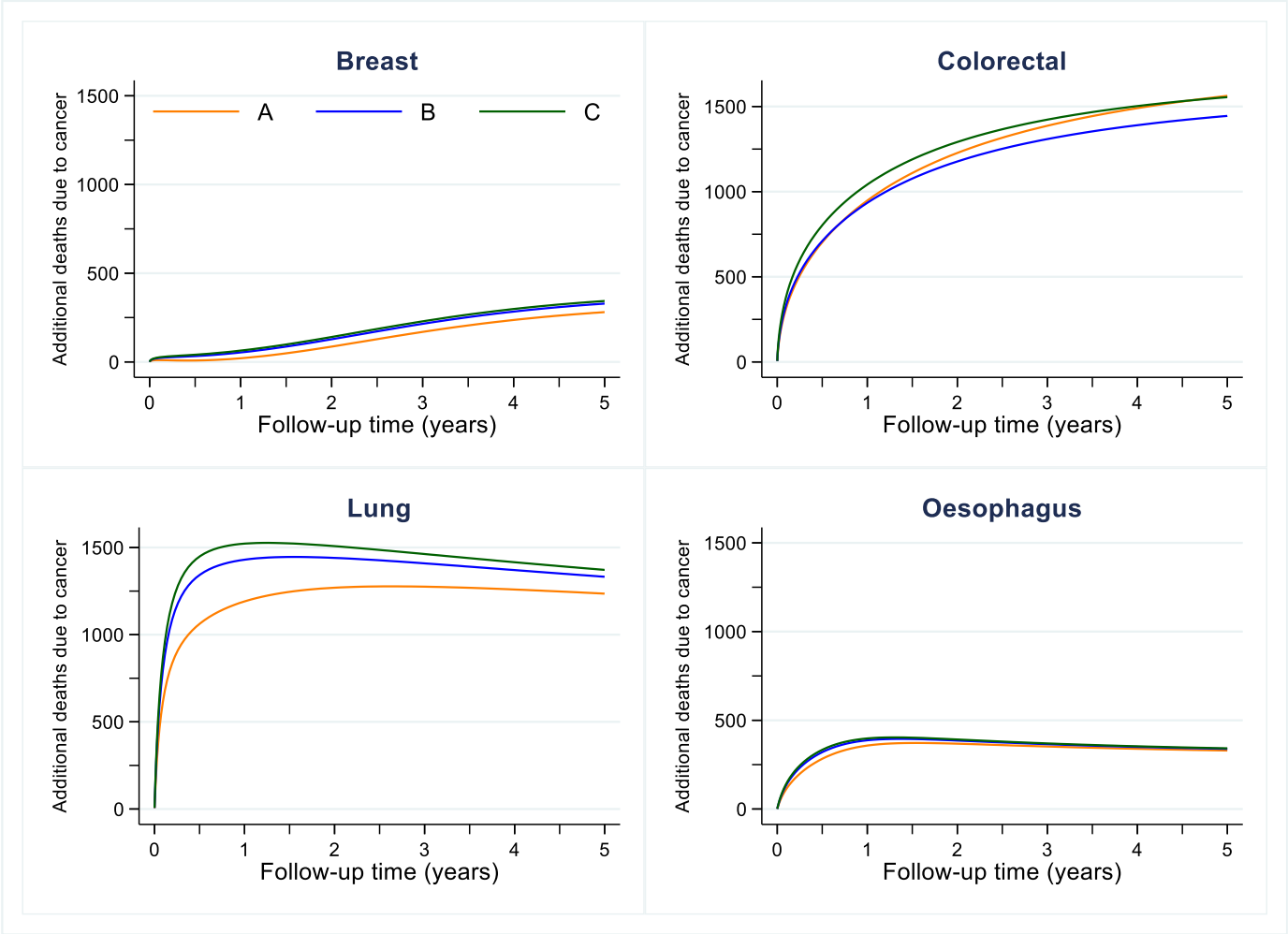
Table 3. Estimated Years of life lost (YLL) resulting from additional deaths due to cancer up to 5 years from diagnosis for each pandemic scenarios A-C.

	N (95% CI)
Breast (N = 32,583)	
Scenario A	8,181 (7,797-8,535)
Scenario B	9,033 (8,638-9,390)
Scenario C	9,261 (8,843-9,631)
Colorectum (N = 24,975)	
Scenario A	27,735 (27,188-28,241)
Scenario B	25,583 (24,792-27,744)
Scenario C	27,043 (26,234-29,968)
Lung (N = 29,305)	
Scenario A	20,537 (20,184-20,947)
Scenario B	20,860 (20,250-21,277)
Scenario C	20,413 (19,833-20,909)
Oesophagus (N = 6,744)	
Scenario A	5,373 (5,227-5,530)
Scenario B	5,152 (5,006-5,301)
Scenario C	5,027 (4,861-5,213)

Notes:

1. For Breast cancer note that in addition to patients on routine pathways only 25% (n= 2700) of patients diagnosed through screening (i.e. the proportion of patients with T3, T4, Node positive, or Metastatic disease) are reallocated to two-week wait (2WW) urgent referrals or emergency presentation (EP) pathways in the pandemic scenarios (see Methods section).
2. Point estimates and 95% confidence intervals were calculated from bootstrap samples of the original data.

Figure 2. Estimated additional numbers of deaths due to cancer for each pandemic scenario A-C, by tumour type.



Technical appendix

The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis: a national population-based modelling study

Dr. Camille Maringe PhD, Prof. James Spicer PhD, Dr Melanie Morris PhD, Prof. Arnie Purushotham MD, Prof. Ellen Nolte PhD, Prof. Richard Sullivan PhD, Prof. Bernard Rachet PhD, Dr Ajay Aggarwal PhD.

1. Re-allocation of patients to new referral pathway

Main analyses: Each patient had equal probabilities to be reallocated to each of the emergency referral routes. We randomly generated their probabilities and selected those patients with random values below the thresholds detailed in the paper, and necessary to maintain proportions of patients re-allocated to the emergency referral pathway in keeping with the original distributions seen in pre-pandemic cohorts (see proportions in Table 1).

2. Quantifying net survival and deaths due to cancer

Baseline, pre-pandemic, levels of cancer-specific survival were assessed through multivariable excess hazard models. We use the *strcs* package in Stata[1]. *strcs* implements a two-step method that incorporates both analytical and numerical integration to estimate the cumulative hazard function required for the log-likelihood function. Flexible parametric survival models are fit using maximum likelihood estimation.

The main assumption of excess hazard models is that the overall mortality of the cohort of patients (λ) is the sum of two forces of mortality: the excess mortality hazard (λ_E), assumed to be the mortality hazard directly or indirectly due to cancer, and the expected or other causes mortality hazard, which is considered to be well approximated by the general population mortality hazard (λ_P).

$$\lambda(t, \boldsymbol{x}) = \lambda_E\,(t, \boldsymbol{x}) + \lambda_P\,(a + t, y + t, \boldsymbol{z}),$$

The cancer mortality hazard, λ_E, at time t for given patient's covariates $\boldsymbol{x}$, such as age at diagnosis (a), deprivation levels, and referral pathway, is what we need to estimate. The following model is fitted:

$$\lambda_E\,(t, \boldsymbol{x}) = \lambda_0\,(t) * exp\,(\beta * \boldsymbol{x})$$

λ_E (i.e. hazard of death due to cancer) was modelled as a function of age at diagnosis (a), deprivation (d), and mode of presentation (p) as follows: non-linear effects of age at diagnosis (restricted cubic splines, a_1 and a_2) and time-dependent effects of each variable were allowed, as

well as interactions between age at diagnosis and deprivation and between age at diagnosis and mode of presentation. The excess hazard at the reference value of all covariables, the baseline hazard, $\lambda_0\ (t)$, was modelled using polynomials of follow-up time defined in three contiguous time intervals (restricted cubic splines with 3 degrees of freedom) and smoothly joined at the intervals' boundaries.

$$\lambda_E\ (t, \boldsymbol{x}) = \lambda_0\ (t) * exp\ (\beta_{a,1}(t) * a_1 + \beta_{a,2}(t) * a_2 + \sum_{j=2}^{5}(\beta_{d,j}(t) * I_{d=j} + \gamma_{a,1,j}(t) * a_1 I_{d=j} + \gamma_{a,2,j}(t) * a_2 I_{d=j}) + \sum_{k=2}^{P}(\beta_{p,k}(t) * I_{p=k} + \alpha_{a,1,k}(t) * a_1 I_{p=k} + \alpha_{a,2,k}(t) * a_2 I_{p=k}))$$

$\beta_{a,1}$ and $\beta_{a,2}$ are the effects of each component of age, $\beta_{d,j}$ are the effects of each deprivation quintile j, $j = 2, \ldots 5$, $\beta_{p,k}$ are the effects of each mode of presentation, and $\gamma_{a,1,j}$, $\gamma_{a,2,j}$, $\alpha_{a,1,k}$, and $\alpha_{a,2,k}$ are the interactive effects on the excess hazard of death. Each effect is allowed to vary with follow-up time t. The best-fitting forms of effects were selected using a hierarchical model selection algorithm designed by Royston and Sauerbrei (mfpigen),[2,3] combined with the Akaike Criteria (AIC).[4] The effects selected are presented in the Table below.

When analysing population-based data, the measure of interest, excess mortality due to cancer, is conventionally retrieved by removing the impact of competing risks of death, i.e. the deaths from causes other than the cancer of interest. These competing risks, derived from general population life tables defined by sex, single years of age, calendar years, deprivation quintile, and Government Office Regions ($\boldsymbol{z}$), were assigned to each patient at their date of last known vital status.

	Main effects				Interactions	
	Age at diagnosis	*Referral pathway*	*Deprivation*	*Sex*	*Age* referral*	*Age * deprivation*
Breast	Non linear, non proportional	Categorical, non proportional	Categorical		Included	Included
Colorectum	Non linear, non proportional	Categorical, non proportional	Categorical	Proportional	Included	
Lung	Linear, non proportional	Categorical, non proportional	Categorical	Proportional	Included	Included, non proportional
Oesophagus	Non linear, non proportional	Categorical, non proportional	Categorical	Non proportional	Included	

Effects selected for each excess hazard model

The final model selected for each cancer was fitted on the pre-pandemic cohorts of patients. The estimated coefficients associated with the effects of each variable and the parameters corresponding to the baseline excess hazard were retained. These inform the prediction of excess hazard of death due to cancer for each patient i at selected times t, $\lambda_{E,i}(t)$. Such predictions were made for each patient in the setting of the observed pre-pandemic cohorts in addition to the three scenarios A-C. From the individual excess hazards, we derived the following quantities:

Cohort net survival: the survival of the cohort of cancer patients, assuming patients can only die of their cancer. $S_{N,i}$ is the individual net survival, and S_N is the cohort net survival, such that:

$$S_{N,i}(t, x_i) = \exp\left(-\int_0^t \lambda_{E,i}(u, x_i)du\right)$$

$$S_N(t) = \frac{1}{N}\sum_{i=1}^{N} S_{N,i}(t, x_i)$$

Crude probability of cancer death: this is the probability of cancer-related death for each patient, $CPD_{C,i}$, or on average in the cohort, in the presence of competing risks of deaths.

$$CPD_{C,i}(t, x_i) = \int_0^t S_{O,i}(u^-|x_i) * \lambda_{E,i}(u, x_i)du$$

$S_{O,i}(u^-)$ represent individual overall survival of patient i, estimated just before time u. These were derived from multivariable hazard models, adjusting for the effects of age at diagnosis, deprivation, sex and referral pathway on the overall (all-cause) hazard of death. We performed model selection identical to that explained for the excess hazard models.

Number of deaths due to cancer at time t, D_C: these are directly derived from the individual crude probabilities of death estimated at time t.

$$D_C(t, x_i) = \sum_{i=1}^{N} CPD_{C,i}(t|x_i)$$

Number of years of life expectancy lost due to cancer: this is the total number of years of life expectancy lost due to cancer-related mortality for the cohort of cancer patients. $LEL_C(a, b, x_i)$ defines the number of years of life expectancy lost due to deaths due to cancer between years a and b.

$$LEL_C(0, t, x_i) = \sum_{i=1}^{N}(CPD_{C,i}(0, t|x_i) - CPD_{C,i}(t, \infty|x_i)) * \int_t^{\infty} {S_i}^*(u|z_i)du$$

$e_{x,i}(t) = \int_t^{\infty} {S_i}^*(u|z_i)du$ is the life expectancy of patient i at time t.

Each of these quantities were compared between the pre-pandemic setting and the 3 scenarios explored up to 5 years following diagnosis. The differences provided an estimated decrease in net survival, additional number of deaths due to cancer and additional numbers of years of life expectancy lost due to cancer, namely:

$$Diff{D_C}^X(t, x_i) = {D_C}^X(t, x_i) - {D_C}^{PP}(t, x_i)$$

Whereby ${D_C}^X$ is the number of deaths due to cancer in Scenario X (X=A, B, or C) and ${D_C}^{PP}$ is the number of deaths due to cancer in the pre-pandemic period, and

$$Diff{LEL_C}^X(0, t, x_i) = {LEL_C}^X(0, t, x_i) - {LEL_C}^{PP}(0, t, x_i)$$

We make the conservative assumption that $CPD_{C,i}(t, \infty|x_i)$ are equivalent in the pre-pandemic cohort and the cohort in each scenario, leading to:

$$Diff{LEL_C}^X(0, t, x_i) = \sum_{i=1}^{N}({CPD_{C,i}}^X(0, t|x_i) - {CPD_{C,i}}^{PP}(0, t|x_i)) * \int_t^{\infty} {S_i}^*(u|z_i)du$$

For the later, only the figures at 5 years were calculated and presented.

We provide the point estimates and their 95% CI around the estimations of CPD_C, D_C, and LEL_C based on bootstrap samples.[5,6]

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Appendix Figure 1

1-, 3- and 5-year net survival, by referral pathway and overall pre-pandemic and by scenarios A-C