The relationship between HbA\textsubscript{1c} and cancer in people with or without diabetes: A systematic review

C. Hope\textsuperscript{1}, A. Robertshaw\textsuperscript{1}, K.L. Cheung\textsuperscript{1}, I. Idris\textsuperscript{1}, E. English\textsuperscript{1*}

Affiliation:

\textsuperscript{1} School of Medicine, University of Nottingham, Royal Derby Hospital, DE22 3DT, UK.

*Corresponding author:

Emma English
Division of Medical Sciences and Graduate Entry Medicine
School of Medicine
University of Nottingham
Royal Derby Hospital Centre
DE22 3DT
UK
+44 1332 724620
Emma.english@nottingham.ac.uk

^ Now at: Cardiovascular Theatres, 2nd Floor East Wing, St Thomas' Hospital, London, SE1 7EH. UK

Keywords: cancer, diabetes, HbA\textsubscript{1c}, neoplasm

No financial funding required.

No conflict of interests to report.

Word count: 4374

Novelty Statement

This review is the first to systematically evaluate the evidence for a link between HbA\textsubscript{1c} and cancer risk. It outlines the relationships between HbA\textsubscript{1c} and the incidence and mortality of all and site-specific cancers. Furthering our understanding of the relationship between HbA\textsubscript{1c} and cancer is of great clinical and academic interest. This review goes some way to outlining these associations and highlighting areas where more research is needed.
Abstract

Aims Cancer is a major public health problem accounting for 8.2 million deaths worldwide in 2012. Glycated Haemoglobin (HbA1c) is associated with the risk of developing certain cancers, though the existing evidence is conflicting. The aim of this systematic review is to identify the relationship between HbA1c and cancers in people with or without diabetes.

Methods Embase, Medline, Cinahl and Cochrane Library were searched. Eligible articles included randomised-controlled trials, cohort studies, case-control studies, systematic reviews and meta-analyses. Participants of either sex, with or without type 1 or 2 diabetes, were included. The studies were assessed using the Scottish Intercollegiate Guidelines Network (SIGN) criteria by two independent assessors. No meta-analysis was performed due to heterogeneity of results.

Results Nineteen studies from 1006 met the inclusion criteria. Fourteen were cohort studies and five nested case control studies. Eight studies investigated outcomes for all cancer sites. Four of these studies reported that higher HbA1c levels were associated with increased incidence and/or mortality risk for all cancers. One study observed a U-shape relationship between HbA1c and cancer incidence and mortality. Increasing HbA1c levels were associated with increased risk of developing colorectal, pancreatic, respiratory and female genital tract cancers. No increased risk was observed for breast cancer, gastrointestinal or urological malignancies.

Conclusion HbA1c appears to be associated with cancer incidence and/or cancer mortality. However, further studies are needed to fully understand the complex relationship between HbA1c and cancer.
**Introduction**

Cancer and diabetes represent two leading causes of morbidity and mortality globally and their increasing prevalence represents a significant public health burden. Cancer incidence in the UK has increased by more than a third since the 1970s [1], resulting in the need for more research to identify and enable modification of risk factors for cancer development. Similarly, diabetes incidence in the UK is increasing with 3.8 million people predicted to be affected by 2020 [2]. Glycated haemoglobin (HbA1c) is the mainstay for monitoring glycaemic control in diabetes and more recently has been advocated for the diagnosis of Type 2 diabetes at a level of 48mmol/mol (6.5%) [3].

Various studies have reported an association between diabetes or the metabolic syndrome with increased cancer risk [4,5]. In a recent study [6], which evaluated 27 meta-analyses investigating type 2 diabetes and the risk of developing or dying from cancer, associations between type 2 diabetes and breast, cholangiocarcinoma, colorectal and endometrial cancers were found. It is unclear whether hyperglycaemia *per se* is associated with increased cancer risk in the absence of diabetes. The exact mechanisms remain unknown but a role for hyperinsulinaemia [7], inflammation and the effects of insulin-like growth factor 1 (IGF-1) has been proposed. HbA1c has also been shown to be an important marker for the metabolic processes that determine insulin [8] and IGF-1 levels [9, 10] and thus may be linked to the disease process in people with type 2 diabetes, highlighted above.

Previous studies have reported an association between increased HbA1c and increased risk of cancer, but these studies have been limited to people with diabetes or used HbA1c values as discrete, rather than continuous variables. Further developing our understanding of the
relationship between HbA1c and cancer aetiology, in specific cancers, is of clinical importance. We aim to assess the relationship between HbA1c and all and site specific cancers in people with or without diabetes.

**Materials and methods**

**Searches**

Medline, Embase, Cochrane and Cinahl were searched for articles evaluating the relationship between cancer risk and HbA1c, published between January 1990-October 2014 (See Fig.1). The search was limited to human studies written in English. The reference lists of included articles were reviewed.

**Study criteria**

Articles included met the following criteria: (i) the association of HbA1c and cancer risk in people with or without diabetes was evaluated, and (ii) the diabetes diagnostic criteria were clearly defined. Randomised-controlled trials, case-control studies, cohort studies and meta-analyses were included in the search. Children (<18 years) and pregnant women were excluded. Case reports, case series studies, and other studies that were not published as full articles were excluded.

**Study selection**

Titles, abstracts and full texts of articles were reviewed by two independent assessors (CH and AR). The quality of the included studies was assessed using SIGN criteria. Methodology checklists for both cohort and case control studies were reviewed, and relevant aspects from each were employed to critically appraise and grade the evidence of included studies. Quality assessment was not used as an exclusion criterion.
**Additional analyses**

No meta-analyses or other statistical analyses were conducted due to the variation within study methodology and heterogeneity of results. Particularly, the categorisation of HbA1c levels varied widely between studies making direct comparison difficult.

**Results**

The searches (Fig. 1) identified 1006 articles. The main reasons for exclusion on reading the full text were an inadequate definition of diabetes or the article did not assess HbA1c and cancer risk. Nineteen met the inclusion criteria and were evaluated and quality assessed.

**Study characteristics**

Of the 19 articles, 14 were cohort studies and 5 were nested case control studies (Table 1). There was considerable variation within study designs, particularly concerning the stratification of HbA1c with both percentage (%) and SI units (mmol/mol) used as units of measurement. Data were included from a range of people with and without diabetes. Most studies were conducted prior to the updated American Diabetes Association (ADA) and World Health Organization (WHO) guidelines recommending the measurement of HbA1c for the diagnosis of diabetes. Therefore, diagnosis of diabetes was based primarily on self-report, fasting plasma glucose concentration and oral glucose tolerance tests. Participants without diabetes were considered those without a formal diagnosis prior to the study commencing.

**All cancers**

Eight studies focused on the relationship between HbA1c and all types of cancer [10-17], summarised in Table 2. All studies were adjusted for age, sex and smoking status.
Three studies investigated HbA\textsubscript{1c} and cancer in people without diabetes. A total of 12,792 individuals were included in a study by Joshu \textit{et al} [10]. The most common incident cancers among women were post-menopausal breast (31%), lung (10%) and colorectal cancer (10%). The study additionally adjusted for body mass index (BMI), ethnicity, systolic blood pressure and education level. Women without diabetes with an HbA\textsubscript{1c} >39mmol/mol (>5.7%) had a 24% higher cancer incidence rate compared to those with HbA\textsubscript{1c} 31-38mmol/mol (5-5.6%) but a 27% increase in cancer incidence rate was also noted in HbA\textsubscript{1c} levels below 31mmol/mol (5%), indicating a U-shape relationship between HbA\textsubscript{1c} and all types of cancer incidence. In contrast, no positive relationship was seen between HbA\textsubscript{1c} levels and cancer risk in men. Prostate made up 39% of the incident cancer cases, with 15% lung and 10% colorectal cancer. The known inverse relationship between prostate cancer and diabetes was taken into account and all cancer and all cancer minus prostate cancer were compared.

In Jonasson’s [14] study of 25,476 people with type 2 diabetes no associations between HbA\textsubscript{1c} and risk for all cancers or site specific cancers were observed. Insulin treatment, duration of diabetes and BMI were adjusted for. Twenty-four percent of cancer cases were made of up gastrointestinal cancer, 22% of prostate, 9% breast and 2% lung cancer.

A study by Travier [15] comprised 46,575 participants. Oral and digestive system cancers made up 18% of new cancer cases, respiratory cancers 12% and colorectal cancer 6%. While, female breast cancer accounted for 34% of new cancer cases found in women. A significantly increased hazard ratio for risk of all cancers was found in those with HbA\textsubscript{1c} 42-52mmol/mol (6%-6.9%) (HR 1.40, CI 95%: 1.11-1.76), compared to those with HbA\textsubscript{1c} <42mmol/mol (<6%). A smaller non-significant 9% increase was observed in levels >53mmol/mol (>7%)
(HR 1.09, CI 95%:0.80-1.48). This study had a short median follow up of 4.4 years and therefore potentially undiagnosed cancers were included. It also lacked any anthropometric data so confounders such as BMI were not accounted for.

Six studies investigated the relationship between HbA1c and cancer mortality. The study by Joshu et al [10] investigated the association between all and site specific cancer mortality rates and HbA1c. Lung cancer was the most commonly reported cause of cancer death in both men and women (35% and 28%), with colorectal cancer conveying an 9% mortality rate in men and 8% in women. A similar U-shape relationship was observed, where women without diabetes with an HbA1c <31mmol/mol (<5%) were found to have an 82% increase in cancer mortality and rates also increased with incremental increases in HbA1c above 39mmol/mol (>5.7%). Cancer mortality in men was not affected by HbA1c level.

Nakanishi et al [11] studied the effects of HbA1c levels on cancer specific mortality in a Japanese cohort. After adjustment for BMI, blood pressure, total cholesterol, smoking and alcohol intake, HbA1c >48mmol/mol (>6.5%) significantly increased the hazard ratios for mortality from malignant neoplasms (HR 1.62; CI 95% 1.00-2.61, p=0.0015). The study provides no breakdown of the type of malignant neoplasm which limits comparison to the other studies.

Parekh et al [12] evaluated the impact of markers of glucose and insulin metabolism on site specific and overall cancer mortality in 15,594 people. Lung cancer made up the majority of cancer deaths (9%), followed by colorectal (2.2%). Breast cancer accounted for 1.5% of cancer mortality as did prostate cancer. There was a borderline significant 22% increased
hazard ratio for death from cancer for each 2mmol/mol (2%) increment in HbA1c (HR: 1.22; 95% CI: 0.96-1.55) after adjusting for age, sex, physical activity, smoking history and BMI.

Saydah et al [13] investigated the relationship between HbA1c and overall cancer mortality rates in 19,025 people of mixed diabetic status. HbA1c levels >64mmol/mol (>8%) were associated with a more than twofold increase in relative risk of cancer mortality compared to those with HbA1c levels <42mmol/mol (<6%). Overall, they concluded that increasing levels of HbA1c were associated with increased cancer mortality, however, no breakdown of the specific types of cancer was provided.

Silbernagel et al [16] reported that HbA1c significantly predicts overall cancer mortality. Lung cancer was analysed separately but other specific cancers were not analysed due to small numbers. BMI and ethnicity were also adjusted for. Participants with HbA1c 48-57mmol/mol (6.5-7.4%) had a significantly higher hazard ratio for cancer mortality than those with HbA1c <31mmol/mol (<5%) [p=0.032]. Additional confounders such as hypertension and cholesterol levels were considered. No details on the specific types of cancer were included. A major limitation of this study was the selection of a non-representative sample as patients were recruited post coronary angiography and only Caucasians were included.

Hsu et al [17] examined the relationship between cancer mortality and glycaemic biomarkers of type 2 diabetes. HbA1c was not found to be related to all-cause cancer mortality among 2,509 people without diabetes.

The above studies combine cancer incidence and mortality. Three studies [10, 14, 15] investigated HbA1c level and the risk of developing all cancers. Of these, a positive
association was observed in two studies [10, 15]. Positive relationships between increasing HbA1c and cancer mortality were also noted [10, 11, 13, 16]. These relationships were noted at the extremes of HbA1c level and seem to affect women more so than men.

Breast Cancer

Four cohort studies investigated the association between HbA1c and breast cancer [10, 14, 15, 18]. All were large cohorts ranging from 12,792 to 46,575 participants. Joshu et al [10] found that women with HbA1c of $\geq 39\text{mmol/mol (} \geq 5.7\% \text{)}$ or $<31\text{mmol/mol (}<5\%)$ did not have significantly higher incidence rates of post-menopausal breast cancer compared to the reference (31-38mmol/mol, 5-5.6%). When compared to women without diabetes, women with diabetes had a non-significant increase in HR for post-menopausal breast cancer [HR 1.30, 95% CI: 0.92-1.83] and mortality [HR 2.34, 95% CI: 0.97-5.62].

Jonasson’s study in type 2 diabetes [14], did not expose a relationship between HbA1c and breast cancer. No significant differences in risk were found between HbA1c levels higher or lower than the cohort median (52mmol/mol, 6.9%). Lin et al [18] investigated whether HbA1c levels could predict breast cancer risk in 27,110 women without diabetes. Overall, they concluded that high HbA1c levels had no effect on breast cancer risk. A weakly inverse relationship was observed among post-menopausal women who had never used hormone replacement therapy ($p=0.06$). Within another cohort without diabetes, Travier et al [15] did not observe an increased risk among all women, or following stratification by menopausal status.

None of the four studies found any significant association between HbA1c and the risk of developing breast cancer. The studies were of considerable sample size and good
methodology. Although, only the studies by Lin and Joshu adjusted for post-menopausal hormone use.

**Colorectal Cancer**

Five cohort studies and three nested case control studies evaluated HbA1c in relation to colorectal cancer [10, 15, 19-24]. In a cross sectional study of 2,776 people with and without diabetes, Hsu et al [19] investigated the association between measures of glycaemic index and colorectal neoplasia, odds ratios were used to measure the associations. Neoplasia included adenomas and cancerous lesions. For analysis the authors divided neoplasia into ‘any neoplasia’ and ‘high risk neoplasia’. It should be noted that only 2 cases had colorectal cancer. HbA1c was found to be an independent risk factor (p<0.001) for colorectal neoplasia for the whole cohort after multivariate analysis. HbA1c was superior to fasting plasma glucose as a risk indicator which led the authors to speculate about the use of HbA1c in colorectal cancer screening programmes.

A large study by Joshu et al [10] identified a non-significant increase in incidence rate of colorectal cancer within men [HR 1.52, 95% CI: 0.88-2.60] and women [HR 1.55, 95% CI: 0.88-2.75] with diabetes, compared to those without diabetes (reference; 31-38mmol/mol, 5.5-5.6%). A significant increase in colorectal cancer [HR 1.84, 95% CI: 1.07-3.18] was also observed for men without diabetes, with HbA1c <31mmol/mol (<5%).

Khaw et al [20] studied 9,605 men and women with and without diabetes. Mean HbA1c concentration was significantly higher within incident colorectal cancer cases [p=0.005]. Those with known or undiagnosed diabetes (HbA1c ≥53mmol/mol, ≥7%, but no reported
diabetes) had a 4-fold increase in incident colorectal cancer rate compared to persons with HbA$_{1c}$ < 31 mmol/mol (<5%) [p for trend < 0.001].

Rinaldi et al [21] enrolled 1,026 colorectal cancer cases, with and without diabetes, and an equal number of matched controls. Increasing HbA$_{1c}$ percentages were associated with increased odds ratios for colorectal cancer incidence [OR 1.10, 95% CI: 1.01-1.19 per 10% rise in HbA$_{1c}$]. This relationship was also true of women separately [OR 1.16, 95% CI: 1.01-1.32]. No such relationship was observed in men. The methodological quality of these studies was good, though minimisation of confounding factors was not thoroughly addressed. Each failed to account for at least one of the following: BMI, race/ethnicity, alcohol intake and smoking.

Three studies focused on cohorts without diabetes only. Saydah et al [22] found that higher HbA$_{1c}$ levels > 40 mmol/mol (>5.8%) were associated with increased risk of colorectal cancer (OR, 1.57; 95% CI, 0.94–2.60; p for trend 0.02) compared to 346 controls matched for age, race, and sex. Risk was 57% higher in the top quartile of HbA$_{1c}$ compared to the bottom quartile, however this did not reach significance.

Travier et al [15] identified no risk increases for colorectal cancer among people without diabetes. Likewise, Platz et al [23] did not find HbA$_{1c}$ to significantly differ between 280 women without diabetes and colorectal cancer and 357 matched controls without colorectal cancer. Additionally among 27,110 women without diabetes [24], HbA$_{1c}$ levels were not correlated to cancers of the proximal colon, distal colon or rectum. The methodological quality of the previous two studies, including assessment of confounding factors, was very good.
Five out of eight studies identified an increased risk of colorectal cancer with higher HbA1c levels. One study also suggested that very low HbA1c levels (<31mmol/mol, <5%) may increase incidence of colorectal cancer. Two of the studies which established a null relationship were of considerably larger sample sizes and subsequently have greater statistical power. However, on balance, the presence of some association cannot be excluded.

**Gastric Cancer**

Three population-based cohort studies investigated the relationship between HbA1c and gastric cancer risk [14, 15, 25]. All three studies adjusted for age, sex and smoking status. Ikeda et al [25] investigated the impact of HbA1c level on gastric cancer occurrence and the interaction with *Helicobacter pylori* (*H. pylori*) in people with and without diabetes. They concluded that HbA1c levels 42-52mmol/mol (6-6.9%) (p=0.003) significantly increased hazard ratios for the risk of gastric cancer, this remained significant after multivariate adjustment for other risk factors including *H.pylori* seropositivity, BMI and alcohol intake. The co-existence of elevated HbA1c ≥42mmol/mol (≥6%) and *H.pylori* infection similarly resulted in increased risk (HR, 4.03; 95% CI: 1.89-8.58; p <0.001). The methodology of this study thoroughly accounted for confounding factors with a moderate sample size of 2603 patients. The two remaining large studies by Travier et al [15] and Jonasson et al [14] (46,575 and 25,476 respectively), found no correlation between HbA1c levels and gastric/gastrointestinal cancer risk in those without diabetes or participants with type 2 diabetes. Neither study, considered *H.pylori* status as a confounder.

Based on the current available evidence, it is not possible to state whether HbA1c effects gastric cancer risk.
Pancreatic cancer

Three studies investigated the relationship between HbA$_{1c}$ and pancreatic cancer [26-28]. All studies comprised male and female participants. All three adjusted for age, sex and smoking status. Two studies [26, 27] included people with and without diabetes. Grote et al [26] investigated the role of HbA$_{1c}$ and C-peptide levels in the development of pancreatic cancer. A total of 466 participants with pancreatic cancer were matched with an equal number of controls, with and without diabetes. A statistically significant increase in odds ratio for pancreatic cancer was observed with increasing HbA$_{1c}$ levels within the whole population [p for trend= 0.002], and within those without diabetes [p for trend= 0.02], even after adjustment for BMI, diabetes status and smoking status. The overall methodology of this prospective study was good however, confounding factors such as alcohol intake and ethnicity were not considered. Also, risk was not given per unit HbA$_{1c}$ which would have enabled further conclusions.

Wolpin et al [28] evaluated HbA$_{1c}$ within a population of 449 participants and 982 matched controls, without diabetes. Again, increasing HbA$_{1c}$ levels were associated with a significant increase in odds ratios [p for trend= 0.04] for pancreatic cancer. The methodological quality of this study was very good. In a study of 127 patients, Cheon et al [27] concluded that elevated HbA$_{1c}$ levels were associated with poor survival in people with pancreatic cancer; however this did not reach significance.

These studies suggest that increasing HbA$_{1c}$ is positively correlated with pancreatic cancer risk. However, the sample sizes are small and there are few studies for comparison.
Other cancers

Four cohort studies [10, 14, 15, 17] reported data regarding HbA1c in relation to other site-specific cancers. No significant difference in incidence of lung and prostate cancers was identified by Joshu [10] in people with or without diabetes.

Jonasson et al [14] investigated risks for respiratory, urological, prostate and female genital cancers in people with type 2 diabetes. Among them, no significant differences between HbA1c level and hazard ratios for cancer were recognised. However, an association was identified by Travier [15] for respiratory cancer incidence among participants not known to have diabetes. A significant increase in respiratory cancer [HR 2.27, 95% CI: 1.34-3.86] was observed in persons with moderate HbA1c elevation (42-52mmol/mol, 6-6.9%), as compared to those with normal levels (<42mmol/mol, <6%). The same authors additionally revealed a significant increase in female genital cancer incidence [HbA1c 42-52mmol/mol/6-6.9%, HR 2.84, 95% CI: 1.35-5.98; HbA1c ≥53mmol/mol/7%, HR 2.01, 95% CI: 0.69-5.89]. No significant increases in urinary or prostate cancers were observed.

Hsu et al [17] found no associations between HbA1c level and lung cancer mortality in a cohort of people with undiagnosed diabetes or impaired fasting blood glucose.

The above studies reveal that HbA1c is not associated with cancers of the prostate or urological tract. One large cohort study revealed that HbA1c increases are positively correlated to respiratory and female genital cancer risk.

Discussion
This review is the first to systematically evaluate the evidence for an association between HbA\textsubscript{1c} and cancer risk/mortality. The studies included in this review report conflicting findings nevertheless, several conclusions can be drawn. The spread of results across the included studies represented a relatively large population size. Correlations generally existed across HbA\textsubscript{1c} ranges, as opposed to being more prevalent within diabetes versus no-diabetes. Therefore, glycaemia \textit{per se} as opposed to a diagnosis of diabetes appears important. The results are consistent with studies reporting a link between the metabolic syndrome and increased cancer risk.

The majority of studies that investigated HbA\textsubscript{1c} levels in relation to the risk of all cancers identified positive associations. Those with positive associations generally had larger sample sizes than those reporting no association. HbA\textsubscript{1c} levels <31 mmol/mol (<5%) also appeared to be associated with increased cancer risk. However, the comparison of results between studies is made difficult by the heterogeneity of the cancer types that exist within each population. Whilst postmenopausal breast cancer or prostate cancer were the most common in the ARIC study [10], followed by lung and then colorectal cancer, lung and colorectal are predominant over prostate and breast cancer in the Japanese population. The data presented on specific cancer types indicates that HbA\textsubscript{1c} may have a greater association with some cancers over others; indeed associations may be specific to sub-types of cancer. Therefore, if any one cancer type is under or over represented in a population, comparing all cancer data interpretation is difficult. In addition, the studies that included all cancers looked at incidence or mortality; however the disease aetiology and progression in different cancer types varies markedly and will significantly impact on outcome data, depending on the dominant forms of cancer in a particular population.
The included studies that explored the relationship between HbA1c and breast cancer were all of good methodological quality and relatively large sample sizes. Among them, no overall increases in breast cancer risk were observed. The studies were carried out on varying populations; one study contained mainly Swedish participants and the other largely Maori participants. Two studies targeted women >45 years while the remaining two included a wider range of ages. Two studies, however, did note known diabetes and HbA1c elevation to be weakly associated with post-menopausal breast cancer. These studies support, to an extent, the findings that where postmenopausal breast cancer is a predominant form of cancer in a population the overall correlation between HbA1c and all cancers is also positive.

The majority of studies that investigated HbA1c levels in relation to colorectal cancer risk identified positive associations. Low HbA1c levels <31 mmol/mol (<5%) were associated with increased colorectal cancer risk in men without diabetes and a three-fold increase in mortality in women in one study. The studies that failed to identify a link between HbA1c and colorectal cancer tended to comprise larger sample sizes than those with positive association. Again the population sampled may have had an impact on the results, the largest study was composed of 70% Maori ethnicity which may not be representative of other ethnic groups. Four of the eight studies were conducted on US populations, however two of these studies reported an association and two did not. All of the studies were nested case control studies with carefully selected controls; this limits the degree of selection and recall bias. Overall, we can conclude cases with colorectal cancer were found to have higher HbA1c levels than the controls; however the possibility of reverse causality cannot be completely excluded. In addition, iron deficiency anaemia is known to increase HbA1c level, subsequently fluctuations in iron status, which is common in colorectal pathology and malignancy can lead to deviations in HbA1c stability which has not been considered in any of the articles [29].
Despite being one of the more prevalent cancers in several populations studied, there was little focus on lung cancer and HbA\textsubscript{1c}, in the articles identified. One study revealed risk increases for respiratory cancer, among people with moderate to high elevation of HbA\textsubscript{1c}. This study included 46,000 participants; therefore the result may be of significance and correlates with a study [5] that discovered that a diagnosis of diabetes may increase the risk of lung cancer, particularly among women.

The three studies that examined HbA\textsubscript{1c} in relation to pancreatic cancer revealed similar findings. Two of the three studies had very similar population sizes and all had a mean age between 62-69 years. In each case, higher levels were associated with increased risk of pancreatic cancer risk and mortality, among people with and without diabetes. Poorer survival was noted with higher levels of HbA\textsubscript{1c}. The relationship between pancreatic cancer and glycaemia is complex and issues surrounding causation and effect make the results of the present studies difficult to interpret.

Of the studies whose aims were to establish the relationship between HbA\textsubscript{1c} and gastric cancer, two of three failed to detect an association. The remaining study found the incidence of gastric cancer to be greater with higher HbA\textsubscript{1c} levels, whilst considering \textit{H. pylori} as a confounder. However, this study was conducted in a Japanese population where gastric cancer is much more common. Studies that revealed a null relationship, failed to consider \textit{H. pylori} as a potential confounder. Therefore, no firm conclusions regarding HbA\textsubscript{1c} and gastrointestinal cancer risk can be made.
All but one of the studies, reporting data for HbA1c in relation to other site-specific cancers, determined no differences in risk for respiratory, urological, female genital or prostate cancers.

Given the results of this review, the monitoring and optimisation of glycaemia, using HbA1c as a measure of hyperglycaemia, could be considered as a modifiable risk factor for certain cancers, along with well-established risk factors such as smoking and alcohol. With further research, HbA1c could aid in informing prognosis for certain cancers as extremes of HbA1c level are correlated with increased cancer mortality. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is ongoing and further research generated from this large cohort study may contribute to our knowledge of HbA1c and cancer risk.

This systematic review has some limitations. One is the inability to perform a meta-analysis due to heterogeneity of the results and study design. Within the studies, little differentiation was made between type 1 and type 2 diabetes yet the two disease progressions may contribute to different risk profiles for cancer which was not accounted for. Furthermore, the role of anti-diabetic treatment on cancer risk has not been accounted for in all of the studies. Most studies only had one HbA1c measurement per case, this means temporal relationships cannot be compared between studies. Finally, reverse causality cannot be excluded in any of the studies.

Since the publication of most of the included studies, standards for HbA1c measurement have improved, further studies should ensure that all HbA1c measurements are performed in alignment with the IFCC and clear quality data should be provided in the reports [30].
Conclusions

In conclusion, there is evidence that HbA1c may predict overall and certain site specific cancer risk/mortality in people with or without diabetes. Further studies looking at specific cancers, where a positive correlation has been shown, are warranted. Whilst data is currently mixed, understanding the role of HbA1c and glycaemia in the aetiology of specific cancers may help to identify where HbA1c can give additional information to support either identification of people at risk of cancers or give some insight into the potential progression of the disease.

Acknowledgements

We would like to thank R. Curtis (Library Services, University of Nottingham, Nottingham, UK) for her help and guidance in constructing the database searches.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest

None to declare.

References


<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study</th>
<th>HbA1c stratification</th>
<th>N (males)</th>
<th>Inclusion Criteria</th>
<th>Diabetes status</th>
<th>Cancer type</th>
<th>Follow up duration</th>
<th>Adjusting factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakanishi et al 2005</td>
<td>Cohort; from Adult Health Study (1986-1994)</td>
<td>Known diabetes and remaining into 4 groups of baseline data</td>
<td>3,710 (1,142)</td>
<td>Male and female; A-bomb survivors and controls; Nagasaki Adult Health Study population excluded</td>
<td>Mixed</td>
<td>Overall</td>
<td>8.83 (mean)</td>
<td>Age; sex; A-bomb kerma dose; BMI; systolic BP; total cholesterol; smoking; alcohol</td>
</tr>
<tr>
<td>Parekh et al 2010</td>
<td>Observational; from NHANES III</td>
<td>Per 2% increments</td>
<td>15,594 (7,594)</td>
<td>Male and female; 20-89 years; subjects meeting at least 3 of the 5 criteria for the IRS5; pregnant women excluded</td>
<td>Mixed</td>
<td>Overall</td>
<td>8.5 (mean) (median)</td>
<td>Age; race; sex; smoking; physical activity; BMI</td>
</tr>
<tr>
<td>Saydah et al 2009</td>
<td>Cohort; from NHANES III</td>
<td>4 groups of baseline data [&lt;6.0, 6.0-&lt;7.0, 7.0-&lt;8.0 and ≥8.0%]</td>
<td>19,025 (8,517)</td>
<td>Male and female≥20 years; participants with complete data for all variables included in the analysis</td>
<td>Mixed</td>
<td>Overall</td>
<td>6-12 (range)</td>
<td>Age; sex; race/ethnicity; education level; smoking; BMI; systolic BP; HDL cholesterol</td>
</tr>
<tr>
<td>Joshua et al 2012</td>
<td>Cohort; from ARIC study (1990-92)</td>
<td>According to diabetic status (diabetic [≤7 and &gt;7%], and non-diabetic [5.0-5.5 and ≥5.7%]) further classified into ≥5.7-6.4 and ≥6.5%</td>
<td>12,792 (5,790)</td>
<td>Male and female; 45-64 years; no prior cancer diagnosis (except non-melanoma skin) by second examination visit within ARIC study</td>
<td>Mixed</td>
<td>Overall/ specific sites</td>
<td>15 (median)</td>
<td>Age; sex; race/ethnicity; education level; smoking; BMI; waist circumference; PM hormone use</td>
</tr>
<tr>
<td>Silbernagel et al 2011</td>
<td>Cohort; from the LURIC health study</td>
<td>6 groups of baseline data [&lt;5.0, 5.0-5.4, 5.5-5.9, 6.0-6.4, 6.5-7.4 and ≥7.5%]</td>
<td>2,696 (1,897)</td>
<td>Male and female; German ancestry; the availability of a coronary angiogram; no acute illnesses/chronic non-cardiac diseases or malignancies within past 5 years</td>
<td>No diabetes</td>
<td>Overall</td>
<td>7.54 (mean)</td>
<td>Sex; age; BMI; hypertension; smoking; GFR; triglycerides; LDL/HDL cholesterol; fasting glucose</td>
</tr>
<tr>
<td>Hsu et al 2013</td>
<td>Cohort; from NHANES III</td>
<td>According to baseline median and [interquartile range] Male = 5.51% [5.16-5.98%]; Female = 5.56% [5.25-5.94%]</td>
<td>2,509 (1,348)</td>
<td>Male and female; ≥80 years; impaired fasting blood glucose/undiagnosed diabetes; no previous history of malignancy</td>
<td>No diabetes</td>
<td>Overall/ lung</td>
<td>11.17 (mean) 0-18.17 (range)</td>
<td>Age; sex; BMI; race/ethnicity; smoking</td>
</tr>
<tr>
<td>Travier et al 2007</td>
<td>Cohort; from a hepatitis B screening programme (1999-2001)</td>
<td>3 groups of baseline data [6.0, 6.0-6.9, and ≥7.0%]</td>
<td>46,575 (20,761)</td>
<td>Male and female; ≥18 years; no participants who had a cancer registered or a diabetes diagnosis before their HbA1c test</td>
<td>No diabetes</td>
<td>Overall/ specific sites</td>
<td>4.4 (median)</td>
<td>Sex; age; ethnicity; smoking</td>
</tr>
<tr>
<td>Jonasson et al 2012</td>
<td>Cohort; from Swedish National Diabetes Register from 1997-99</td>
<td>According to cohort median [≤58 mmol/mol (7.5%), &gt;58 mmol/mol] – baseline and updated mean</td>
<td>25,476 (14,259)</td>
<td>Male and female; 25-90 years; no cancer diagnosis or death before the start of follow-up</td>
<td>Type 2 diabetes</td>
<td>Overall/ specific sites</td>
<td>11-13 (range)</td>
<td>Age; sex; diabetes duration; BMI; smoking; insulin treatment</td>
</tr>
<tr>
<td>Cheon et al 2014</td>
<td>Cohort; admitted to Konkuk University Medical Center from 2005 to 2011</td>
<td>&lt;7.0% and ≥7.0%</td>
<td>127 (60)</td>
<td>Male and female; 43-90 years; stage 3 or above pancreatic cancer</td>
<td>Mixed</td>
<td>Pancreatic</td>
<td>7 (mean)</td>
<td>Age; sex; TNM; BMI; alcohol; smoking; chemotherapy; Ca19-9</td>
</tr>
<tr>
<td>Grote et al 2011</td>
<td>Nested case-control; conducted within EPIC</td>
<td>Quintiles of baseline data [4.8-5.4, 5.5-5.7, 5.8-5.9, 6.0-6.4 and 6.5-11.0%]</td>
<td>466 (225)</td>
<td>Male and female; 30-76 years; no occurrence of other malignant tumours preceding pancreatic cancer diagnosis</td>
<td>Mixed</td>
<td>Pancreatic</td>
<td>5.3 (mean) 0-13 (range)</td>
<td>Age; sex; smoking; BMI; diabetes status; fasting time</td>
</tr>
<tr>
<td>Wolphin et al 2011</td>
<td>Nested case-control; quintile 1 median [4.77%]</td>
<td>Case 449</td>
<td>Male and female≥30 years; pancreatic</td>
<td>No diabetes Pancreatic 10-26</td>
<td>Sex; age; BMI; smoking; race; fasting status; smoking; diabetes status; smoking; insulin treatment; BMI; systolic BP; total cholesterol; smoking; alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Study Description</td>
<td>Cohort Details</td>
<td>Baseline Data</td>
<td>Study Details</td>
<td>Diagnosis</td>
<td>Stage</td>
<td>Age/Other Factors</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------------------</td>
<td>----------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>from 5 prospective studies</td>
<td>4 groups of baseline data with 1% intervals [≤5.0, 5.0-5.9, 6.0-6.9] and [≥7.0%]</td>
<td>Male and female; ≥80 years; no prior history of gastrectomy or gastric cancer</td>
<td>Mixed</td>
<td>Gastric</td>
<td>Age; sex; Helicobacter pylori seropositivity; history of peptic ulcer disease; BMI; total serum cholesterol; alcohol; smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>Cohort; from a voluntary health check-up programme</td>
<td>2,776 (1,506)</td>
<td>Male and female; 18-86 years; no participants whose colonoscopy failed cecal intubation</td>
<td>Mixed</td>
<td>Colorectal</td>
<td>Age; sex; BMI; smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Cohort; from EPIC-Norfolk study</td>
<td>9,605 (4,445)</td>
<td>Male and female; 45-79 years; available HbA1c, measurement; no prevalent cancer at baseline survey</td>
<td>Mixed</td>
<td>Colorectal</td>
<td>Age; sex; BMI; smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Nested case-control; conducted within EPIC</td>
<td>Colon case/control 1,644 (342) Rectum case/control 1,382 (219)</td>
<td>Male and female; 35-69 years; cases who developed colon/rectum cancers after recruitment and before end of study; anal cancer excluded; controls free of cancer (except non-melanoma skin) at time of diagnosis of the index case</td>
<td>Mixed</td>
<td>Colorectal</td>
<td>Age; sex; menopausal status; waist to hip ratio; alcohol; diabetes status; fasting status; follow-up time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Nested case-control; conducted within the Nurses' Health Study</td>
<td>Tertiles of baseline data (tertile 1 median [5.2%], tertile 2 median [5.5%], tertile 3 median [5.8%])</td>
<td>Cancer case/control 79 (0) / 156 (0) DA case/control 201 (0)</td>
<td>No diabetes</td>
<td>Colorectal</td>
<td>Age; weight; BMI; physical activity; smoking; alcohol; red meat intake; folic acid; methionine; aspirin use; PM hormone use; fasting status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Nested case control; conducted within CLUE II cohort</td>
<td>Quartiles of baseline data (quartile cut points = 5.38, 5.54 and 5.78%)</td>
<td>Case 173 (NA) Control 346 (NA)</td>
<td>No diabetes</td>
<td>Colorectal</td>
<td>Age; sex; race; date of blood draw; time since last meal; other circulating markers included in study×</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Cohort; from the Women’s Health Study</td>
<td>Quartiles of baseline data [2.3-4.8, &gt;4.8-5.0, &gt;5.0-5.2 and ≥5.2%]</td>
<td>Female only; ≥45 years; free of cancer and cardiovascular disease at time of enrolment in 1993</td>
<td>No diabetes</td>
<td>Colorectal</td>
<td>Age; RA; BMI; family history; history of colon polyps; physical activity; smoking; red meat intake; alcohol; multivitamin use; menopausal status; PM hormone use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Cohort; from the Women’s Health Study</td>
<td>Quartiles of baseline data</td>
<td>Female only; ≥45 years; free of cancer and cardiovascular disease at time of enrolment in 1993</td>
<td>No diabetes</td>
<td>Breast</td>
<td>Age; RA; BMI; family history; history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Women’s Health Study</td>
<td>cancer and cardiovascular disease at time of enrolment in 1993</td>
<td>of benign breast disease; physical activity; alcohol; age at menarche/first birth; menopausal status; PM hormone use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>----------------------</td>
<td>-------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤4.80, &gt;4.80–4.94, &gt;4.94–5.07, &gt;5.07–5.25 and &gt;5.25%</td>
<td>5 groups of clinically-relevant cut-offs [≤5.0, 5.0–&lt;5.5, 5.5–&lt;6.0, 6.0–&lt;6.5 and ≥6.5%]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI = body mass index, BP = blood pressure, FPG = fasting plasma glucose, GFR = glomerular filtration rate, HDL = high-density lipoprotein, IRS = insulin resistance syndrome, LDL = low-density lipoprotein, NA = not available, PM = post-menopausal, RTA = random treatment assignment. *Other studied circulating markers include: plasma insulin, the ratio of total cholesterol:HDL cholesterol, triglycerides and IGFBP-1.  

*a Five criteria for the insulin resistance syndrome: (1) insulin resistance [fasting glucose ≥6.1 mmol/l], (2) hypertension [systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg], (3) hypertriglyceridemia [triglycerides ≥1.7 mmol/l], (4) low high-density cholesterol levels [<1.0mmol/l in men or <1.3mmol/l in women], and (5) abdominal obesity [waist circumference >102 cm in men or >88 cm in women].  

*b Other studied circulating markers include: plasma insulin, the ratio of total cholesterol:HDL cholesterol, triglycerides and IGFBP-1.  

*c Five prospective studies = Health Professionals Follow-up Study (HPFS), Nurses’ Health Study (NHS), Physicians’ Health Study (PHS), Women’s Health Initiative-Observational Study (WHI-OS) and Women’s Health Study (WHS).
Table 2. A summary of the results of studies that investigated HbA₁c in relation to all cancers.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject Groups</th>
<th>≤5.0%</th>
<th>5.0-5.6%</th>
<th>5.5-5.9%</th>
<th>≥5.7%</th>
<th>6.0-6.4%</th>
<th>≥6.5%</th>
<th>≤58 mmol/mol</th>
<th>&gt;58 mmol/mol</th>
<th>Diabetes</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al. (2013)</td>
<td>Male</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.24(0.90-1.70)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.97(0.57-1.65)</td>
</tr>
<tr>
<td>Jonasson et al. (2012)</td>
<td>All</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Joshu et al. (2012)</td>
<td>Male incidence*</td>
<td>1.04 (0.85-1.27)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.08(0.95-1.22)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.85(0.69-1.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male mortality*</td>
<td>1.16 (0.90-1.50)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.11(0.95-1.31)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.96(0.74-1.24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Minus prostate</td>
<td>0.97 (0.67-1.40)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.08(0.87-1.33)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.92(0.66-1.30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male incidence*</td>
<td>0.89 (0.60-1.32)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.01(0.80-1.26)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.30(1.06-1.60)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female incidence</td>
<td>1.27 (1.02-1.58)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.24(1.07-1.44)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.96(1.40-2.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female mortality</td>
<td>1.82 (1.25-2.64)</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1.58(1.23-2.05)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nakanishi et al. (2005)</td>
<td>All</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1.10(0.77-1.56)</td>
<td>-</td>
<td>1.30(0.85-2.00)</td>
<td>1.70(1.02-2.82)</td>
<td>-</td>
<td>-</td>
<td>1.82(1.20-2.76)</td>
</tr>
</tbody>
</table>

Study | Subject Groups | <5% | 5.0-5.4% | 5.5-5.9% | <6% | 6.0-6.4% | 6.0-6.9 | 6.5-7.4 | 7.0-7.9% | ≥7.0% | ≥7.5% | ≥8.0% | Per 2% Increment |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Parekh et al. (2010)</td>
<td>All</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.22(0.96-1.55)</td>
</tr>
<tr>
<td>Saydah et al. (2009)</td>
<td>All</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>0.73 (0.5-1.1)</td>
<td>-</td>
<td>0.93 (0.4-2.2)</td>
<td>-</td>
<td>-</td>
<td>2.64 (1.2-6.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>0.20(0.05-0.90)</td>
<td>-</td>
<td>0.43(0.08-2.28)</td>
<td>-</td>
<td>-</td>
<td>1.04(0.25-4.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>0.8 (0.6-1.2)</td>
<td>-</td>
<td>0.6 (0.1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Hazard Ratio (95% Confidence Interval) for HbA₁c Categorisations.
<table>
<thead>
<tr>
<th>Study</th>
<th>All</th>
<th>0.82 (0.39-1.72)</th>
<th>1</th>
<th>0.93 (0.50-1.74)</th>
<th>-</th>
<th>1.85 (0.98-3.48)</th>
<th>-</th>
<th>1.67 (0.46-6.11)</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silbernagel et al. (2011)</td>
<td>All</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.40 (1.11-1.76)</td>
<td>-</td>
<td>-</td>
<td>1.09 (0.80-1.48)</td>
<td>-</td>
</tr>
<tr>
<td>Travier et al. (2007)</td>
<td>All</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Appendix 1. Embase/Medline search strategy

1. neoplasm/
2. "neoplasm*".ti.
5. "malignan*".ti.
7. 1 or 2 or 3 or 4 or 5 or 6
8. diabetes mellitus/
9. "diabet*".ti,ab.
10. "nondiabet*".ti,ab.
11. insulin blood level/ or insulin resistance/ or human insulin/ or insulin dependence/ or insulin sensitivity/ or insulin deficiency/ or non insulin dependent diabetes mellitus/ or insulin release/ or insulin dependent diabetes mellitus/ or insulin metabolism/ or insulin/
12. "insulin*".ti,ab.
13. "insulin resistant*".ti,ab.
14. "insulin insensitiv*".ti,ab.
15. "insulin dependen*".ti,ab.
16. "noninsulin dependen*".ti,ab.
17. "non-insulin dependen*".ti,ab.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. blood glucose monitoring/ or glucose intolerance/ or glucose/ or glucose metabolism/ or glucose blood level/ or glucose tolerance/
22. "glycemi*".ti,ab.
23. "hyperglycemi*".ti,ab.
24. 20 or 21 or 22 or 23
25. glycosylated hemoglobin/ or diabetes mellitus/
26. "a1c".ti.
27. "hba1c".ti.
30. 25 or 26 or 27 or 28 or 29
31. risk/ or cancer risk/
32. "risk*".ti.
33. "predict*".ti.
34. "associat*".ti.
35. "factor*".ti.
37. "predispos*".ti.
38. "mortalit*".ti.
39. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 7 and 19 and 24 and 30 and 39