Glycemic index, glycemic load, and risk of digestive tract neoplasms: a systematic review and meta-analysis

Helen G Mulholland, Liam J Murray, Chris R Cardwell, and Marie M Cantwell

ABSTRACT

Background: Habitual consumption of diets with a high glycemic index (GI) and a high glycemic load (GL) may influence cancer risk via hyperinsulinaemia and the insulin-like growth factor axis.

Objective: The objective was to conduct a systematic review to assess the association between GI, GL, and risk of digestive tract cancers.

Design: Medline and Embase were searched for relevant publications from inception to July 2008. When possible, adjusted results from a comparison of cancer risk of the highest compared with the lowest category of GI and GL intake were combined by using random-effects meta-analyses.

Results: Cohort and case-control studies that examined the risk between GI or GL intake and colorectal cancer (n = 12) and adenomas (n = 2), pancreatic cancer (n = 6), gastric cancer (n = 2), and squamous-cell esophageal carcinoma (n = 1) were retrieved. Most case-control studies observed positive associations between GI and GL intake and these cancers. However, pooled cohort study results showed no associations between colorectal cancer risk and GI intake [relative risk (RR): 1.04; 95% CI: 0.92, 1.12; n = 7 studies] or GL intake (RR: 1.06; 95% CI: 0.95, 1.17; n = 8 studies). Furthermore, no significant associations were observed in meta-analyses of cohort study results of colorectal cancer subsites and GI and GL intake. Similarly, no significant associations emerged between pancreatic cancer risk and GI intake (RR: 0.99; 95% CI: 0.83, 1.19; n = 5 studies) or GL intake (RR: 1.01; 95% CI: 0.86, 1.19; n = 6 studies) in combined cohort studies.

Conclusions: The findings from our meta-analyses indicate that GI and GL intakes are not associated with risk of colorectal or pancreatic cancers. There were insufficient data available regarding other digestive tract cancers to make any conclusions about GI or GL intake and risk. Am J Clin Nutr 2009;89:568–76.

INTRODUCTION

Dietary glycemic index (GI) values rank carbohydrate-containing foods according to the 2-h blood glucose response induced after consumption of a set portion of food in comparison with that induced by a standard food, usually glucose or white bread (1). An additional measure, the glycemic load (GL), was introduced more recently to reflect overall glucose demand by incorporating both the GI value and the total carbohydrate content in usual portion sizes of foods (2).

In recent years, numerous authors have suggested that habitual consumption of high-GI and high-GL diets may increase the risk of cancer, particularly colorectal cancer (3–7). Several biologically plausible mechanisms have been put forward in the literature to explain the potential association between GI intake, GL intake, and the development of cancers of the digestive tract. High GI and GL intakes may produce chronic elevations in blood glucose concentrations and have been positively associated with the risk of type 2 diabetes mellitus (8). Hyperglycemia and the presence of diabetes have been linked with both increased incidence of, and mortality from, colorectal, pancreatic, gastric, and esophageal cancers (9–14).

Additionally, hyperglycemia induced by high GI and GL intakes may in turn lead to chronic hyperinsulinaemia. Substantial epidemiologic evidence suggests that insulin and its associated growth factors are directly related to colon cancer in particular (15). It has also been proposed that high-GI and high-GL diets may promote weight gain over time (16). Being overweight or obese has been associated with esophageal adenocarcinoma and colorectal cancer risk in several meta-analyses (17–20).

In view of these biologically plausible mechanisms, many studies have investigated the association between dietary GI and GL intakes and the risk of cancers of the digestive tract; however, results from case-control and cohort studies are conflicting (21). A systematic review of the literature to date would help to clarify any potential associations between GI, GL, and gastrointestinal cancer risk, and analyses by site may provide some indication of the most likely mechanisms involved. The aim of our systematic review, therefore, was to establish whether an association exists between dietary GI, GL, and cancers of the digestive tract and to quantify, when possible, associations via meta-analyses.

SUBJECTS AND METHODS

Study selection

The electronic databases Ovid Medline (US National Library of Medicine, Bethesda, MD) and Embase (Reed Elsevier PLC, Amsterdam, Netherlands) were searched for relevant studies that

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2 Supported by a PhD studentship from the Department for Employment & Learning, Northern Ireland (to HGM).

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included at least one keyword or Medical Subject Heading from each of the following: 1) glyc(a)emic index, glyc(a)emic load, blood glucose, blood sugar(s); 2) diet, nutrition, dietary carbohydrate(s), carbohydrate(s), dietary fiber/fiber, fiber/fiber, dietary sugar(s), and dietary sucrose; and 3) cancer, neoplasms, neoplasia, adenoma, adenocarcinoma, or carcinoma. The search strategy excluded reviews and animal studies but did not impose any language restrictions. Observational studies published up to July 2008 were considered for inclusion if they described a study population in which dietary GI and/or GL intake had been measured and reported information regarding cancer incidence to give a statistical risk estimate and corresponding 95% CIs. Potentially relevant articles were screened by 2 independent reviewers (HGM and MMC), initially by abstract and then by full text when necessary to determine whether they met the inclusion criteria; any discrepancies were resolved by discussion. The reference lists of the identified articles were searched for additional studies.

Data extraction
The reviewers extracted information from each publication on study design and location, sample size, number of cancer cases and case definitions, population demographics, exclusion criteria, methods of exposure ascertainment and dietary assessment, GI and GL intakes, adjustments for confounders, and results from each study.

Statistical analysis
Meta-analyses were conducted for colorectal and pancreatic cancers by comparing cancer risk in the highest reported category of GI or GL intake with the lowest reported category. Too few studies were published to consider a meta-analysis of gastric and esophageal cancers. Most studies categorized intake using quartiles or quintiles. Adjusted relative risk (RR), odds ratios (ORs) or hazard rate ratios, and 95% CIs were combined and weighted to produce pooled RRs with the use of a random-effects model. Random-effects models were deemed suitable for our analysis because of anticipated heterogeneity between the observational studies, the extent of which was investigated by using the chi-square test and $I^2$ statistic (22). Study estimates were plotted against their corresponding SEs to produce funnel plots, which were checked for asymmetry to investigate publication bias in each meta-analysis (23). Separate analyses were conducted for cohort and case-control studies, males and females, and American and European studies (for colorectal cancer only) and by systematically removing each individual study. In combined male and female meta-analyses, if only sex-specific estimates were available from a study, they were pooled before analysis. One study reported results for different genetic polymorphisms (24), which were pooled before our analysis. For colorectal cancer, meta-analyses were also conducted by cancer subsite (ie, colon, distal colon, proximal colon, and rectal cancer) and after including studies of colorectal adenomas. Statistical analysis was conducted by using Intercooled STATA version 9.2 (2005; StataCorp, College Station, TX).

RESULTS
The electronic search strategy identified a total of 465 potentially relevant publications, from which 51 were selected as fulfilling the inclusion criteria for all cancer sites. Four articles were then excluded, 3 because of multiple publications (25–27) and 1 because of insufficient information (28), and an additional article was retrieved after a hand-search of reference lists of the included articles (29). Thus, a total of 48 articles were identified, of which just fewer than 50% described cancers of the digestive tract: colorectal cancer ($n = 12$), pancreatic cancer ($n = 6$), stomach cancer ($n = 2$), and esophageal cancer ($n = 1$). Two additional studies examined the association between GI or GL intake and risk of colorectal adenomas (30, 31).

Colorectal cancer and adenomas
Twelve studies examined the association between GI, GL, and colorectal cancer risk (24, 32–42), and an additional 2 studies examined colorectal adenoma risk (30, 31), all of which were conducted in Europe or Northern America and are described in Table 1. Median GI intakes varied from 49 to 80; however, Murtaugh et al (24) reported anomalous mean intakes that ranged from 197 in controls to 234 among cases. Median daily GL intakes ranged from 67 to 210.

The association between GI intake and colorectal cancer risk is illustrated in Figure 1. The study by Slattery et al (25) was not included in this forest plot, because it presented results for colon cancer risk only, which is dealt with in a further site-specific subanalysis. As shown in Figure 1, the small but nonsignificant increased risk of colorectal cancer in the highest category of GI intake when all studies were combined was largely attributable to case-control study results and was subject to marked heterogeneity ($I^2 = 77\%$, $P < 0.01$). No significant associations were observed between the highest compared with the lowest category of GI intake and colorectal cancer risk when results from cohort studies were combined (RR: 1.04; 95% CI: 0.92, 1.16), and evidence of heterogeneity was also reduced ($I^2 = 39\%$, $P = 0.13$). Similarly, as shown in Figure 2, no evidence of an association between the highest compared with the lowest category of GI intake and colorectal cancer risk when cohort study results were pooled (RR: 1.06; 95% CI: 0.95, 1.17; $I^2 = 23\%$, $P = 0.25$). There was no evidence of publication bias observed in funnel plots (data not shown) of either GI or GL and colorectal cancer risk.

When possible, we also performed analyses after including studies of colorectal adenomas and by cancer subsite, ie, colon, proximal colon, distal colon, and rectum (Table 2). Most of these explorations did not result in markedly different associations, with the exception of a positive association emerging between rectal cancer risk and high GI (RR: 1.20; 95% CI: 1.02, 1.40) and high GL (RR: 1.22; 95% CI: 1.00, 1.49) intakes when all study results were combined. However, again, these results were largely attributable to case-control studies, and pooled cohort study results showed no significant associations between GI (RR: 1.08; 95% CI: 0.89, 1.33) or GL (RR: 1.12; 95% CI: 0.91, 1.38) and rectal cancer risk. Several studies indicated that they had performed subgroup analyses based on strata of body mass index (BMI) categories; however, variation in cutoffs used or lack of information presented hindered further robust investigation of these associations via meta-analysis. Two studies observed positive associations between GI and GL intake and colorectal cancer risk among participants with an above-normal BMI (36, 41), whereas others
<table>
<thead>
<tr>
<th>Authors, date, location</th>
<th>Study</th>
<th>Study design (mean follow-up)</th>
<th>Cases</th>
<th>Controls/ cohort size</th>
<th>Diet assessment</th>
<th>Median GI (IQ range)</th>
<th>Median GL (IQ range)</th>
<th>Adjusted confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kabat et al, 2008, USA (32)</td>
<td>Women's Health Initiative</td>
<td>Prospective cohort (7.8 y)</td>
<td>1476</td>
<td>157,324</td>
<td>Self-reported 122-item FFQ</td>
<td>52 (49–55)</td>
<td>87 (62–127)</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Weijenberg et al, 2008, Netherlands (33)</td>
<td>Netherlands Cohort Study</td>
<td>Prospective cohort (11.3 y)</td>
<td>1811</td>
<td>120,852</td>
<td>Self-reported 150-item FFQ</td>
<td>587, 61 (37–78)</td>
<td>1022, 136 (19–240)</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Stayer et al, 2007, USA (34)</td>
<td>BCDDP Cohort</td>
<td>Prospective cohort (8.5 y)</td>
<td>490</td>
<td>45,561</td>
<td>Self-reported 62-item FFQ</td>
<td>49 (42–55)</td>
<td>67 (47–89)</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Larsson et al, 2007, Sweden (35)</td>
<td>Swedish Mammography Cohort</td>
<td>Prospective cohort (15.7 y)</td>
<td>870</td>
<td>61,433</td>
<td>Self-reported 67-item FFQ</td>
<td>80 (76–83)</td>
<td>186 (164–200)</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>McCarl et al, 2006, USA (36)</td>
<td>Iowa Women’s Health Study</td>
<td>Prospective cohort (15 y)</td>
<td>954</td>
<td>49,521</td>
<td>Self-reported 127-item FFQ</td>
<td>85 (81–89)</td>
<td>170 (146–193)</td>
<td>X X X X X</td>
</tr>
<tr>
<td>Murtagh et al, 2006, USA (24)</td>
<td>Population-based case-control</td>
<td>Interviewed diet history</td>
<td>2450</td>
<td>2821</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Michaud et al, 2005, USA (37)</td>
<td>Nurses’ Health Study and HPFUS</td>
<td>Prospective cohort (&lt;20 y)</td>
<td>1809</td>
<td>131,349</td>
<td>Multiple Self-reported 61 + item FFQs</td>
<td>747, 76 (65–82)</td>
<td>1192, 177 (80–223)</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Hlegenboetham et al, 2004, USA (38)</td>
<td>Women’s Health Study</td>
<td>Prospective cohort (7.9 y)</td>
<td>174</td>
<td>38,451</td>
<td>Self-reported 131-item FFQ</td>
<td>53 (49–57)</td>
<td>117 (92–143)</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Terry et al, 2003, Canada (39)</td>
<td>National Breast Screening Study</td>
<td>Prospective cohort (16.5 y)</td>
<td>616</td>
<td>49,124</td>
<td>Self-reported FFQ</td>
<td>—</td>
<td>137 (82–217)</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Levi et al, 2002, Switzerland (40)</td>
<td>Hospital-based case-control</td>
<td>Interviewed 79-item FFQ</td>
<td>323</td>
<td>1145</td>
<td>Interviewed 79-item FFQ</td>
<td>80 (74–86)</td>
<td>—</td>
<td>X X X X X X X X</td>
</tr>
<tr>
<td>Franceschi et al, 2001, Italy (41)</td>
<td>Hospital-based case-control</td>
<td>Interviewed FFQ</td>
<td>1953</td>
<td>4154</td>
<td>Interviewed FFQ</td>
<td>75 (71–80)</td>
<td>210 (151–285)</td>
<td>X X X X X X X X</td>
</tr>
<tr>
<td>Flood et al, 2006, USA (30)</td>
<td>PLCO Screening Study</td>
<td>Nested case-control</td>
<td>3696</td>
<td>34,817</td>
<td>Self-reported 137-item FFQ</td>
<td>547, 55 (51–58)</td>
<td>1162, 145 (102–166)</td>
<td>X X X X X X X X X</td>
</tr>
<tr>
<td>Oh et al, 2004, USA (51)</td>
<td>Nurses’ Health Study</td>
<td>Prospective cohort (&lt;18 y)</td>
<td>1,715</td>
<td>34,428</td>
<td>Self-reported 61 + item FFQs</td>
<td>75 (69–80)</td>
<td>136 (104–167)</td>
<td>X X X X X X X X X</td>
</tr>
</tbody>
</table>

1 Adjusted confounders: age, BMI or body weight, energy, energy intake, family history of colorectal cancer, smoking, education, alcohol intake, physical activity, nonsteroidal antiinflammatory drug use (eg, aspirin use), fiber intake, red or processed meat intake, folate intake, calcium intake, and hormone replacement therapy use in women. NSAIDs, nonsteroidal antiinflammatory drugs; PA, physical activity; BCDDP, Breast Cancer Detection Demonstration Project; HPFUS, Health Professionals Follow-Up Study; IQ, interquartile; FFQ, food-frequency questionnaire; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer; HRT, hormone replacement therapy. Xs represent potential confounders that were adjusted for in individual study analyses.

2 Values for females.

3 Values for males.

4 Energy-adjusted value using the residual method.
observed no associations in any BMI strata (31–33, 35) and indeed an additional study detected an inverse association between GI or GL intake and colorectal cancer risk among sedentary overweight individuals (34). Studies that excluded patients with diabetes in stratified analyses also produced inconsistent results (33, 36).

Pancreatic cancer
To date, 6 studies have been published that investigated GI or GL intake and pancreatic cancer risk (29, 43–47), and the main characteristics of these studies are summarized in Table 3. Most of the cohorts originated from North America (29, 44–47); only one study was conducted in Europe (43). Notably, only half of all studies included men in their study population (43, 45, 46). All studies adjusted for smoking, age, and energy intake in multivariate analysis, whereas history of diabetes and BMI were included as confounders in most studies.

As shown in Figure 3 and Figure 4, the meta-analyses showed no significant associations between pancreatic cancer risk and either GI (RR: 0.99; 95% CI: 0.83, 1.19) or GL (RR: 1.01; 95% CI: 0.86, 1.19) in a comparison of the highest with the lowest category of intake. There was little evidence of heterogeneity of estimates for GI ($I^2 = 0\%$, $P = 0.78$) or GL ($I^2 = 4\%$, $P = 0.39$), and the funnel plots (data not shown) provided no evidence of publication bias. Results did not change when individual studies were removed or when the studies that included data for females only were considered. There were insufficient data to conduct separate analysis on data for males only. Five studies stratified the analyses by BMI and/or physical activity subgroups (29, 43–46), and most of these studies did not report any significant findings, with only one exception (44).

Stomach cancer
As detailed in Table 3, only 2 studies described GI and GL intakes in relation to stomach cancer risk (48, 49). No significant associations were seen between GI intake and stomach cancer risk in either study. There was a direct association between GL and stomach cancer risk in the case-control study in a comparison of those in the highest category of GL intake with those in the lowest category of GL intake (OR: 1.94; 95% CI: 1.47, 2.55), and the association was accentuated in females. However, these results were not replicated in the cohort study (RR: 0.85; 95% CI: 0.50, 1.43). The authors of both studies indicated that their results did not change when the participants were stratified by BMI category.

Esophageal cancer
One Italian hospital-based case-control study addressed the relation between GI and GL and squamous cell carcinoma of the esophagus, as outlined in Table 3 (50). Borderline significant associations were observed between squamous cell esophageal cancer risk and each 10-unit/d increase in GI intake (OR: 1.1; 95% CI: 0.9, 1.5) and 100-unit/d increment in GL intake (OR: 1.2; 95% CI: 1.0, 1.5). The authors described an even greater risk in overweight people consuming a high-GI or high-GL diet, although this analysis included results for squamous cell esophageal, laryngeal, oral, and pharyngeal cancers combined.
DISCUSSION

The results of this systematic review and meta-analyses, which is the most comprehensive to date, do not strongly support an association between dietary GI or GL and colorectal or pancreatic cancer.

TABLE 2

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>No. of studies (references)</th>
<th>Heterogeneity</th>
<th>Heterogeneity</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>Cohorts</td>
<td>Case-control</td>
</tr>
<tr>
<td>Glycemic index</td>
<td></td>
<td>r^2</td>
<td>P value</td>
<td>r^2</td>
</tr>
<tr>
<td>Colon</td>
<td>7 (24, 33, 35, 37, 40–42)</td>
<td>1.20 (0.98, 1.47)</td>
<td>79 &lt;0.01</td>
<td>0.97 (0.77, 1.23)</td>
</tr>
<tr>
<td>Proximal colon</td>
<td>5 (32, 33, 35, 37, 42)</td>
<td>1.16 (0.99, 1.37)</td>
<td>28 0.20</td>
<td>1.07 (0.91, 1.26)</td>
</tr>
<tr>
<td>Distal colon</td>
<td>5 (32, 33, 35, 37, 42)</td>
<td>0.98 (0.82, 1.17)</td>
<td>30 0.19</td>
<td>0.89 (0.73, 1.08)</td>
</tr>
<tr>
<td>Rectal</td>
<td>6 (32, 33, 35, 37, 40, 41)</td>
<td>1.20 (1.02, 1.40)</td>
<td>2 0.42</td>
<td>1.08 (0.89, 1.33)</td>
</tr>
<tr>
<td>CRC and adenomas</td>
<td>13 (24, 30–41)</td>
<td>1.12 (0.99, 1.27)</td>
<td>76 &lt;0.01</td>
<td>1.03 (0.95, 1.12)</td>
</tr>
<tr>
<td>Glycemic load</td>
<td></td>
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</tr>
<tr>
<td>Colon</td>
<td>5 (33, 35, 37, 39, 41)</td>
<td>1.08 (0.85, 1.38)</td>
<td>81 0.01</td>
<td>0.99 (0.83, 1.18)</td>
</tr>
<tr>
<td>Proximal colon</td>
<td>5 (32, 33, 35, 37, 39)</td>
<td>0.93 (0.77, 1.12)</td>
<td>11 0.34</td>
<td>0.93 (0.77, 1.12)</td>
</tr>
<tr>
<td>Distal colon</td>
<td>5 (32, 33, 35, 37, 39)</td>
<td>0.94 (0.75, 1.18)</td>
<td>26 0.23</td>
<td>0.94 (0.75, 1.18)</td>
</tr>
<tr>
<td>Rectal</td>
<td>6 (32, 33, 35, 37, 40, 41)</td>
<td>1.22 (1.00, 1.49)</td>
<td>24 0.24</td>
<td>1.12 (0.91, 1.38)</td>
</tr>
<tr>
<td>CRC and adenomas</td>
<td>12 (24, 30–39, 41)</td>
<td>1.10 (0.95, 1.28)</td>
<td>79 &lt;0.01</td>
<td>1.06 (0.95, 1.17)</td>
</tr>
</tbody>
</table>

Other cancers of the digestive tract

Our electronic search found no studies of GI or GL intake that were related to the risk of cancer of the liver or the biliary tract.

FIGURE 2. Forest plot of glycemic load and colorectal cancer risk. *Test for heterogeneity: χ^2 = 9.1, df = 7, P = 0.25; I^2 = 23% (95% CI: 0%, 65%). **Test for heterogeneity: χ^2 = 34.9, df = 8, P < 0.01; I^2 = 77% (95% CI: 56%, 88%).

^Meta-analyses of case-control studies were not possible for some cancer subsites because of insufficient numbers.
<table>
<thead>
<tr>
<th>Authors, date, location</th>
<th>Study design (mean follow-up)</th>
<th>Cases</th>
<th>Controls/ cohort size</th>
<th>Diet assessment</th>
<th>Median GI (IQ range)</th>
<th>Median GL (IQ range)</th>
<th>Adjusted confounders</th>
</tr>
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<tbody>
<tr>
<td><strong>Pancreatic cancer</strong></td>
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<tr>
<td>Heinen et al, 2008, Netherlands (43)</td>
<td>Netherlands Cohort Study</td>
<td>408</td>
<td>120,852</td>
<td>Self-reported cohort (13.3 y)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>58&lt;sup&gt;3&lt;/sup&gt;, 61&lt;sup&gt;4&lt;/sup&gt; (37–78)</td>
<td>102&lt;sup&gt;3&lt;/sup&gt;, 136&lt;sup&gt;4&lt;/sup&gt; (19–240)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Nöthlings et al, 2007, USA (45)</td>
<td>Multiethnic Cohort Study</td>
<td>434</td>
<td>162,150</td>
<td>Self-reported cohort (8 y)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>—</td>
<td>147 (78–272)</td>
<td>X X X X X X X</td>
</tr>
<tr>
<td>Patel et al, 2007, USA (46)</td>
<td>CPS II Nutrition Cohort</td>
<td>401</td>
<td>124,907</td>
<td>Self-reported cohort (9 y)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>74 (68–80)</td>
<td>113 (95–132)</td>
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<tr>
<td>Silvera et al, 2005, Canada (47)</td>
<td>National Breast Screening Study</td>
<td>112</td>
<td>49,111</td>
<td>Self-reported cohort (16.4 y)</td>
<td>74 (63–92)</td>
<td>148 (125–169)</td>
<td>X X X X X X</td>
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<tr>
<td>Johnson et al, 2005, USA (29)</td>
<td>Iowa Women’s Health Study</td>
<td>181</td>
<td>33,551</td>
<td>Self-reported cohort</td>
<td>85 (82–89)</td>
<td>170 (151–188)</td>
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<tr>
<td>Michaud et al, 2002, USA (44)</td>
<td>Nurses’ Health Study</td>
<td>180</td>
<td>88,802</td>
<td>Self-reported cohort (18 y)</td>
<td>74 (65–81)</td>
<td>119 (80–167)</td>
<td>X X X X X X</td>
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<tr>
<td><strong>Stomach cancer</strong></td>
<td></td>
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<td>Larsson et al, 2006, Sweden (48)</td>
<td>Swedish Mammography Cohort</td>
<td>156</td>
<td>61,433</td>
<td>Self-reported cohort (18 y)</td>
<td>80 (76–83)</td>
<td>179 (157–207)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Augustin et al, 2004, Italy (49)</td>
<td>Hospital-based case-control</td>
<td>769</td>
<td>2081</td>
<td>Interviewed 29-item FFQ</td>
<td>—</td>
<td>—</td>
<td>X X X X X X X</td>
</tr>
<tr>
<td><strong>Squamous-cell esophageal cancer</strong></td>
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<tr>
<td>Augustin et al, 2003, Italy (50)</td>
<td>Hospital-based case-control</td>
<td>304</td>
<td>743</td>
<td>Interviewed 78-item FFQ</td>
<td>77 (71–81)</td>
<td>238 (163–298)</td>
<td>X X X X X X X</td>
</tr>
</tbody>
</table>

<sup>1</sup> Adjusted confounders: age, sex: male/female, energy intake, family history of diabetes, race, smoking, physical activity, red and processed meat intake, alcohol intake, diabetes, history of diabetes (exclusion criteria for Nöthlings et al and Patel et al), and height. PA, physical activity; CPS, Cancer Prevention Study; FFQ, food-frequency questionnaire; IQ, interquartile. Xs represent potential confounders that were adjusted for in individual study analyses.

<sup>2</sup> Total follow-up length.

<sup>3</sup> Values for females.

<sup>4</sup> Values for males.
cancer risk. Furthermore, only limited evidence from hospital-based case-control studies indicates an association between high GL intake and an increased risk of gastric cancer and esophageal squamous cell carcinoma.

Our findings contrast with those of a previous meta-analysis, which reported significant positive associations between GI and GL intakes and colorectal cancer risk and incorporated marked heterogeneity (51). In their analysis, Gnagnarella et al (51) combined the results from cohort and case-control studies and then performed statistical adjustment for study design in metaregression models. This approach, in addition to the extra study included in our analysis (32), may explain the lack of consistency with our findings. A smaller previous meta-analysis of cohort studies illustrated a borderline positive association between high GI intake and colorectal cancer risk, but observed no associations for high-GL diets (52). In our analysis, separate meta-analyses were conducted for colorectal, colon, distal colon, proximal colon, and rectum subsites. There was no strong association between GI or GL intake and risk of cancer at any of the subsites investigated when cohort study results were combined. When the results of case-control studies were also considered, an association between GI intake and rectal cancer risk was suggested. This may be explained by the high range of GI and GL intakes observed among the European hospital-based case-control study participants (40, 41); however, a European cohort study observed similar intakes among their population in Sweden and found no significant association with colorectal cancer risk (35). Therefore it is plausible that the results of case-control studies may have been positively skewed by dietary recall bias (40, 41).

The lack of a strong association between GI or GL intake and colorectal cancer is particularly surprising because one of the main hypothesized mechanisms for this association is via hyperinsulinemia, markers of which have been strongly linked with elevated colon cancer risk (9, 53, 54). Additionally, nonfasting plasma C-peptide (a marker of insulin secretion), rather than fasting C-peptide has been shown to be directly related to pancreatic cancer risk in nested case-control studies (55–57), which implies that insulin concentrations in the postprandial state may be the relevant exposure for pancreatic carcinogenesis. However, our findings provide little support for an influence of dietary GI and GL on the risk of either cancer; therefore, it is speculated that dietary GI and GL may not significantly affect blood insulin concentrations. Others have noted that the plasma insulin response is not proportional to the blood glucose response and that other dietary components, such as protein and fat intake, may be

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Relative Risk (95% CI)</th>
<th>Relative weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heinen 2008 (43)</td>
<td>Men + women</td>
<td>0.87 (0.59, 1.29)</td>
<td>22</td>
</tr>
<tr>
<td>Patel 2007 (46)</td>
<td>Men + women</td>
<td>0.93 (0.69, 1.25)</td>
<td>39</td>
</tr>
<tr>
<td>Silvera 2005 (47)</td>
<td>Women</td>
<td>1.43 (0.56, 3.65)</td>
<td>4</td>
</tr>
<tr>
<td>Johnson 2005 (29)</td>
<td>Women</td>
<td>1.08 (0.74, 1.58)</td>
<td>23</td>
</tr>
<tr>
<td>Michaud 2002 (44)</td>
<td>Women</td>
<td>1.16 (0.69, 1.97)</td>
<td>12</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.99 (0.83, 1.19)*</td>
<td>100</td>
</tr>
</tbody>
</table>

**FIGURE 3.** Forest plot of glycemic index and pancreatic cancer risk. *Test for heterogeneity: $\chi^2 = 1.8$, df = 4, $P = 0.78$; $I^2 = 0$% (95% CI: 0%, 79%).

**FIGURE 4.** Forest plot of glycemic load and pancreatic cancer risk. *Test for heterogeneity: $\chi^2 = 5.2$, df = 5, $P = 0.39$; $I^2 = 4$% (95% CI: 0%, 76%).
more relevant than GI in promoting insulin secretion, regardless of blood glucose concentrations (58).

It has also been proposed that GI and GL intake may affect cancer risk via the insulin-like growth factor (IGF) axis, independently of insulin (59). Elevated insulin concentrations have been shown to lower concentrations of IGF-binding proteins (IGFBPs), which in turn contribute to an increase in bioavailable IGF-1 concentrations—a pathway that has several implications that favor carcinogenesis (15). An increased risk of colorectal cancer has been shown for individuals in the highest serum GI-1 category compared with those in the lowest category in a well-conducted meta-regression analysis (60)—a finding that has since been confirmed in a later study (61). However, a small comparison study of postprandial IGF responses after consumption of a high-GI compared with a low-GI food showed minimal differences in IGF-1 concentrations, although serum concentrations of IGFBP-3 were markedly elevated after consumption of the low-GI food (62). Unfortunately, studies to date have not found strong associations between IGFBP-3 concentrations and colorectal, pancreatic, and gastric cancers (57, 60, 63).

The limited evidence uncovered by our systematic review is only suggestive of a link between GI, GL, and gastric and esophageal cancer risks. Incidence rates of proximal gastric cardia cancers and esophageal adenocarcinomas are increasing, in contrast with static or falling numbers of distal noncardia gastric cancers and esophageal squamous cell carcinomas (64–66). It may be important to discern between these subsites in dietary investigations of gastric and esophageal cancers to conceal any potential associations arising from their different etiologies. Neither of the reports of GI, GL, and gastric cancer in our review distinguished between subsites and our search found only one study describing squamous cell esophageal carcinoma. Being overweight elevates the risk of gastric cardia cancers (67) and esophageal adenocarcinomas (20); therefore, future research on GI and GL intakes in relation to the risk of these cancer subsites is especially warranted.

It could be argued that we did not show an association between GI and GL intakes and cancer risk because of dietary measurement error, and therefore because of a misclassification of individuals according to GI and GL intake, in the studies in the meta-analyses. The quality of dietary assessment tools used varied widely from a 29-item food-frequency questionnaire (49) to a 200-item food-frequency questionnaire (45) or interviewer administered diet history (24, 42). Most studies used only one measure of dietary intake and perhaps failed to capture any changes in habitual diet that may have occurred over long follow-up time periods and subsequently influenced cancer development. Notably, no studies assessed GI or GL intakes in childhood or adolescence in relation to risk of digestive tract neoplasms in later life. Two studies assessed GI and GL intakes in relation to the risk of colorectal adenomas; no association was observed in women (30, 31), and an inverse association was observed in men (30). These findings suggest that GI and GL intakes are not of etiologic importance in the initiation stages of colorectal cancer development. Moreover, most of the participants in the included studies were women; therefore, it is highly likely that men were underrepresented in our estimates. This may also explain the inconsistent results observed in sensitivity analyses by body mass strata between studies. If there is a relation between GI or GL intake and cancers of the digestive tract, it is likely to be a weak association that may be more difficult to detect.

Potential limitations of our meta-analyses include the relatively small number of studies involved, which make estimates of publication bias and heterogeneity difficult to interpret. Furthermore, adjustment for potential confounders was inconsistent between studies; therefore, it is possible that there was residual confounding from factors such as physical activity. In addition, we only compared the risk of cancer for those in the highest category of GI and GL intakes with those in the lowest category of GI and GL intakes, and these categories of intake varied between studies. In summary, this systematic review provides little evidence of an association between dietary GI or GL intake and the risk of cancers of the digestive tract.

The authors’ responsibilities were as follows—HGM, MMC, and LJM: designed the study; HGM and MMC: conducted the literature search and extracted the data; CRC: provided statistical advice; and HGM: conducted the statistical analysis and prepared the first draft of the manuscript. All authors contributed to the writing, editing, and proofreading of the final manuscript. None of the authors had any conflicts of interest to declare.

REFERENCES


