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Original Article

Hyperglycaemia and Survival in Solid Tumours: A Systematic Review and Meta-analysis

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Abstract

Aims: Diabetes is associated with adverse cancer outcomes. However, the effect of hyperglycaemia in non-diabetic cancer patients is unclear.
Materials and methods: A systematic search of electronic databases identified publications exploring the effect of hyperglycaemia on overall survival, disease-free survival (DFS) or progression-free survival (PFS). Data from studies reporting a hazard ratio and 95% confidence interval and/or a *P*-value were pooled in a meta-analysis using generic inverse-variance and random effects modelling. Subgroup analyses were conducted based on method of hyperglycaemia measurement (HbA1c, other) and stage (early, advanced, mixed). Meta-regression was performed to evaluate the influence of clinical characteristics including baseline diabetes status on the hazard ratio for overall survival.
Results: Twelve studies comprising a total of 9872 patients were included. All studies reported hazard ratios for overall survival. Three studies reported DFS; two reported PFS outcomes. Definitions of hyperglycaemia and cut-offs varied between studies. Hyperglycaemia was associated with worse overall survival (hazard ratio 2.05, 95% confidence interval 1.67–2.51; $P < 0.001$) and DFS (hazard ratio 1.98, 95% confidence interval 1.20–3.27; $P = 0.007$), but did not affect PFS (hazard ratio 1.08, 95% confidence interval 0.72–1.62; $P = 0.71$). The association with worse overall survival was maintained in subgroups based on method of hyperglycaemia measurement (subgroup difference $P = 0.46$) and stage ($P = 0.14$). Meta-regression showed a significantly greater magnitude of association between hyperglycaemia and decreased overall survival in studies with higher proportions of women and diabetic patients.
Conclusions: Hyperglycaemia is associated with adverse overall survival and DFS in patients with cancer. The therapeutic role of glycaemic control in cancer patients warrants further investigation.

Key words: Cancer; Diabetes; Hyperglycaemia; Meta-analysis; Survival

Introduction

Chronic hyperglycaemia is thought to increase the risk of developing several types of cancer [1]. In patients with established malignancy, diabetes and hyperinsulinaemia have also been associated with higher mortality and poor outcomes [2,3]. Hyperglycaemic states can also exist in non-diabetic patients, often indicating a stress response to acute and chronic illness [4], and may lead to adverse treatment-related outcomes [5]. In patients with acute leukaemia, stress hyperglycaemia during induction chemotherapy has been associated with higher mortality [5,6], as well as a shorter duration of complete remission [6]. In non-diabetic patients with febrile neutropenia secondary to cancer-directed therapy, stress hyperglycaemia has also been linked to increased mortality [7]. In addition, this phenomenon has been associated with adverse outcomes in surgical patients and those with acute cardiovascular events. A study of critically ill patients showed higher

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mortality in newly hyperglycaemic patients than in those with known diabetes [8,9].

It has also been proposed that hyperglycaemia may negatively affect prognosis in patients with cancer. Early preclinical data have shown that malignant tissue relies on aerobic glycolysis for energy and thus uses glucose at higher rates than normal tissue [10]. Hyperglycaemic states may also worsen prognosis in malignancy due to increased tumour cell proliferation, inhibition of apoptosis and facilitation of invasion and metastasis [11,12] and potentially lead to chemotherapy resistance and increased treatment-related toxicity [5]. The innate immune system can also be negatively affected by hyperglycaemic conditions [13]. In particular, hyperglycaemia can cause abnormal monocyte cytokine production and dysfunction of neutrophils, macrophages and gamma delta T cells [13]. However, the prognostic impact of hyperglycaemia independent of diabetes in patients with cancer remains unclear. We carried out a systematic review and meta-analysis to explore the effect of hyperglycaemia on outcomes of patients with solid tumours and the influence of diabetes and other clinical factors on this association.

Materials and Methods

Data Sources and Searches

This analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The following electronic databases were searched: Medline (host: OVID), Medline in Process, Medline Epub Ahead of Print (host: OVID), EMBASE (host: OVID) and Cochrane Database of Systematic Reviews. All databases were initially searched up to May 2016 with no language restrictions and the full literature search was updated in November 2017. The list of citations was screened manually to ensure that the search strategy was appropriate. The full search strategy from Medline is outlined in the Appendix.

Study Selection

Studies were included based on the following criteria: (i) studies of adults with solid tumours; (ii) baseline measure of blood sugar after cancer diagnosis (glycosylated haemoglobin [HbA1c], fasting glucose or random glucose) included in univariable or multivariable analysis; (iii) reporting of a hazard ratio for overall survival, disease-free survival (DFS) or progression-free survival (PFS) and corresponding 95% confidence interval and/or *P*-value; (iv) available as full-text publication; (v) clinical trials, cohort or case-control studies; and (vi) English language publication. Case reports, conference abstracts and letters to editors were excluded. Titles identified by the initial search were evaluated and potentially relevant publications were retrieved in full. Two authors (RB and JE) reviewed full articles independently for both eligibility and data collection. Disagreements were resolved by consensus.

Data Extraction

The following data were collected from included studies using a predesigned abstraction form: name of first author, year of publication, journal, number of patients included in analysis, median age, proportion female sex, primary malignancy, disease stage (stage I–III defined as early and all others metastatic), proportion of patients with diabetes, definition of hyperglycaemia, number of patients with hyperglycaemia, number of patients on glucose-modifying medications (insulin, oral hypoglycaemic or steroids) and hazard ratios with associated 95% confidence interval for overall survival, DFS and/or PFS. The criteria for hyperglycaemia and diabetes were defined as reported in individual studies.

Statistical Analyses

Extracted data were pooled using RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark). A meta-analysis was conducted for all included studies for each of the end points of interest. The primary outcome of interest was overall survival. Secondary end points were intermediate outcomes, namely DFS and PFS. Estimates for hazard ratios were pooled and weighted by generic inverse variance and computed by random effects modelling. Given the presence of substantial clinical heterogeneity, random effects modelling was used in all analyses. Subgroup analyses were conducted based on the definition of hyperglycaemia (HbA1c versus other) and disease stage (early [defined as stage 1, 2 or 3] versus metastatic [defined as stage 4]) using methods described by Deeks *et al.* [15]. Meta-regression was carried out to evaluate the effects of individual study median age and the proportion of patients with female sex, metastatic stage, diabetes, use of hypoglycaemic medications and glucose-modifying medications on the natural log of the hazard ratio (Ln[HR]) for overall survival. Meta-regression comprised a univariable linear regression weighted by individual study inverse variance and was carried out using SPSS version 24 (IBM Corp, Armonk, New York, USA). Multivariable meta-regression was not carried out due to the small number of eligible studies leading to an undesirable risk of over-fitting. Publication bias was assessed by visual inspection of funnel plots. All statistical tests were two-sided and statistical significance was defined as $P < 0.05$. No correction was applied for multiple statistical testing. To address the potential influence of multiple significance testing and control for type 1 errors, where the null hypothesis is incorrectly rejected, we computed false discovery rates as described by Benjamini and Hochberg [16]. This method estimates whether significant values are likely true or false discoveries.

Results

Twelve retrospective studies comprising 9872 patients were included (Figure 1). The characteristics of included

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