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Does cancer risk increase with HbA_{1c}, independent of diabetes?

J C de Beer[1] and L Liebenberg*[,1,2]

[1]Center for Research and Continued Engineering Development, North-West University (Pretoria Campus), Suite No. 91, Private Bag X30, Lynnwood Ridge, Pretoria 0040, South Africa and [2]TEMM International (Pty) Ltd, Pretoria, South Africa

Background: The risks for several cancer types are increased in people with diabetes. Hyperglycaemia, hyperinsulinaemia, inflammation and altered hormonal concentrations are common characteristics between the two diseases and can all be linked to hyperglycaemia.

Methods: Here, we use glycated haemoglobin (HbA_{1c}) as a biomarker for chronic hyperglycaemia. We explore whether cancer risk increases with HbA_{1c}, independent of diabetes, and, therefore, if risk is already increased below the diabetic HbA_{1c} range, by analysing data from current studies linking HbA_{1c} to risk of several cancer types.

Results: The data reveal that chronic hyperglycaemia correlates with increased cancer risk for a number of cancers, except prostate cancer. Evidence is also provided that risk is already increased in the pre-diabetic and normal ranges for several cancers.

Conclusions: These results merit urgent investigation into the risks and advantages of updating recommendations for stricter glycaemic control in diabetic and non-diabetic subjects, as this could help reduce the risk of cancer incidence and mortality.

People with established diabetes have an increased risk of developing certain cancer types compared with non-diabetics; the strongest associations are seen for endometrial, liver and pancreatic cancer, followed by kidney, oesophageal, colorectal, breast and bladder cancer, and leukaemia (Giovannucci *et al*, 2010; Habib and Rojna, 2013). It is, however, not clear whether hyperglycaemia, a hallmark of diabetes, correlates with increased cancer risk *independent of diabetes*. If such an association exists, then the cancer risk in persons with glucose levels lower than that required to diagnose diabetes might already be increased. This would have important diagnostic and therapeutic ramifications, which we investigate here.

Research surrounding the increasing prevalence of cancer and diabetes (Mathers and Loncar, 2006; Giovannucci *et al*, 2010; World Health Organization, 2010; Wagner and Brath, 2012) has established direct pathogenetic commonalities between these two chronic diseases. These include hyperinsulinaemia, hyperglycaemia, inflammation and altered concentrations of endogenous hormones.

The association of most cancers and diabetes with chronic inflammation (Pollak, 2012; Coussens *et al*, 2013) and the direct link between increased inflammatory signalling and high blood glucose levels in cancer models (Habib and Rojna, 2013) support the possibility that chronic hyperglycaemia may have a pivotal role in cancer risk in humans. Increased production of endogenous hormones can also be indirectly linked to hyperglycaemia via hyperinsulinaemia and obesity, and, therefore, also to diabetes and cancer risk (Montaruli *et al*, 2012; Patterson *et al*, 2013; Robien *et al*, 2013). Chronic hyperglycaemia in diabetes patients seems to be directly linked with the ubiquitous reliance of most cancer cells on high glucose flux (Hanahan and Weinberg, 2011; Mathews and Liebenberg, 2013). Onodera *et al* (2014) found that an increase in glucose uptake can activate oncogenic pathways in breast cells. This could potentially provide another pathway by which hyperglycaemia increases cancer incidence risk.

Chronic hyperglycaemia may be evaluated by measuring glycated haemoglobin (HbA_{1c}) (American Diabetes Association, 2013), a biomarker of the average blood glucose concentration for a prolonged period of time (Travier *et al*, 2007; Habib and Rojna, 2013). Importantly, HbA_{1c} may also be a good indicator of metabolic processes influencing levels of insulin (Saydah *et al*, 2003)

*Correspondence: Professor L Liebenberg; E-mail: lliebenberg@researchtoolbox.com

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or insulin-like growth factors, important for cancer pathogenesis (Habib and Rojna, 2013).

Most studies focus on the association between cancer risk and diabetes. This approach, however, does not provide evidence for the potential causal links between the two diseases (Giovannucci *et al*, 2010).

One study (Pisani, 2008) performed a meta-analysis on epidemiological studies linking hyperglycaemia and risk for colorectal and pancreatic cancers. The researcher only assessed risk in the highest compared with the lowest categories of exposure. Another study (Johnson and Bowker, 2011) performed a meta-analysis on the impact of glycaemic control in type 2 diabetic patients and found no decrease in cancer risk with increased glycaemic control. This meta-analysis may have been influenced by confounding factors such as insulin usage, which could increase cancer risk (Pollak, 2012). Habib and Rojna (2013) reviewed some of the most important studies on the association between cancer risk and hyperglycaemia. They, however, did not attempt to consolidate the evidence per cancer type or provide a dose–response relation.

No meta-analysis has yet been published that consolidates risk of different types of cancers with different HbA_{1c} ranges, including glycaemic levels lower than that associated with diabetes. If cancer risk is lower at low HbA_{1c} levels, then the incidence of cancer in the diabetic and non-diabetic populations could potentially be lowered by decreasing glucose levels. This could be achieved by means of appropriate lifestyle or therapeutic interventions, and by imposing stricter recommendations for glycaemic control.

Here, we perform dose–response meta-analyses on the current published evidence regarding HbA_{1c} levels and risk of various cancers. This *post hoc* analysis attempts to establish whether cancer risk is already elevated in normal and pre-diabetic HbA_{1c} ranges. The overall goal is to determine whether HbA_{1c} concentrations can effectively quantify cancer risk *independent of diabetes*.

MATERIALS AND METHODS

Study selection. Only English-language articles were included. Studies from 1960 to the present (date last searched – 9 January 2014) were included in the search. Articles using the following risk measures were included: relative risk (RR), odds ratio (OR) or hazard ratio (HR). For studies to be included in the quantitative meta-analysis, they had to provide risk data for at least three HbA_{1c} levels. Literature searches were performed using Science Direct and Scopus to identify articles that relate HbA_{1c} to the risk of cancer incidence (primary or recurrence) or mortality. More articles were identified from the reference lists of surveyed articles.

Search terms included a number of MeSH terms and were combinations of the following: ('cancer' OR 'malignancy' OR 'tumor' OR 'tumour' OR 'neoplasm' OR 'neoplasia') AND ('hemoglobin a1c' OR 'hba1c' OR 'glycated hemoglobin' OR 'glycosylated hemoglobin' OR 'a1c' OR 'haemoglobin a1c' OR 'glycated haemoglobin' OR 'glycosylated haemoglobin' OR 'glycohemoglobin a' OR 'glycohaemoglobin a') in the title of the study.

The trends adjusted for the most confounding variables were used, where sufficient information was available on that trend. This was done so that the effects of most of the potential confounders could be adjusted for. This may, however, have increased the heterogeneity between studies, as not all studies adjusted for the same confounders. Only studies providing data on specific cancer types were included (not studies referring to cancer in general).

It was assumed that all studies used the National Glycohemoglobin Standardization Program (NGSP) HbA_{1c} reference, unless explicitly stated otherwise in a specific study. Suitable conversion to the NGSP reference was performed for three studies (Stocks *et al*, 2007, 2008; Cust *et al*, 2009) that used the Swedish monoS standard, using the relation NGSP (%) = (monoS + 0.8925)/0.9718. Using the NGSP reference, 'diabetes' is deemed to exist at HbA_{1c} levels greater than 6.5% (American Diabetes Association, 2013); 'pre-diabetes' if HbA_{1c} levels are between 5.7% and 6.4% (American Diabetes Association, 2013). The 'normal glycaemic' range is taken to span from ~4–5.7% (American Diabetes Association, 2013).

Data extraction. The following data were extracted from the studies: reference details, number of cases per HbA_{1c} level for OR, RR and HR, number of controls per HbA_{1c} level for OR, total number of persons per HbA_{1c} level for RR, number of person-years per HbA_{1c} level for HR, gender, cancer site, whether the risk was measured in RR, OR or HR, the risk per HbA_{1c} range, HbA_{1c} range or level and the 95% confidence intervals (CIs) per HbA_{1c} level. Additional information was obtained from the authors of two studies to be able to include these studies in the quantitative analysis.

Statistical analyses. When a range of HbA_{1c} values was provided, a single value was chosen per HbA_{1c} category using method 1 in Hartemink *et al* (2006). It is acknowledged that the method that is used to select a single value per dose–response category could potentially affect the outcome (Hartemink *et al*, 2006). The method works as follows. Where a range was specified for a dose, the midpoint of the range was selected as the point representing that range; where an open-ended range was specified, the dose for the lower open-ended range was calculated by subtracting half of the width of the second lowest range from the lowest value specified (the top value of the bottom open-ended range) (Hartemink *et al*, 2006); the dose for the upper open-ended range was calculated by adding the width of the second highest range to the highest value specified (bottom value of the upper open-ended range) (Hartemink *et al*, 2006).

Dose–response meta-analyses were performed per cancer type and for cancer incidence and mortality separately using the *dosresmeta* R package (Crippa, 2013; R Core Team, 2013). This is the R-equivalent of the *GLST* Stata-module developed by Orsini *et al* (2006, 2012).

Risk estimates were transformed using the natural logarithm (*ln*). The reference HbA_{1c} level per study was subtracted from each HbA_{1c} level in the study, resulting in a model fitted through the origin (i.e., no intercept).

Linear and restricted cubic spline (RCS) models (with three knots, located at the 10th, 50th and 90th percentiles of the data) of the natural logarithm-transformed risk estimates were developed using random-effects meta-analysis methods, to incorporate heterogeneity. If, for a certain cancer type, only a single study was available, and that study had fewer than six exposure levels, only a linear model was fitted, as the function that develops the RCS models requires at least six data points. The graphical displays of the statistically significant models obtained during the analyses were referenced to the lowest HbA_{1c} level for all the studies included in a model.

To assess non-linearity, the null hypothesis that the coefficient of the second spline is zero was tested. A significance level of $P < 0.05$ was used.

Lack of goodness of fit and heterogeneity was determined by assessing whether the *P*-value from the chi-squared test was smaller than 0.1. I^2 values were determined for each model.

Combined and separate models for RR, OR and HR were developed to assess whether the risk measure, and in effect the type of study, could influence the results.

RESULTS

The study selection process is illustrated in Figure 1. Thirty-six studies were identified through database searching. Thirty-two studies were identified from the reference lists of surveyed articles. Two duplicate studies were removed. The remaining 66 records were screened. Ten articles were not relevant to the study aims (e.g., they did not address cancer). For six of the records, full-text articles were not available or referred to conference abstracts. Fifty full-text articles were assessed. Of these, 18 articles were excluded as they either did not provide data on a specific cancer type (9 studies), they did not provide data on cancer (2 studies) or they used glycaemic measures other than HbA_{1c} (7 studies). Thirty-two studies remained that were relevant for the qualitative synthesis. Eighteen studies were excluded from the quantitative analysis as they did not provide information on cancer incidence or mortality, but rather on stage or grade of cancer (4 studies), they provided information on cancer pre-cursors, such as adenoma, adenomatous polyps or benign neoplasia (5 studies), they did not provide data on RR, OR or HR (2 studies), they specified fewer than three HbA_{1c} ranges (4 studies), the study population was already included in another study (2 studies) or enough information on the number of cases or person-years per HbA_{1c} level was not available (1 study). Fourteen studies remained that were included in the quantitative meta-analyses. Of these, thirteen studies provided data on cancer incidence only, while one study provided data on cancer incidence as well as mortality (Joshu *et al*, 2012).

The statistically significant or border-line significant models that were obtained during the dose–response analyses are shown in Figures 2–8. The plots are referenced to the lowest HbA_{1c} level in the studies included in each model.

Female genital cancer

Quantitative analysis. Two studies (Travier *et al*, 2007; Miao Jonasson *et al*, 2012) on female genital cancer incidence were included in the quantitative analysis. Both used the HR as a risk measure. No statistically significant models were obtained in the analysis ($P = 0.2961$ for increasing log-linear model, $P_{non\text{-}linearity} = 0.3274$ for increasing-decreasing RCS model).

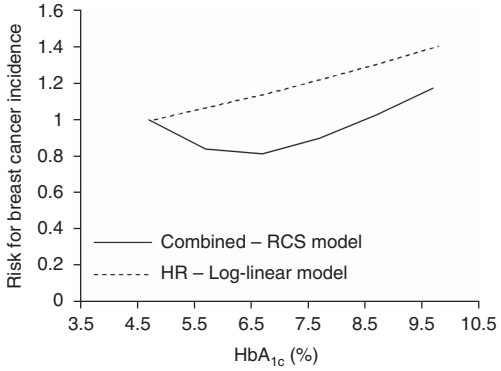

Figure 2. Relationship between risk for breast cancer incidence and HbA_{1c}.

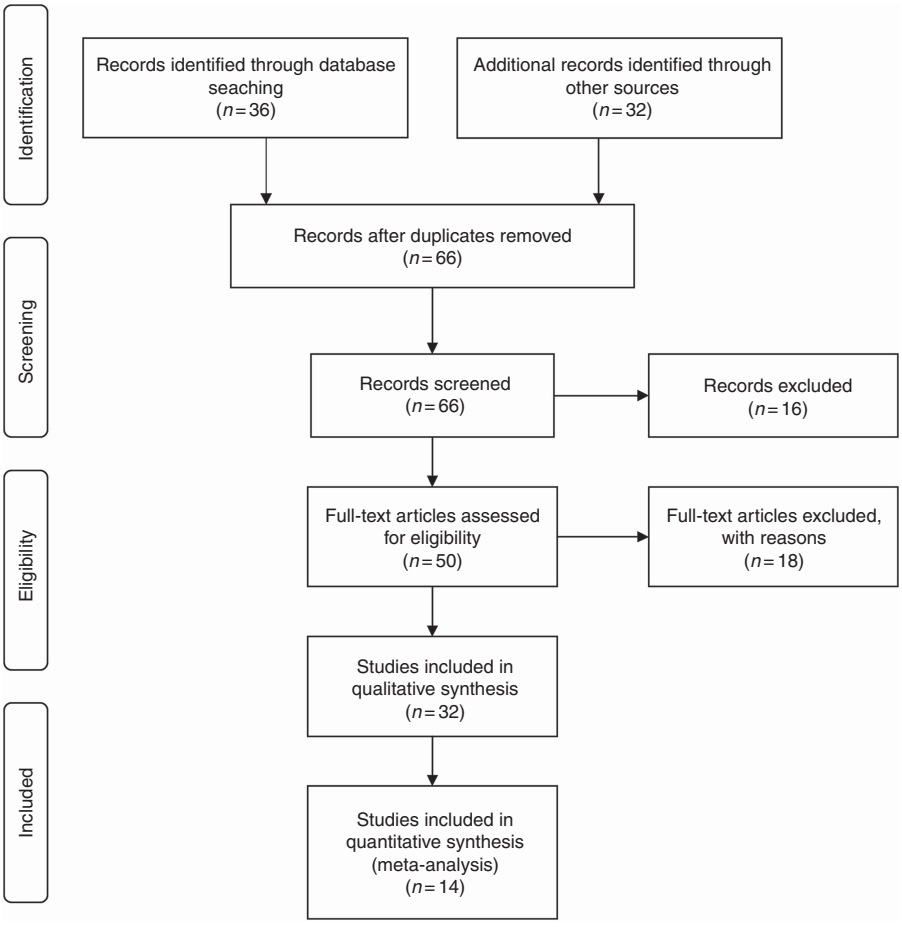

Figure 1. Flow diagram showing the study selection process (Moher *et al*, 2009).

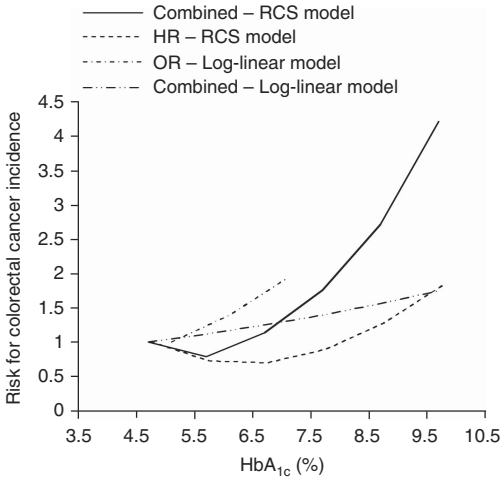

Figure 3. Relationship between risk for colorectal cancer incidence and HbA_{1c}.

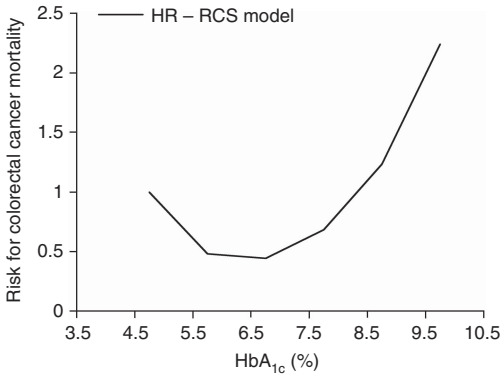

Figure 4. Relationship between risk for colorectal cancer mortality and HbA_{1c}.

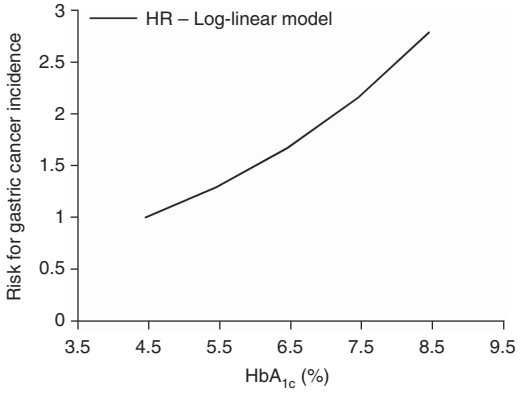

Figure 5. Relationship between risk for gastric cancer incidence and HbA_{1c}.

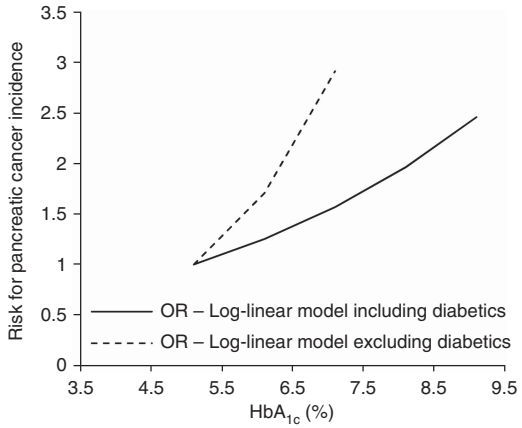

Figure 6. Relationship between risk for pancreatic cancer incidence and HbA_{1c}.

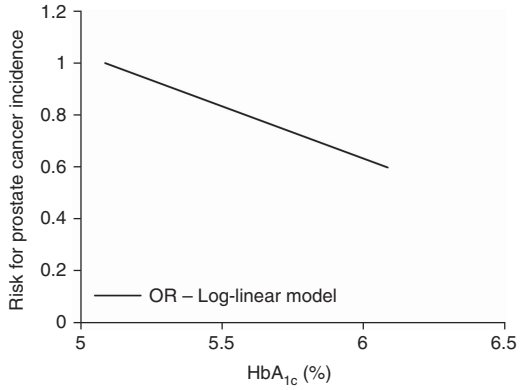

Figure 7. Relationship between risk for prostate cancer incidence and HbA_{1c}.

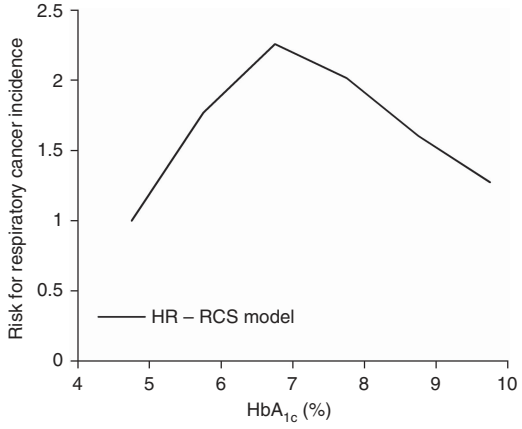

Figure 8. Relationship between risk for respiratory cancer incidence (including lung cancer) and HbA_{1c}.

Qualitative analysis. Travier *et al* (2007) found a statistically significant (HR = 2.84, 95% CI = 1.35–5.98) increased risk in the 6% to 7% HbA_{1c} range, compared with the reference risk in the <6% range. The risk was also increased in the >7% range, but not significantly (HR = 2.01, 95% CI = 0.69–5.89). Miao Jonasson *et al* (2012) found no statistically significant associations for cancer risk in the baseline (slightly decreased HRs) or updated mean (slightly increased HRs) HbA_{1c} groups for a group of people with type 2 diabetes. Levran *et al* (1984) revealed an increased number of endometrial cancer cases with HbA_{1c} above 6.5%, as compared with below 6.5%. The distribution of controls was more even across all of the HbA_{1c} ranges. They, however, did not provide risk measures for comparison. Levitan *et al* (2008) found no statistically significant trend ($P = 0.53$) for uterine or ovarian cancer mortality risk. Stevens *et al* (2012) found some evidence of increased endometrial cancer stage with increasing HbA_{1c}, but this was not statistically significant ($P = 0.07$).

Liver cancer

Quantitative analysis. One study (Travier *et al*, 2007) was included in the quantitative analysis for liver cancer incidence. The increasing log-linear HR model obtained from this study was not statistically significant ($P = 0.5737$).

Qualitative analysis. Two studies that were excluded from the quantitative analysis as they did not provide enough HbA_{1c} levels (Donadon *et al*, 2010; Kaneda *et al*, 2012) found changes in hepatocellular carcinoma (HCC) risk as HbA_{1c} increased. Kaneda *et al* (2012) found a large risk (HR = 3.551, $P = 0.03$) for HCC recurrence as the HbA_{1c} level increased above 6.5% for patients with diabetes. Donadon *et al* (2010) found that the OR for HCC increased by 1.508 for each percentage increase in HbA_{1c} for type 2 diabetic patients compared with controls with liver cirrhosis ($P = 0.0005$). Compared with the normal control group, the OR increased by 1.265 per 1% increase in HbA_{1c} – this was, however, not statistically significant ($P = 0.1172$).

Pancreatic cancer

Quantitative analysis. One study (Grote *et al*, 2011) was included in the quantitative analysis. The OR increasing log-linear model, including diabetic participants, was statistically significant ($P = 0.0049$). The increasing log-linear model, excluding diabetic participants, was also statistically significant ($P = 0.0148$).

Qualitative analysis. Another study (Levitan *et al*, 2008) found no statistically significant trends for pancreatic cancer mortality ($P = 0.40$), with decreased risk (RR = 0.86) in the lower normal HbA_{1c} range of 4.88–5.08% and increased risk (RR = 1.36) in the upper normal range (5.09–5.59%), compared with the reference group (2.27–4.87%).

Prostate cancer

Quantitative analysis. Four studies were included in the quantitative analysis for prostate cancer incidence (Stocks *et al*, 2007; Travier *et al*, 2007; Joshu *et al*, 2012; Miao Jonasson *et al*, 2012), while only one study (Joshu *et al*, 2012) was included in the analysis for mortality. The OR decreasing log-linear model obtained from the Stocks *et al* (2007) study was border-line statistically significant ($P = 0.0596$), while none of the other models were statistically significant ($P = 0.1114$ for the decreasing combined log-linear model, $P = 0.1783$ for the decreasing HR log-linear model, $P = 0.6502$ for the decreasing HR mortality log-linear model).

Qualitative analysis. Rusu *et al* (2011) found that HbA_{1c} was statistically significantly ($P = 0.0001$) lower in patients with prostate cancer ($HbA_{1c} = 6\%$) than in those without cancer ($HbA_{1c} = 7.1\%$) or in patients with benign prostatic hyperplasia ($HbA_{1c} = 7.4\%$). No adjustments were made for confounders in this study.

Kim *et al* (2010a) revealed statistically significant ($P = 0.001$) increased risks for higher pathological Gleason score cancer with increasing HbA_{1c} level in a population of diabetic men. Hong *et al* (2009) found a significantly higher rate of high pathological Gleason score cancers ($P = 0.005$) and extraprostatic extension ($P = 0.043$) in diabetic men with HbA_{1c} levels $\geqslant 6.5\%$ than in those with HbA_{1c} levels lower than 6.5%.

Colorectal cancer

Quantitative analysis. Nine studies presented data on colorectal cancer incidence. Two of these studies (Platz *et al*, 1999; Khaw *et al*, 2004) were excluded from the quantitative analysis as they provided data from the same cohorts as other studies already included. Seven studies remained that were included in the quantitative analysis (HR – Joshu *et al*, 2012; RR – Lin *et al*, 2005; OR – Rinaldi *et al*, 2008; OR – Saydah *et al*, 2003; OR – Stocks *et al*, 2008; HR – Travier *et al*, 2007; OR – Wei *et al*, 2005). One study also presented data on colorectal cancer mortality (HR – Joshu *et al*, 2012). The colorectal cancer incidence combined RCS model ($P_{non\text{-}linearity} = 0.0068$, $P_{heterogeneity} = 0.2046$, $I^2 = 21.4\%$) and HR RCS model ($P_{non\text{-}linearity} = 0.0261$, $P_{heterogeneity} = 0.8494$, $I^2 = 1\%$) both showed a decreased risk at lower HbA_{1c} levels followed by an increased risk at higher HbA_{1c} levels. The combined log-linear model ($P = 0.0325$, $P_{heterogeneity} = 0.1526$, $I^2 = 33.2\%$) and OR log-linear model ($P = 0.0072$, $P_{heterogeneity} = 0.2945$, $I^2 = 18.9\%$) both showed statistically significant increasing trends. The mortality RCS HR model was also statistically significant ($P_{non\text{-}linearity} = 0.0180$, $P_{heterogeneity} = 0.9849$, $I^2 = 1\%$), with decreasing risk at lower HbA_{1c} levels, and increasing risk at higher HbA_{1c} levels. The other models were not statistically significant ($P = 0.3089$ for increasing HR log-linear model, $P = 0.1486$ for OR RCS decreasing-increasing model, $P = 0.3942$ for decreasing RR log-linear model).

Qualitative analysis. Further to the results from the dose–response relation, Khaw *et al* (2004) found a significantly increased risk as HbA_{1c} increased in the combined ($P < 0.001$), men-only group ($P < 0.001$) and women-only group ($P = 0.03$). The risk in the women-only group was decreased in the 5–5.9% range (RR = 0.7), but increased above this range. Continuous analysis per 1% increase in HbA_{1c} revealed an increase of RR = 1.30 for the combined group ($P = 0.02$), RR = 1.35 for the men-only group ($P = 0.02$) and RR = 1.20 for the women-only group ($P = 0.26$). The authors found that the increased risk for colorectal cancer in diabetic patients was largely due to the increase in HbA_{1c} and not due to diabetes status. Platz *et al* (1999) and Siddiqui *et al* (2008a) found a significant increase in risk for advanced-stage colorectal cancer with higher HbA_{1c}levels ($P = 0.02$ and $P = 0.002$, respectively).

The risks for colorectal cancer pre-cursors (adenomatous and/or advanced adenomatous polyps) were significantly increased with increasing HbA_{1c} levels in diabetic and non-diabetic subjects (Siddiqui *et al*, 2008b; Kim *et al*, 2010b). Hsu *et al* (2012) found an increase of OR = 1.25 in colorectal neoplasia for each percentage increase in HbA_{1c} level for men and women ($P = 0.02$). HbA_{1c} was not statistically significantly associated with colorectal adenoma, distal colorectal adenoma or advanced adenoma in two studies (Wei *et al*, 2006; Yang *et al*, 2010).

Breast cancer

Quantitative analysis. Six studies on breast cancer incidence (HR – Joshu *et al*, 2012; HR – Miao Jonasson *et al*, 2012; HR – Travier *et al*, 2007; HR – Erickson *et al*, 2011; OR – Cust *et al*, 2009; RR – Lin *et al*, 2006) and one study on cancer mortality (HR – Joshu *et al*, 2012) were included in the quantitative analysis. A statistically significant RCS model for combined risk ($P_{non\text{-}linearity} = 0.0260$, $P_{heterogeneity} = 0.6457$, $I^2 = 1\%$), which showed decreased risk at lower HbA_{1c} levels and increased risk at higher HbA_{1c} levels, as well as a border-line statistically significant increasing log-linear model for HR ($P = 0.0783$, $P_{heterogeneity} = 0.6948$, $I^2 = 1\%$) was obtained. The other models were all statistically non-significant ($P = 0.2329$ for increasing combined log-linear model, $P_{non\text{-}linearity} = 0.3118$ for HR decreasing-increasing RCS model, $P = 0.2323$ for decreasing OR log-linear model, $P_{non\text{-}linearity} = 0.2844$ for increasing-decreasing RCS model, $P = 0.2007$ for decreasing RR log-linear model, $P = 0.1789$ for increasing HR log-linear mortality model).

Qualitative analysis. Two studies did not adjust for confounders and found contrasting results. Yadav *et al* (2012) observed that

HbA_{1c} increased in pre- and post-menopausal breast cancer cases. Contrarily, Nemesure *et al* (2009) found decreased HbA_{1c} in pre- and post-menopausal breast cancer cases.

Levitan *et al* (2008) found no statistically significant linear trend for breast cancer mortality with increasing HbA_{1c} level ($P = 0.23$).

Gastric cancer

Quantitative analysis. Two studies on gastric (stomach) cancer incidence were included in the quantitative analysis (HR – Ikeda *et al*, 2009; HR – Travier *et al*, 2007). The increasing log-linear trend obtained from these studies was statistically significant ($P = 0.0171$, $P_{heterogeneity} = 0.9439$, $I^2 = 1\%$).

Qualitative analysis. No additional studies were available for discussion.

Respiratory cancer, including lung cancer

Quantitative analysis. Two studies on respiratory or lung cancer incidence were included in the quantitative analysis (HR – Joshu *et al*, 2012; HR – Travier *et al*, 2007). The RCS model obtained from these studies was statistically significant ($P_{non\text{-}linearity} = 0.0353$, $P_{heterogeneity} = 0.1537$, $I^2 = 40.1\%$), with increasing risk at lower HbA_{1c} levels, and decreasing risk at higher HbA_{1c} levels. Neither the increasing log-linear HR mortality model ($P = 0.1573$), nor the increasing-decreasing RCS HR mortality model from the Joshu *et al* (2012) study was statistically significant ($P_{non\text{-}linearity} = 0.2996$).

Qualitative analysis. The Levitan *et al* (2008) study found increasing lung cancer mortality risk with increased HbA_{1c} level, but the linear trend was not statistically significant ($P = 0.22$).

Other cancers

Quantitative analysis. Results from other cancer types investigated were not statistically significant. These cancer types included lymphoma and leukaemia ($P = 0.5427$ for the decreasing log-linear model), as well as melanoma ($P = 0.5514$ for the increasing log-linear model). One study (HR – Travier *et al*, 2007) presented results on each type of cancer.

Qualitative analysis. Levitan *et al* (2008) found an increase in RR for lymphoma or leukaemia mortality as HbA_{1c} increased. This was, however, not statistically significant ($P = 0.18$ for a linear trend).

DISCUSSION

Quantitative analysis. Results from the dose–response meta-analysis revealed the following statistically significant or borderline significant results:

- Increasing log-linear models for breast cancer (HR), colorectal cancer (OR and combined), gastric cancer (HR) and pancreatic cancer (OR).
- Decreasing log-linear model for prostate cancer (OR).
- Increased risk above 8.5% for breast cancer (combined) and colorectal cancer (HR for incidence and mortality), above 6.5% for colorectal cancer (combined) and increasing trend up to 7% and decreasing risk above 7% for respiratory cancer (HR).

The following relations were not statistically significant:

- Increasing log-linear models for female genital cancer (HR), liver cancer (HR), colorectal cancer (HR), breast cancer (combined and HR mortality), respiratory (HR) and melanoma (HR).
- Decreasing log-linear models for prostate cancer (combined, HR and HR mortality), colorectal (RR), breast (OR and RR) and lymphoma and leukaemia (HR).

Qualitative analysis. The qualitative analysis revealed some additional information. Cancer stage for female genital cancer was found to be non-significantly increased with increasing HbA_{1c}. Liver cancer incidence increased significantly for diabetics and in patients with HbA_{1c} above 6.5%. A significantly higher rate of high-grade prostatic tumours and extraprostatic extension was present with increasing HbA_{1c}. For colorectal cancer, advanced stage colorectal cancer incidence and pre-cursor incidence increased with increasing HbA_{1c} level. Respiratory/lung cancer, as well as lymphoma and leukaemia, mortality was non-significantly increased with increasing HbA_{1c} level.

CONCLUSIONS

Our study corroborates that cancer sites should be investigated separately, as the observed trends differ between cancer sites. Evidence is provided that indicates:

- Cancer incidence risk is already increased in the pre-diabetic and normal ranges for colorectal, gastric, pancreatic and respiratory cancers, although the results are not the same for all risk measures.
- Cancer incidence is higher at HbA_{1c} levels in the diabetic range for colorectal, gastric, pancreatic, breast and liver cancers.

There is possible evidence for:

- Decreased risk of prostate cancer incidence with increasing HbA_{1c} level, and already in the pre-diabetic and normal ranges.
- Increased risk of breast cancer incidence in the diabetic, pre-diabetic and normal ranges.

Our study reveals that chronic hyperglycaemia, as quantified by HbA_{1c} levels, correlates with increased cancer risk in colorectal, gastric, liver and pancreatic cancers, and possibly breast cancer, while correlating with decreased prostate cancer risk. The relations for other cancer types investigated are not statistically significant. It is also clear that there is increased risk for higher cancer stage/grade and cancer pre-cursor incidence for some cancer types with increasing HbA_{1c} level.

The near-linear association of HbA_{1c} levels with risk of several cancers supports the conjecture that it might be possible to use HbA_{1c} as an independent metabolic biomarker for cancer risk in diabetic or non-diabetic persons. Significantly, the study also provides preliminary evidence for an already increased cancer risk in the normal and pre-diabetic categories for a number of cancers. The incidence of cancer in the diabetic and non-diabetic populations could, therefore, potentially be reduced by decreasing glucose levels. This could be achieved by means of appropriate lifestyle or therapeutic interventions, and by imposing stricter recommendations for glycaemic control (Krone and Ely, 2005).

The risks and advantages of updating recommendations for stricter glycaemic control (in diabetic and non-diabetic subjects) merit urgent investigation. Indications are that such stricter glycaemic control measures could help reduce the risk for cancer incidence and mortality (Krone and Ely, 2005) as long as care is taken to ensure that stricter glycaemic control does not result in hypoglycaemia, which may have other deleterious effects.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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