Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis

British Journal of Nutrition (2012), **108**, 1934–1947
doi:10.1017/S0007114512003984

Review Article

Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis

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(Submitted 12 March 2012 – Final revision received 26 July 2012 – Accepted 8 August 2012 – First published online 18 October 2012)

Abstract

Diets high in glycaemic index (GI) or glycaemic load (GL) have been hypothesised to increase the risks of certain cancers by increasing blood glucose or insulin concentrations. We aimed to conduct a meta-analysis of prospective cohort studies to evaluate the association between GI or GL and diabetes-related cancers (DRC), including bladder, breast, colon–rectum, endometrium, liver and pancreas, which are associated with an increased risk for diabetes, and prostate cancer, which is associated with a reduced risk for diabetes. We searched Pubmed, EMBASE and MEDLINE databases up to September 2011 and reference lists of relevant articles. Relative risks (RR) and 95 % CI for the highest *v.* the lowest categories were extracted and pooled using a random-effects model. Thirty-six prospective cohort studies with a total of 60 811 DRC cases were included in the present meta-analysis. In a comparison of the highest and lowest categories, the pooled RR of DRC were 1·07 (95 % CI 1·04, 1·11; *n* 30) for GI and 1·02 (95 % CI 0·96, 1·08; *n* 33) for GL. In an analysis of site-specific cancer risks, we found significant associations for GI in relation to breast cancer (RR 1·06; 95 % CI 1·02, 1·11; *n* 11) and colorectal cancer (RR 1·08; 95 % CI 1·00, 1·17; *n* 9 studies). GL was significantly associated with the risk of endometrial cancer (RR 1·21; 95 % CI 1·07, 1·37; *n* 5). In conclusion, the findings of the present study suggest a modest-to-weak association between a diet that induces a high glucose response and DRC risks.

Key words: Glycaemic index: Glycaemic load: Diabetes-related cancers: Meta-analysis

Diabetes and cancer are common chronic diseases that have contributed to many deaths worldwide. Recently, a consensus report of experts[1] representing the American Diabetes Association and the American Cancer Society reviewed the relationship between diabetes and cancers, and suggested that individuals with diabetes (primarily type 2) are more susceptible to developing cancers of the liver, pancreas, endometrium, colon/rectum, breast and bladder; however, they also have a lower risk of prostate cancer. This consensus report also discussed several possible biological mechanisms that may explain the direct link between diabetes and cancers, such as hyperinsulinaemia, hyperglycaemia and inflammation, but an explanation remains elusive.

The glycaemic index (GI) is, by definition, a unit of measurement used to rank carbohydrate-containing foods (scores ranging from 0 to 100) based on the postprandial blood glucose response compared with an equivalent amount of carbohydrate from a reference food (either glucose or white bread)[2]. A related measure, the glycaemic load (GL), of a serving of a specific food is the product of the GI and the grams of carbohydrate content in a serving of a food, reflecting both the quality and quantity of dietary carbohydrates[3–5]. Validation studies have shown that GL may be applicable to measuring degrees of overall postprandial plasma glucose and insulin response[6,7]. Prospective cohort studies have shown that high-GI or -GL diets are associated with increased

Abbreviations: DRC, diabetes-related cancer; GI, glycaemic index; GL, glycaemic load; RR, relative risk.

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risks of adverse health outcomes, including CHD[8], the metabolic syndrome[9] and type 2 diabetes[10,11] compared with low GI or GL. Additionally, a number of epidemiological studies have been conducted for the associations between GI or GL and the risk of common cancer sites, although results have been mixed (generally positive or null, not showing a clear association). Given the evidence for the potential link between GI or GL and cancer risks, presumably through effects of a diet stimulating postprandial glucose or insulin response, it is important to evaluate the hypothesis that GI and GL can be potential predictive factors for cancer risks, particularly those related to high levels of blood glucose or insulin.

We therefore assessed the associations between GI or GL and diabetes-related cancers (DRC) in a meta-analysis of observational prospective cohort studies. We did not include case–control studies because recall and selection bias is often encountered in case–control studies of diet and cancer risk.

Materials and methods

Literature search

A single author (Y. C.) conducted a literature search of the published studies using Pubmed, EMBASE and MEDLINE databases up to September 2011, and another author (J. E. L.) checked the extracted studies. The keyword 'glycemic index' OR 'glycemic load' was combined with the following search terms in each turn: (1) 'liver cancer' OR 'liver neoplasm' OR 'liver carcinoma' OR 'hepatocellular carcinoma'; (2) 'pancreas' OR 'pancreatic cancer' OR 'pancreatic neoplasm' OR 'pancreatic carcinoma'; (3) 'endometrium' OR 'endometrial cancer' OR 'endometrial neoplasm' OR 'corpus uteri' OR 'endometrial carcinoma'; (4) 'colorectal cancer" OR 'colon cancer' OR 'rectal cancer' OR 'colorectal neoplasm' OR 'colorectal carcinoma'; (5) 'breast cancer' OR 'breast carcinoma' OR 'breast neoplasm'; (6) 'bladder cancer' OR 'bladder neoplasm' OR 'bladder carcinoma'; (7) 'prostate cancer' OR 'prostate neoplasm' OR 'prostate carcinoma'. We also reviewed the reference lists of the retrieved articles to identify additional studies.

Study selection

Studies were included if they met the following criteria: (1) a cohort with GI or GL as an exposure and cases of DRC as an outcome were described; (2) estimates of relative risk (RR) and corresponding 95 % CI were provided; and (3) it was published in English. If multiple publications from one study were found, the most recent study was included in the present meta-analysis.

Data extraction

The following data were retrieved from the publications: the first author's last name, the year of publication, the sex of the participants, the study name, the country where the study was performed, the duration of follow-up, the age at baseline, the number of cases, the sample size, the dietary assessment, the comparison level (the highest intake category *v.* the lowest) of the GI and GL and confounding factors included in the multivariable-adjusted model. For each study, we used the most fully adjusted RR in the multivariate

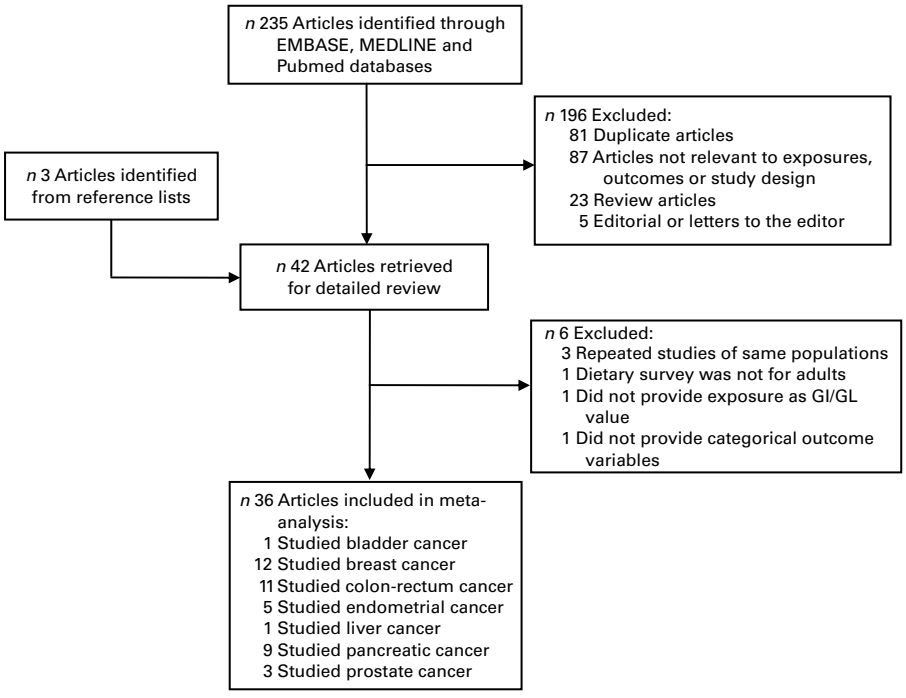

Fig. 1. Flowchart of the study selection process in the meta-analysis. GI, glycaemic index; GL, glycaemic load.

Table 1. Characteristics of the studies included in the meta-analysis

Study (sex)	Study name	Study location and follow-up (years)†	Age at baseline (years)	Cases (*n*)	Cohort size (*n*)	Dietary assessment	Comparison level (highest *v.* lowest)*		Study quality	Adjustment for confounders
							Glycaemic index	Glycaemic load		
Bladder cancer										
George *et al.*[14] (M, F)	NIH-AARP	USA (1995–2003)	50–71	F: 235	183 535	FFQ(s) 124 items	F: 56·6–83·9 *v.* 33·6–50·4	F: 135·3–593·7 *v.* 4·6–66·9	8	Age, race, education, marital status, BMI, FH of any cancer, PA, smoking, alcohol, TEI, menopausal HRT (women only)
				M: 1246	262 642		M: 57·0–84·1 *v.* 33·5–51·3	M: 164·4–740·2 *v.* 7·08–83·2		
Breast cancer										
Shikany *et al.*[28] (F)	WHI	USA (8)	50–79	6115	148 767	FFQ(s) 122 items	57 *v.* 47·8	52·9 *v.* 150·4	7	Age, race, education, hormone therapy trial randomisation, dietary modification trial randomisation, Ca and vitamin D trial randomisation, smoking, alcohol, PA, BMI, AAM, age at first birth, parity, age at menopause, oral contraceptive use, postmenopausal hormone use, breast cancer in first-degree relative, mammogram within 2 years prior to enrollment, TEI
George *et al.*[14] (F)	NIH-AARP	USA (1995–2003)	50–71	5478	183 535	FFQ(s) 124 items	56·6–83·9 *v.* 33·6–50·4	135·3–593·7 *v.* 4·6–66·9	8	Age, race, education, marital status, BMI, FH of any cancer, PA, smoking, alcohol, TEI, menopausal HRT
Wen *et al.*[29] (F)	SWHS	China (7·4)	40–70	616	74 942	FFQ(l) 71 items	76·8 *v.* 63·9	239·4 *v.* 163·8	7	Age, TEI, education, BMI, age at first birth, breast cancer history in first-degree relative, personal history of benign breast disease, PA
Larsson *et al.*[30] (F)	SMC	Sweden (17·4)	40–74	2952	61 433	FFQ(s) 67 items	≥83·4 *v.* <75·8	≥200 *v.* <164	7	Age, education, BMI, height, parity, age at first birth, AAM, TEI, age at menopause, oral contraceptives/HRT, FH of breast cancer, history of benign breast disease, intakes of alcohol, coffee and energy-adjusted cereal fibre
Lajous *et al.*[27] (F)	MGEN	France (9)	42–72	1812	62 739	FFQ(l) 208 items	65·6 *v.* 44·3	165 *v.* 84	7	Age, 2 years follow-up period, region of residence, education, FH of breast cancer, history of benign breast disease, AAM, parity, breastfeeding, years since last use of oral contraceptives, age at menopause, year of HRT, regular mammographic evaluation, height, PA, BMI, vitamin supplement use, TEI, intakes of folate and alcohol
Sieri *et al.*[31] (F)	ORDET	Italy (11·5)	34–70	289	8926	FFQ(s) 107 items	>57·5 *v.* <53·5	>133·7 *v.* <103·2	8	Age, height, weight, AAM, smoking, education, oral contraceptive use, parity, TEI, intakes of alcohol, fibre and saturated fat
Silvera *et al.*[32] (F)	NBSS	Canada (16·6)	40–59	1461	49 613	FFQ(s) 86 items	>96 *v.* < 60	>175 *v.* <119	7	Age, BMI, menopausal status, alcohol, menopausal status, HRT use, oral contraceptive use, parity, AAM, age at first-birth, breast cancer history in first-degree relative, history of benign breast disease, TEI, alcohol intake, energy-adjusted total fibre intake, study centre, randomisation group
Nielsen *et al.*[24] (F)	DDCHS	Denmark (6·6)	50–65	634	23 870	FFQ(s) 192 items	10 units/d	100 units/d	7	Age, parity, age at first birth, education, HRT use, duration of HRT, BMI, alcohol intake

Table 1. *Continued*

Study (sex)	Study name	Study location and follow-up (years)†	Age at baseline (years)	Cases (*n*)	Cohort size (*n*)	Dietary assessment	Comparison level (highest *v.* lowest)*		Study quality	Adjustment for confounders
							Glycaemic index	Glycaemic load		
Holmes *et al.*[19] (F)	NHS	USA (18)	34–59	4092	88,678	FFQ(s) 61 items	81 *v.* 69	186 *v.* 116	7	Age, BMI, 2 years time period, TEI, alcohol intake, parity, age at first birth, height, AAM, FH of breast cancer, history of benign breast disease, AAM (postmenopausal women only: age at menopause, HRT use, duration of menopause)
Higginbotham *et al.*[33] (F)	WHS	USA (6·8)	≥45	946	39 876	FFQ(s) 131 items	55 *v.* 50	143 *v.* 92	7	Age, BMI, alcohol, smoking, AAM, age at first pregnancy, parity, oral contraceptive use, postmenopausal hormone use, FH of breast cancer, PA, TEI, energy-adjusted total fat, fibre, folate
Jonas *et al.*[34] (F)	CPSII	USA (5)	40–87	1442	63 307	FFQ(s) 68 items	85 *v.* 65	147 *v.* 83	8	Age, AAM, age at menopause, parity, age at first birth, HRT, oral contraceptive use, FH of breast cancer in a mother or sister, personal history of breast cysts, education, BMI, adult weight gain from age 18 years, location of body weight gain, height, PA, TEI, diethylstilbestrol use, alcohol use, race, smoking
Cho *et al.*[35] (F)	NHS II	USA (8)	26–46	714	90 655	FFQ(s) 133/142 items	82 *v.* 70	211 vs .138	7	Age, smoking, height, parity, age at first birth, BMI, AAM, FH of breast cancer, history of benign breast disease, oral contraceptive use, menopausal status, TEI, intakes of alcohol and animal fat
Colon-rectum cancer										
Li *et al.*[36] (F)	SWHS	China (9·1)	40–70	475	73 061	FFQ(s) 71 items	76 *v.* 64·4	225·9 *v.* 159·7	8	Age, education, income, BMI, PA, FH of colorectal cancer, TEI, HRT
George *et al.*[14] (M, F)	NIH-AARP	USA (1995–2003)	50–71	F: 1457 M: 3031	183 535 262 642	FFQ(s) 124 items	F: 56·6–83·9 *v.* 33·6–50·4 M: 57·0–84·1 *v.* 33·5–51·3	F: 135·3–593·7 *v.* 4·6–66·9 M: 164·4–740·2 *v.* 7·08–83·2	8	Age, race, education, marital status, BMI, FH of any cancer, PA, smoking, alcohol, TEI, menopausal HRT (women only)
Howarth *et al.*[15] (M, F)	MEC	USA (8)	45–75	F: 1086 M: 1293	105 106 85 898	FFQ(s) >180 items	– –	F: ≥156·9 *v.* Q1(ref) M: ≥188·5 *v.* Q1(ref)	7	Age, race, time since cohort entry, FH of colorectal cancer, history of colorectal polyps, pack-years of cigarette smoking, BMI, hours of vigorous activity, nonsteroidal anti-inflammatory drug use, multivitamin use, TEI, HRT use (women only), intakes of alcohol, red meat, folate, vitamin D, Ca and dietary fibre
Kabat *et al.*[37] (F)	WHI	USA (7·8)	50–79	1476	158 800	FFQ(s) 122 items	≥55·4 *v.* <49·4	≥126·6 *v.* <62·4	7	Age, education, cigarettes smoked per d, BMI, height, hormone therapy, history of diabetes, FH of colorectal cancer in first-degree relative, PA, observational study component participant, TEI, intakes of total dietary fibre and Ca
Weijenberg *et al.*[16] (M, F)	NLCS	The Netherlands (11·3)	55–69	F: 755 M: 1082	62 843 58 009	FFQ(s) 150 items	61·9 *v.* 53·7 64·5 *v.* 56·6	123·6 *v.* 82·5 165·4 *v.* 108·7	7	Age, BMI, FH of colon cancer, smoking, TEI, intakes of Ca, alcohol and processed meat, education, PA
Strayer *et al.*[38] (F)	BCDDP	USA (8·5)	61·9‡	490	45 561	FFQ(s) 62 items	>52·5 *v.* <45	>79·5 *v.* <55·3	7	Age, TEI, NSAID use, smoking, menopausal female hormone use, screened for colorectal cancer, BMI, fibre intake (intakes of dietary Ca and fibre were not adjusted for glycaemic load)

Table 1. *Continued*

Study (sex)	Study name	Study location and follow-up (years)†	Age at baseline (years)	Cases (*n*)	Cohort size (*n*)	Dietary assessment	Comparison level (highest *v.* lowest)*		Study quality	Adjustment for confounders
							Glycaemic index	Glycaemic load		
Larsson *et al.*[39] (F)	SMC	Sweden (15·7)	40–76	870	61 443	FFQ(s) (67 items)	≥ 83·4 *v.* <75·8	≥200 *v.* <164	7	Age, year of entry, education, BMI, TEI, quartiles of intakes of alcohol, cereal fibre, folate, Ca, Mg and red meat
McCarl *et al.*[40] (F)	IWHS	USA (15)	55–69	954	35 197	FFQ(s) 127 items	>89·3 *v.* <81	>193 *v.* <146	8	Age, TEI, activity level, multivitamin use, diabetes, smoking, BMI, waist:hip ratio
Michaud *et al.*[17] (M; F)	NHSI HPFS	USA (20)	30–55 40–75	F: 1113 M: 696	83 927 47 422	FFQ(s) 61/131 items	F: 81 *v.* 65 M: 82 *v.* 69	F: 167 *v.* 80 M: 223 *v.* 131	7	Age, FH of colon cancer, prior endoscopy screening, aspirin use, height, BMI, pack-years of smoking before age 30 years, PA, intakes of cereal fibre, alcohol, Ca, folate, processed meat, and beef, pork or lamb as main dish
Higginbotham *et al.*[41] (F)	NHS	USA (7·9)	≥ 45	174	38 451	FFQ(s) 131 items	57 *v.* 53	143 *v.* 117	7	Age, BMI, history of oral contraceptive use, postmenopausal hormone use, smoking, alcohol, PA, FH of colorectal cancer, non-steroidal anti-inflammatory use, TEI, energy-adjusted total fibre, total fat, folate, Ca, vitamin D
Terry *et al.*[42] (F)	NBSS	USA (16·5)	40–59	616	49 124	FFQ(s) 86 items	–	≥185 *v.* <99	8	Age, TEI, study centre, treatment allocation, BMI, smoking, education, PA, oral contraceptive use, HRT use, parity, intakes of alcohol, red meat and folic acid
Endometrial cancer										
George *et al.*[14] (F)	NIH-AARP	USA (1995–2003)	50–71	1041	183 535	FFQ(s) 124 items	56·6–83·9 *v.* 33·6–50·4	4·6–66·9 *v.* 135·3–593·7	8	Age, race, education, marital status, BMI, FH of any cancer, PA, smoking, alcohol, TEI, menopausal HRT
Cust *et al.*[43] (F)	EPIC	10 western EU (6·4)	20–85	710	288 428	FFQ(s/l)	Q1 *v.* Q4	Q1 *v.* Q4	8	Age, centre, TEI, BMI, height, PA, smoking
Larsson *et al.*[44] (F)	SMC	Sweden (15·6)	NA	608	61 226	FFQ(s) 67 items	≥84·4 *v.* <75·7	≥200 *v.* <164	7	Age, year of enrollment, education, BMI, AAM, oral contraceptive use, age at first birth, parity, age at menopause, postmenopausal hormone use, menopausal status, TEI
Silvera *et al.*[45] (F)	NBSS	Canada (16·4)	40–59	426	49 613	FFQ(s) 86 items	>77 *v.* <67	>169 *v.* <125	8	Age, BMI, menopausal status, smoking, alcohol, HRT use, oral contraceptive use, parity, AAM, PA, TEI, study centre, treatment allocation
Folsom *et al.*[46] (F)	IWHS	USA (15)	55–69	415	23 335	FFQ(s) 126 items	≥89·3 *v.* <81	≥193·5 *v.* <147·4	8	Age, TEI, BMI, waist:hip ratio, diabetes, hypertension, alcohol intake, AAM, age at menopause, HRT use, smoking
Liver cancer										
George *et al.*[14] (M, F)	NIH-AARP	USA (1995–2003)	50–71	F: 72 M: 238	183 535 262 642	FFQ(s) 124 items	F: 56·6–83·9 *v.* 33·6–50·4 M: 57·0–84·1 *vs.* 33·5–51·3	F: 135·3–593·7 *v.* 4·6–66·9 M: 164·4–740·2 *v.* 7·1–83·2	8	Age, race, education, marital status, BMI, FH of any cancer, PA, smoking, alcohol, TEI, menopausal HRT (women only)
Pancreatic cancer										
Simon *et al.*[47] (F)	WHI	USA (8)	50–79	332	161 809	FFQ(s) 122 items	56 *v.* 48	150 *v.* 105	7	Age, race, income, BMI, PA, history of diabetes, alcohol intake, smoking
Meinhold *et al.*[48] (C)	PLCO	USA (6·5)	55–74	266	109 175	FFQ(s) 124 items	≥56·2 *v.* ≤50·9	≥73·6 *v.* ≤54·3	7	Age, sex, BMI, smoking, TEI, excluding self-reported diabetics
George *et al.*[14] (M, F)	NIH-AARP	USA (1995–2003)	50–71	F:348 M: 601	183 535 262 642	FFQ(s) 124 items	F: 56·6–83·9 *v.* 33·6–50·4 M: 57·0–84·1 *v.* 33·5–51·3	F: 135·3–593·7 *v.* 4·6–66·9 M: 164·4–740·2 *v.* 7·08–83·2	8	Age, race, education, marital status, BMI, FH of any cancer, PA, smoking, alcohol, TEI, menopausal HRT (women only)

Table 1. *Continued*

Study (sex)	Study name	Study location and follow-up (years)†	Age at baseline (years)	Cases (*n*)	Cohort size (*n*)	Dietary assessment	Comparison level (highest *v.* lowest)*		Study quality	Adjustment for confounders
							Glycaemic index	Glycaemic load		
Heinen *et al.*[49] (C)	NLCS	USA (13·3)	55–69	408	120 852	FFQ(s) 150 items	64 *v.* 55	156 *v.* 88	8	Age, sex, TEI, smoking, alcohol intake, history of diabetes or hypertension, BMI, intakes of vegetables, fruit and fibre
Nothlings *et al.*[50] (C)	MEC	USA (8)	45–75	434	162 150	FFQ(s) 200 items	–	≥82·3 *v.* <63·3	7	Age, sex, time on study, race, smoking, BMI, pack-years of smoking, FH of pancreatic cancer, TEI, intakes of red meat and processed meat
Patel *et al.*[18] (M, F)	CPSII	USA (9)	50–74	401	124 907	FFQ(s) 68 items	F: >79·96 *v.* ≤68·4 M: >81·8 *v.* ≤69·6	F: >132·4 *v.* ≤ 95·1 M: >169·9 *v.* ≤ 119·0	8	Age, sex, race, BMI, history of gallstones, smoking, TEI, FH of pancreatic cancer, location of weight gain, sedentary behaviour
Silvera *et al.*[51] (F)	NBSS	Canada (16·5)	40–59	112	49 613	FFQ(s) 86 items	>92 *v.* <63	>169 *v.* <125	8	Age, BMI, alcohol intake, smoking, parity, TEI, study centre, randomisation group
Johnson *et al.*[52] (F)	IWHS	USA (16)	55–69	190	34 699	FFQ(s) 126 items	>89 *v.* <82	>188 *v.* <151	7	Age, smoking, pack-years, diabetes, multivitamin use
Michaud *et al.*[26] (F)	NHS	USA (18)	30–55	180	88 802	FFQ(s) 61 items	81 *v.* 65	167 *v.* 80	7	Age, BMI, height, TEI, PA, pack-years of smoking, history of diabetes and cholecystectomy
Prostate cancer										
Shikany *et al.*[53] (M)	PLCO	USA (9·2)	55–74	2436	30 482	FFQ(s) 137 items	≥58·1 *v.* ≤52·1	≥194 *v.* ≤ 103·2	7	Age, year of entry, centre, compliant for baseline screen, marital status, BMI, vigorous PA, smoking, history of diabetes, history of cancer, aspirin use, FH of prostate cancer, any prostate problems, prior PSA test, prostate biopsy prior to entry, TEI, intakes of total fat, red meat, processed meat, dairy, Ca, vitamin D, vitamin E, lycopene and Se
Nimptsch *et al.*[54] (M)	HPFS	USA (1986–2007)	40–75	5112	49 934	FFQ(s) 131 items	≥55·98 *v.* ≤ 50·4	≥145 *v.* ≤ 103	7	Age, BMI, height, history of diabetes, FH of prostate cancer, race, smoking, vigorous PA, TEI, intakes of alcohol, Ca, α-linolenic acid and tomato sauce
George *et al.*[14] (M)	NIH-AARP	USA (1995–2003)	50–71	15 949	262 642	FFQ(s) 124 items	M: 57·0–84·1 *v.* 33·5–51·3	M: 164·4–740·2 *v.* 7·1–83·2	8	Age, race, education, marital status, BMI, FH of any cancer, PA, smoking, alcohol, TEI, menopausal HRT

M, males; F, females; NIH-AARP, National Institutes of Health–American Association of Retired Persons; FFQ(s), self-reported FFQ; FH, family history; PA, physical activity; TEI, total energy intakes; HRT, hormone replacement therapy; WHI, Women's Health Initiative; AAM, age at menarche; SWHS, Shanghai Women's Health Study; FFQ(I), interviewed FFQ; SMC, Swedish Mammography Cohort; MGEN, Mutuelle Générale de l'Education Nationale; ORDET, Ormoni e Dieta nella Eziologia dei Tumori (Hormones and Diet in the Etiology of Breast Cancer); NBSS, National Breast Screening Study; DDCHS, Danish Diet, Cancer, and Health Study; NHS, Nurses' Health Study; WHS, Women's Health Study; CPSII, Cancer Prevention Study II; MEC, Multiethnic Cohort study; Q, quartiles or quintiles; ref, reference; NLCS, Netherlands Cohort Study; BCDDP, Breast Cancer Detection Demonstration Project; NSAID, non-steroidal anti-inflammatory drug; IWHS, Iowa Women's Health Study; HPFS, Health Professional Follow-Up Study; EPIC, European Prospective Investigation into Cancer and Nutrition; EU, European Union; NA, not available; C, males and females; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen.

* Value expressed as mean, median value or range corresponding to the category (g/d).

† Value expressed as mean or median; baseline and end of follow-up years given for the studies by George *et al.*[14] and Nimptsch *et al.*[54].

‡ Value expressed as mean.

model. The two authors (Y. C. and J. E. L.) independently assessed the study quality using the Newcastle–Ottawa Scale, which ranged from 1 to 9 stars (poor to excellent, respectively)[12], and disagreements were resolved through consensus.

Statistical analysis

As a primary analysis, we pooled the RR estimates by comparing the highest intake category with the lowest from each study for site-specific cancer risks and overall DRC risk according to the GI and GL. The pooled RR estimates with corresponding 95 % CI were derived using a random-effects analysis, which considers both within- and between-study variance components[13]. For studies that only provided separate estimates by sex[14–18] and the one study that reported breast cancer risk by menopausal status[19], we included the results separately. Studies describing relationships between the GI or GL and prostate cancer, which is considered to be inversely associated with diabetes[1], were not included in the main analysis to examine the hypothesis that the GI or GL was positively associated with some cancers that are associated with an increased risk for diabetes. The statistical heterogeneity between the studies was tested with Q statistics and I^2 statistics[20]. We also evaluated the non-linearity of the association using restricted cubic splines[21–23] for studies that provided the number of participants or person-years and two or more categories of GI or GL intake. We conducted sensitivity analyses by omitting each study, one at a time, to evaluate whether the pooled estimates were influenced substantially by any single study. For studies[24] that provided RR as continuous variables only, we recalculated them into estimates per ten increments in GI and per 100 increments in GL (treated as top and bottom estimates) and then pooled them with categorical variables in the additional analysis. We also performed subgroup analyses (highest intake *v.* lowest intake) and random-effects meta-regression analyses to explore potential sources of heterogeneity between the studies by selected study characteristics, including the cancer site, the geographic region (North America, Europe and Asia), sex (males, females and both sexes), obesity status (<25 *v.* $\geq 25\,kg/m^2$), study quality and the exclusion of diabetic individuals. Potential publication bias was assessed with Egger's regression asymmetry test[25]. $P<0{\cdot}05$ was considered statistically significant. All analyses were two-sided and performed using STATA software (version 11; StataCorp) and SAS statistical software, version 9.2 (SAS Institute).

Results

Study characteristics

Fig. 1 shows the detailed literature search steps. The preliminary literature search resulted in the retrieval of 235 articles. Of these, thirty-nine articles and three additional relevant articles were considered to be of interest for the full-text review. After the full-text review, six articles were excluded for the reasons described in the flowchart and thirty-six were included in the final meta-analysis. The characteristics of the included articles are shown in Table 1. Overall, the meta-analysis for GI was based on thirty-three prospective cohort studies (n 44 RR estimates) and the meta-analysis for GL was based on thirty-six prospective cohort studies (n 48 RR estimates). The total number of cases of DRC was 60 811 (bladder, n 1481; breast, n 26 551; colon–rectum, n 16 793; endometrium, n 3200; liver, n 310; pancreas, n 3272; and prostate, n 9204), with a mean follow-up duration ranging from 5 to 21 years. To assess the habitual diet, all studies used either self- or interviewer-administered FFQ that included sixty-one[17,19,26] to 208 food items[27]. For dietary GI intake, twenty-seven studies used a single dietary assessment and four studies used a cumulative average dietary assessment. For dietary GL intake, thirty studies used a single dietary assessment and four studies used a cumulative average dietary assessment. All studies were given a score of 7 or 8 stars, representing the high quality of studies of the studies, twenty-six were conducted in North America, seven in Europe and two in Asia.

Glycaemic index and glycaemic load intake associated with the risk of overall diabetes-related cancers and each cancer site

Figs. 2 and 3 show the associations between DRC risk and either GI or GL, respectively, when comparing the highest with the lowest category intake.

Overall diabetes-related cancer risk

We combined thirty prospective studies of GI and thirty-three studies of GL that examined associations with potential diabetes-induced cancers, including bladder cancer[14], breast cancer[14,19,27–35], colorectal cancer[14–17,36–42], endometrial cancer[14,43–46], liver cancer[14] and pancreatic cancer[14,18,26,47–52]. We pooled three risk estimates of prostate cancer[14,53,54]separately, which could possibly be lower among diabetic individuals[1]. When comparing the highest intake category with the lowest category, the pooled multivariable-adjusted RR of the overall DRC risk were 1·07 (95 % CI 1·04, 1·11) for GI, with no evidence of heterogeneity ($P=0{\cdot}36$, $I^2=6{\cdot}1\,\%$) across studies, and 1·02 (95 % CI 0·96, 1·08) for GL, with modest heterogeneity ($P<0{\cdot}001$, $I^2=45{\cdot}4\,\%$). Egger's regression test showed no evidence of a publication bias for GI ($P=0{\cdot}99$) or GL ($P=0{\cdot}54$). When we added one more study[24] that provided RR for continuous GI or GL, RR comparing the highest with the lowest category were 1·07 (95 % CI 1·03, 1·10) for GI and 1·02 (95 % CI 0·97, 1·08) for GL. When we evaluated whether there were non-linear relationships between the GI or GL and overall DRC risks, we found modestly suggestive evidence of non-linearity for GI ($P=0{\cdot}06$) or GL ($P=0{\cdot}21$) intakes.

The subgroup analyses, meta-regression and sensitivity analysis were performed on the associations of the overall DRC risk in relation to the GI and GL (highest *v.* lowest intake; Table 2). In the meta-regression analyses, we could not find any evidence of between-study heterogeneity in

the overall risk estimates by cancer site (*P* for difference: *P*=0·23 for GI, *P*=0·06 for GL), geographic location (*P* for difference: *P*=0·99 for GI, *P*=0·22 for GL), sex (*P* for difference: *P*=0·13 for GI, *P*=0·64 for GL) or obesity (*P* for difference: *P*=0·59 for GI, *P*=0·37 for GL). When we examined whether associations differed by contrast in levels in the comparison categories, we found similar associations, with a pooled RR of 1·08 (95 % CI, 1·02, 1·13) for a difference of ≥12 in the GI and 1·06 (1·00–1·14) for a difference of <12 in the GI. With respect to the GL, the pooled RR were 0·98 (0·91–1·06) for a difference of ≥65 and 1·07 (0·98–1·16) for a difference of <65. Additionally, the associations did not vary by study quality (*P* for difference: *P*≤0·6 for GI or GL) or the exclusion of diabetic individuals

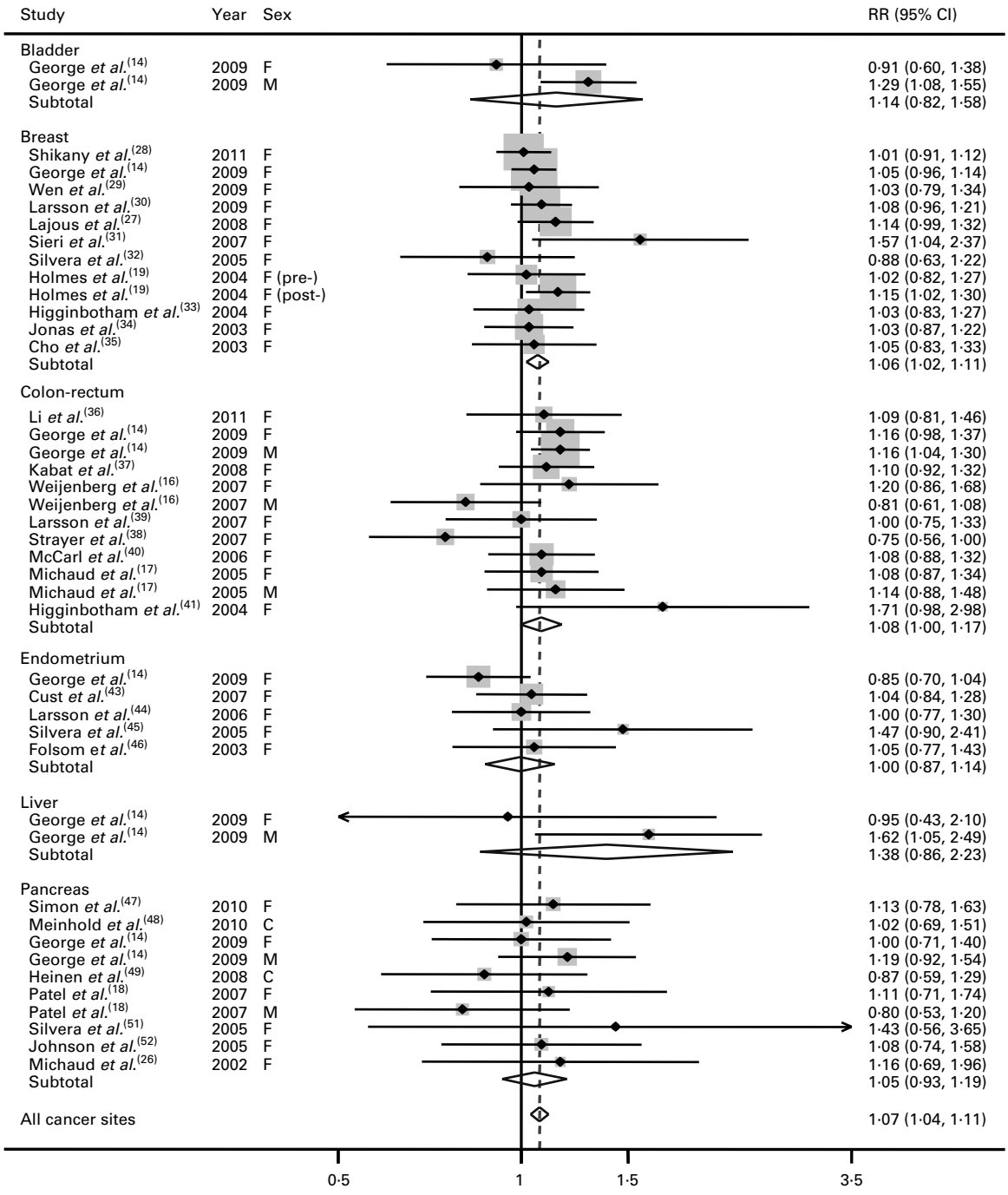

Fig. 2. The pooled relative risks (RR) and 95 % CI of the glycaemic index in association with diabetes-related cancer and each cancer site. The pooled RR estimates were obtained using a random-effects model. On the *x* axis, the centre of each square indicates the RR of the study with its corresponding 95 % CI (the horizontal line). The size of the ■ indicates the relative sample sizes in each study. The ◆ indicates the pooled RR estimates for each cancer site and the ◇ at the bottom indicates the pooled RR estimate for total cancers. F, females; M, males; pre-, premenopausal status; post-, postmenopausal status; C, both sexes.

(*P* for difference: $P \leq 0{\cdot}6$ for GI or GL). Although there were no statistically significant differences, a significant positive association between GI and overall DRC risk was more apparent in the thirty-three combined estimates conducted in North America (RR 1·07; 95 % CI 1·03, 1·12) compared to other regions. A significant positive association between GI and overall DRC risk was observed in the twenty-seven combined estimates for women (RR 1·06; 95 % CI 1·02, 1·10; *n* 34 RR estimates). In the sensitivity analyses, where one study was omitted at a time, no particular study unduly influenced the pooled RR estimates for overall cancer sites or the *P* for heterogeneity.

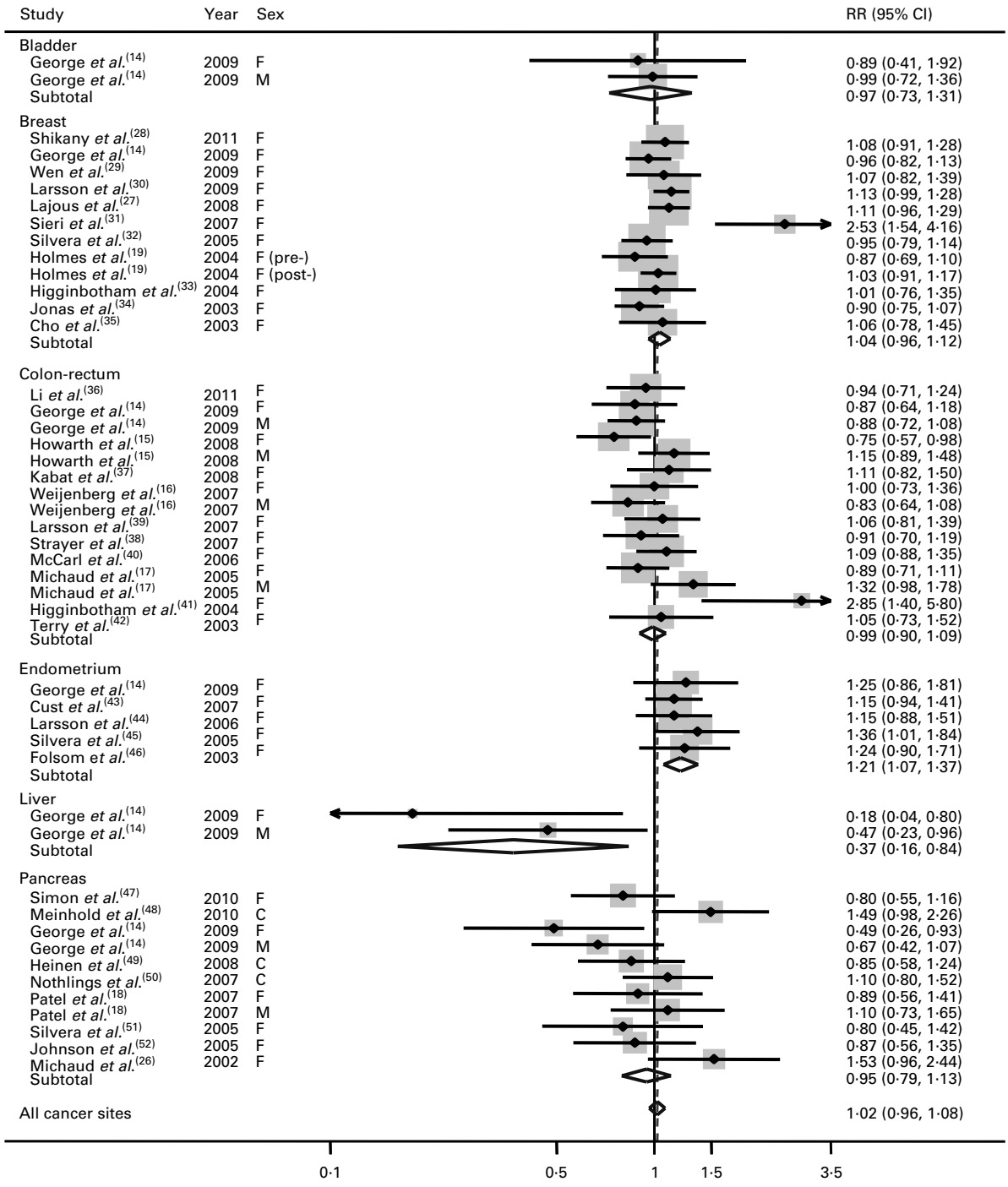

Fig. 3. The pooled relative risks (RR) and 95 % CI of the glycemic load in association with diabetes-related cancer and each cancer site. The pooled RR estimates were obtained using a random-effects model. On the *x* axis, the centre of each square indicates the RR of the study with its corresponding 95 % CI (the horizontal line). The size of the ■ indicates the relative sample sizes in each study. The ◆ indicate the pooled RR estimates for each cancer site, and the ◇ at the bottom indicates the pooled RR estimate for total cancers. F, females; M, males; pre-, premenopausal status; post-, postmenopausal status; C, both sexes.

Table 2. Subgroup analysis and meta-regression for the effects of characteristics on diabetes-related cancer risk*

(Relative risks (RR) and 95 % confidence intervals)

	GI				GL			
Characteristic	*n*†	RR‡	95 % CI	*P*§	*n*†	RR‡	95 % CI	*P*§
Geographic location				0·99				0·22
North America	33	1·07	1·03, 1·12		37	0·99	0·93, 1·06	
Europe	8	1·07	0·98, 1·17		8	1·11	0·99, 1·26	
Asia	2	1·06	0·87, 1·29		2	1·01	0·83, 1·22	
Sex				0·13				0·64
Females	34	1·06	1·02, 1·10		36	1·03	0·97, 1·09	
Males	7	1·13	0·99, 1·29		8	0·95	0·81, 1·12	
Both	2	0·94	0·71, 1·24		3	1·11	0·82, 1·49	
Obesity‖				0·59				0·37
BMI $<25\,kg/m^2$	16	1·09	0·97, 1·21		17	1·05	0·93, 1·18	
BMI $\geq 25\,kg/m^2$	18	1·04	0·90, 1·20		21	1·14	1·00, 1·31	

* Prostate cancer was excluded from the analysis.
† The number of RR estimates.
‡ All pooled RR estimates for the comparison of the highest *v.* lowest categories were calculated from random- effects model.
§ *P* value for test of heterogeneity.
‖ The analysis included studies that assessed the associations by BMI; data were available for cancers of breast, colon–rectum, pancreas and endometrium.

Bladder cancer risk

One large prospective study of older US adults examined the associations between GI or GL and bladder cancer risk. The RR (95 % CI) for men and women combined were 1·14 (0·82, 1·58) for GI and 0·97 (0·73, 1·31) for GL. Notably, a significant positive association between GI and bladder cancer for the comparisons of the highest with the lowest category of intake was found among men but not women. The author speculated, however, that there may be a residual confounding effect of smoking in this association. We were not able to test for a publication bias due to limited number of studies.

Breast cancer risk

Eleven studies evaluated GI and GL intake in relation to breast cancer risk. The majority of the prospective studies were conducted in North America and Europe; only one study was conducted in China. The meta-analysis suggested that the highest GI intake was associated with a 6 % relative increase in breast cancer risk compared with the lowest intake (95 % CI 1·02, 1·11); however, no significant associations were found between GL and breast cancer risk (RR 1·04; 95 % CI 0·96, 1·12). Statistical heterogeneity was not observed for GI ($P=0·64$, $I^2=0\,\%$), but it was observed for GL ($P=0·03$, $I^2=49·2\,\%$). Although heterogeneity was observed in the association between GL and breast cancer risk, this heterogeneity disappeared when a study by Sieri *et al.*[31] was omitted, resulting in a pooled estimate of 1·03 (95 % CI 0·97, 1·08; $P=0·52$, $I^2=0\,\%$). We found no indications of a publication bias for either GI ($P=0·75$) or GL ($P=0·41$) using Egger's test. In an additional analysis, where we added one more study[24] that provided RR for continuous GI or GL, RR for breast cancer comparing the highest with the lowest category were 1·06 (95 % CI 1·01, 1·10) for GI and 1·04 (95 % CI 0·97, 1·11) for GL. In a further subgroup analysis of breast cancer by menopausal status[19,27,29,31–33], the pooled RR were 1·05 (95 % CI 0·83, 1·33) for GI and 1·28 (95 % CI 0·94, 1·75) for GL among pre-menopausal woman, and 1·07 (95 % CI 0·88, 1·28) for GI and 1·11 (95 % CI 0·91, 1·36) for GL among post-menopausal woman.

Colorectal cancer risk

Nine studies for GI and eleven studies for GL were included in the meta-analysis of colorectal cancer risk. The meta-analysis of nine prospective studies showed a borderline positive association between GI and colorectal cancer risk when comparing the highest with the lowest category of intake (RR 1·08; 95 % CI 1·00, 1·17); there was no evidence of heterogeneity ($P=0·16$, $I^2=29·4\,\%$) or a publication bias ($P=0·44$). No significant association was observed between GL intake and colorectal cancer risk (RR 0·99; 95 % CI 0·90, 1·09) with modest heterogeneity ($P=0·04$, $I^2=42·2\,\%$) and evidence of a publication bias ($P=0·03$). When a study by Higginbotham *et al.*[41] was omitted from the analysis of GL intake and colon–rectal cancer, however, no heterogeneity was found among the remaining ten studies ($P=0·28$, $I^2=15·9\,\%$), and the pooled RR for the highest *v.* lowest category of GL intake was 0·97 (95 % CI 0·90, 1·05).

Endometrial cancer risk

Five prospective studies examined the association of endometrial cancer with either GI or GL intake. There was no significant association with endometrial cancer for the highest *v.* the lowest GI intake (RR 1·00; 95 % CI 0·87, 1·14). In contrast, the highest category of GL intake was significantly associated with a 21 % greater risk of developing endometrial cancer compared with the lowest category of intake (95 % CI 1·07, 1·37). No statistical heterogeneity among studies was observed

for either GI ($P=0{\cdot}28$, $I^2=21{\cdot}6\,\%$) or GL ($P=0{\cdot}91$, $I^2=0\,\%$); we also found no evidence of a publication bias using Egger's test ($P=0{\cdot}08$ for GI and $P=0{\cdot}23$ for GL).

Liver cancer risk

Only one longitudinal study (National Institutes of Health – American Association of Retired Persons) evaluated the association of GI or GL intake with the risk of liver cancer. A combined analysis of men and women together showed no evidence of an association between GI intake and liver cancer risk. In contrast, the comparison of the highest *v.* lowest category of GL intake showed a significant reduction in the risk of liver cancer (RR 0·37; 95 % CI 0·16, 0·84). We could not test for a publication bias due to the limited number of studies.

Pancreatic cancer risk

With regard to pancreatic cancer, eight studies for GI and nine studies for GL were conducted in North America. There was no association between the GI and pancreatic cancer risk when comparing the highest with the lowest intake (RR 1·05; 95 % CI 0·93, 1·19), with little evidence of heterogeneity ($P=0{\cdot}87$, $I^2=0\,\%$). Similarly, no association was found for the highest GL intake compared with lowest intake (RR 0·95; 95 % CI 0·79, 1·13; *P* for heterogeneity $P=0{\cdot}06$, $I^2=43{\cdot}5\,\%$).

Prostate cancer risk

We pooled three RR estimates of prostate cancer, the risk of which has been suggested to be lower among diabetic individuals, and found no significant associations. The pooled RR were 0·97 (95 % CI 0·91, 1·04) for GI and 0·90 (95 % CI 0·74, 1·11) for GL when comparing the highest with lowest category of intake. There was no evidence of a publication bias, as determined by Egger's regression test for GI ($P=0{\cdot}99$) or GL ($P=0{\cdot}54$).

Discussion

To our knowledge, the present study is the first systematic literature review and meta-analysis of the association between the risks of DRC and the GI or GL. The present results from the meta-analysis of prospective cohort studies suggest that high GI was modestly associated with overall DRC risks, whereas high GL was not related to overall DRC risks. In the cancer-specific analysis, we found that high GI was weakly, but significantly, associated with an increased risk of breast or colorectal cancer. We also found that high GL was significantly associated with an increased risk of developing endometrial cancer.

We could draw several inferences from other studies that may be likely explanations for the modest-to-weak associations between GI or GL and DRC risks observed in the present study. Of several aetiological hypotheses on cancer, insulin resistance, hyperinsulinemia and an increased level of insulin-like growth factor-I may be most probable as currently understood, as they have been implicated as key mediators in the underlying mechanism relating dietary and associated lifestyle factors to carcinogenesis[1,55]. Elevated circulating insulin levels could promote carcinogenesis, either directly by stimulating the production of insulin receptors or indirectly by suppressing insulin-like growth factor-binding proteins 1 and 3, which may increase the bioavailability of insulin-like growth factor-I for its receptors[56]. Growing evidence from epidemiological studies has supported the mechanisms described earlier. Elevated levels of insulin (or C-peptide as a surrogate) and insulin-like growth factor-I have also been associated with an increased risk of several DRC cancers[57–60]. The increasing evidence for an association between hyperinsulinaemia and cancer risk has led to interest in examining factors that increase insulin in relation to various cancers[61]. Epidemiological studies have shown an elevated risk of cancers with factors that increase insulin levels and a reduced risk of cancers with factors related to decreased insulin levels: increased cancer risks among individuals who had obesity (or visceral obesity)[62] or consumed a C-peptide dietary pattern[63] or western dietary patterns enriched in fat and red meat[64,65], and reduced cancer risks among those with high physical activity[66,67] or who were coffee drinkers[68,69].

The lack of association or modest association for GI and GL in the present meta-analysis may suggest that a mechanism linking insulin to cancer development could be more plausible than the effect of blood glucose on cancer development[1]. Experimental study[70] has shown that rats that were hyperglycaemic and insulin deficient, a condition similar to human type 1 diabetes, had reduced tumour cell proliferation, as assessed by the size, number and aggressiveness of the tumour. The differences in cancer development between type 1 and 2 diabetes partly support this hypothesis. Hyperglycaemia occurs in both type 1 and 2 diabetes, but insulin resistance and endogenous hyperinsulinaemia are only observed in type 2 diabetes[71]. Cancers frequently observed in association with type 2 diabetes are bladder, breast, colorectal, endometrial, liver and pancreatic cancers[1], and those associated with type 1 diabetes are stomach and squamous cell skin carcinomas and leukaemia[72]. The finding that no association was identified with colorectal cancer among those who have been diagnosed with type 2 diabetes for more than 15 years[73], possibly under a condition of insulin deprivation (the Starling Curve of the pancreas)[74], could also support the hypothesis that hyperinsulinaemia may be a more important contributor to tumour development than hyperglycaemia. The dietary insulin index is another approach that has been recently developed to directly quantify the postprandial plasma insulin secretion compared with a reference food[75], and it has been found to be more precise in assessing the insulin response than the GL or carbohydrate amount[76]. The evidence that postprandial insulin concentrations do not change proportionally with the blood glucose response[75] and that GI or GL, measures of the carbohydrates in blood glucose levels, may not ideally predict insulin secretion through the consumption of no or low carbohydrate-containing food, may suggest that the dietary insulin index is a more acceptable measure for assessing insulin secretion and cancer

risk. Only a few studies, however, have been conducted regarding insulin index/load or C-peptide, an indicator of insulin production[76], in relation to cancer risks, which warrants further observational studies to investigate indicators reflecting insulin secretion and its effect on cancer risks.

Other conceptual and practical considerations may contribute to the weak association observed in the present study. From a conceptual perspective, GI and GL may be relatively moderate contributors to overall insulin exposure, which is influenced by genetic factors, adiposity level, physical activity and non-carbohydrate components in foods that influence insulin secretion, and dietary factors, such as coffee, that influence insulin resistance but not insulin secretion directly. From a practical perspective, the attenuation of associations could also be explained by a potential measurement error or between-study variation in the estimated amount of carbohydrates, as measured through the different types of FFQ, given the likely influence of heterogeneity by diets with a high GL. Although we could not clearly identify the sources of heterogeneity in the relationship between diets with a high GL and overall DRC risks, the significant heterogeneity observed in the association of diets with a high GL with risks of breast cancer and colorectal cancer disappeared after omitting individual studies from the breast cancer studies[31] and from the colorectal studies[41] that had extreme values compared to the other studies. A better understanding requires further prospective cohort studies for each site of DRC.

A previous meta-analysis of both case–control and prospective cohort studies[77] observed increased risks of colorectal cancer, breast cancer and endometrial cancer with the highest *v.* the lowest levels of GI and/or GL diets. The present meta-analysis was restricted to observational prospective cohort studies because such a design minimises the possible effects of selection and recall bias compared to case–control studies, showing a weaker association for GI and GL in relation to colorectal, breast or endometrial cancers than a meta-analysis of both case–control and prospective cohort studies.

There are possible limitations to the present study. First, measurement error with regard to random variation in the estimated GI values might have occurred in some studies included in the present analysis because the GI values of some foods are presently based on the results provided in only one or two GI calculation studies, which frequently had small sample sizes[3]. Second, because most of the studies assessed diets using a single FFQ, which may have contained a measurement error, the possibility of misclassification of GI or GL cannot be precluded[78]. Third, the limited number of studies for certain cancer sites (e.g. liver and bladder cancer) did not allow us to draw conclusive summaries for those sites. Lastly, the majority of studies included in the present meta-analysis were conducted in Western countries, thus it is uncertain whether the present findings for different geographic locations or populations are generalised, especially in Asian populations whose typical diets on average consist of a greater proportion of carbohydrates. Further studies should provide information on the potential differences based upon geographic location or ethnic difference. However, the present study also has several major strengths, including the inclusion of many prospective studies with long durations of follow-up and a large number of cases of DRC. The present results were also unlikely to be attributed to publication bias with regard to GI or GL and DRC risk based on Egger's regression test.

In conclusion, the findings of the present meta-analysis suggest a modest or weak association between a diet inducing high glucose response and the risks of overall cancers, particularly those positively related to diabetes. GI or GL may not be strong predictors of DRC risks, and presumably other factors associated with insulin response *per se* may contribute relatively more to DRC risks. The present findings warrant further studies to explore a diet that stimulates the postprandial insulin response in relation to cancer risk.

Acknowledgements

The present study was supported by the National Research Foundation of Korea (NRF) grant, which was funded by the Korean government (no. 2012-0003287), and by the SRC Research Center for Women's Diseases of Sookmyung Women's University (2011). The authors' responsibilities were as follows: Y. C. contributed to the concept and design of the study, data collection, statistical analysis and writing of the manuscript; E. G. provided invaluable advice and consultations during draft development and critically revised the manuscript for important intellectual content; and J. E. L. contributed to the concept and design of the study, provided guidance during study selection, data analysis, draft development and final submission. All authors were responsible for the critical interpretation of the findings, and all contributed to the final manuscript and gave final approval of the version to be published. None of the authors had a conflict of interest.

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