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Influence of dietary insulin scores on survival in colorectal cancer patients

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Background: Although hyperinsulinemia is hypothesised to be involved in colorectal carcinogenesis, it remains unclear whether a diet inducing an elevated insulin response influences colorectal cancer (CRC) survival.

Methods: We examined the association of post-diagnosis dietary insulin scores with survival among 2006 patients from two large prospective cohorts who were diagnosed with CRC from 1976 to 2010. Dietary insulin load was calculated as a function of the food insulin index. Dietary insulin index was calculated by dividing insulin load by total energy intake. Cox proportional hazards models were used to calculate hazard ratios (HRs) for CRC-specific mortality and overall mortality, adjusted for other risk factors for cancer survival.

Results: The adjusted HRs for CRC-specific mortality comparing the highest to the lowest quintiles were 1.82 (95% CI: 1.20–2.75, $P_{trend} = 0.006$) for dietary insulin load and 1.66 (95% CI: 1.10–2.50, $P_{trend} = 0.004$) for dietary insulin index. We also observed an increased risk for overall mortality, with adjusted HRs of 1.33 (95% CI: 1.03–1.72, $P_{trend} = 0.03$) for dietary insulin load and 1.32 (95% CI: 1.02–1.71, $P_{trend} = 0.02$) for dietary insulin index, comparing extreme quintiles. The increase in CRC-specific mortality associated with higher dietary insulin scores was more apparent among patients with body mass index (BMI) $\geqslant 25\,kg\,m^{-2}$ than BMI $< 25\,kg\,m^{-2}$ ($P_{interaction} = 0.01$).

Conclusions: Higher dietary insulin scores after CRC diagnosis were associated with a statistically significant increase in CRC-specific and overall mortality.

Hyperinsulinemia and insulin resistance are hypothesised to play important roles in the development of colorectal cancer (CRC). Many of the established risk factors for CRC, including obesity (Giovannucci, 2003a; Moghaddam *et al*, 2007), sedentary lifestyle (Samad *et al*, 2005) and type 2 diabetes mellitus (Larsson *et al*, 2005), are characterised by hyperinsulinemia and insulin resistance. Higher circulating insulin and C-peptide (a marker of insulin resistance and long-term insulin secretion) have also been associated with an increased risk of CRC in many studies (Schoen *et al*, 1999; Kaaks *et al*, 2000; Ma *et al*, 2004; Wei *et al*, 2005).

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Beyond cancer risk, increasing evidence indicates that the same host factors, including obesity (Meyerhardt *et al*, 2003), sedentary lifestyle (Meyerhardt *et al*, 2006a), and high intake of a Western pattern diet (Meyerhardt *et al*, 2007) are associated with an increased risk of recurrence or death among CRC patients.

The association between hyperinsulinemia and CRC suggests that a diet inducing an elevated insulin response may contribute to tumour growth. Dietary glycaemic load and dietary glycaemic index have been used to quantify the influence of carbohydrate intake on blood glucose. A recent study showed that higher dietary glycaemic load, but not dietary glycaemic index, was associated with an increased risk of recurrence and death in stage III colon cancer patients (Meyerhardt *et al*, 2012). However, dietary glycaemic scores, which only reflect carbohydrate intake, may be suboptimal indicators of insulin response since protein and fat intake can also increase insulin secretion.

A novel insulin score was therefore developed to quantify postprandial insulin response for various food items, including those with low or no carbohydrate content (Holt *et al*, 1997). Using this new measure, the insulin response to overall diets, represented by dietary insulin load and dietary insulin index, can be calculated. In a validation study, dietary insulin index was strongly correlated with actual circulating insulin concentrations ($r = 0.78$, $P = 0.0016$), and led to a more accurate prediction of insulin demand evoked by composite meals than carbohydrate content or dietary glycaemic load (Bao *et al*, 2009).

In this study, we used these two dietary insulin scores to investigate whether diets high in foods that increase postprandial insulin concentrations influence survival among CRC patients from two large prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS). We also examined the association of dietary insulin scores with CRC survival across strata of relevant biomarkers, including adiponectin (Chong *et al*, 2015), C-peptide (Wolpin *et al*, 2009), and insulin-like growth factor binding protein (IGFBP)-1 (Wolpin *et al*, 2009), among a subset of patients with plasma samples collected before cancer diagnosis.

MATERIALS AND METHODS

Study population. NHS was initiated in 1976 when 121 700 U.S. female nurses aged 30–55 years completed a mailed questionnaire describing demographics, lifestyle choices, and medical history (Colditz *et al*, 1997). HPFS was initiated in 1986 when 51 529 U.S. men aged 40–75 years working in health professions completed a mailed questionnaire on health-related behaviours and medical history (Rimm *et al*, 1991). Since then, participants have updated information through biennial follow-up questionnaires. All participants were enrolled at baseline. This study was approved by the Human Subjects Committee at the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and all participants provided informed consent.

Identification of study patients. NHS and HPFS participants with pathologically confirmed colorectal adenocarcinoma were identified after return of the baseline questionnaire (NHS: 1976; HPFS: 1986) through 2010. When a participant (or next of kin for decedents) reported a diagnosis of CRC during the previous two years on follow-up questionnaires, we asked permission to obtain hospital records and pathology reports. Blinded study physicians then reviewed these records and recorded information on important tumour characteristics. For nonrespondents, the National Death Index was used to discover deaths and ascertain any diagnosis of CRC that contributed to death or was a secondary diagnosis. We estimate that 96–97% of patients were identified through these methods (Giovannucci *et al*, 1994a,b). We excluded participants who had reported any cancer (other than nonmelanoma skin cancer) before CRC diagnosis, who had diabetes at CRC diagnosis (because diabetic patients usually limit intake of insulinogenic foods), and who died within three months of dietary assessment (to minimise bias by occult recurrence or impeding death).

Mortality assessment. Ascertainment of deaths included reporting by family or postal authorities, and interrogation of names of persistent nonresponders in the National Death Index (Sathiakumar *et al*, 1998). More than 98% of deaths have been identified by these methods (Stampfer *et al*, 1984). Cause of death was assigned by blinded physicians.

Dietary assessment. Dietary intake was obtained from NHS participants via validated semiquantitative food-frequency questionnaires (FFQs) in 1980, 1984, 1986, and every 4 years thereafter, and from HPFS participants every 4 years starting in 1986. Participants were asked to report their average frequency of intake over the preceding year for a specified serving size of each food. Individual nutrient intakes were calculated by multiplying the frequency of each food consumed by the nutrient content of the specified portion size, and then summing the contributions from all foods.

The insulin index value for each food item compares the postprandial plasma insulin response induced by that food relative to that of a reference food (glucose or white bread). Insulin index values for foods that appeared in the FFQ were obtained either from published estimates (31 foods) (Holt *et al*, 1997) or from direct testing of food items at the University of Sydney, Australia (73 foods; provided by Jennie Brand-Miller). U.S. food samples were shipped to the laboratory in Sydney for testing. The testing procedure has been described in detail previously (Bao *et al*, 2009): each person consumed a variety of test foods on separate days, with insulin measured every 15 min for 2 h after consumption. The food insulin index value was calculated by dividing the area under the insulin response curve for 1000 kJ of a test food by the area under the insulin response curve for 1000 kJ of the reference food. The insulin index value for each food represented the mean responses of 11–13 participants.

Using these insulin index values, we calculated the average dietary insulin load for each participant by multiplying the insulin index value of each food by the total energy intake contributed by that food, and summing values for all food items reported:

$$\text{Dietary insulin load} = \sum \begin{bmatrix} \text{food insulin index} \times \text{energy content of food} \\ (\text{kcal/serving}) \times \text{frequency of consumption} \\ (\text{servings/day}) \end{bmatrix}$$

Each unit represents the equivalent insulin response generated by 1 kilocalorie of the reference food. The dietary insulin index for the overall diet, which is the weighted mean of the insulin index values for each of the component foods, was calculated by dividing insulin load by total energy intake:

$$\text{Dietary insulin index} = \text{dietary insulin load} \Big/ \sum \begin{bmatrix} \text{energy content of food(kcal/serving)} \\ \times \text{frequency of consumption} \\ (\text{servings/day}) \end{bmatrix}$$

Dietary insulin load and dietary insulin index were energy-adjusted by the residual method (Willett and Stampfer, 1986). The FFQ was found to be a reasonably accurate measure of a person's food intake (Salvini *et al*, 1989; Feskanich *et al*, 1993). For top food sources contributing to dietary insulin load, the Pearson

Table 1. Baseline characteristics among patients with colorectal cancer by quintile of post-diagnosis dietary insulin score

	Dietary insulin load					Dietary insulin index				
Characteristic	**Quintile 1**	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	**Quintile 1**	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**
No. of patients	401	404	400	402	399	400	401	402	402	401
Age at diagnosis, years, mean (s.d.)	66.9 (9.9)	67.1 (9.7)	66.4 (10.0)	66.7 (9.2)	68.8 (8.7)	66.7 (10.3)	67.0 (9.5)	66.2 (10.1)	67.5 (8.9)	68.6 (8.8)
Sex, No. (%)										
Female	262 (65.3)	266 (65.8)	262 (65.5)	264 (65.7)	260 (65.2)	261 (65.3)	264 (65.8)	263 (65.4)	263 (65.4)	263 (65.6)
Male	139 (34.7)	138 (34.2)	138 (34.5)	138 (34.3)	139 (34.8)	139 (34.8)	137 (34.2)	139 (34.6)	139 (34.6)	138 (34.4)
Race, No. (%)										
White	385 (96.0)	392 (97.0)	382 (95.5)	385 (95.8)	381 (95.5)	384 (96.0)	389 (97.0)	385 (95.8)	386 (96.0)	381 (95.0)
Black	4 (1.0)	3 (0.7)	9 (2.3)	4 (1.0)	3 (0.8)	4 (1.0)	3 (0.7)	7 (1.7)	5 (1.2)	4 (1.0)
Other	2 (0.5)	4 (1.0)	6 (1.5)	4 (1.0)	7 (1.8)	2 (0.5)	4 (1.0)	7 (1.7)	3 (0.7)	7 (1.7)
Unknown	10 (2.5)	5 (1.2)	3 (0.8)	9 (2.2)	8 (2.0)	10 (2.5)	5 (1.2)	3 (0.7)	8 (2.0)	9 (2.2)
Current smoker, No. (%)	47 (11.7)	38 (9.4)	23 (5.8)	18 (4.5)	15 (3.8)	47 (11.8)	35 (8.7)	25 (6.2)	18 (4.5)	16 (4.0)
Body mass index, kg m^{-2}, mean (s.d.)[a]	25.8 (4.3)	25.6 (4.5)	25.8 (4.7)	25.8 (4.5)	25.5 (4.6)	25.9 (4.3)	25.7 (4.5)	25.7 (4.8)	25.8 (4.5)	25.4 (4.5)
Physical activity, MET-h per week, median (range)[a]	11.2 (0–221.9)	10.1 (0–145.9)	10.9 (0–172.0)	9.6 (0–168.4)	9.8 (0–125.0)	11.2 (0–221.9)	10.2 (0–145.9)	10.4 (0–172.0)	10.1 (0–168.4)	9.7 (0–125.0)
Alcohol intake, g d^{-1}, median (range)	14.0 (0–88.5)	3.1 (0–76.8)	1.8 (0–65.0)	0.9 (0–41.4)	0 (0–47.0)	14.3 (0–88.5)	3.3 (0–63.9)	1.8 (0–65.0)	0.9 (0–41.4)	0 (0–47.0)
Vitamin D intake, IU d^{-1}, energy-adjusted, median (range)	488 (15–3179)	400 (29–2955)	444 (14–2635)	425 (29–2543)	523 (21–2436)	490 (15–3179)	398 (14–2955)	416 (29–2635)	446 (29–2543)	517 (21–2436)
Carbohydrate intake, g d^{-1}, energy-adjusted, median (range)	182 (49–317)	206 (116–339)	222 (143–352)	232 (146–335)	259 (194–394)	181 (49–317)	204 (111–349)	222 (143–352)	232 (146–348)	258 (172–394)
Protein intake, g d^{-1}, energy-adjusted, median (range)	74 (36–141)	76 (31–135)	74 (35–129)	73 (41–133)	70 (27–129)	74 (36–141)	75 (43–135)	74 (31–129)	72 (43–133)	69 (27–129)
Total fat intake, g d^{-1}, energy-adjusted, median (range)	66 (24–140)	63 (18–108)	59 (31–98)	55 (26–94)	47 (23–85)	66 (24–140)	63 (18–108)	59 (31–98)	56 (26–94)	47 (23–85)
Energy intake, kcal d^{-1}, median (range)	1716 (601–4004)	1705 (660–3993)	1749 (627–3838)	1729 (611–3761)	1655 (611–4194)	1713 (601–4004)	1722 (660–3993)	1747 (627–3838)	1722 (628–3770)	1649 (611–4194)
Stage, No. (%)										
I	142 (35.4)	134 (33.2)	109 (27.3)	132 (32.8)	119 (29.8)	141 (35.3)	139 (34.7)	111 (27.6)	126 (31.3)	119 (29.7)
II	111 (27.7)	103 (25.5)	118 (29.5)	122 (30.3)	114 (28.6)	109 (27.3)	103 (25.7)	116 (28.9)	128 (31.8)	112 (27.9)
III	85 (21.2)	92 (22.8)	103 (25.8)	84 (20.9)	91 (22.8)	89 (22.3)	85 (21.2)	103 (25.6)	83 (20.6)	95 (23.7)
IV	22 (5.5)	28 (6.9)	22 (5.5)	22 (5.5)	24 (6.0)	22 (5.5)	27 (6.7)	24 (6.0)	23 (5.7)	22 (5.5)
Unknown	41 (10.2)	47 (11.6)	48 (12.0)	42 (10.4)	51 (12.8)	39 (9.8)	47 (11.7)	48 (11.9)	42 (10.4)	53 (13.2)
Grade of tumour differentiation, No. (%)										
Well	167 (41.6)	175 (43.3)	154 (38.5)	166 (41.3)	169 (42.4)	166 (41.5)	168 (41.9)	153 (38.1)	177 (44.0)	167 (41.6)
Moderate	133 (33.2)	114 (28.2)	130 (32.5)	130 (32.3)	129 (32.3)	130 (32.5)	117 (29.2)	140 (34.8)	116 (28.9)	133 (33.2)
Poor	81 (20.2)	97 (24.0)	94 (23.5)	88 (21.9)	84 (21.1)	84 (21.0)	98 (24.4)	87 (21.6)	92 (22.9)	83 (20.7)
Unknown	20 (5.0)	18 (4.5)	22 (5.5)	18 (4.5)	17 (4.3)	20 (5.0)	18 (4.5)	22 (5.5)	17 (4.2)	18 (4.5)
Location of primary tumour, No. (%)										
Proximal colon	70 (17.5)	57 (14.1)	53 (13.3)	67 (16.7)	44 (11.0)	70 (17.5)	60 (15.0)	45 (11.2)	71 (17.7)	45 (11.2)
Distal colon	213 (53.1)	218 (54.0)	235 (58.8)	216 (53.7)	243 (60.9)	213 (53.3)	215 (53.6)	236 (58.7)	226 (56.2)	235 (58.6)
Rectum	54 (13.5)	59 (14.6)	50 (12.5)	55 (13.7)	47 (11.8)	53 (13.3)	53 (13.2)	58 (14.4)	52 (12.9)	49 (12.2)
Unknown	64 (16.0)	70 (17.3)	62 (15.5)	64 (15.9)	65 (16.3)	64 (16.0)	73 (18.2)	63 (15.7)	53 (13.2)	72 (18.0)

Abbreviations: MET = metabolic equivalent; s.d. = standard deviation.
[a]Analysis restricted to participants with available information.

correlation coefficients between FFQ and one-week diet records were listed in Supplementary Table 1.

Covariates. Stage of disease, grade of tumour differentiation, primary tumour location, and year of diagnosis (as a surrogate for treatment) were extracted from the medical record. Body mass index, physical activity, and smoking status were taken from the same questionnaire that assessed dietary insulin scores.

Measurement of biomarkers. In NHS, a total of 32 826 women between 43 and 69 years of age returned a mailed blood collection kit by overnight courier in 1989 and 1990. In HPFS, blood was collected from 18 225 men and returned in a mailed blood collection kit by overnight courier in 1993 through 1995. Approximately 95% of samples were received within 24 h of blood collection.

Plasma levels of adiponectin were measured using ELISA from ALPCO Diagnostics. Plasma levels of C-peptide and IGFBP-1 were measured by enzyme-linked immunosorbent assays with reagents from Diagnostic Systems Laboratory (Webster, TX, USA) in the laboratory of Michael Pollak (McGill University, Montreal, Canada). The mean intra-assay coefficients of variation for these biomarkers were all $<13\%$.

Statistical analyses. The primary exposure was post-diagnosis dietary insulin load and dietary insulin index, calculated from the first dietary assessment within 4 years of diagnosis (median, 21 months). We categorised the dietary insulin score into quintiles, with cutoffs determined separately within NHS and HPFS, and combined the cohorts for pooled analysis. Follow-up time was calculated from post-diagnosis dietary assessment to death or last follow-up dates, June 2012 in NHS, or January 2012 in HPFS,

Table 2. HRs for CRC-specific and overall mortality among patients with colorectal cancer by quintile of post-diagnosis dietary insulin score

Dietary insulin score	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}
Dietary insulin load						
Median (range)						
Nurses' Health Study	582 (298–625)	652 (626–674)	697 (675–714)	736 (715–763)	804 (765–1104)	
Health Professionals Follow-up Study	693 (428–748)	783 (749–810)	837 (811–862)	888 (863–923)	967 (924–1258)	
CRC-specific mortality						
Events/patients	47/401	69/404	77/400	72/402	78/399	
Age-adjusted HR (95% CI)	Referent	1.44 (0.99–2.08)	1.62 (1.13–2.33)	1.42 (0.99–2.06)	1.70 (1.18–2.44)	0.01
Multivariable-adjusted HR (95% CI)[a]	Referent	1.31 (0.89–1.94)	1.55 (1.04–2.29)	1.48 (0.99–2.21)	1.82 (1.20–2.75)	0.006
Overall mortality						
Events/patients	145/401	166/404	157/400	171/402	176/399	
Age-adjusted HR (95% CI)	Referent	1.09 (0.87–1.37)	1.02 (0.81–1.28)	1.02 (0.82–1.28)	1.11 (0.89–1.39)	0.48
Multivariable-adjusted HR (95% CI)[a]	Referent	1.13 (0.89–1.43)	1.11 (0.87–1.41)	1.17 (0.92–1.50)	1.33 (1.03–1.72)	0.03
Dietary insulin index						
Median (range)						
Nurses' Health Study	36 (20–39)	41 (39–42)	44 (42–45)	46 (45–48)	50 (48–70)	
Health Professionals Follow-up Study	35 (21–37)	39 (37–40)	42 (41–43)	44 (43–46)	48 (46–63)	
CRC-specific mortality						
Events/patients	50/400	62/401	74/402	82/402	75/401	
Age-adjusted HR (95% CI)	Referent	1.21 (0.84–1.76)	1.42 (0.99–2.04)	1.58 (1.11–2.25)	1.51 (1.05–2.16)	0.008
Multivariable-adjusted HR (95% CI)[a]	Referent	1.17 (0.79–1.73)	1.32 (0.89–1.95)	1.60 (1.09–2.36)	1.66 (1.10–2.50)	0.004
Overall mortality						
Events/patients	142/400	160/401	156/402	186/402	171/401	
Age-adjusted HR (95% CI)	Referent	1.09 (0.87–1.36)	1.00 (0.79–1.25)	1.17 (0.94–1.46)	1.08 (0.86–1.35)	0.39
Multivariable-adjusted HR (95% CI)[a]	Referent	1.17 (0.92–1.49)	1.07 (0.83–1.37)	1.35 (1.06–1.72)	1.32 (1.02–1.71)	0.02

Abbreviations: CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio.
[a]Adjusted for age at diagnosis (continuous), sex, race (White, Black, other, unknown), smoking status (never, past, current, unknown), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, ⩾35.0 kg m^{-2}, or unknown), physical activity (quintiles or unknown), alcohol intake (0, 0.1–4.9, 5.0–14.9, ⩾15.0 g d^{-1}), cancer stage (I–IV or unknown), grade of tumour differentiation (well, moderate, poor, unknown), location of primary tumour (proximal, distal, rectum, unknown) and year of diagnosis (continuous).

whichever came first. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) of death or death as a result of CRC. Test for trend was performed using the median value for each quintile as a continuous variable in the regression models. The Cox models were tested for and met the assumption of proportionality. Survival curves by tertile of dietary insulin scores were generated using the Kaplan–Meier method, and statistical significance was measured using the log-rank test. Tertiles were used instead of quintiles for ease of graphical viewing.

In multivariable analyses, we adjusted for known prognostic factors and potential confounders for CRC survival, including age at diagnosis, sex, cancer stage, grade of tumour differentiation, primary tumour location, year of diagnosis, BMI, physical activity, smoking status, and alcohol intake. We calculated partial Spearman correlation coefficients between dietary insulin scores and relevant biomarkers, adjusted for age at blood collection, sex, BMI, and energy intake. Tests of interaction between dietary insulin scores and potential effect modifiers were assessed by entering in the model the cross product of dietary insulin score as a continuous variable and the stratification variable, evaluated by the likelihood ratio test. All analyses were performed with SAS 9.4 statistical package. All *P*-values were two sided.

RESULTS

Among 2006 eligible participants with CRC, there were 815 deaths, 343 of which were documented as CRC-specific deaths. The median follow-up period from date of diagnosis for patients who were alive was 12.7 years (range: 2–35.9 years). Baseline characteristics of the 2006 patients are shown in Table 1 by quintile of post-diagnosis dietary insulin score. In general, patients with higher dietary insulin index were older and less likely to smoke, and consumed more carbohydrates and less fat, protein, and alcohol.

Higher post-diagnosis dietary insulin scores were associated with a statistically significant increase in the risk of both CRC-specific and overall mortality (Table 2). Kaplan–Meier curves by dietary insulin score are shown in Figure 1. The pooled adjusted HRs for CRC-specific mortality comparing the highest to the lowest quintiles were 1.82 (95% CI: 1.20–2.75, $P_{trend} = 0.006$) for dietary insulin load and 1.66 (95% CI: 1.10–2.50, $P_{trend} = 0.004$) for dietary insulin index. We also observed an increased risk of overall mortality, with adjusted HRs of 1.33 (95% CI: 1.03–1.72, $P_{trend} = 0.03$) for dietary insulin load and 1.32 (95% CI: 1.02–1.71, $P_{trend} = 0.02$) for dietary insulin index, comparing extreme quintiles. Though correlated with post-diagnosis dietary insulin scores ($r = 0.67$ and 0.55 for dietary insulin load and dietary insulin index, respectively), pre-diagnosis dietary insulin scores were not statistically significantly associated with survival (data not shown). After further adjustment for pre-diagnosis dietary insulin scores, post-diagnosis dietary insulin scores remained statistically significantly associated with survival.

We next evaluated whether the association of dietary insulin scores with CRC-specific mortality could be explained away by other dietary characteristics. Although post-diagnosis dietary glycaemic load and glycaemic index were associated with survival (Supplementary Table 2), inclusion of dietary glycaemic scores into the multivariable model did not change the statistically significant association between dietary insulin scores and CRC-specific mortality (Supplementary Table 3). The association also remained materially unchanged after further adjustment for consumption of red meat, vegetables, and fruits, as well as overall dietary patterns (Supplementary Table 3). Despite the addition of single food items in Supplementary Table 1 into the model both singly and in combination, we continued to observe a statistically significant association between higher dietary insulin scores and worse outcome.

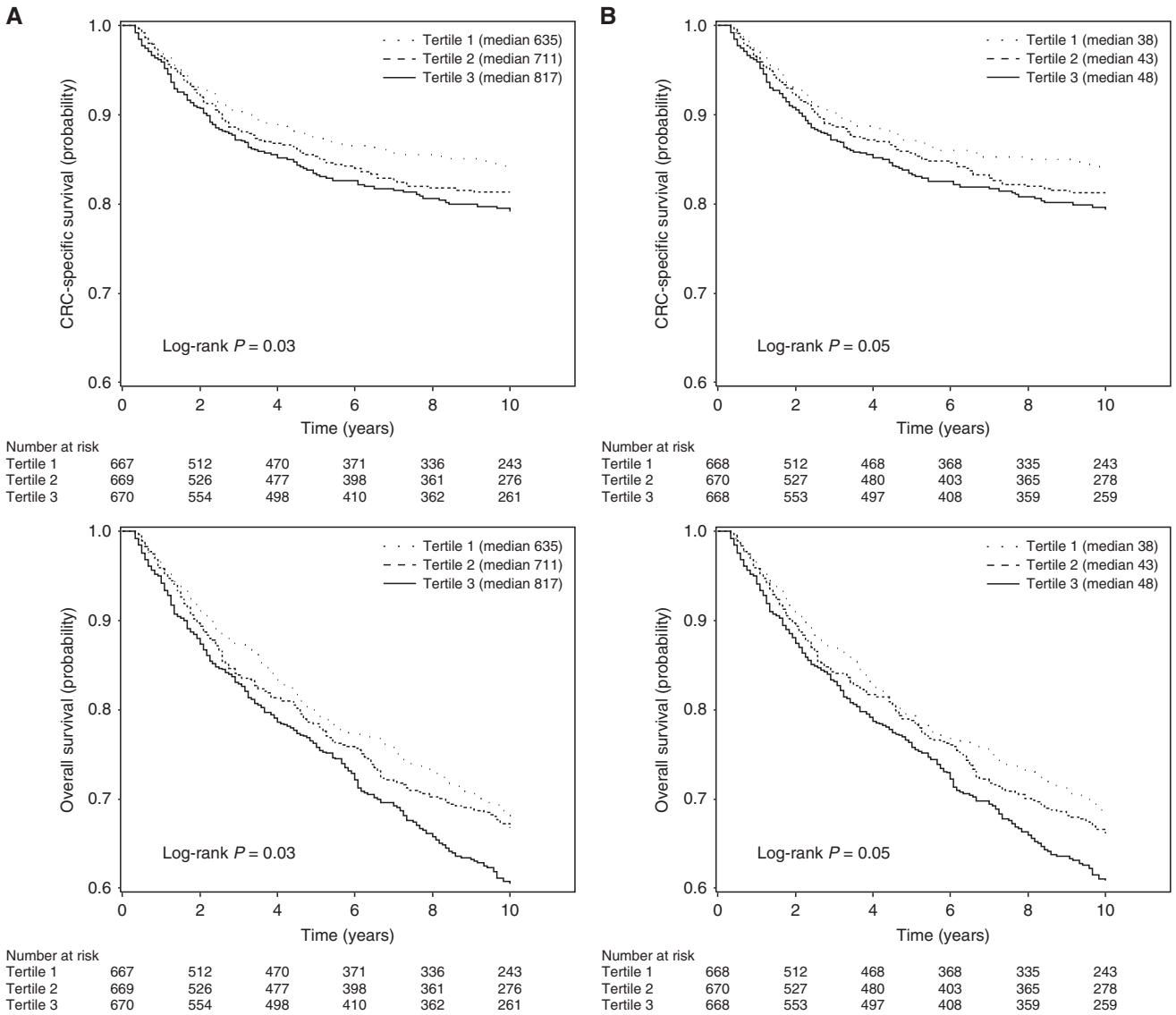

Figure 1. Kaplan–Meier curves of colorectal cancer-specific and overall survival among patients with colorectal cancer by tertile of post-diagnosis (**A**) dietary insulin load or (**B**) dietary insulin index. Log-rank *P*-values were calculated using extreme tertiles.

To address the possibility that changes in dietary habits could reflect occult recurrence or impending death, we excluded patients who died within 3 months of dietary assessment in our primary analyses. We also conducted sensitivity analyses by extending the exclusion period to 6 months or by excluding patients with stage IV disease, but our results remained statistically significant. To address the possible impact of active treatment on diet, we conducted sensitivity analyses by excluding patients with dietary assessment collected within 9 months after diagnosis, but continued to see a consistent relationship between higher dietary insulin scores and worse survival.

We examined the correlation between dietary insulin scores and relevant biomarkers at the time of blood collection. We observed a negative correlation of dietary insulin scores with adiponectin ($P = 0.02$ and 0.05 for dietary insulin load and dietary insulin index, respectively) and no correlation with C-peptide or IGFBP-1.

We also examined the association of dietary insulin index with CRC-specific mortality stratified by predictors of patient outcome (Table 3) and relevant biomarkers (Table 4). The increase in CRC-specific mortality associated with higher dietary insulin index was more apparent among patients with BMI $\geqslant 25\,kg\,m^{-2}$ (HR: 2.32; 95% CI: 1.21–4.46) than BMI $< 25\,kg\,m^{-2}$ (HR: 1.14; 95% CI: 0.67–1.93; $P_{interaction} = 0.01$). No statistically significant interactions were seen with age, sex, physical activity, alcohol intake, diagnosis period, time between diagnosis and dietary assessment, cancer stage, grade of tumour differentiation, location of primary tumour, or levels of adiponectin, C-peptide, or IGFBP-1. Dietary insulin load had similar interactions with these covariates (data not shown).

DISCUSSION

Higher dietary insulin load and dietary insulin index after diagnosis of CRC were associated with increased risk of CRC-specific and overall mortality. Moreover, the increased mortality associated with higher dietary insulin scores was principally observed among patients who were overweight or obese.

Dietary insulin scores have not been extensively studied in relation to development and progression of CRC. In a nested case-control study, we observed that higher dietary insulin load or index was not associated with an increase in CRC risk (Bao *et al*, 2010).

Table 3. HRs for CRC-specific mortality among patients with colorectal cancer by quintile of post-diagnosis dietary insulin index stratified by predictors of patient outcome

		Dietary insulin index					
Stratification covariate	**No. of patients**	**Quintile 1**	**Quintile 2 HR (95% CI)[a]**	**Quintile 3 HR (95% CI)[a]**	**Quintile 4 HR (95% CI)[a]**	**Quintile 5 HR (95% CI)[a]**	**$P_{interaction}$**
Age at diagnosis, years[b]							0.56
⩽67	999	Referent	1.39 (0.84–2.29)	1.50 (0.91–2.47)	1.92 (1.16–3.17)	1.79 (1.04–3.07)	
>67	1007	Referent	0.90 (0.49–1.67)	1.09 (0.61–1.96)	1.24 (0.71–2.18)	1.44 (0.82–2.54)	
Sex							1.00
Female	1314	Referent	0.99 (0.62–1.58)	1.24 (0.78–1.95)	1.53 (0.97–2.42)	1.58 (0.98–2.54)	
Male	692	Referent	1.70 (0.86–3.37)	1.50 (0.74–3.02)	1.73 (0.89–3.39)	1.81 (0.89–3.67)	
BMI, kg m^{-2}							0.01
<25.0	890	Referent	1.13 (0.69–1.85)	0.80 (0.47–1.35)	0.97 (0.57–1.63)	1.14 (0.67–1.93)	
⩾25.0	966	Referent	1.10 (0.55–2.22)	2.24 (1.21–4.14)	2.93 (1.59–5.40)	2.32 (1.21–4.46)	
Physical activity, MET-h per week[b]							0.40
⩽10.2	917	Referent	1.47 (0.80–2.68)	1.84 (1.02–3.31)	2.28 (1.29–4.02)	2.37 (1.30–4.30)	
>10.2	908	Referent	1.07 (0.57–2.00)	0.98 (0.53–1.82)	1.04 (0.55–1.97)	1.47 (0.79–2.72)	
Alcohol intake, g d^{-1}[b]							0.38
⩽1.9	1011	Referent	0.76 (0.40–1.43)	0.88 (0.47–1.62)	1.09 (0.61–1.95)	1.01 (0.56–1.82)	
>1.9	995	Referent	1.32 (0.82–2.13)	1.45 (0.90–2.33)	1.63 (0.99–2.69)	2.26 (1.34–3.81)	
Diagnosis period[b]							0.82
1976–1997	1056	Referent	1.30 (0.78–2.16)	1.28 (0.77–2.11)	2.02 (1.24–3.31)	1.60 (0.94–2.72)	
1998–2010	950	Referent	0.99 (0.54–1.82)	1.53 (0.85–2.76)	0.96 (0.52–1.79)	1.72 (0.97–3.07)	
Time between diagnosis and dietary assessment, years							0.14
0<2	1105	Referent	1.15 (0.72–1.83)	1.52 (0.96–2.43)	1.54 (0.98–2.43)	2.11 (1.33–3.37)	
2–4	901	Referent	1.21 (0.61–2.41)	1.17 (0.61–2.24)	1.68 (0.86–3.27)	1.05 (0.51–2.18)	
Stage							1.00
I/II	1204	Referent	1.44 (0.71–2.88)	1.83 (0.92–3.63)	2.12 (1.09–4.12)	1.63 (0.80–3.34)	
III/IV	573	Referent	1.21 (0.73–2.00)	1.17 (0.71–1.92)	1.38 (0.83–2.29)	1.73 (1.05–2.83)	
Grade of tumour differentiation							0.17
Well/moderate	1416	Referent	1.15 (0.69–1.92)	1.63 (1.01–2.63)	1.81 (1.12–2.92)	2.05 (1.24–3.39)	
Poor	265	Referent	1.62 (0.76–3.42)	1.09 (0.51–2.37)	0.97 (0.42–2.25)	1.09 (0.43–2.74)	
Location of primary tumour							0.75
Colon	1467	Referent	1.33 (0.82–2.17)	1.56 (0.98–2.50)	1.82 (1.14–2.90)	1.79 (1.09–2.92)	
Rectum	444	Referent	0.87 (0.44–1.73)	0.88 (0.42–1.80)	1.14 (0.57–2.27)	1.35 (0.67–2.72)	

Abbreviations: BMI = body mass index; CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; MET = metabolic equivalent.
[a]Adjusted for age at diagnosis (continuous), sex, race (White, Black, other, unknown), smoking status (never, past, current, unknown), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, ⩾35.0 kg m^{-2}, or unknown), physical activity (quintiles or unknown), alcohol intake (0, 0.1–4.9, 5.0–14.9, ⩾15.0 g d^{-2}), cancer stage (I–IV or unknown), grade of tumour differentiation (well, moderate, poor, unknown), location of primary tumour (proximal, distal, rectum, unknown) and year of diagnosis (continuous), excluding the stratification covariate.
[b]Cutpoints chosen based on median values.

Table 4. HRs for CRC-specific mortality among patients with colorectal cancer by quintile of post-diagnosis dietary insulin index stratified by relevant biomarkers

		Dietary insulin index			
Stratification covariate	**No. of patients**	**Tertile 1**	**Tertile 2 HR (95% CI)[a]**	**Tertile 3 HR (95% CI)[a]**	**$P_{interaction}$**
Adiponectin, μg ml^{-1}[b]					0.47
⩽6.65	207	Referent	1.59 (0.60–4.23)	0.93 (0.33–2.65)	
>6.65	207	Referent	1.44 (0.50–4.15)	2.13 (0.72–6.33)	
C-peptide, ng ml^{-1}[b]					0.83
⩽2.05	179	Referent	1.18 (0.43–3.20)	1.47 (0.55–3.97)	
>2.05	178	Referent	1.64 (0.46–5.91)	2.11 (0.58–7.64)	
IGFBP-1, ng ml^{-1}[b]					0.21
⩽20.45	157	Referent	2.00 (0.60–6.68)	2.33 (0.67–8.08)	
>20.45	157	Referent	0.85 (0.26–2.80)	1.08 (0.34–3.37)	

Abbreviations: CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; IGFBP = insulin-like growth factor binding protein.
[a]Adjusted for age at diagnosis (continuous), sex, race (White, Black, other, unknown), smoking status (never, past, current, unknown), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, ⩾35.0 kg/m^2, or unknown), physical activity (quintiles or unknown), alcohol intake (0, 0.1–4.9, 5.0–14.9, ⩾15.0 g/d), cancer stage (I to IV or unknown), grade of tumour differentiation (well, moderate, poor, unknown), location of primary tumour (proximal, distal, rectum, unknown) and year of diagnosis (continuous).
[b]Cutpoints chosen based on median values.

In the current study, pre-diagnosis dietary insulin scores were not associated with CRC survival. Moreover, we did not observe a correlation between pre-diagnosis dietary insulin scores and pre-diagnosis plasma C-peptide, a more stable biomarker of insulin secretion than plasma insulin. One possible explanation is that the insulinogenic content of a diet as represented by the dietary insulin load or index may not contribute to sustained hyperinsulinemia among healthy participants, which is largely determined by the degree of insulin resistance. In this study, however, dietary insulin load and dietary insulin index were both strongly associated with worse patient outcome, suggesting that tumour progression among CRC patients may be influenced by acute postprandial insulin secretion in response to food intake. Our findings are consistent with a recent study using a subset of this population with measured tumour molecular markers ($N = 1160$), in which the overall HR for CRC-specific mortality was 1.19 (95% CI: 1.02–1.38) for an increase of one standard deviation in dietary insulin index (Keum *et al*, 2017).

BMI, physical activity, and diet are established risk factors for several types of cancer, including CRC (Friedenreich and Orenstein, 2002; Giovannucci, 2002; Calle *et al*, 2003; Johnson and Lund, 2007), and these modifiable behaviours are now increasingly recognised as potentially important risk factors for CRC recurrence, progression, and death (Meyerhardt *et al*, 2003; Dignam *et al*, 2006; Haydon *et al*, 2006; Meyerhardt *et al*, 2006a, b, 2007). Although the biological mediators of this increased risk of recurrence and death are poorly defined, hyperinsulinemia and perturbations in the insulin-like growth factor axis have been proposed as underlying mechanisms for these observations (Sandhu *et al*, 2002; Giovannucci, 2003b; Calle and Kaaks, 2004; Davies *et al*, 2006). This hypothesis is supported by laboratory studies of intestinal epithelial cells and colon cancer cell lines, in which insulin binds to the insulin receptor on the cancer cell surface and stimulates cell growth, while inhibiting apoptosis, suggesting that insulin may act directly as a mitogen for colon cancer cells (Tran *et al*, 1996; Desbois-Mouthon *et al*, 2000; Taniguchi *et al*, 2006; Tran *et al*, 2006; Shi *et al*, 2007; Sun and Jin, 2008). Among patients with non-metastatic CRC, elevated levels of plasma C-peptide were associated with an increased risk of CRC-specific mortality (Wolpin *et al*, 2009). In addition, the association between dietary insulin scores and CRC survival appeared more apparent when CRC is negative for *PIK3CA* mutation and fatty acid synthase (FASN), two molecular markers linked to the insulin signalling pathway (Keum *et al*, 2017). A recent study demonstrated that dietary sugar intake increases liver tumour incidence in female mice (Healy *et al*, 2016), suggesting that a higher dietary insulin index may affect CRC progression by promoting metastasis to the liver.

We noted a greater association of higher dietary insulin scores with increased CRC-specific mortality among overweight or obese patients, suggesting that dietary factors may play a more critical role among those with established insulin resistance. Interestingly, among healthy participants, those with higher dietary insulin scores had increased plasma concentrations of triglycerides (a marker of insulin secretion), and this association was strongest among obese participants (Nimptsch *et al*, 2011).

The current study has several strengths, including the prospective design, large sample size, long follow-up period, high follow-up rate, and detailed information on other prognostic factors. The procedure for developing the food insulin index was performed under highly standardised conditions (Holt *et al*, 1997) and shown to be an accurate measure of actual postprandial insulin response evoked by composite meals (Bao *et al*, 2009). Additionally, dietary insulin scores were correlated with plasma levels of relevant biomarkers, including triglyceride in a healthy population (Nimptsch *et al*, 2011) and adiponectin in this study, confirming that the estimates of dietary insulin scores are able to predict an expected biological response.

Our work has several limitations. Patients with either occult cancer recurrence or other poor prognostic characteristics may have consumed a high insulinogenic diet as an alternative source of needed calories. To minimise this potential bias, we excluded patients who died within 3 months of dietary assessment. When we extended this restriction to 6 months, we continued to observe a statistically significant association between higher dietary insulin scores and worse survival.

We also considered the possibility that patients who consumed a high insulinogenic diet after cancer diagnosis may have consumed a similar diet before diagnosis and acquired biologically more aggressive tumours. However, we did not observe any statistically significant association between dietary insulin scores and tumour-related characteristics associated with survival, including stage and grade of tumour differentiation. Furthermore, with the availability of repeated dietary measures in NHS and HPFS, we were able to control for pre-diagnosis dietary insulin scores, with no appreciable change in our results.

Another potential concern with the food insulin index values is that they were derived from lean university students (Holt *et al*, 1997), whose absolute insulin response may be different from that of the older and heavier individuals; however, the method is valid if the increase in insulin levels induced by a food, that is, the relative insulin response, is comparable between the two groups. Indeed, in the biomarker validation study (Nimptsch *et al*, 2011), the association observed between dietary insulin index and triglyceride concentrations was strongest among obese participants, indicating that the general method used to develop the insulin index also applies to heavier individuals.

CONCLUSIONS

In summary, consumption of a dietary pattern characterised by higher dietary insulin scores was statistically significantly associated with increased cancer-specific and overall mortality among CRC patients from two large prospective cohort studies. These data offer further support for the link between energy balance factors and CRC progression and reinforces the need for continued research into the role of these pathways in CRC pathogenesis. Our findings will help to guide dietary recommendations for CRC patients and offer potentially modifiable opportunities to improve patient survival.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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