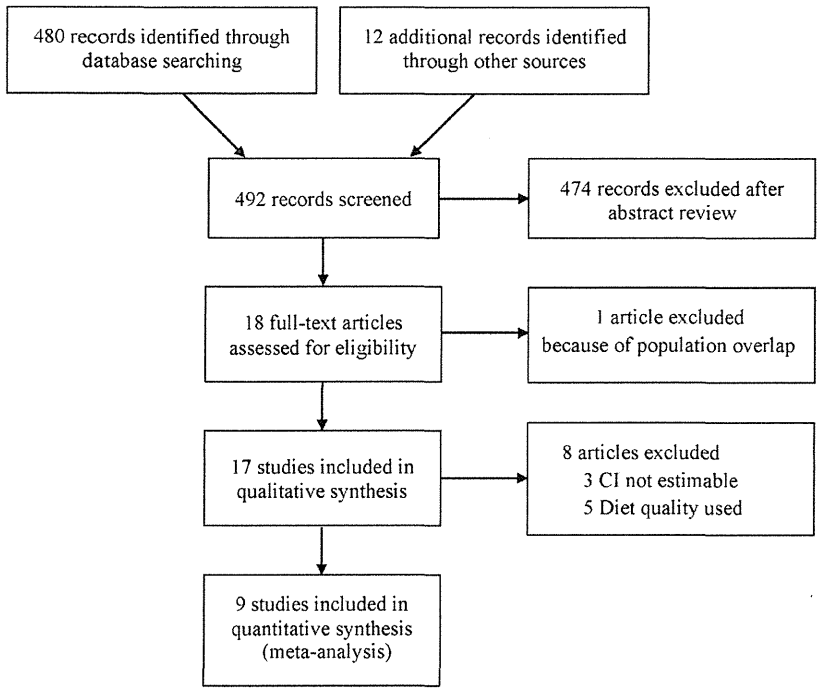

Figure 1. Flow diagram of study selection.
doi:10.1371/journal.pone.0055030.g001

durations were long enough for the outcomes to occur. Although the majority of the enrolled subjects were middle-aged and free of such chronic comorbidities as diabetes and coronary heart disease, healthcare professionals dominated in the US cohorts, who may not truly represented the average population in the community.

All-cause mortality was assessed in 7 reports. Four cohort studies using the low-carbohydrate score [7,10,11,32] and two using the LC-HP score [11,12] showed a significant increase associated with low-carbohydrate diets (relative risk range 1.12–25.0). One diet quality study suggested 0.27 shorter years of life in 10 years, which was statistically significant. [28] Only two out of five studies demonstrated a significantly elevated risk of CVD mortality (relative risk range 2.17–3.52) evaluated by the LC-HP score. [11,12] One article showed a significantly elevated risk of CVD incidence estimated by the low-carbohydrate score and the LC-HP score (relative risk range 1.42–1.55), [9] whereas three diet quality researches suggested a significantly increased risk of incident CVD (relative risk range 1.30–1.56). [14,26,27] Neither of the studies that calculated regression coefficients showed a significant correlation between low-carbohydrate diets and CVD. [23,24] Some studies suggested that low-carbohydrate diets might increase the risk of mortality and CVD in animal-based dietary patterns whereas they might decrease the risk in plant-based diets. [7,9,30].

The estimates in all the other analyses using either score were non-significant and none of these studies revealed that low-carbohydrate diets were associated with a significantly decreased risk of these outcomes.

Quantitative Summary (Meta-analysis)

A total of 9 articles that provided sufficient information using the low-carbohydrate score and/or the LC-HP score were included in the meta-analysis (**Fig. 1**). All the ascertainment of diagnosis was based on the valid registries but only a few specified the diagnostic criteria for CVD. [12,29,30] The follow-up rate was more than about 90% in each study. Carbohydrate intake was assessed by the residual method in 5 studies [8–12] and by the density method in 4 studies. [7,29–31] Of the 272,216 people in 4 cohort studies using the low-carbohydrate score, 15,981 (5.9%) cases of death from all-cause were reported. **Fig. 2** illustrates the significantly increased risk of all-cause mortality among those adherent to low-carbohydrate diets: the pooled RR (95% CI) 1.31 (1.07–1.59); $p = 0.007$; $I^2 = 53\%$ ($p = 0.09$). Analysis using the LC/HP score yielded a similar significant increase in the risk of all-cause mortality: RR 1.30 (1.01–1.68); $p = 0.04$; $I^2 = 65\%$ ($p = 0.04$). A dose-response was observed in 2 analyses. [7,12] Since heterogeneity among reports in the all-cause mortality using the low-carbohydrate score was statistically significant, we conducted a subgroup analysis according to the possible predictors. The pooled RRs of the studies conducted in Europe [10–12] and the United States [7] (RR 1.42 [1.18–1.72] vs 1.12 [1.01–1.24]) were both significantly elevated; and the diet assessment method (residual method [10–12] or density method [7]) coincided with these regions; the studies with follow-up length shorter than 10 years [10,12] were associated with a statistically high RR while those with follow-up length longer than 10 years [7,11] were not (RR 1.40 [1.12–1.74] vs 1.27 [0.88–1.84]); The pooled RR for men [7,10] was statistically elevated while that for women [7,9,10] was not (RR 1.19 [1.08–1.31] vs 1.34 [0.96–1.87]). We were unable to perform a subgroup analysis according to the body-mass index because the mean values were not stated or estimable in the majority of the reports.

A total of 3,214 (1.3%) cases of CVD death among 249,272 subjects in 3 cohort studies and 5,081 (2.3%) incident CVD cases among 220,691 women in different 4 cohort studies were reported. As summarized in **Fig. 3** and **Fig. 4**, the RRs of CVD mortality

Table 1. Study characteristics.

Source	Country, region/cohort	Follow-up, yr	N (women, %)	Age, yr	Diabetes, %	Coronary heart disease, %	Outcome, n
Garcia-Palmieri, 1980* [23]	USA, Puerto Rico	6	8218 (0)	45–64	NR	0	Myocardial infarction or coronary heart disease death 286
McGee, 1984* [24]	USA, Japanese ancestry	10	7088 (0)	45–68	NR	0	Coronary heart disease 456
McCullough, 2000* [25]	USA, NHS	12	67272 (100)	45–64	0	0	All CVD 1427
McCullough, 2000* [26]	USA, HPFS	8	51529 (0)	40–75	0	0	All CVD 1092
McCullough, 2002* [14]	USA,	8–12					
	a. NHS		a. 67271 (100)	a. 30–55	0	0	a. All CVD 1365
	b. HPFS		b. 38615 (0)	b. 40–75	0	0	b. All CVD 1092
Fung, 2001* [27]	USA, NHS	12	69017 (100)	38–63	0	0	Coronary heart disease 821
Diehr, 2003* [28]	USA, US Cardiovascular Health Study	10	5888 (58)	73	11	25	Coronary heart disease 2179
Oh, 2005 [29]	USA, NHS	18	78779 (100)	30–55	0	0	All stroke 1020
							Ischemic stroke 515
							Hemorrhagic stroke 279
Halton, 2006 [30]	USA, NHS	20	82802 (100)	30–55	0	0	Coronary heart disease 1994
Beulens, 2007 [31]	Netherland, Prospect-EPIC	Mean 9	15714 (100)	49–70	0	0	All CVD 799
							Coronary heart disease 556
							Stroke 243
Lagiou, 2007 [11]	Sweden, Scandinavian Women's Lifestyle and Health Cohort	Mean 12	42237 (100)	30–49	0	0	All-cause death 588
							CVD death 75
Massimino, 2007* [32]	Brazil, Japanese-Brazilians	8	647 (52)	Mean 63.5	20	NR	All-cause death 71
Trichopoulou, 2007 [12]	Greece, EPIC	Mean 4.9	22944 (59)	Adults	0	0	All-cause death 455
							CVD death 193
Fung, 2010 [7]	USA,						
	a. NHS	a. 26	a. 85168 (100)	a. 34–59	a. 0	a. 0	a. All-cause death 12555
							CVD death 2458
	b. HPFS	b. 20	b. 44548 (0)	b. 40–75	b. 0	b. 0	b. All-cause death 8678
							CVD death 2746
Sjögren, 2010 [8]	Sweden, Uppsala	Mean 10.1	924 (0)	Mean 71	0	0	All-cause death 215
							CVD death 88
Lagiou, 2012 [9]	Sweden, Uppsala Longitudinal Study of Adult Men cohort	Mean 15.7	43396 (100)	30–49	NR	0	All CVD 1268
							Ischemic heart disease 701

Table 1. Cont.

Source	Country, region/cohort	Follow-up, yr	N (women, %)	Age, yr	Diabetes, %	Coronary heart disease, %	Outcome, n
							Ischemic stroke 294
							Hemorrhagic stroke 70
							Subarachnoid hemorrhage 121
							Peripheral arterial disease 82
Nilsson, 2012 [10]	Sweden, Västerbotten Intervention Program	Median 10	77319 (51)	Median 49	3	NR	All-cause death 2383
							CVD death 681

NR: not reported, CVD: cardiovascular disease, LCHP: low-carbohydrate/high-protein,
*not included in meta-analysis, NHS: Nurses' Health Study, HPFS: Health Professionals Follow-up Study, EPIC: European Prospective Investigation into Cancer and Nutrition.
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and incidence were not statistically significant: RR 1.10 (0.98–1.24); p = 0.12; I^2 = 0% (p = 0.41), RR 0.98 (0.78–1.24); p = 0.87; I^2 = 53% (p = 0.09), respectively. The RR in CVD mortality using the LC/HP score was not statistically significant, either: RR 1.53 (0.88–2.67); p = 0.13; I^2 = 61% (p = 0.05). There was only one study on CVD incidence using the LC/HP score, which showed a significantly elevated risk. [9] There was a positive dose-response in 2 analyses. [7,9].

Discussion

Our systematic review and meta-analyses of worldwide reports suggested that low-carbohydrate diets were associated with a significantly higher risk of all-cause mortality in the long run. They also suggested that low-carbohydrate diets might not be protective or harmful in terms of CVD mortality and incidence. These findings support the hypothesis that the short-term benefits of low-carbohydrate diets for weight loss are potentially irrelevant. [13] In light of the fact that the number of people with obesity is exponentially increasing worldwide and obesity is one of the leading risk factors of mortality, [15] our findings have substantial clinical and public implications on a global scale and point to the need for the further investigation of the long-term health effects of low-carbohydrate diets and other nutritional factors.

The strength of our present study is that the analysis was mainly based on long-term large population-based data originating from multiple nations and was performed with a high level of precision and this is the first meta-analysis, to our best knowledge, on the health effects of low-carbohydrate diets. The included data were good in quality and apparently had power enough to detect the differences in the risk of these outcomes. The outcome ascertainment tools were valid, and each result was adjusted for multiple confounders and the significantly increased pooled RRs for all-cause mortality were robust in that the RRs based on both of the methods were almost identical and statistically significant. Heterogeneity of the results of the component studies was modest: low heterogeneity suggests that the each result was consistent and most variation was attributable to chance alone, and the large I^2 values in some analyses indicated that the range of the plausible risk estimates was wide, generally because of the diversity of study design, population backgrounds and ethnicities. The subgroup analysis suggested that the possible major source of heterogeneity was the region or the nutrition assessment method in addition to the publication bias. The main dietary source of protein and the obesity prevalence differ across countries [33]. The length of follow-up and the gender were possibly other sources of heterogeneity but these hypotheses cannot be statistically tested in light of the scarcity of data.

Evidence has been accumulating to suggest that low-carbohydrate diets and their combination with high-protein diets are effective in weight loss [1–3] and may have favorable short-term effects on the risk markers of CVD. [4–6] Low-carbohydrate diets may be nutritionally safe and valid insofar as the carbohydrates are simple and refined, and the main source of the protein is plants. Despite these facts, our study did not find a cardiovascular benefit and supports their potential long-term health harm when such nutritional quality is not considered. Low-carbohydrate diets tend to result in reduced intake of fiber and fruits, and increased intake of protein from animal sources, cholesterol and saturated fat, [27,30,34] all of which are risk factors for mortality and CVD. [13,14] It is postulated that differences in dietary bioactive components such as specific free fatty acids, protein, fiber, minerals, vitamins and phytochemicals are involved. [7] Subgroup analyses suggested that low-carbohydrate diets might increase the

Table 2. Methodological assessments of the included studies.

Source	Parameter	Outcome measures	Referent	Comparator	Adjustment factors
Garcia-Palmieri, 1980* [23]	Carbohydrate intake	Coefficient			Alcohol, systolic blood pressure, cholesterol, cigarettes smoked, and blood glucose
McGee, 1984* [24]	Carbohydrate intake	Coefficient			Energy intake, blood pressure, serum cholesterol, cigarettes smoked per day, body weight (in pounds), and physical activity index
McCullough, 2000* [25]	Healthy eating index-f	Relative risk	Quintile 5	Quintile 1	Age (5-y categories), smoking (never, past, 1–14 cigarettes/d, 15–24 cigarettes/d, or ≥25 cigarettes/d), time period, body mass index (quintiles), alcohol intake (7 categories), physical activity (6 categories of metabolic equivalents), history of hypertension or hypercholesterolemia at baseline, total energy intake (quintiles), postmenopausal status, postmenopausal hormone use, multivitamin and vitamin E supplement use
McCullough, 2000* [26]	Healthy eating index-f	Relative risk	Quintile 5	Quintile 1	Age (5-y categories), body mass index (quintiles), smoking (never, past, 1–14 cigarettes/d, 15–24 cigarettes/d, ≥25 cigarettes/d), alcohol intake (7 categories), physical activity (6 categories), total energy intake (quintiles), time period, multivitamin use, vitamin E use, and diagnosis of hypercholesterolemia and hypertension at baseline
McCullough, 2002* [14]	Recommended Food Score	Relative risk	Quintile 5	Quintile 1	Age (5-y categories), smoking (never, past, 1–14 cigarettes/d, 15–24 cigarettes/d, >25 cigarettes/d), time period, body mass index (quintiles), physical activity (6 categories of metabolic equivalents), total energy intake (quintiles), history of hypertension or hypercholesterolemia at baseline, vitamin E and multivitamin supplement, and for women, postmenopausal hormone use
Fung, 2001* [27]	Prudent pattern/ Western pattern	Relative risk	Quintiles 4,5/1	Quintiles 1/4,5	Age, period, smoking, body mass index, hormone replacement therapy, aspirin use, caloric intake, family history, history of hypertension, multivitamin and vitamin E use, and physical activity
Diehr, 2003* [28]	Diet quality	Years of life in 10 yr, CVD incidence	Healthy diet	Unhealthy diet (high fat, low fiber, low carbohydrate, high protein, high calorie)	Demographics, health, behaviors, and baseline health variables
Oh, 2005 [29]	Carbohydrate intake	Relative risk	Quintile 5	Quintile 1	Age (5-year categories), body mass index (five categories), smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day), alcohol intake (four categories), parental history of myocardial infarction, history of hypertension, hypercholesterolemia, and diabetes, menopausal status and postmenopausal hormone use, aspirin use (five categories), multivitamin use, vitamin E supplement use, physical activity (hours/week, five categories), energy, cereal fiber (quintiles), saturated fat, monounsaturated fat, polyunsaturated fat, trans-fat, and omega-3 fatty acids (quintiles)
Halton, 2006 [30]	Low carbohydrate score	Relative risk	Decile 1	Decile 10	Age (in 5-year categories), body-mass index (<22.0, 22.0 to 22.9, 23.0 to 23.9, 24.0 to 24.9, 25.0 to 27.9, 28.0 to 29.9, 30.0 to 31.9, 32.0 to 33.9, 34.0 to 39.9, or ≥40.0), smoking status (never, past, or current [1 to 14, 15 to 24, or ≥25 cigarettes a day]), postmenopausal hormone use (never, current use, or past use), hours of physical activity per week (<1, 1 to 2, 2 to 4, 4 to 7, or >7), alcohol intake (0, <5 g per day, 5 to 14 g per day, or ≥15 g per day), number of times aspirin was used per week (<1, 1 to 2, 3 to 6,7 to 14, or ≥15), use of multivitamins (yes or no), use of vitamin E supplement (yes or no), history of hypertension (yes or no), history of hypercholesterolemia (yes or no), parental history of myocardial infarction (yes or no), and total calories
Beulens, 2007 [31]	Carbohydrate intake	HR	Quartile 4	Quartile 1	Age, hypertension, cholesterolemia, smoking (never/past/current smoking of 1 to 10, 11 to 20, and ≥20 cigarettes), body mass index, mean systolic blood pressure, total physical activity, menopausal status (pre or post), hormone replacement therapy use, oral contraceptives use, alcohol intake (≤10, 11 to 25, 26 to 50, ≥50 g/day energy-adjusted), total energy intake (in quintiles) and energy-adjusted intake of vitamin E, protein, dietary fiber, folate, saturated fat, and poly- and monounsaturated fat
Lagiou, 2007 [11]	Low carbohydrate score	HR	Per decreasing tenth of carbohydrate intake		Height (cm, continuously), body mass index (<25, 25–29.99 and 30 kg m2, categorically), smoking status (never smokers, former smokers of <10 cigarettes, former smokers of 10–14 cigarettes, former smokers of 15–19 cigarettes, former smokers of 20 or more cigarettes, current smokers of <10 cigarettes, current smokers of 10–14 cigarettes, current smokers of 15–19 cigarettes, current smokers of 20 or more cigarettes, categorically), physical activity [from 1 (low) to 5 (high), categorically], education (0–10, 11–13 and 14 or more years in school, categorically), energy intake (per 1000 kJ day), continuously), saturated lipid intake (per 10 g, continuously) and alcohol intake (<5, 5–25 or >25 g day, categorically).

Table 2. Cont.

Source	Parameter	Outcome measures	Referent	Comparator	Adjustment factors
	LCHP score	HR	Per increasing 2 points		
Massimino, 2007* [32]	Carbohydrate intake	HR	Tertile 3	Tertile 1	Gender (male/female), age (in years), generation (second versus first), physical activity (other versus heavy/very heavy), arterial pressure (systolic and diastolic, in mmHg), degree of glucose tolerance ("dummy": normal glucose tolerance, altered fasting blood glucose, impaired glucose tolerance, and diabetes mellitus), presence of dyslipidemia (yes/no), and smoking (smoker/non-smoker)
Trichopoulou, 2007 [12]	Carbohydrate intake	HR	Per decreasing tenth of carbohydrate intake		Energy intake, gender (men, women; categorically), age (<45 years, 45–54 years, 55–64 years, ≥65 years; categorically), years of schooling (<6, 6–11, 12, ≥13; categorically), smoking (never, former and 1–10 cigs per day, 11–20 cigs per day, 21–30 cigs per day, 31–40 cigs per day, ≥41 cigs per day; ordered), body mass index (per quintile; ordered), physical activity (per quintile; ordered), and ethanol intake (<10 g per day, 10–30 g per day, ≥30 g per day; categorically).
	LCHP score	HR	Per increasing 2 points for CVD death		
			Lowest group (2–6 points) for all-cause death	Highest group (16–20 points)	
Fung, 2010 [7]	Low carbohydrate score	HR	Decile 1	Decile 10	Age, physical activity, body mass index, energy intake, alcohol intake, menopausal status and postmenopausal hormone use (women only), history of hypertension, smoking status, and multivitamin use.
Sjögren, 2010 [8]	LCHP score	HR	Lowest group (2–6 points)	Highest group (16–20 points)	Energy intake, smoking, social class, type 2 diabetes, the metabolic syndrome, lipid-lowering treatment, blood pressure–lowering treatment, waist circumference, diastolic blood pressure, insulin, C-reactive protein
Lagiou, 2012 [9]	Low carbohydrate score	HR	Per decreasing tenth of carbohydrate intake		Height (cm, continuously), body mass index (<25, 25–29.99, and ≥30, categorically), smoking status (never smokers, former smokers of <10 cigarettes, former smokers of 10–14 cigarettes, former smokers of 15–19 cigarettes, former smokers of ≥20 cigarettes, current smokers of <10 cigarettes, current smokers of 10–14 cigarettes, current smokers of 15–19 cigarettes, and current smokers of ≥20 cigarettes, categorically), physical activity (from 1 (low) to 5 (high), categorically), education (≤10, 11–13, and ≥14 years in school, categorically), diagnosis of hypertension (ever versus never), energy intake (per 1000 kJ/day, continuously), unsaturated lipid intake (per 10 g/day, continuously), saturated lipid intake (per 10 g/day, continuously), and alcohol intake (<5 g/day, 5–25 g/day, and >25 g/day, categorically)
	LCHP score	HR	Per increasing 2 points		
Nilsson, 2012 [10]	Carbohydrate intake	HR	Per decreasing tenth of carbohydrate intake		Age, body mass index, sedentary lifestyle, education, current smoking, intake of energy, alcohol, and saturated fat
	LCHP score	HR	Lowest group (2–8 points)	Highest group (14–20 points)	

CVD: cardiovascular disease, LCHP: low-carbohydrate/high-protein, HR: hazard ratio,
*not included in meta-analysis.
doi:10.1371/journal.pone.0055030.t002

risk of mortality and CVD in animal-based dietary patterns whereas they might decrease the risk in plant-based diets. [7,9,30] In our analysis, the increment in the all-cause mortality might have been partly attributable to the increased risks for CVD mortality and morbidity although they were not significant. It is possible that the beneficial effect of plant protein may have been offset by the adverse effect of animal protein in our calculations. Low-carbohydrate diets may be linked to an array of other chronic health problems. A positive cancer risk has been reportedly related to the intake of animal protein, [7] and red and processed meat consumption, [35] although the risk of cancer was found to be non-significant in our analysis. [11,12] Little is known about the

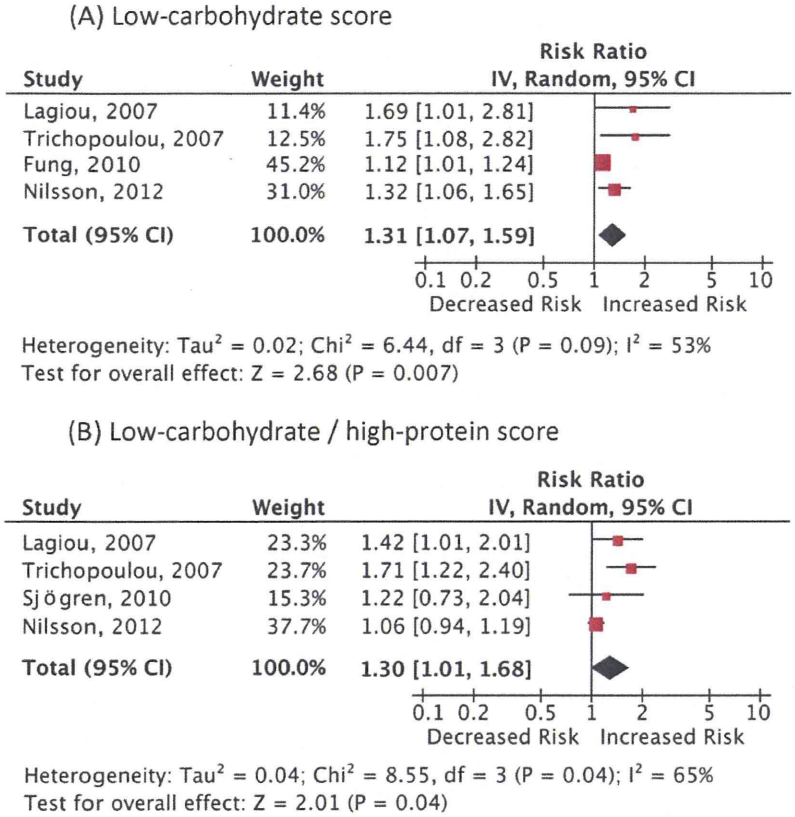

Figure 2. Adjusted risk ratios for all-cause mortality associated with low-carbohydrate diets. Analysis was done based on (A) the low-carbohydrate score and (B) the low-carbohydrate/high-protein score. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. IV, inverse-variance.
doi:10.1371/journal.pone.0055030.g002

consequences of low-carbohydrate diets with respect to kidney disease, osteoporosis, and mental condition. The biology that underlies the positive correlation between low-carbohydrate diets and all-cause death is not fully explained. Further studies to clarify the mechanism are eagerly awaited.

Given the facts that low-carbohydrate diets are likely unsafe and that calorie restriction has been demonstrated to be effective in weight loss regardless of nutritional composition, [36] it would be prudent not to recommend low-carbohydrate diets for the time being. Further detailed studies to evaluate the effect of protein source are urgently needed.

Limitations

Although the quality of the included studies might not be an issue, our analysis should be interpreted in the context of the following limitations. The observational studies were scarce and moderately heterogeneous, and thus a publication bias and a residual confounding bias may have existed although we cannot assess these hypotheses. In the analysis of CVD mortality risk, there may not have been enough statistical power and the representativeness of the cohort may be poor since the data of healthcare professionals [7] dominated (**Fig. 3A**). Next, the relation may not necessarily be causal, particularly in the observational studies [37] because of possible confounding factors and biases that may not have been fully adjusted for, which may have rendered the results less valid. In our analysis, the adjustment in each component study was adequate and fair. Confounding by treatment indication [38] might bias the effect of diets. However, most of the target populations were free of chronic disease at baseline and it is less likely that the dietary habits had been modulated according to their previous health status. A dose-response of relative risk was confirmed in few studies, which might make the results less plausible. Dietary patterns may vary over the course of follow-up but updating dietary information was not done in many studies and thus the magnitude of risk may have been diluted as suggested by our subgroup analysis of the flow-up periods and the supplementary analysis by Lagiou, et al. [9] Furthermore, it is difficult to distinguish the effects of individual nutritional component. For all these limitations, however, observational studies provide good available evidence regarding potential benefit and harm, and the overall pooled estimates were robust, the temporal sequence of the events was appropriate, and the results among the included studies seemed consistent. Moreover, evidence has been accumulating to support these potential adverse outcomes. [39] With regards to external validity, it is also important to realize that the participants of the studies may not represent general populations most likely because the majority of the studies were done in Western countries and healthcare professionals dominated. It remains unclear if these diets exert a similar influence on the clinical outcome in diabetic patients.

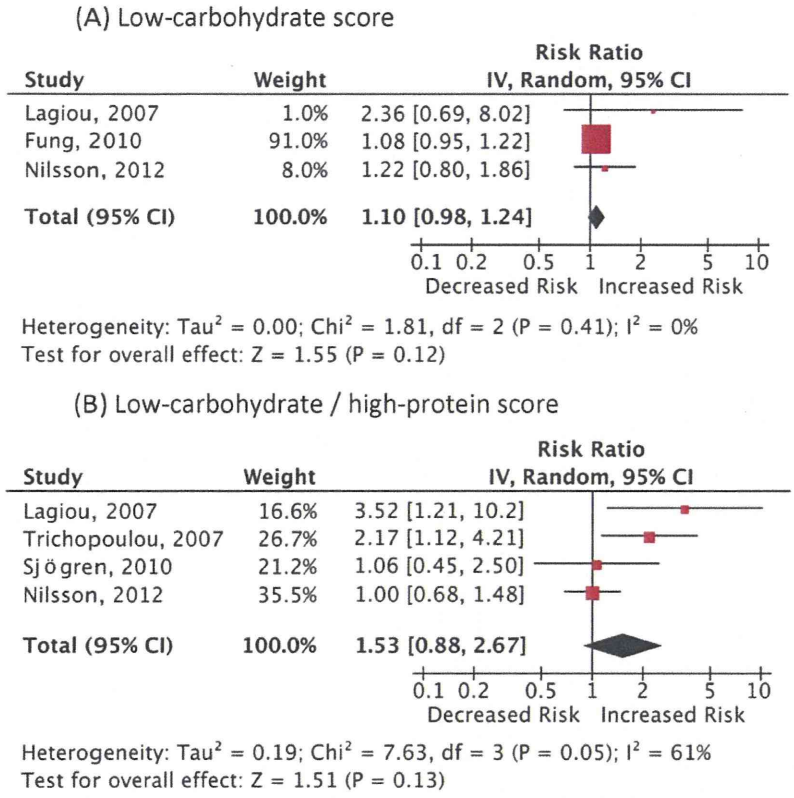

Figure 3. Adjusted risk ratios for CVD mortality associated with low-carbohydrate diets. Analysis was done based on (A) the low-carbohydrate score and (B) the low-carbohydrate/high-protein score. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. IV, inverse-variance.
doi:10.1371/journal.pone.0055030.g003

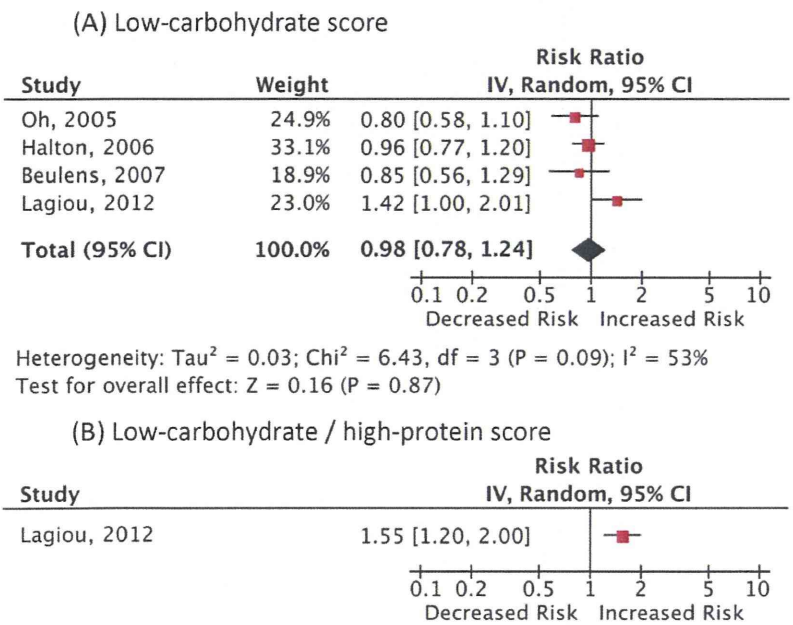

Figure 4. Adjusted risk ratios for CVD incidence associated with low-carbohydrate diets. Analysis was done based on (A) the low-carbohydrate score and (B) the low-carbohydrate/high-protein score. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. IV, inverse-variance.
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Even with these limitations, none of the included studies showed a significantly reduced risk and our analysis does not favor long-term benefits of low-carbohydrate diets, which should provide physicians with an incentive to pay attention to the considerable potential adverse effects on health if such diets are implemented without considering the nature of the carbohydrates and the source of protein. [9].

Conclusions

Our meta-analysis supported long-term harm and no cardiovascular protection with low-carbohydrate diets. However, the observational studies were limited and moderately heterogeneous. Our findings underscore the imminent need for large-scale trials on the complex interactions between low-carbohydrate diets and long-term outcomes.

Supporting Information

Table S1 Newcastle-Ottawa quality assessments of the included studies.
(DOCX)

Acknowledgments

Disclaimer: All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions

Conceived and designed the experiments: HN MN. Performed the experiments: HN AG TT. Analyzed the data: HN AG TT. Contributed reagents/materials/analysis tools: HN AG TT. Wrote the paper: HN.

References

1. Hession M, Rolland C, Kulkarni U, Wise A, Broom J (2009) Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. Obesity Reviews 10: 36–50.
2. Bravata DM, Sanders L, Huang J, Krumholz HM, Olkin I, et al. (2003) Efficacy and safety of low-carbohydrate diets: a systematic review. JAMA 289: 1837–1850.
3. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, et al. (2003) A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 348: 2074–2081.
4. Gogebakan O, Kohl A, Osterhoff MA, van Baak MA, Jebb SA, et al. (2011) Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: the diet, obesity, and genes (DiOGenes) study: a randomized, controlled trial. Circulation 124: 2829–2838.
5. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, et al. (2003) A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 348: 2082–2090.
6. Noakes M, Keogh JB, Foster PR, Clifton PM (2005) Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. Am J Clin Nutr 81: 1298–1306.
7. Fung TT, van Dam RM, Hankinson SE, Stampfer M, Willett WC, et al. (2010) Low-carbohydrate diets and all-cause and cause-specific mortality: two cohort studies. Ann Intern Med 153: 289–298.
8. Sjogren P, Becker W, Warensjo E, Olsson E, Byberg L, et al. (2010) Mediterranean and carbohydrate-restricted diets and mortality among elderly men: a cohort study in Sweden. Am J Clin Nutr 92: 967–974.
9. Lagiou P, Sandin S, Lof M, Trichopoulos D, Adami HO, et al. (2012) Low carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: prospective cohort study. BMJ 344: e4026.
10. Nilsson LM, Winkvist A, Eliasson M, Jansson JH, Hallmans G, et al. (2012) Low-carbohydrate, high-protein score and mortality in a northern Swedish population-based cohort. Eur J Clin Nutr 66: 694–700.
11. Lagiou P, Sandin S, Weiderpass E, Lagiou A, Mucci L, et al. (2007) Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. J Intern Med 261: 366–374.
12. Trichopoulou A, Psaltopoulou T, Orfanos P, Hsieh CC, Trichopoulos D (2007) Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. Eur J Clin Nutr 61: 575–581.
13. Floegel A, Pischon T (2012) Low carbohydrate-high protein diets. BMJ 344: e3801.
14. McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, et al. (2002) Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. Am J Clin Nutr 76: 1261–1271.
15. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ (2006) Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 367: 1747–1757.
16. Schulz KF, Altman DG, Moher D (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 152: 726–732.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, et al. (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 61: 344–349.
18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, et al. (Accessed 2012 December 3) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. http://wwwohrica/programs/clinical_epidemiology/oxfordasp.
19. Manzoli L, Villari P, G MP, Boccia A (2007) Marital status and mortality in the elderly: a systematic review and meta-analysis. Soc Sci Med 64: 77–94.
20. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, et al. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283: 2008–2012.
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151: W65–94.
22. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, et al. (2000) A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 71: 1455–1461.
23. Garcia-Palmieri MR, Sorlie P, Tillotson J, Costas R, Jr., Cordero E, et al. (1980) Relationship of dietary intake to subsequent coronary heart disease incidence: The Puerto Rico Heart Health Program. Am J Clin Nutr 33: 1818–1827.
24. McGee DL, Reed DM, Yano K, Kagan A, Tillotson J (1984) Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. Am J Epidemiol 119: 667–676.
25. McCullough ML, Feskanich D, Stampfer MJ, Rosner BA, Hu FB, et al. (2000) Adherence to the Dietary Guidelines for Americans and risk of major chronic disease in women. Am J Clin Nutr 72: 1214–1222.
26. McCullough ML, Feskanich D, Rimm EB, Giovannucci EL, Ascherio A, et al. (2000) Adherence to the Dietary Guidelines for Americans and risk of major chronic disease in men. Am J Clin Nutr 72: 1223–1231.
27. Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB (2001) Dietary patterns and the risk of coronary heart disease in women. Arch Intern Med 161: 1857–1862.
28. Diehr P, Beresford SAA (2003) The relation of dietary patterns to future survival, health, and cardiovascular events in older adults. J Clin Epidemiol 56: 1224–1235.
29. Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, et al. (2005) Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. Am J Epidemiol 161: 161–169.
30. Halton TL, Willett WC, Liu SM, Manson JE, Albert CM, et al. (2006) Low-carbohydrate-diet score and the risk of coronary heart disease in women. N Engl J Med 355: 1991–2002.
31. Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, et al. (2007) High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. J Am Coll Cardiol 50: 14–21.
32. Massimino FC, Gimeno SGA, Ferreira SRG, Japanese Brazilian Diabetes S (2007) All-cause mortality among Japanese-Brazilians according to nutritional characteristics. Cadernos De Saude Publica 23: 2145–2156.
33. Willett WC (2007) Low-carbohydrate diets: A place in health promotion? J Intern Med 261: 363–365.
34. Astrup A, Meinert Larsen T, Harper A (2004) Atkins and other low-carbohydrate diets: hoax or an effective tool for weight loss? Lancet 364: 897–899.
35. Larsson SC, Wolk A (2006) Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. Int J Cancer 119: 2657–2664.
36. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, et al. (2009) Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 360: 859–873.
37. Johnson JA, Gale EA (2010) Diabetes, insulin use, and cancer risk: are observational studies part of the solution-or part of the problem? Diabetes 59: 1129–1131.
38. Yang YX (2009) Do diabetes drugs modify the risk of pancreatic cancer? Gastroenterology 137: 412–415.
39. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, et al. (2006) Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials (Structured abstract). Archives of Internal Medicine. 285–293.

Table S1. Newcastle-Ottawa quality assessments of the included studies.

Study	Selection				Comparability	Outcome			Total quality score
	(1) Representativeness of the exposed cohort	(2) Selection of the non-exposed cohort	(3) Ascertainment of exposure	(4) Demonstration that outcome of interest was not present at start of study	(1) Comparability of cohorts on the basis of the design or analysis[a]	(1) Assessment of outcome	(2) Was follow-up long enough for outcomes to occur?[b]	(3) Adequacy of follow up of cohorts[c]	
Oh, 2005 [29]		★	★	★	★★	★	★	★	8
Halton, 2006 [30]		★	★	★	★★	★	★	★	8
Beulens, 2007 [31]	★	★	★	★	★★	★		★	8
Lagiou, 2007 [11]	★	★	★	★	★★	★	★	★	9
Trichopoulou, 2007 [12]	★	★	★	★	★★	★		★	8
Fung, [7]		★	★	★	★★	★	★	★	8
Sjögren, 2010 [8]	★	★	★	★	★★	★	★	★	9
Lagiou, 2012 [9]	★	★	★	★	★★	★	★	★	9
Nilsson, 2012 [10]	★	★	★	★	★★	★	★		8

a: A maximum of 2 stars can be awarded for this item. A study controlling for age receives one star, and a study controlling for other major risk factors for CHD and death receives an additional star.

b: A study with a follow-up period ≥10 years receives one star.

c: A study with a follow-up rate >90% receives one star.

発表論文

2) Noto H, Goto A, Tsujimoto T, Osame K, Noda M:
Latest insights into the risk of cancer in diabetes.
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Latest insights into the risk of cancer in diabetes

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ABSTRACT

A growing body of evidence from observational studies and meta-analyses of the data suggest that diabetes mellitus is associated with an increased risk of cancer. Meta-analyses have shown that diabetes increases the risks of total cancer, and of site-specific cancers of the breast, endometrium, bladder, liver, colorectum and pancreas, and that it decreases the risk of prostate cancer. Insulin resistance and secondary hyperinsulinemia is the most frequently proposed hypothesis, and hyperglycemia itself might promote carcinogenesis. In addition to several facets of lifestyle including obesity, smoking and lack of exercise, treatment for diabetes might affect the risk of cancer. For instance, metformin, an insulin sensitizer, reportedly has a potential anticancer effect. In light of the exploding global epidemic of diabetes, even a modest increase in the cancer risk will translate into a substantial socioeconomic burden. The current insights underscore the need for clinical attention and better-designed studies of the complex interactions between diabetes and cancer. (J Diabetes Invest, doi: 10.1111/jdi.12068, 2013)

KEY WORDS: Cancer, Diabetes, Risk factors

INTRODUCTION

Emerging evidence from observational studies and meta-analyses of the data suggest that diabetes mellitus is associated with an increased risk of cancer. The mechanisms are yet to be investigated, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis, as insulin might have a possible mitogenic effect through binding the insulin-like growth factor-1 receptor[1]. In addition, hyperglycemia itself might promote carcinogenesis by increasing oxidative stress[2–5].

In light of the fact that cancer is the second leading cause of death worldwide, diabetes is the 12th[6], the current worldwide diabetes epidemic and the higher mortality in cancer patients with diabetes[7,8], elucidating the association between these diseases in general populations is crucial for making timely, rational, and informed decisions, not only in the areas of public health and socioeconomy, but also for the prevention and targeted management of diabetes in daily clinical practice. The American Diabetes Association and the American Cancer Society recently published a consensus statement that reviewed evidence regarding the association between diabetes and cancer incidence or prognosis, risk factors common to both diabetes and cancer, possible biological links between diabetes and cancer risk, and whether diabetes treatments influence risk of cancer or cancer prognosis[9].

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EPIDEMIOLOGY

Several meta-analyses have shown that diabetes is associated with increased risks of site-specific cancers of the liver, endometrium, pancreas, colorectum, bladder, breast and total cancer (Table 1). The evidence for non-Hodgkin's lymphoma remains inconclusive[18]. Exceptionally, the risk of prostate cancer in diabetes is significantly decreased[17].

Evidence has been accumulating to suggest that diabetic patients have a higher risk of cancer death than non-diabetic peo-

Table 1 | Cancer risk in diabetes: meta-analysis

Site	Risk ratio (95% CI)
Cancer incidence	
Overall[10]	
Men	1.14 (1.06-1.23)
Women	1.18 (1.08-1.28)
Combined	1.10 (1.04-1.17)
Liver[11]	2.50 (1.93-3.24)
Endometrium[12]	2.10 (1.75-2.53)
Pancreas[13]	1.82 (1.66-1.89)
Colorectum[14]	1.30 (1.20-1.40)
Bladder[15]	1.24 (1.08-1.42)
Breast[16]	1.20 (1.12-1.28)
Prostate[17]	0.84 (0.76-0.93)
Cancer mortality	
Overall[10]	
Men	1.10 (0.98-1.23)
Women	1.24 (1.11-1.40)
Combined	1.16 (1.03-1.30)

CI, confidence interval.

ple (Table 1)[10,19]. Furthermore, cancer patients with pre-existing diabetes have higher short-term[8] and long-term[7] mortalities.

The same as in Western countries, the prevalence of diabetes is markedly increasing in Asia. This trend is presumably attributable to the rapid Westernization of lifestyle, a trend that is likely shared by the majority of Asian populations[20]. Although cardiovascular disease is the main cause of mortality in Western countries, and patients with diabetes have a high risk of such disease, cancer is emerging as a major cause of death in Asian countries[21–23]. Our meta-analysis[24] showed that the pooled adjusted risk ratio (RR) of all-cancer mortality in diabetics was significantly higher than in non-diabetic people (RR 1.32, 95% confidence interval [CI] 1.20–1.45 for Asians; RR 1.16, 95% CI 1.01–1.34 for non-Asians). Diabetes was also associated with an increased RR of incidence across all cancer types (RR 1.23, 95% CI 1.09–1.39 for Asians; RR 1.15, 95% CI 0.94–1.43 for non-Asians). The RR of incident cancer for Asian men was significantly higher than for non-Asian men ($P = 0.021$).

MECHANISMS

Hyperinsulinemia

Type 2 diabetes is characterized by insulin resistance and compensatory hyperinsulinemia, and people with type 2 diabetes are typically obese and lead sedentary lives, both of which also contribute to their hyperinsulinemia. Multiple and complex mechanisms are postulated. First, insulin might bind and activate its structurally related insulin-like growth factor-1 (IGF-1) receptor, which is the most frequently proposed mechanism to explain the clearly increased risk of cancer in diabetic patients (Figure 1)[1,25]. Second, hyperinsulinemia might increase cancer risk by unregulated insulin receptor signaling, leading to proliferative and anti-apoptotic effects[26]. Finally, the mitogenic activity of insulin might be enhanced at the cellular level by postreceptor molecular mechanisms including insulin residence time on the receptor and the intracellular upregulation of the insulin mitogenic pathway[27]. It has been reported that this mitogenic pathway, unlike the metabolic pathway, might not be blunted in the condition of insulin resistance[28].

Several findings were consistent with this insulin supply hypothesis. Pancreatic cancer has been reportedly induced more effectively with a carcinogen or by implantation of cancer cells when experimental insulin-deficient animals were given supplemental insulin[29]. In humans, patients with type 1 diabetes, who are insulin deficient, have a lower risk of cancer than patients with type 2 diabetes[30], although the evidence of the risk as compared with that in the general population remains inconclusive[31]. However, these speculations need to be interpreted with caution, as they are derived from retrospective observational studies and might not necessarily show causality because of possible biases and confounders, such as coexisting obesity

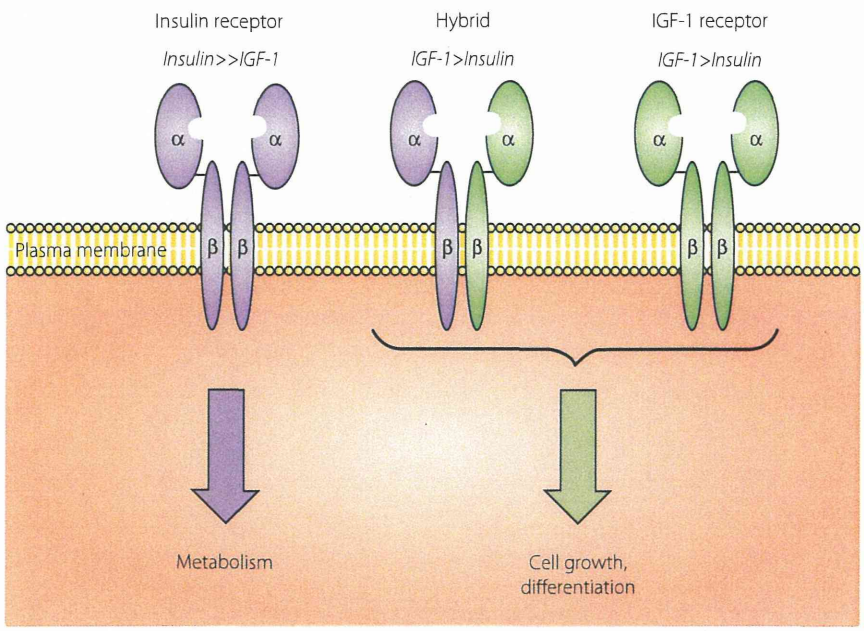

Figure 1 | *The insulin/insulin-like growth factor-1 (IGF-1) receptor. Both the insulin receptor and the IGF receptor are encoded by single genes,* which are processed into an α-chain and β-chain that remain linked by disulfide bonds. These α/β complexes can either homodimerize to form insulin receptors or IGF receptors, or heterodimerize to form hybrid receptors. Insulin binds preferentially to the insulin receptor, whereas IGF-1 binds preferentially to the IGF-1 and hybrid receptors. Although there is a great deal of overlap in their function, the insulin receptor is more closely linked with metabolic effects, whereas the hybrid receptor and IGF receptor are more closely linked with proliferation. Adapted from Biddinger *et al.*[25] with permission.

and age[32]. In fact, more recent studies have shown no or minimal increments in cancer risk[33], and the data from insulin-treated patients are controversial[34].

Of interest, diabetes has been reported to protect against the development of prostate cancer[17,35], which is testosterone-dependent. Testosterone deficiency is common in men with diabetes, because they have low levels of sex hormone-binding globulin, and testosterone levels have been shown to be partly influenced by insulin resistance[36]. The degree of the decrease in cancer risk as a result of testosterone deficiency is likely to be higher than the magnitude of the increase in cancer risk as a result of insulin resistance, and thus this effect of diabetes on prostate cancer might have contributed to the attenuation of the increase in cancer risk in men[19]. However, those meta-analyses[17,35] were mainly based on data for Caucasian men, and the reported risks for Asian men have been either significantly elevated in Taiwan[37,38] or non-significant in Japan[39] and Korea[3], which points to the possibility that the effect of diabetes on prostate cancer might not be universal, probably secondary to genetic/cultural/socioeconomic factors.

Hyperglycemia

Hyperglycemia has also been reported to promote carcinogenesis and cancer metastasis in type 2 diabetes[40]. Indeed, this forms the basis for 18F-fluorodeoxyglucose-positron emission tomography of cancers, which detects tissues with high rates of glucose uptake. In addition, hyperglycemia itself might promote carcinogenesis by generating oxidative stress[2,41], which is frequently observed to be increased in a variety of cells in diabetes. The increase in oxidative stress would damage DNA, the initial step in carcinogenesis[5]. Community-based prospective surveys have documented associations between plasma glucose levels and the risk of cancer[2,3,42]. The results of our study[24] support this hypothesis, because the results showed that the risk of both cancer incidence and mortality is also generally higher among Japanese[19] and Korean[3] patients with diabetes, who have been deemed to be insulinopenic[20,43]. However, a meta-analysis of large randomized-controlled trials (RCTs) of intensified glycemic control did not support the hypothesis that hyperglycemia is causally linked to increased cancer risk[44].

These observations point to the crucial need for understanding the role of glucose metabolism and insulin resistance in carcinogenesis[20,45].

Confounding Factors

Potential common risk factors of cancer and diabetes need to be addressed, because it remains to be clarified whether the association between diabetes and the risk of cancer is mainly a result of shared risk factors or whether diabetes itself causes some types of cancer.

First, several comorbidity confounders exist. Diabetes and cancer share multiple lifestyle-related risk factors (Table 2). For example, coexisting obesity and a sedentary lifestyle, which induce hyperinsulinemia, might be the true causes, and diabetes might merely be an innocent bystander. A meta-analysis showed that obesity is associated with increased risk for pancreas cancer, thyroid cancer, non-Hodgkin's lymphoma, leukemia and myeloma[46], whereas bariatric surgery resulted in 60% reduction in cancer mortality over the course of 7 years[47]. Exercise is suggestively associated with overall cancer, colon cancer, hepatocellular cancer, pancreas cancer and gastric cancer[48]. The other possible confounding factors include age, sex, diet, alcoholic intake, smoking, cirrhosis, hepatitis C viral infection[49] and the indication of insulin therapy. These factors are generally interrelated, and thus it is difficult to assess the contribution of each factor. Second, an alternative explanation is that diabetic patients might receive medical care more frequently and have more opportunities for cancer detection than non-diabetic subjects. Third, diabetes might develop as a consequence of cancer, as cancers generally cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis-α[50]. Fourth, the previous studies might have left room for confounding by treatment indication; differences between the treatment of cancer according to whether or not they had diabetes might have contributed to the increased mortality of the subjects. Diabetic patients often have other diabetes-related comorbidities that might influence the treatment decisions and prognosis. For example, diabetes might be accompanied by a higher risk of infection, and the diagnosis of cancer might result in inappropriate glucose management.

Table 2 | Shared risk factors of diabetes and cancer

Age
Sex
Genetic factors
Obesity
Diets
Lack of exercise
Smoking
Alcohol intake

MEDICAL TREATMENT OF DIABETES AND CANCER

Insulin, Sulfonylureas and Glinides

As discussed earlier, insulin injection might increase the risk of cancer because of its structural similarity to IGF-1. In fact, several reports based on observational studies suggested that insulin glargine usage might be associated with an elevated risk of cancer[51–54]. However, these observational studies were subject to considerable biases[34,55,56]: retrospective studies only show an association, and not necessarily causality; it is very difficult to adjust all possible confounders in observational studies; the effects of treatment by indication and informative censoring cannot be excluded. In contrast, the oncogenic effect of hyperinsulinemia might be offset by the cancer-protective effect through amelioration of hyperglycemia. RCTs and more recent cohort studies have not shown significant associations of insulin with cancer risk[57–62].

Table 3 | Metformin and cancer risk in diabetes: meta-analysis[69]

Site	Risk ratio (95% CI)
Cancer incidence*	
Overall	0.67 (0.53–0.85)
Liver	0.20 (0.07–0.88)
Lung	0.67 (0.45–0.99)
Colorectum	0.68 (0.53–0.88)
Cancer mortality	
Overall	0.66 (0.49–0.88)

*Risk ratios for the cancer of pancreas, breast, stomach and bladder were not statistically significant. CI, confidence interval.

Sulfonylureas and glinides induce hyperinsulinemia, and thus there is a concern of increased cancer risks[54,63–66]. However, the estimates in other reports are inconsistent[67]. Further investigations are required to verify its oncogenic safety.

Metformin

Metformin is an insulin sensitizer that is the drug of first choice in the management of type 2 diabetes[68], given its safety profile and lower cost. Our recent meta-analysis including observational studies and RCTs showed that metformin usage is associated with a lower risk of cancer incidence and mortality in diabetes[69] (Table 3), and similar effects have been seen across different regions in the world[38,65,67,70–73].

As shown in Figure 2, metformin activates activating adenosine 5′-mono-phosphate-activated protein kinase (AMPK) through LKB-1, a tumor suppressor protein kinase. AMPK, the mammalian target of rapamycin (mTOR) and the insulin-signaling pathway represent three interrelated components of a complex mechanism controlling cell responses to nutrient availability. AMPK inhibits protein synthesis and gluconeogenesis during cellular stress and inhibits mTOR, a downstream effector of growth factor signaling, which is frequently activated in malignant cells. In human breast cancer cells, it reduces HER-2 protein expression by inhibiting mTOR. Metformin also induces cell cycle arrest and apoptosis, and reduces growth factor signaling. To support the hypothesis of these direct effects, metformin reportedly potentiated the effect of neoadjuvant chemotherapy in early-stage breast cancer[74], decreased the risk of colorectal cancer in a small RCT involving non-diabetic subjects[75], and was associated with a decreased cancer risk while another insulin-sensitizer, thiazolidinedione, was not[76–79].

Our research[69] showed that metformin use is associated with reduced mortality and incidence of cancer at any site, supporting the generalizability of the proposed anticancer mechanisms. In contrast, the magnitude of the risk reduction

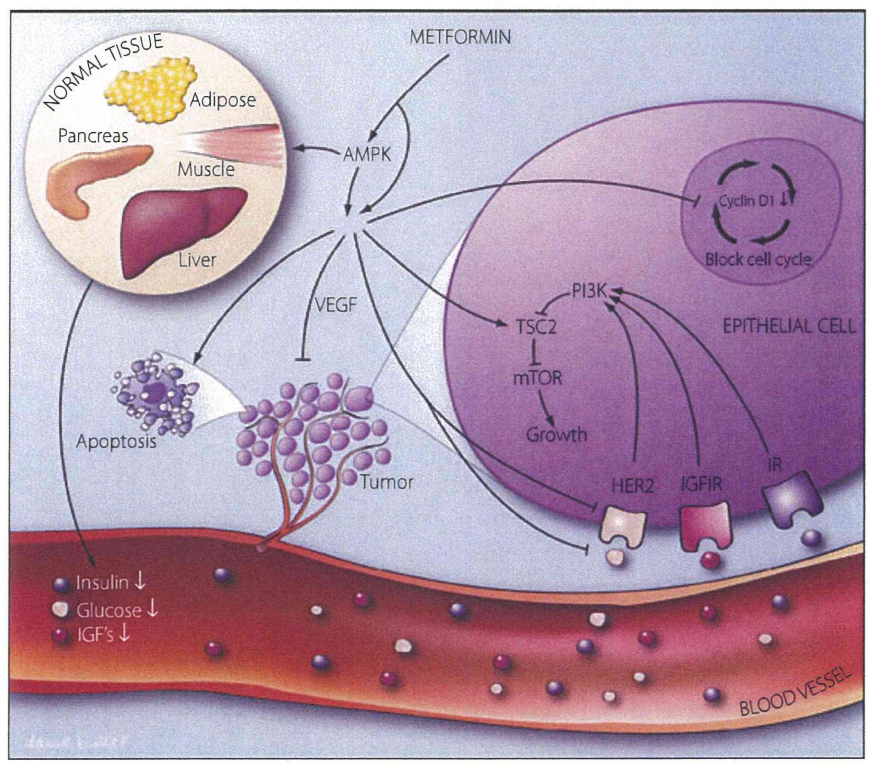

Figure 2 | Mechanisms of anti-oncogenic effect of metformin. AMPK, adenosine 5′-mono-phosphate-activated protein kinase; HER2, epithelial growth factor receptor 2; IGF, insulin-like growth factor; IGF-1R, insulin-like growth factor 1; IR, insulin receptor; mTOR, mammalian target of rapamycin; PI3K, phosphinositide 3-kinase; TSC2, tuberous sclerosis complex 2; VEGF, vascular endothelial growth factor. Adapted from Jalving *et al.*[87] with permission.

Table 4 | Risk of bladder cancer in pioglitazone users

	Hazard ratio (95% CI)
Exposure to pioglitazone	1.2 (0.9–1.5)
Cumulative treatment periods (months)	
<12	0.8 (0.6–1.3)
12–24	1.4 (0.9–2.1)
≥24	1.4 (1.03–2.0)
P_{trend}	0.03
Cumulative dosage (mg)	
1–10,500	1.0 (0.7–1.5)
10,500–28,000	1.2 (0.8–1.8)
>28,000	1.4 (0.96–2.1)
P_{trend}	0.08

Adapted from Lewis *et al.*[79] with permission. CI, confidence interval.

varies among site-specific cancers. This variance might result from differences in carcinogenesis at certain sites. For instance, elevated levels of insulin and glucose might exert an important influence in the development or growth of epithelial malignant tumors of the colon[80–82], pancreas[83,84] and breast[85], and metformin reportedly prevents incident colon cancer in non-diabetic subjects[75]. An animal study suggested that metformin prevented smoking-related lung cancer in mice, probably by inducing some hormone from the liver[86]. The fact that one preliminary study suggested a promising effect of metformin on pathological complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer[74] might point to the possibility that metformin simply augmented the efficacy of chemotherapy for breast cancer[77,87]. Several prospective clinical trials to evaluate its safety and efficacy are currently ongoing[34,87].

Pioglitazone

Pioglitazone is another insulin sensitizer that activates peroxisome proliferator-activated receptor-γ. Recent reports including meta-analyses have suggested that it might significantly increase the risk of bladder cancer in a exposure/dose-response pattern[73,78,79,88–94] (Table 4), whereas its effect on total cancer or cancers at other sites might be neutral[95]. The carcinogenic effect was also seen in an animal study[96], although the mechanism is not clarified yet. The risk is not conclusive at present[65,73,97,98], and several surveys are in progress. It is currently not on the market in France and Germany because of this potential harm.

α-Glucosidase Inhibitors

Data on the cancer risk associated with α-glucosidase inhibitors are sparse. An increased risk of bladder cancer was reported in one study[78], whereas it was not confirmed in another[65].

Glucagon-Like Peptide-1 Analogs and Dipeptidyl Peptidase-4 Inhibitors

The risk of pancreas cancer and thyroid cancer was reportedly elevated among exenatide, a glucagon-like peptide-1 analog, users[99]. An increased risk of thyroid C-cell cancer was seen in rodent studies. The risk of pancreas cancer might be increased with sitagliptin, a DPP-4 inhibitor[99]. Although a meta-analysis suggested oncogenic safety of dipeptidyl peptidase-4 (DPP-4) inhibitors[100], the included studies were of short follow-up periods and the long-term effect remains elusive.

FUTURE DIRECTIONS

In light of the exploding global epidemic of diabetes, a modest increase in the risk of cancer will translate into a substantial socioeconomic burden. The present review underscores the need for diabetes prevention, particularly by weight management, and for investigation of effective cancer prevention, screening policies and implementation of diabetes treatment with potentially protective effects against cancer. Attention should be directed to elucidating the association between these diseases in populations with increased risks to make timely, rational and informed decisions, not only in the public health area and socioeconomic area, but also for the prevention and targeted management of diabetes in routine clinical practice. For the time being, healthful diets, physical activity and weight management should be promoted for all. Patients with diabetes should be strongly encouraged by their healthcare professionals to undergo appropriate cancer screenings as recommended for all people of their age and sex, and cancer risk should not be a major factor in choosing between available diabetes therapies for the average patient[9].

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The authors have declared that no competing interests exist.

REFERENCES

1. White MF. The insulin signalling system and the IRS proteins. *Diabetologia* 1997; 40(Suppl 2): S2–S17.
2. Barclay AW, Petocz P, McMillan-Price J, *et al.* Glycemic index, glycemic load, and chronic disease risk – a meta-analysis of observational studies. *Am J Clin Nutr* 2008; 87: 627–637.
3. Jee SH, Ohrr H, Sull JW, *et al.* Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; 293: 194–202.
4. Stocks T, Rapp K, Bjorge T, *et al.* Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. *PLoS Med* 2009; 6: e1000201.
5. Abe R, Yamagishi S. AGE-RAGE system and carcinogenesis. *Curr Pharm Des* 2008; 14: 940–945.
6. Lopez AD, Mathers CD, Ezzati M, *et al.* Global and regional burden of disease and risk factors, 2001: systematic

analysis of population health data. *Lancet* 2006; 367: 1747–1757.
7. Barone BB, Yeh HC, Snyder CF, *et al.* Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008; 300: 2754–2764.
8. Barone BB, Yeh HC, Snyder CF, *et al.* Postoperative mortality in cancer patients with preexisting diabetes: systematic review and meta-analysis. *Diabetes Care* 2010; 33: 931–939.
9. Giovannucci E, Harlan DM, Archer MC, *et al.* Diabetes and cancer: a consensus report. *Diabetes Care* 2010; 33: 1674–1685.
10. Noto H, Tsujimoto T, Sasazuki T, *et al.* Significantly increased risk of cancer in patients with diabetes mellitus. *Endocr Pract* 2011; 17: 616–628.
11. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; 4: 369–380.
12. Friberg E, Orsini N, Mantzoros CS, *et al.* Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 2007; 50: 1365–1374.
13. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, *et al.* Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005; 92: 2076–2083.
14. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* 2005; 97: 1679–1687.
15. Larsson SC, Andersson SO, Johansson JE, *et al.* Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men. *Eur J Cancer* 2008; 44: 2655–2660.
16. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer* 2007; 121: 856–862.
17. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2056–2062.
18. Chao C, Page JH. Type 2 diabetes mellitus and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis. *Am J Epidemiol* 2008; 168: 471–480.
19. Noto H, Osame K, Sasazuki T, *et al.* Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. *J Diabetes Complications* 2010; 24: 345–353.
20. Chan JC, Malik V, Jia W, *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
21. Hotta N, Nakamura J, Iwamoto Y, *et al.* Causes of death in Japanese diabetics: a questionnaire survey of 18,385 diabetics over a 10-year period. *J Diabetes Invest* 2010; 1: 66–76.
22. Tseng CH. Mortality and causes of death in a national sample of diabetic patients in Taiwan. *Diabetes Care* 2004; 27: 1605–1609.
23. Yang X, So WY, Kong AP, *et al.* Development and validation of a total coronary heart disease risk score in type 2 diabetes mellitus. *Am J Cardiol* 2008; 101: 596–601.
24. Noto H, Tsujimoto T, Noda M. Significantly increased risk of cancer in diabetes mellitus patients: a meta-analysis of epidemiologic evidence in Asians and non-Asians. *J Diabetes Invest* 2012; 3: 24–33.
25. Biddinger S, Emanuelli B. Insulin Resistance in the Metabolic Syndrome. In: Ahima A (ed). *Metabolic Basis of Obesity*, 1st edn. Springer, New York, 2011; 175–198.
26. Gallagher EJ, Leroith D. Minireview: IGF, Insulin, and Cancer. *Endocrinology* 2011; 152: 2546–2551.
27. Vigneri P, Frasca F, Sciacca L, *et al.* Diabetes and cancer. *Endocr Relat Cancer* 2009; 16: 1103–1123.
28. Corbould A, Zhao H, Mirzoeva S, *et al.* Enhanced mitogenic signaling in skeletal muscle of women with polycystic ovary syndrome. *Diabetes* 2006; 55: 751–759.
29. Fisher WE, Boros LG, O'Dorisio TM, *et al.* GI hormonal changes in diabetes influence pancreatic cancer growth. *J Surg Res* 1995; 58: 754–758.
30. Lindblad P, Chow WH, Chan J, *et al.* The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologia* 1999; 42: 107–112.
31. Zendehdel K, Nyren O, Ostenson CG, *et al.* Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Natl Cancer Inst* 2003; 95: 1797–1800.
32. Johnson JA, Gale EA. Diabetes, insulin use, and cancer risk: are observational studies part of the solution-or part of the problem? *Diabetes* 2010; 59: 1129–1131.
33. van Staa TP, Patel D, Gallagher AM, *et al.* Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. *Diabetologia* 2012; 55: 654–665.
34. McFarland MS, Cripps R. Diabetes mellitus and increased risk of cancer: focus on metformin and the insulin analogs. *Pharmacotherapy* 2010; 30: 1159–1178.
35. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* 2004; 47: 1071–1078.
36. Grossmann M, Thomas MC, Panagiotopoulos S, *et al.* Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab* 2008; 93: 1834–1840.
37. Tseng CH. Prostate cancer mortality in Taiwanese men: increasing age-standardized trend in general population and increased risk in diabetic men. *Ann Med* 2011; 43: 142–150.
38. Tseng CH. Diabetes and risk of prostate cancer: a study using the National Health Insurance. *Diabetes Care* 2011; 34: 616–621.
39. Inoue M, Iwasaki M, Otani T, *et al.* Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med* 2006; 166: 1871–1877.

40. Richardson LC, Pollack LA. Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Pract Oncol* 2005; 2: 48–53.
41. Gapstur SM, Gann PH, Lowe W, *et al.* Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 2000; 283: 2552–2558.
42. Seshasai SR, Kaptoge S, Thompson A, *et al.* Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; 364: 829–841.
43. Kadowaki T, Miyake Y, Hagura R, *et al.* Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 1984; 26: 44–49.
44. Stefansdottir G, Zoungas S, Chalmers J, *et al.* Intensive glucose control and risk of cancer in patients with type 2 diabetes. *Diabetologia* 2011; 54: 1608–1614.
45. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell* 2006; 124: 823–835.
46. Renehan AG, Tyson M, Egger M, *et al.* Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; 371: 569–578.
47. Adams TD, Gress RE, Smith SC, *et al.* Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; 357: 753–761.
48. Inoue M, Yamamoto S, Kurahashi N, *et al.* Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. *Am J Epidemiol* 2008; 168: 391–403.
49. Noto H, Raskin P. Hepatitis C infection and diabetes. *J Diabetes Complications* 2006; 20: 113–120.
50. McCall JL, Tuckey JA, Parry BR. Serum tumour necrosis factor alpha and insulin resistance in gastrointestinal cancer. *Br J Surg* 1992; 79: 1361–1363.
51. Hemkens LG, Grouven U, Bender R, *et al.* Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 2009; 52: 1732–1744.
52. Jonasson JM, Ljung R, Talback M, *et al.* Insulin glargine use and short-term incidence of malignancies – a population-based follow-up study in Sweden. *Diabetologia* 2009; 52: 1745–1754.
53. Colhoun HM. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 2009; 52: 1755–1765.
54. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009; 52: 1766–1777.
55. Smith U, Gale EA. Does diabetes therapy influence the risk of cancer? *Diabetologia* 2009; 52: 1699–1708.
56. Hernandez-Diaz S, Adami HO. Diabetes therapy and cancer risk: causal effects and other plausible explanations. *Diabetologia* 2010; 53: 802–808.
57. Rosenstock J, Fonseca V, McGill JB, *et al.* Similar risk of malignancy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: findings from a 5 year randomised, open-label study. *Diabetologia* 2009; 52: 1971–1973.
58. Home PD, Lagarenne P. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. *Diabetologia* 2009; 52: 2499–2506.
59. The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in Dysglycemia. *N Engl J Med* 2012; 367: 319–328.
60. Fagot JP, Blotiere PO, Ricordeau P, *et al.* Does insulin glargine increase the Risk of cancer compared with other basal insulins?: a French nationwide cohort study based on national administrative databases. *Diabetes Care* 2013; 36: 294–301.
61. Morden NE, Liu SK, Smith J, *et al.* Further exploration of the relationship between insulin glargine and incident cancer: a retrospective cohort study of older Medicare patients. *Diabetes Care* 2011; 34: 1965–1971.
62. Yang X, Ko GT, So WY, *et al.* Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. *Diabetes* 2010; 59: 1254–1260.
63. Monami M, Lamanna C, Balzi D, *et al.* Sulphonylureas and cancer: a case-control study. *Acta Diabetol* 2009; 46: 279–284.
64. Hsieh MC, Lee TC, Cheng SM, *et al.* The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. *Exp Diabetes Res* 2012; 2012: 413782.
65. Tseng CH. Diabetes and risk of bladder cancer: a study using the National Health Insurance database in Taiwan. *Diabetologia* 2011; 54: 2009–2015.
66. Chang CH, Lin JW, Wu LC, *et al.* Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2012; 97: E1170–E1175.
67. Yang X, So WY, Ma RC, *et al.* Use of sulphonylurea and cancer in type 2 diabetes – The Hong Kong Diabetes Registry. *Diabetes Res Clin Pract* 2010; 90: 343–351.
68. Nathan DM, Buse JB, Davidson MB, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32: 193–203.
69. Noto H, Goto A, Tsujimoto T, *et al.* Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. *PLoS ONE* 2012; 7: e33411. doi:33410.31371/journal.pone.0033411.
70. Lee MS, Hsu CC, Wahlqvist ML, *et al.* Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. *BMC Cancer* 2011; 11: 20.

71. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology* 2004; 127: 1044–1050.
72. Lai SW, Chen PC, Liao KF, *et al.* Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. *Am J Gastroenterol* 2012; 107: 46–52.
73. Chang CH, Lin JW, Wu LC, *et al.* Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. *Hepatology* 2012; 55: 1462–1472.
74. Jiralerspong S, Palla SL, Giordano SH, *et al.* Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol* 2009; 27: 3297–3302.
75. Hosono K, Endo H, Takahashi H, *et al.* Metformin suppresses azoxymethane-induced colorectal aberrant crypt foci by activating AMP-activated protein kinase. *Mol Carcinog* 2010; 49: 662–671.
76. Li D, Yeung SC, Hassan MM, *et al.* Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009; 137: 482–488.
77. Decensi A, Puntoni M, Goodwin P, *et al.* Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev Res (Phila)* 2010; 3: 1451–1461.
78. Piccinni C, Motola D, Marchesini G, *et al.* Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care* 2011; 34: 1369–1371.
79. Lewis JD, Ferrara A, Peng T, *et al.* Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011; 34: 916–922.
80. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr* 2007; 86: s836–s842.
81. Zakikhani M, Dowling RJ, Sonenberg N, *et al.* The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of AMP-activated protein kinase. *Cancer Prev Res (Phila)* 2008; 1: 369–375.
82. Algire C, Amrein L, Zakikhani M, *et al.* Metformin blocks the stimulative effect of a high-energy diet on colon carcinoma growth *in vivo* and is associated with reduced expression of fatty acid synthase. *Endocr Relat Cancer* 2010; 17: 351–360.
83. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. *Nat Rev Gastroenterol Hepatol* 2009; 6: 699–708.
84. Schneider MB, Matsuzaki H, Haorah J, *et al.* Prevention of pancreatic cancer induction in hamsters by metformin. *Gastroenterology* 2001; 120: 1263–1270.
85. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *Am J Clin Nutr* 2007; 86: s823–s835.
86. Memmott RM, Mercado JR, Maier CR, *et al.* Metformin prevents tobacco carcinogen–induced lung tumorigenesis. *Cancer Prev Res (Phila)* 2010; 3: 1066–1076.
87. Jalving M, Gietema JA, Lefrandt JD, *et al.* Metformin: taking away the candy for cancer? *Eur J Cancer* 2010; 46: 2369–2380.
88. Hillaire-Buys D, Faillie JL, Montastruc JL. Pioglitazone and bladder cancer. *Lancet* 2011; 378: 1543–1544; author reply 1544-1545.
89. Neumann A, Weill A, Ricordeau P, *et al.* Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia* 2012; 55: 1953–1962.
90. Azoulay L, Yin H, Filion KB, *et al.* The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ* 2012; 344: e3645.
91. Mamtani R, Haynes K, Bilker WB, *et al.* Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. *J Natl Cancer Inst* 2012; 104: 1411–1421.
92. Actos. Product information as approved by the CHMP on 20 October 2011, pending endorsement by the European Commission. 2011. Available at: http://www.ema. europa.eu/docs/en_GB/document_library/Other/2011/07/WC500109185.pdf (accessed December 20 2011).
93. Zhu Z, Shen Z, Lu Y, *et al.* Increased risk of bladder cancer with pioglitazone therapy in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2012; 98: 159–163.
94. Colmers IN, Bowker SL, Majumdar SR, *et al.* Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. *CMAJ* 2012; 184: E675–E683.
95. Ramos-Nino ME, MacLean CD, Littenberg B. Association between cancer prevalence and use of thiazolidinediones: results from the Vermont Diabetes Information System. *BMC Med* 2007; 5: 17.
96. Suzuki S, Arnold LL, Pennington KL, *et al.* Effects of pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, on the urine and urothelium of the rat. *Toxicol Sci* 2010; 113: 349–357.
97. Tseng CH. Pioglitazone and bladder cancer: a population-based study of Taiwanese. *Diabetes Care* 2012; 35: 278–280.
98. Li W, Macdonald TM, Mackenzie IS. Pioglitazone and bladder cancer: a propensity score matched cohort study. *Br J Clin Pharmacol* 2013; 75: 254–259.
99. Elashoff M, Matveyenko AV, Gier B, *et al.* Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; 141: 150–156.
100. Monami M, Dicembrini I, Martelli D, *et al.* Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011; 27 (Suppl 3): 57–64.

1）朝日新聞（2013 年 1 月 27 日）

朝日新聞デジタル：糖質制限ダイエット、長期は危険？　死亡率高まる恐れ

糖質制限ダイエット、長期は危険？ 死亡率高まる恐れ

【桜井林太郎】ご飯やパンなどの糖質を控える「糖質制限食（ダイエット）」を５年以上続けると、死亡率が高くなるかもしれないとする解析結果を、国立国際医療研究センター病院糖尿病・代謝・内分泌科の能登洋医長らが２６日、米科学誌プロスワンで発表した。死亡率が高まる理由はよく分かっていない。

糖質制限食は「低炭水化物ダイエット」などとも呼ばれ、短期的には減量や血糖値の改善につながるという報告が出ているが、長く続けても安全かははっきりしていない。能登さんらは昨年９月１２日までに発表された糖質制限食に関する４９２の医学論文から動物実験などを除き、人間での経過を５年以上追跡して死亡率などを調べた海外９論文を分析した。

対象は、とくに病気がない地域住民や医療スタッフら計約２７万人。摂取した総カロリーに占める糖質の割合に応じて１０のグループに分けた。

5?２６年の追跡期間中、計約１万６千人が死亡していたが、糖質摂取量の割合が最も少ないグループの死亡率は最も多いグループの１・３１倍で、統計上の明確な差が出た。

糖質制限食は「肉食中心になりがちで、心筋梗塞（こうそく）や脳卒中などのリスクが高まる可能性がある」との指摘がある。そこで、心筋梗塞などによる死亡率や発症率との関係を調べたが、はっきりした差はなかった。

能登さんは「なぜ死亡率が高まるのか、原因の究明が課題だが、糖質制限食の長期的な利点は少ないのではないか。日本人も含めたさらなる検証の必要性がある」と話す。

2）読売新聞（2013 年 1 月 28 日）

低炭水化物ダイエット、死亡率高まる可能性：科学：YOMIURI ONLINE（読売新聞）

低炭水化物ダイエット、死亡率高まる可能性

ご飯やパンなどの炭水化物の摂取が、長期にわたって少ない人は、多い人よりも死亡率が高まる可能性があるとする調査結果を、厚生労働省の研究班がまとめ、科学誌プロスワンに発表した。

炭水化物の摂取を極力控えるダイエット法に一石を投じる成果として注目される。

国立国際医療研究センターの能登洋・糖尿病代謝内分泌科医長らが、米国と欧州で、７０代～３０代の男女２０万人以上を２６～５年にわたり追跡した住民健康調査などのデータを解析した。その結果、総摂取カロリーに炭水化物が占める割合が４０％以下と、低い人の死亡率は、炭水化物の摂取割合が高い人（同６０％以上）の１・３倍だった。

炭水化物を抑えた食事は、短期的には血糖値が下がり、コレステロールの値が改善するなど、心疾患のリスクを下げるとの報告がある。ところが、今回の解析では、長期間の低炭水化物食が、心疾患のリスクを下げる傾向は見られなかった。能登医長は「低炭水化物食は短期的には減量などに効果があっても、長年続けることには慎重になった方が良い」と指摘する。

（2013年1月28日15時30分　読売新聞）