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

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Novelty Statement

This review is the first to systematically evaluate the evidence for a link between HbA_{1c} and cancer risk. It outlines the relationships between HbA_{1c} and the incidence and mortality of all and site-specific cancers. Furthering our understanding of the relationship between HbA_{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 (HbA_{1c}) 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 HbA_{1c} 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 HbA_{1c} levels were associated with increased incidence and/or mortality risk for all cancers. One study observed a U-shape relationship between HbA_{1c} and cancer incidence and mortality. Increasing HbA_{1c} 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 HbA_{1c} appears to be associated with cancer incidence and/or cancer mortality. However, further studies are needed to fully understand the complex relationship between HbA_{1c} 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 (HbA_{1c}) 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. HbA_{1c} 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 HbA_{1c} and increased risk of cancer, but these studies have been limited to people with diabetes or used HbA_{1c} values as discrete, rather than continuous variables. Further developing our understanding of the

relationship between HbA_{1c} and cancer aetiology, in specific cancers, is of clinical importance. We aim to assess the relationship between HbA_{1c} 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 HbA_{1c}, 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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_{1c} and cancer in people without diabetes. A total of 12,792 individuals were included in a study by Joshu *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_{1c} >39mmol/mol (>5.7%) had a 24% higher cancer incidence rate compared to those with HbA_{1c} 31-38mmol/mol (5-5.6%) but a 27% increase in cancer incidence rate was also noted in HbA_{1c} levels below 31mmol/mol (5%), indicating a U-shape relationship between HbA_{1c} and all types of cancer incidence. In contrast, no positive relationship was seen between HbA_{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_{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_{1c} 42-52mmol/mol (6%-6.9%) (HR 1.40, CI 95%: 1.11-1.76), compared to those with HbA_{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 HbA_{1c} and cancer mortality. The study by Joshu *et al* [10] investigated the association between all and site specific cancer mortality rates and HbA_{1c}. 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 HbA_{1c} <31mmol/mol (<5%) were found to have an 82% increase in cancer mortality and rates also increased with incremental increases in HbA_{1c} above 39mmol/mol (>5.7%). Cancer mortality in men was not affected by HbA_{1c} level.

Nakanishi *et al* [11] studied the effects of HbA_{1c} levels on cancer specific mortality in a Japanese cohort. After adjustment for BMI, blood pressure, total cholesterol, smoking and alcohol intake, HbA_{1c} >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 HbA_{1c} (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 HbA_{1c} and overall cancer mortality rates in 19,025 people of mixed diabetic status. HbA_{1c} levels >64mmol/mol (>8%) were associated with a more than twofold increase in relative risk of cancer mortality compared to those with HbA_{1c} levels <42mmol/mol (<6%). Overall, they concluded that increasing levels of HbA_{1c} were associated with increased cancer mortality, however, no breakdown of the specific types of cancer was provided.

Silbernagel *et al* [16] reported that HbA_{1c} 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 HbA_{1c} 48-57mmol/mol (6.5-7.4%) had a significantly higher hazard ratio for cancer mortality than those with HbA_{1c} <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. HbA_{1c} 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 HbA_{1c} level and the risk of developing all cancers. Of these, a positive

association was observed in two studies [10, 15]. Positive relationships between increasing HbA_{1c} and cancer mortality were also noted [10, 11, 13, 16]. These relationships were noted at the extremes of HbA_{1c} level and seem to affect women more so than men.

Breast Cancer

Four cohort studies investigated the association between HbA_{1c} 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 HbA_{1c} of ≥39mmol/mol (≥5.7%) or <31mmol/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 HbA_{1c} and breast cancer. No significant differences in risk were found between HbA_{1c} levels higher or lower than the cohort median (52mmol/mol, 6.9%). Lin *et al* [18] investigated whether HbA_{1c} levels could predict breast cancer risk in 27,110 women without diabetes. Overall, they concluded that high HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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. HbA_{1c} was found to be an independent risk factor ($p<0.001$) for colorectal neoplasia for the whole cohort after multivariate analysis. HbA_{1c} was superior to fasting plasma glucose as a risk indicator which led the authors to speculate about the use of HbA_{1c} 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, 5-5.6%). A significant increase in colorectal cancer [HR 1.84, 95% CI: 1.07-3.18] was also observed for men without diabetes, with HbA_{1c} <31mmol/mol (<5%).

Khaw *et al* [20] studied 9,605 men and women with and without diabetes. Mean HbA_{1c} concentration was significantly higher within incident colorectal cancer cases [p=0.005]. Those with known or undiagnosed diabetes (HbA_{1c} ≥53mmol/mol, ≥7%, but no reported

diabetes) had a 4-fold increase in incident colorectal cancer rate compared to persons with HbA_{1c} <31mmol/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 >40mmol/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 HbA_{1c} levels. One study also suggested that very low HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} level on gastric cancer occurrence and the interaction with *Helicobacter pylori* (*H.pylori*) in people with and without diabetes. They concluded that HbA_{1c} 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 HbA_{1c} ≥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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 [HbA_{1c} 42-52mmol/mol/ 6-6.9%, HR 2.84, 95% CI: 1.35-5.98; HbA_{1c} ≥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 HbA_{1c} level and lung cancer mortality in a cohort of people with undiagnosed diabetes or impaired fasting blood glucose.

The above studies reveal that HbA_{1c} is not associated with cancers of the prostate or urological tract. One large cohort study revealed that HbA_{1c} 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_{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_{1c} ranges, as opposed to being more prevalent within diabetes versus no-diabetes. Therefore, glycaemia *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_{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_{1c} levels <31mmol/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_{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 HbA_{1c} 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 >45years while the remaining two included a wider range of ages. Two studies, however, did note known diabetes and HbA_{1c} 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 HbA_{1c} levels in relation to colorectal cancer risk identified positive associations. Low HbA_{1c} levels <31mmol/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 HbA_{1c} 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 HbA_{1c} levels than the controls; however the possibility of reverse causality cannot be completely excluded. In addition, iron deficiency anaemia is known to increase HbA_{1c} level, subsequently fluctuations in iron status, which is common in colorectal pathology and malignancy can lead to deviations in HbA_{1c} 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_{1c}, in the articles identified. One study revealed risk increases for respiratory cancer, among people with moderate to high elevation of HbA_{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_{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_{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_{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_{1c} levels, whilst considering *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 *H. pylori* as a potential confounder. Therefore, no firm conclusions regarding HbA_{1c} and gastrointestinal cancer risk can be made.

All but one of the studies, reporting data for HbA_{1c} 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 HbA_{1c} 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, HbA_{1c} could aid in informing prognosis for certain cancers as extremes of HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} measurement have improved, further studies should ensure that all HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} and glycaemia in the aetiology of specific cancers may help to identify where HbA_{1c} 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.

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Conflicts of interest

None to declare.

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Table 1. Summary of all study characteristics

Author/Year	Study	HbA1c stratification	N (males)	Inclusion Criteria	Diabetes status	Cancer type	Follow up duration	Adjusting factors
Nakanishi *et al* 2005	Cohort; from Adult Health Study (1986-1994)	Known diabetes and remaining into 4 groups of baseline data [<5.5%, ≥5.5 - <6.0%, ≥6.0 - <6.5% and ≥6.5%]	3,710 (1,142)	Male and female; A-bomb survivors and controls; Nagasaki Adult Health Study population excluded	Mixed	Overall	8.83 (mean)	Age; sex; A-bomb kerma dose; BMI; systolic BP; total cholesterol; smoking; alcohol
Parekh *et al* 2010	Observational; from NHANES III	Per 2% increments	15,594 (7,594)	Male and female; 20-89 years; subjects meeting at least 3 of the 5 criteria for the IRS[a]; pregnant women excluded	Mixed	Overall	8.5 (mean) 8.55 (median)	Age; race; sex; smoking; physical activity; BMI
Saydah *et al* 2009	Cohort; from NHANES III	4 groups of baseline data [<6.0, 6.0- <7.0, 7.0- <8.0 and ≥8.0%]	19,025 (8,517)	Male and female;≥20 years; participants with complete data for all variables included in the analysis	Mixed	Overall	6-12 (range)	Age; sex; race/ethnicity; education level; smoking; BMI; systolic BP; HDL cholesterol
Joshu *et al* 2012	Cohort; from ARIC study (1990-92)	According to diabetic status (diabetic [≤7 and >7%], and non-diabetic [<5.0, 5.0-5.6 and ≥5.7%] ≥5.7% further classified into ≥5.7-6.4 and ≥6.5%)	12,792 (5,790)	Male and female; 45-64 years; no prior cancer diagnosis (except non-melanoma skin) by second examination visit within ARIC study	Mixed	Overall/ specific sites	15 (median)	Age; sex; race/ethnicity; education level; smoking; BMI; waist circumference; PM hormone use
Silbernagel *et al* 2011	Cohort; from the LURIC health study	6 groups of baseline data [<5.0, 5.0-5.4, 5.5-5.9, 6.0-6.4, 6.5-7.4 and ≥7.5%]	2,696 (1,897)	Male and female; German ancestry; the availability of a coronary angiogram; no acute illnesses/chronic non-cardiac diseases or malignancies within past 5 years	No diabetes	Overall	7.54 (mean)	Sex; age; BMI; hypertension; smoking; GFR; triglycerides; LDL/HDL cholesterol; fasting glucose
Hsu *et al* 2013	Cohort; from NHANES III	According to baseline median and [interquartile range] Male = 5.51% [5.16-5.98%] Female = 5.56% [5.25-5.94%]	2,509 (1,348)	Male and female; ≥40 years; impaired fasting blood glucose/undiagnosed diabetes; no previous history of malignancy	No diabetes	Overall/ lung	11.17 (mean) 0-18.17 (range)	Age; sex; BMI; race/ethnicity; smoking
Travier *et al* 2007	Cohort; from a hepatitis B screening programme (1999-2001)	3 groups of baseline data [6.0, 6.0-6.9, and ≥7.0%]	46,575 (20,761)	Male and female; ≥18 years; no participants who had a cancer registered or a diabetes diagnosis before their HbA_{1c} test	No diabetes	Overall/ specific sites	4.4 (median)	Sex; age; ethnicity; smoking;
Jonasson *et al* 2012	Cohort; from Swedish National Diabetes Register from 1997-99	According to cohort median [≤58 mmol/mol (7.5%), >58 mmol/mol] – baseline and updated mean	25,476 (14,259)	Male and female; 25-90 years; no cancer diagnosis or death before the start of follow-up	Type 2 diabetes	Overall/ specific sites	11-13 (range)	Age; sex; diabetes duration; BMI; smoking; insulin treatment
Cheon *et al* 2014	Cohort; admitted to Konkuk University Medical Center from 2005 to 2011	<7.0%, ≥7.0%.	127 (60)	Male and female; 43-90 years; stage 3 or above pancreatic cancer	Mixed	Pancreatic	7 (mean)	Age; sex; TNM; BMI; alcohol; smoking; chemotherapy;Ca19-9
Grote *et al* 2011	Nested case-control; conducted within EPIC	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%]	Case/control 466 (225)	Male and female; 30-76 years; no occurrence of other malignant tumours preceding pancreatic cancer diagnosis	Mixed	Pancreatic	5.3 (mean) 0-13 (range)	Age; sex; smoking; BMI; diabetes status; fasting time
Wolphin *et al*	Nested case-control;	quintile 1 median [4.77%]	Case 449	Male and female;≥30 years; pancreatic	No diabetes	Pancreatic	10-26	Sex; age; BMI; smoking; race; fasting status;

2013	from 5 prospective studies[c]	quintile 2 median [4.95%] quintile 3 median [5.09%] quintile 4 median [5.24%] quintile 5 median [5.50%]	(128) Control 982 (288)	adenocarcinoma cases diagnosed through 2008 with available plasma and no prior cancer (except non-melanoma skin); controls without cancer at case patient's diagnosis			(range)	fasting time
Ikeda *et al* 2009	Cohort; from 1988 screening survey in Hisayama, Japan	4 groups of baseline data with 1% intervals [≤4.9, 5.0-5.9, 6.0-6.9 and ≥7.0%]	2,603 (1,070)	Male and female; ≥40 years; no prior history of gastrectomy or gastric cancer	Mixed	Gastric	14 (mean)	Age; sex; *Helicobacter pylori* seropositivity; history of peptic ulcer disease; BMI; total serum cholesterol; alcohol; smoking
Hsu *et al* 2012	Cohort; from a voluntary health check-up programme	According to status of colorectal neoplasia (any/high-risk/none)	2,776 (1,506)	Male and female; 18-86 years; no participants whose colonoscopy failed cecal intubation	Mixed	Colorectal	2 (mean)	Age; sex; BMI; smoking; alcohol; diabetes status; FPG; physical activity; LDL/HDL; family history
Khaw *et al* 2004	Cohort; from EPIC-Norfolk study	Known diabetes, likely undiagnosed diabetes [≥7%] and 3 groups of baseline with 1% intervals [<5.0, 5.0-5.9 and 6.0-6.9%]	9,605 (4,445)	Male and female; 45-79 years; available HbA_{1c} measurement; no prevalent cancer at baseline survey	Mixed	Colorectal	6 (mean)	Age; sex; BMI; smoking
Rinaldi *et al* 2008	Nested case-control; conducted within EPIC	Quintiles of baseline data [≤5.4, 5.4-5.6, 5.6-5.8, 5.8-6.1 and >6.1%]	Colon case/control 644 (342) Rectum case/control 382 (219)	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	Mixed	Colorectal	3-10 (range)	Age; sex; menopausal status; waist to hip ratio; alcohol; diabetes status; fasting status; follow-up time
Platz *et al* 1999	Nested case-control; conducted within the Nurses' Health Study	Tertiles of baseline data (tertile 1 median [5.2%], tertile 2 median [5.5%], tertile 3 median [5.8%]	Cancer case/control 79 (0) / 156 (0) DA case/control 201 (0)	Female only; 30-55 years; controls who supplied blood sample in 1989-90 and were free of diagnosed cancer (except non-melanoma skin); cases who received colorectal cancer diagnosis after date of blood return and through 31 May 1994	No diabetes	Colorectal	8 (mean)	Age; weight; BMI; physical activity; smoking; alcohol; red meat intake; folic acid; methionine; aspirin use; PM hormone use; fasting status
Saydah *et al* 2003	Nested case control; conducted within CLUE II cohort	Quartiles of baseline data (quartile cut points = 5.38, 5.54 and 5.78%)	Case 173 (NA) Control 346 (NA)	Male and female; cases whose colorectal cancers diagnosed after date of blood draw, through December 2000, and did not have a prior cancer diagnosis (except non-melanoma skin). Controls who did not have cancer diagnosis through December 2000	No diabetes	Colorectal	11 (mean)	Age; sex; race; date of blood draw; time since last meal; other circulating markers included in study[b]
Lin *et al* 2005	Cohort; from the Women's Health Study	Quartiles of baseline data [2.3-4.8, >4.8-5.0, >5.0-5.2 and ≥5.2%]	27,110 (0)	Female only; ≥45 years; free of cancer and cardiovascular disease at time of enrolment in 1993	No diabetes	Colorectal	10 (mean)	Age; RTA; BMI; family history; history of colon polyps; physical activity; smoking; red meat intake; alcohol; multivitamin use; menopausal status; PM hormone use
Lin *et al*	Cohort; from the	Quintiles of baseline data	27,110 (0)	Female only; ≥45 years; free of	No diabetes	Breast	10 (mean)	Age; RTA; BMI; family history; history

2006	Women's Health Study	[≤4.80, >4.80-4.94, >4.94-5.07, >5.07-5.25 and >5.25%], 5 groups of clinically-relevant cut-offs [<5.0, 5.0-<5.5, 5.5-<6.0, 6.0-<6.5 and ≥6.5%]		cancer and cardiovascular disease at time of enrolment in 1993				of benign breast disease; physical activity; alcohol; age at menarche/first birth; menopausal status; PM hormone use

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. [b] 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 HbA_{1c} in relation to all cancers.

Study	Subject Groups	Hazard Ratio (95% Confidence Interval) for HbA_{1c} Categorisations										
		≤5.0%	5.0-5.6%	≤5.5%	5.5-5.9%	≥5.7%	6.0-6.4%	≥6.5%	≤58 mmol/ mol	>58 mmol/mol	Diabetes	Overall
Hsu *et al.* (2013)	Male	-	-	-	-	-	-	-	-	-	-	1.24(0.90-1.70)
	Female	-	-	-	-	-	-	-	-	-	-	0.97(0.57-1.65)
Jonasson *et al.* (2012)	All	-	-	-	-	-	-	-	1	1.02 (0.95-1.09)	-	-
Joshu *et al*. (2012)	Male incidence*	1.04 (0.85-1.27)	1	-	-	1.08(0.95-1.22)	-	-	-	-	0.85(0.69-1.05)	-
	*Minus prostate	1.16 (0.90-1.50)	1	-	-	1.11(0.95-1.31)	-	-	-	-	0.96(0.74-1.24) 0.92(0.66-1.30)	-
	Male mortality*	0.97 (0.67-1.40)	1	-	-	1.08(0.87-1.33)	-	-	-	-	0.92(0.65-1.30)	-
	*Minus prostate	0.89 (0.60-1.32)	1	-	-	1.01(0.80-1.26)	-	-	-	-	1.30(1.06-1.60) 1.96(1.40-2.76)	-
	Female incidence	1.27 (1.02-1.58)	1	-	-	1.24(1.07-1.44)	-	-	-	-		-
	Female mortality	1.82 (1.25-2.64)	1	-	-	1.58(1.23-2.05)	-	-	-	-		-
Nakanishi *et al.* (2005)	All	-	-	1	1.10(0.77-1.56)	-	1.30(0.85-2.00)	1.70(1.02-2.82)	-	-	1.82(1.20-2.76)	-

Study	Subject Groups	Hazard Ratio (95% Confidence Interval) for HbA_{1c} Categorisations										
		<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
Parekh *et al.* (2010)	All	-	-	-	-	-	-	-	-	-	-	-	1.22(0.96-1.55)
Saydah *et al.* (2009)	All	-	-	-	1	-	0.73 (0.5-1.1)	-	0.93 (0.4-2.2)	-	-	2.64 (1.2-6.0)	-
	Diabetes	-	-	-	1	-	0.20(0.05-0.90)	-	0.43(0.08-2.28)	-	-	1.04(0.25-4.24) 0.8 (0.3-2.5)	-
	No diabetes	-	-	-	1	-	0.8 (0.6-1.2)	-	0.6 (0.1-	-	-		-

									2.3)				
Silbernagel *et al.* (2011)	All	2.03 (0.76-5.40)	0.82 (0.39-1.72)	1	-	0.93(0.50-1.74)	-	1.85 (0.98-3.48)	-	-	1.67 (0.46-6.11)	-	-
Travier *et al.* (2007)	All	-	-	-	-	-	1.40(1.11-1.76)	-	-	1.09 (0.80-1.48)	-	-	-

Appendix 1. Embase/Medline search strategy

1. neoplasm/

2. "neoplasm*".ti.

3. "cancer*".ti.

4. "tumo?r*".ti.

5. "malignan*".ti.

6. "carcinogen*".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 resistan*".ti,ab.

14. "insulin insensitiv*".ti,ab.

15. "insulin dependen*".ti,ab.

16. "noninsulin dependen*".ti,ab.

17. "non-insulin dependen*".ti,ab.

18. "hyperinsulin?emi*".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/

21. "glucose".ti,ab.

22. "glyc?emi*".ti,ab.

23. "hyperglyc?emi*".ti,ab.

24. 20 or 21 or 22 or 23

25. glycosylated hemoglobin/ or diabetes mellitus/

26. "a1c".ti.

27. "hba1c".ti.

28. "glyc* h?emoglobin".ti.

29. "glycoh?emoglobin".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.

36. "relationship*".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