





# BMJ Open Factors associated with cancer treatment delay: a protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Treatment delays are significantly associated with increased mortality risk among adult cancer patients; however, factors associated with these delays have not been robustly evaluated. This review and meta-analysis will evaluate factors associated with treatment delays among patients with five common cancers.

**Methods and analysis** Scientific databases including Ovid MEDLINE, Elsevier Embase, EBSCOhost CINAHL Plus Full Text, Elsevier Scopus and ProQuest Dissertations and Theses Global will be searched to identify relevant articles published between January 2000 and October 2021. Research articles published in the USA evaluating factors associated with treatment delay among breast, lung, prostate, cervical or colorectal adult cancer patients will be included. The primary outcome of the meta-analysis will be the pooled adjusted and unadjusted odds of treatment delay for patient, disease, provider and system-level factors defined according to specified time intervals. The secondary outcomes will be mean or median treatment delay for each cancer site according to first treatment and the influence of factors on the pooled mean treatment delay for each cancer site (via meta-regression analyses). Results from qualitative and mixed-methods studies will be narratively synthesised. Three reviewers will independently screen records generated from the search and two reviewers will independently extract data following a consensus agreement. Statistical heterogeneity will be assessed with a standard  $I^2$  test and funnel plots will be conducted to evaluate publication bias. Risk of bias will be assessed independently by two authors using validated tools according to the article's study design.

**Ethics and dissemination** Formal ethical approval is not required because the work is being carried out on publicly accessible studies. The findings of this review will be disseminated through a peer-reviewed scientific journal, academic conferences, social media, and key stakeholders.

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## INTRODUCTION

Ensuring cancer patients receive treatment in a timely manner has the potential to decrease both overall mortality<sup>1</sup> and to a greater extent,

## STRENGTHS AND LIMITATION OF THIS STUDY

- ⇒ To the best of our knowledge, this study will be first meta-analysis of patient, disease, provider and system factors associated with treatment delay for patients with five common screenable cancers (breast, lung, prostate, cervical and colorectal).
- ⇒ A rigorous search strategy was developed including comprehensive medical subject headings and text words in multiple databases and inclusion of grey literature.
- ⇒ Factors will be quantified for each cancer site and further by first treatment modality to ensure the clinical relevance of findings.
- ⇒ Wide treatment delay intervals will be used to pool findings from studies that employed various treatment delay cut-offs.
- ⇒ Randomised controlled trials were not used as the preferred source of information.

disease-specific mortality.<sup>2</sup> The total time between a formal cancer diagnosis and initiation of treatment, hereby referred to as *treatment delay* (also referred to as *time-to-treatment*), has been found to be a key determinant of outcomes in cancer.<sup>3</sup> Hannah and colleagues conducted an international systematic review and meta-analysis of high-quality research articles to evaluate the increased risk of mortality associated with each 4-week treatment delay from any cause across seven cancers and three treatment modalities.<sup>1</sup> For surgery, each 4-week delay was associated with a 6%–8% increase in risk of death with even greater risk for radiotherapy and systemic therapy options.<sup>1</sup> In the USA, Bleicher and colleagues separately analysed two sources of national, population-based data and found that the effect of shorter time-to-breast cancer surgery on survival was comparable in magnitude to the effect of extending adjuvant tamoxifen from 5 to 10 years after adjusting for demographic, tumour-related

and treatment-related variables.<sup>2,4</sup> Taken together, these data highlight the potential benefits gained in survival by reductions in the pretreatment interval with evidence pointing towards an even greater benefit for those with early-stage disease.<sup>2,5</sup>

However, less understood are the factors contributing to these delays in the time between diagnosis and initiation of treatment. A theoretical model for studying delays in the cancer patient pathway, originally proposed by Andersen *et al*<sup>6</sup> and later revised by Walter *et al*,<sup>3</sup> identifies a range of multilevel barriers contributing to delays in the prediagnostic and postdiagnostic patient pathway.<sup>3</sup> Patient factors (eg, demographic, psychological, social and cultural), healthcare provider and system factors (eg, access, policy and delivery), as well as disease factors (eg, cancer site, size and growth rate) likely contribute to delays in diagnosis and initiation of cancer treatment.<sup>3</sup> More recently, the SARS-CoV-2 pandemic compounded pre-existing contributors to delayed care across the spectrum of oncological services.<sup>7</sup> A cross-sectional study of nearly 800 000 patients in the USA previously diagnosed with breast, colorectal, lung, pancreatic, cervical, gastric, oesophageal or prostate cancer found the mean monthly number of new cancer diagnoses decreased by nearly 30%, 10% and 19% in the first, second and third pandemic periods, respectively.<sup>8</sup> Other disruptions to the healthcare system as a result of the pandemic include reductions in medical visits, operations, chemotherapy, radiotherapy and outpatient visits mediated by disruptions to system, structural and process-related factors such as supply chain shortages, personnel and service availability.<sup>9</sup> Pre-pandemic factors found to be associated with delays in the initiation of cancer treatment include age,<sup>10–12</sup> race and ethnicity,<sup>10 11 13 14</sup> mental illness,<sup>15</sup> social determinants of health (eg, public vs private insurance, insurance coverage, geographic region in the USA),<sup>10 13 14 16</sup> clinical staging or size of tumour,<sup>11 12</sup> number of comorbidities,<sup>11 16</sup> treatment facility<sup>11</sup> and preoperative components (eg, imaging and biopsy type).<sup>10 13</sup>

While a small number of reviews have evaluated factors associated with treatment delays,<sup>17</sup> no study, to the best of our knowledge, has robustly quantified the relative impact of these factors on treatment delays in a meta-analysis. Calculating point estimates for the odds of time-to-treatment delay occurring within a specific time interval for patient, provider, disease and system-level factors has the potential to identify the most relevant factors contributing to treatment delay. This will inform efforts to manage and triage recently diagnosed cancer patients based on risk of delay as well as multilevel intervention strategies aimed at reducing treatment delay. Therefore, the purpose of this comprehensive meta-analysis and systematic review is to pool the odds ratios (OR) from previously identified factors on time-to-treatment for five common cancer sites (breast, lung, prostate, cervical and colorectal cancer). To ensure the clinical relevance of our findings, we will present pooled effects for factors separately for each cancer site and further by first treatment

modality (ie, delays in breast cancer surgery after diagnosis will be evaluated independently from delays in neoadjuvant chemotherapy and radiotherapy for breast cancer). Additionally, the review will identify and discuss potential modifiable targets to guide future research and interventions aimed at reducing treatment delay. This robust synthesis is timely given the SARS-CoV-2 pandemic has exacerbated existing delays in cancer diagnosis and treatment.<sup>18</sup>

## METHODS AND ANALYSIS

### Study registration

This protocol is being reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol statement.<sup>19</sup> Ethics approval is not required since data is from publicly accessible studies. This protocol is registered with the International Prospective Register of Systematic Reviews.

### Eligibility criteria

We will include eligible studies published in the USA from scientific journal articles, grey literature (ie, meeting abstracts, theses and dissertations) and preprints evaluating at least one factor associated with delays in initiation of treatment among patients diagnosed with breast, cervical, prostate, lung or colorectal cancer. We have chosen to include both quantitative and qualitative reports to acknowledge the limitations and strengths of both types of approaches and enrich our understanding of why greater time-to-treatment occurs among a particular patient population. Additionally, salient themes identified in the included qualitative studies will provide a lens by which to attempt to contextualise and make sense of the study's quantitative findings. We have chosen to limit the review to articles published in the USA given differences in healthcare systems and delivery across countries. Studies will be selected according to the criteria in [table 1](#).

### Search strategy

The following databases will be searched: Ovid MEDLINE, Elsevier Embase, EBSCOhost CINAHL Plus Full Text, Elsevier Scopus and ProQuest Dissertations and Theses Global. Given the clinical and health services focus of this review and the evolution of cancer care and treatment over the last two decades, we have chosen to apply a time restriction to include studies published from the year 2000 and on. No language restrictions will be used. The search strategy was first designed in MEDLINE using a combination of MeSH controlled vocabulary as well as text-words and then translated to the subsequent resources. Given the lack of standardisation of terms related to cancer treatment delay and lack of specificity when using terms such as 'delay' and 'time', the authors designed a search strategy using various combinations of free text and standardised subject terms to balance specificity in conjunction with reviewing the free text terminology and indexing for relevant articles identified

**Table 1** Population, exposure, comparator, exposure and study design framework for eligible studies

PECOS strategy	Inclusion criteria	Exclusion criteria
P - Population	Adult (18+) cancer patients diagnosed with breast, lung, prostate, cervical or colorectal cancer	Patients with recurrent cancer, patients who cannot or choose not to undergo cancer treatment, studies that do not separate patients by first treatment modality (ie, studies that do not indicate which treatment occurred first)
E - Exposure	Studies must have evaluated at least one factor in relation to treatment delay	We have no plans to exclude any factors at this time
C - Comparison	N/A	N/A
O - Outcome	Quantitative studies must have reported the outcome of treatment delay as OR, risk ratio, relative risk or beta-coefficient for each individual exposure	We have no exclusion criteria based on outcome at this time
S - Study design	Retrospective cohort studies, prospective cohort studies, cross-sectional studies, case-control studies, qualitative studies and mixed-methods studies	Reviews, randomised controlled trials, case reports and case series

N/A, not applicable.

through preliminary exploration of the literature. An example search strategy from MEDLINE is provided in the online supplemental file 1.

Additionally, a search of the American Society of Clinical Oncology Meeting Library will be conducted. The authors also plan to review the references of key studies and relevant reviews as well as the final articles included in the review to identify additional potentially relevant studies.

#### Data management

Records generated from the search will be imported by AAS into Endnote Desktop 20 citation manager<sup>20</sup> where duplicate records will be removed. The Endnote file will then be imported into a web-based systematic review software (*DistillerSR.V.2.35*. Evidence Partners; 2021) by AAS. Screening of records and extracting of study information will be conducted within the DistillerSR software.

#### Study selection

Relevance of the identified records will be assessed by three independent evaluators (KEM, RR-M and ML-P) in three phases. Records will be divided into three equal sections (A, B and C) and each evaluator will review two sections (A+B, A+C and B+C). In the first phase, KEM, RR-M and ML-P will independently screen records based on title. If a record is considered potentially relevant, its abstract will be reviewed in the next phase by the three evaluators independently as in the first phase. In the final phase, full-text articles will be read by all three evaluators independently. Discrepancies will be reviewed by all three reviewers and resolved through discussion. If consensus cannot be reached, a fourth research team member with content expertise will be asked to review and resolve discrepancies.

In the case of overlapping study samples across different studies, study selection will be made as a consensus based

on the most representative study (ie, most current and largest sample size).

#### Data extraction

As part of the data extraction process, KEM and RR-M will independently extract the following general study information: study citation, publication type (eg, full report, abstract and dissertation/thesis), institution or data set (eg, Surveillance, Epidemiology and End Results) and study objective(s). Additionally, information/data related to the study's population, setting and outcome(s) will be extracted including the following: study design, study period, cancer site, treatment modality (eg, surgery, neoadjuvant chemotherapy), participant inclusion and exclusion criteria, population description (eg, age, sex, race/ethnicity and tumour characteristics), study definition of delay and/or time-to-treatment intervals (eg, 30±15 days, 60±15 days and 90±15 days) mean or median time from diagnosis to first treatment, factors evaluated in relation to treatment delays, study results and information related to methodological quality. To support meta-analysis, study sample size and effect size or measures of proportion specific to study factors (eg, mean, median, SD, IQR, unadjusted and adjusted HRs, ORs, risk ratios, relative risk, and/or beta-coefficients and 95% CI) will be extracted. All data extraction forms will be created and piloted on three included studies within the DistillerSR software by KEM and RR-M independently. The two authors will then meet to discuss the need for any modifications to the forms before each author independently extracts information/data from the remaining studies.

In the event that information is missing, KEM will contact the study's corresponding author via email up to three times as this method has been successful in prior research.<sup>21</sup>

### Outcomes and prioritisation

The primary outcome of the meta-analysis will be the pooled adjusted and unadjusted odds of treatment delay defined according to specified intervals (30±15 days, 60±15 days and 90±15 days). Factors associated with treatment delay will be quantified for individual patient, disease, provider and system-level factors for each cancer site and further stratified by first treatment (eg, radiation vs surgery). The secondary outcomes will be: (1) mean or median treatment delay for each cancer site according to first treatment (eg, radiation vs surgery) and (2) influence of identified risk factors or characteristics of the population on the pooled mean treatment delay for each cancer site (via meta-regression analyses).

### Risk of bias

Two reviewers (KEM and RR-M) will independently assess the quality of the selected studies. Quality assessment of observational studies will be carried out using the Newcastle-Ottawa Scale for case-control studies and cohort studies.<sup>22</sup> Using this tool, each study will be judged on three dimensions: selection of the study groups, comparability of the group and ascertainment of the exposure. One star will be given for each signalling question among each dimension; out of a total of nine possible stars, studies with seven or more will be considered as high-quality. For qualitative studies, quality will be assessed using the Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach.<sup>23</sup> CERQual provides an assessment of confidence in a review finding and includes four components: methodological limitations, coherence, adequacy of data and relevance.<sup>23</sup> For mixed-methods studies, methodological and reporting quality will be assessed using an appraisal tool developed for studies with heterogeneous designs called The Quality Assessment for Diverse Studies tool.<sup>24</sup>

### Data synthesis

Extracted results from quantitative studies, including findings from mixed-methods studies, will be pooled in a meta-analysis. For studies that report the relationship between a characteristic and a particular treatment delay interval as relative risk or as a beta-coefficient, we will convert these to an OR so that we may summarise odds of treatment delay occurring within a specific time interval for a particular characteristic for each cancer site. For the primary outcome, a generic meta-analysis by the inverse of the variance will be used for pooling the adjusted ORs from each study using random-effects model as the preferred method despite the statistical heterogeneity. For the secondary outcomes, the pooled mean will be used as the pooled effect size by single mean analysis using random-effects modelling (weighting by inverse of variance) along with Clopper-Pearson 'exact' method for calculation of CIs. In case of a small number of studies (two or less), the fixed-effects model will be preferred over the random-effects model due to the poor precision

of the random-effects for estimating between-study variance in such cases.<sup>25</sup> Between-study heterogeneity/variability will be assessed using the tau<sup>2</sup>,  $\chi^2$  (Cochrane Q) and I<sup>2</sup> statistics. Results will be assessed using forest plots and presented as proportions. Publication bias will be assessed by funnel plot in the case of more than five studies per outcome.

We have chosen to retain the meta-regression as a secondary analysis as it permits inclusion of the broadest possible range of study types, reducing the risk of publication bias. It also provides an opportunity to determine the robustness of observed associations in the primary analysis when investigated via a different method. Factors related to treatment delay will be pooled as proportions and mean or medians according to each study. To assess the influence of factors on treatment delay for each cancer site, a meta-regression will be performed when appropriate including all factors as predictors and the final pooled mean of delay for that cancer site as the main regression outcome. Coefficients with  $p < 0.05$  will be considered statistically significant and will be considered to have an influence on the pooled result.

Findings from qualitative and mixed-methods studies will be displayed in a table summarising study characteristics and major themes and will be narratively synthesised within the text. Narrative synthesis aims to critically and conceptually explain findings and influencing factors and identify potential patterns.<sup>26</sup> Factors contributing to treatment delay identified from both quantitative and qualitative studies will be grouped and discussed as patient, disease, provider and system-level factors in accordance with the Andersen Model of Total Patient Delay.<sup>3</sup> Our search encompasses years of publication which capture significant policy in the USA which may influence treatment delay, including the passage of the Affordable Care Act<sup>27</sup> and the SARS-CoV-2 pandemic, which will be taken into consideration during synthesis. For example, depending on the number of eligible studies that assessed the influence of the SARS-CoV-2 pandemic on treatment delay, we may analyse the effect of this event on treatment delay separately.

### Subgroup analysis

We will stratify our analyses conducted for each cancer site further by first treatment (eg, radiation or surgery) to investigate whether the relationship between factors and treatment delay differs by first treatment.

### Sensitivity analysis

We will conduct a sensitivity analysis excluding studies not classified as high-quality based on the proposed risk of bias and quality assessment. We may conduct two separate additional sensitivity analyses (1) excluding studies that did not exclude patients with a time-to-treatment of 0 days and (2) excluding studies that did not use a discernable biopsy date as the date of diagnosis (eg, studies that defined the date of diagnosis as the date imaging was conducted).



## Patient and public involvement

The research team includes a cancer survivor and patient advocate (LS). The Guidance for Reporting Involvement of Patients and Public (GRIPP2) short form checklist<sup>28</sup> will be used to describe the involvement of LS in the review. The aim of the research was discussed with LS prior to the drafting of this protocol and LS will support interpretation of findings, review drafts of the manuscript and assist in the dissemination of the review to key stakeholders.

## ETHICS AND DISSEMINATION

Formal ethical approval is not required because the work is being carried out on published, publicly accessible documents. The findings of this review will be disseminated through a peer-reviewed scientific journal, academic conference, social media and key stakeholders.

In the case, an amendment to this protocol is needed following publication, a detailed description of the deviation will be included in the final published manuscript.

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**Contributors** The authors confirm contribution to the paper as follows: guarantor of the review: KEM; study conception and design: KEM, RR-M, ML-P, RJMP, AAS, TPH; draft manuscript preparation: KEM, RR-M, ML-P, RJMP, AAS, MBS, TR, ETJ, JDA, RH, LS, TPH. All authors reviewed and provided feedback on the protocol and each draft of the manuscript. All authors approved the final manuscript draft.

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**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

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