Glycemic Index: The State of the Science, Part 4:
Glycemic Index and Cancer Risk
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This review is the fourth in the series of papers emanating from the Wheat Foods Council’s White Paper on the Glycemic Index. The complete paper plus the updated summaries are found on the website. The first paper is an overall review of the glycemic index and its variability; the second is its role in weight control and satiety; and the third is its role in coronary heart disease. The fifth one will come out early in 2011 and will address the Glycemic Index in inflammation, metabolic syndrome and diabetes.

Introduction

The role of nutrients and the prevention of cancer is a subject of continuing interest and study. Macronutrients and micronutrients, total caloric intake, and certain dietary patterns have all been suggested as modulators of cancer risk. With respect to macronutrients, total fats and certain types of fat and protein can impact cancer risk. More recently there has been an effort to try to sort out the effect of carbohydrate (CHO) quality as determined either by its glycemic index (GI) or glycemic load (GL).

Interest in this topic is especially keen because of a potential of the glycemic excursion to influence insulin levels and insulin-like growth factors (IGFs). (1) Growth of normal and malignant tissues has been linked to IGFs. This part of the review will assess the strength of evidence between GI and GL and various forms of cancer.

GI, GL and Breast Cancer

Most large epidemiological studies fail to show any relationship between dietary GI or GL and breast cancer risk. These were the findings of a meta-analysis (2) and a review. (3) Authors who reviewed the prospective epidemiologic study concluded that “there is no association that is consistent, strong, and statistically significant for any dietary variables and breast cancer, including GI or GL.” (3) The review noted that the lack of relationship held even when populations were stratified according to body mass index (BMI), physical activity, or hormone use. It needs to be pointed out that in this case, while the majority of findings pointed in this direction, not all studies agree, so controversy remains.

Epidemiological and case-control studies done after these reviews generally support the lack of association between GI and GL and breast cancer. However, a few studies stratified either by BMI or menopausal status do show associations. The problem in looking at the findings is that there is a high degree of variability among the studies, so that determining the precise effect of either menopausal status or BMI is difficult.
Effects of Menopausal Status and BMI

Some sub-cohorts based on menopausal status or BMI do show a relationship between GI and or GL and breast cancer. For example, a prospective epidemiological study of nearly 9,000 Northern Italian women showed that while total CHO intake was not associated with breast cancer incidence, there was an association between GI of high CHO foods and increased breast cancer risk. (4) When data were analyzed with respect to menopausal status and body weight, breast cancer risk for those eating a high GL diet increased sharply only in those women who were premenopausal and of normal body weight (BMIs < 25). In this case, the trifecta of elevated dietary GL, being premenopausal and normal body weight increased breast cancer risk 4-to-6 fold.

In an Italian case-control study, those eating diets with the highest GI or GL had a slightly increased risk. (5) But in this case, these were the findings regardless of menopausal status. In a small case-control study of Mexican women, (6) the results were different from the Italian studies. GI was unrelated to breast cancer risk, but GL was. However in the Mexican cohort, high GL diets doubled the risk for postmenopausal women.

Data from the Italian prospective study indicated that BMI might modulate risk. This was the case in several studies that showed no relationship between breast cancer risk and dietary GI or GL for the cohort considered in totality. However, there was a significant relationship between GL and breast cancer when the cohort was partitioned according to menopausal status and BMI. For example, in the Western New York Exposure and Breast Cancer Study (1,166 cases, 2,105 controls), dietary GL for premenopausal women with BMIs > 25 more than doubled the risk of breast cancer. (7) For postmenopausal women, a high GI or GL dietary pattern was associated with over a 30% reduced risk of breast cancer, and this was more pronounced in overweight women (BMI > 25). Interestingly, these US data are at odds with the Italian data where the risk increased in premenopausal women of normal weight (BMI < 25).

Dietary GI or GL was not related to breast cancer incidence in premenopausal women in the US Nurses’ Health Study II (n=90,655 women aged 26-46 years). (8) For women with normal BMIs (< 25), the relative risk of breast cancer decreased with increasing CHO or GL (but not GI), so those in the quintile eating the most CHO or highest GL had a 38% lower risk of breast cancer than those eating the least CHO or the lowest GL. The opposite was true among premenopausal women with BMIs > 25; the relative risk of breast cancer increased with increasing CHO or GL. The overweight women in the quintile with the highest dietary CHO or GL (not GI) had a 47% higher risk of breast cancer than those with the lowest dietary intakes. (8)

This study taken by itself would indicate that premenopausal women with BMI above normal have increased risk with high GI diets, but premenopausal women with BMIs less than 25 may have lower breast cancer risk when dietary GI or GL is high. However, this finding is not consistent as postmenopausal women in the New York study also showed decreased breast cancer risk with high GL diets. (7) Further, inconsistency in the findings come from a cohort of Chinese women (n=78,942). In this cohort CHO and GL were both related to premenopausal breast cancer incidence. There was no relationship to GI. (9)

Data from the Swedish mammography cohort indicate that the estrogen receptor status may need to be considered in doing these associations. (10) In this cohort, GL (but not CHO or GI) was weakly positively
associated with overall breast cancer risk. However, analyses stratified by estrogen receptor (ER) and progesterone receptor (PR) status of the breast tumors showed statistically significant positive associations between CHO intake, GI and GL with risk of ER+/PR-breast cancer. No associations were observed for ER+/PR+ or ER-/PR- breast tumors.

Thus, data among the different cohorts vary and may depend on a number of factors. Such findings demand more study and analysis in order to assess other potential differences that may occur among the cohorts and research designs.

The following prospective studies show no association of GI and GL with breast cancer:

- In Australian women (n=12,273) there were no significant associations between breast cancer and GI or GL; (11)
- In US women in the Nurses’ Health Study (n= 88,678), there was no association of GI or GL on either pre- or post-menopausal breast cancer; (12)
- In US women in the Women’s Health Study (n=39,876), there was no relationship between GI and GL and post-menopausal breast cancer; (13)
- In US postmenopausal women (n=63,307, age 40-87 years) in the Cancer Prevention Study II Nutrition Cohort, there was no association of GI or GL on breast cancer; (14) in US postmenopausal women (n=34,703) in the Iowa Women’s Health Study, there was no association of GI or GL on breast cancer; (15)
- In a case-control study in South Korea, with 362 women aged 30-65 years old and matched controls, there was no association with GI or GL or total CHO, but there was 20% increase in risk associated with white rice intake, but not mixed rice, and a 25% decrease in risk with brown rice. (16)

**Summary** – These data suggest that there is no clear relationship of GI or GL with risk of breast cancer. Factors such as menopausal status, body weight, tumor type (estrogen-receptor positive and negative tumors), the effects of body weight, hormones and genetic differences and potential mechanisms need to be teased out in future studies.

**GI, GL and Colorectal and Gut Cancer Risk**

Early studies suggested that foods with a high GI or GL could possibly increase the risk of colorectal cancer. (17) However, many studies do not support this theory, even though elevated circulating insulin and resulting high levels of IGF-1 from elevated glucose has been suggested as having an impact. The only animal study that assessed the issue of GI and GL and colon cancer found no relationship despite the fact that the rats were fed a known carcinogen. There was no difference in the formation of abnormal colonic cells (aberrant crypts), a precursor to colon cancer, when the diet varied in GI or GL. (18)

Some epidemiological studies even showed that high GI or GL reduced risk. In the Netherlands Cohort Study (n=120,852 men and women), men eating in the highest quintile of GI or GL reduced their RR for colorectal cancer by nearly 20% compared with those eating in the lowest quintile of GI and GL. (19) In the Prostate, Lung, Colorectal, and Ovarian screening trial (n= 34,817), men and women were screened for polyps and adenomas using flexible sigmoidoscopy. (20) High intakes of CHO or high GL (not high GI) decreased the risk of adenomas by nearly 30% in men. The small decrease seen in women did not reach statistical significance. For the women in Breast Cancer Detection Demonstration Project follow-up cohort (n=45,561), the risk of colon cancer was significantly reduced with diets high in CHO intake and GI. (21)
While some studies showed decreased colorectal cancer risk at least in part of the population, dietary GI or GL did not impact risk in a number of studies. There was no decrease in risk for the following:

1. Women in the Netherlands Cohort Study, (19)
2. Women in a Swedish Mammography Study (n=61,433).(22)
3. Women in previously cited Prostate, Lung, Colorectal, and Ovarian screening trial, (20) and
4. Women in the US Nurses’ Health Study and men in the Health Professionals Follow-up Study. In this cohort neither intakes of dietary CHO, GL, overall GI, sucrose, or fructose were associated with colorectal cancer risk.(23) For men in the latter cohort, dietary GL slightly increased relative risk (RR=1.32) and the association was stronger among men with BMI over 25.

BMI was shown to modulate the association when a subgroup of a study was analyzed. In the Iowa Women’s Health Study (n=35,197 postmenopausal women), CHO intake, GI, and GL were not associated with risk of colorectal cancer. (24) However, classification by BMI showed both GI and GL were positively associated with colorectal cancer incidence in obese women (BMI > 30). The RR was 1.66 for the highest versus lowest quintiles of GI and 1.79 for GL. No such increased risk was observed when the data from the Swedish Mammography cohort was analyzed according to BMI. (22) One possible explanation for differences in the data between the US and the European cohorts may be due to a greater percentage of obese and extremely obese women in US cohorts.

Case-control studies were more likely than prospective cohort studies to show a slight increase colon cancer risk related to dietary GI. Colorectal cancer risk of 1,125 Italian men and 828 women was higher for those in the quintile eating diets with the highest GI or GL compared to those eating in the lowest quintile. (25) The ORs were 1.7 and 1.8, respectively. One study looked at mutations associated with the production of p53 in nearly 1500 patients. This analysis suggested that subjects with a high GL diet (relative to lowest intake) were more likely to have mutations that could lead to increased cancer risk. (26)

In summary, many studies show that dietary GI or GL is not associated with increased risk of colorectal cancer, and even a few studies suggest the dietary GI or GL is associated with reduced risk. This is the conclusion of a recent review that stated that there was no consistent relationship when the results of prospective cohort studies were pooled. (27) While these data fail to show an association, there are few studies suggesting that dietary GI or GL might not affect colorectal cancer risk in the population overall, but that it might be affected by gender or BMI. The puzzling thing about these attributes is that there is not consistency among studies. Perhaps the variation in results is due to differences in the cohort, in overall diet and lifestyle patterns, or the foods in the diet making them low or high GI. Diet quality in terms of dietary fiber and its co-travelers can vary as the GI or GL vary. Such attributes can have positive impacts on colonic health. Further research is needed to clarify the role of particular foods that make a diet low GI or GL, other diet and lifestyle factors, gender and BMI to fully understand the role of GI and GL and its impact on the risk of colorectal cancer. Also, data on possible mechanisms are needed.

**GI, GL and Pancreatic Cancer**

Epidemiological evidence strongly suggests that glucose intolerance and Type 2 diabetes are risk factors for pancreatic cancer, thus some researchers thought that it could be possible that GI or GL would be a risk factor for pancreatic cancer. However, data from a variety of cohorts fail to provide support for

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1 Inactivation of the p53 tumor suppressor gene is a common event in the development of colon cancer.
this hypothesis. GL/GI was not related to pancreatic cancer risk in the following prospective studies.

1. The American Cancer Society Cancer Prevention Study II (CPS-II) (n=124,907 men and women) followed for 9 years. (28)
2. The National Breast Screening Study (n =49,613 Canadian women) followed for 16.5 years. (29)
3. The Nurses’ Health Study (n=88,802) female nurses followed for 18 years. (30)
4. The Hawaii-Los Angeles Multiethnic Cohort (n =162,150) residents of California and Hawaii. (31)
5. The Women’s Health Initiative (n=161,809 postmenopausal women of ages 50-79 years) followed for 8 years. (32)
6. The NIH-AARP Diet and Health Study (n= 482,362) followed for 7 years. Interestingly, while there was no association with either GI or GL, both sugar and fructose intakes were associated with increased risk. (33)

In two of the studies, (30, 31) there was a trend that BMI and other dietary constituents might impact the risk. For the women in the Nurses’ Health study, there was a statistically, non-significant increase in risk of pancreatic cancer for women with a high GL. The risk became stronger among sedentary women with BMIs over 25. In the Hawaii-Los Angeles Multiethnic Cohort, pancreatic cancer risk did not seem to be related to dietary GI or GL, but was increased for those who had both high BMIs and high sucrose intakes.

In summary, the data to date indicate that an association between GI or GL and pancreatic cancer is not very likely. If such an association does exist in the overweight, the elevation of risk appears to be small. This was also the conclusion of the systematic review by Mulholland and colleagues. (27) Further research is needed to see how BMI, other aspects of the diet such as total CHOs or sugars impact the relationship of GI/GL and pancreatic cancer.

**GI, GL and Other Cancers**

Cancers of the thyroid (as well as those of the stomach and upper gastrointestinal tract) have been related to intake of refined grain. (34) Some hypothesize the high GI of GL of a refined grain diet could explain the observations. To date, there are very few studies on GI and GL and thyroid cancer. The only study referenced in MedLine is a case-control study conducted in Italy with 399 patients with thyroid cancer and 616 controls. (35) Those in the highest tertile of GI or GL intake compared with the lowest tertile had their RRs increase to 1.73 and 2.17, respectively.

In terms of stomach cancer, there are more published studies, but most are case-control studies. In two different Italian studies, one with 200 cases and one with 800 cases, diets with a high GL, especially those low in fruits and vegetables, at least doubled the risk of stomach cancer compared to controls (36, 37). Unlike the increased risk observed with GL, no association was seen between dietary GI and stomach cancer risk in either Italian study. (37)

The opposite results were shown in a Serbian study with 102 cases, 204 controls. (38) Gastric cancer risk was unrelated to either GI or GL. In fact, diets high in carbohydrate or mono- and disaccharides reduced the risk by 80% or more. Diets high in polysaccharide intake increased risk for one type of stomach cancer (the diffuse type) only.

The role of GI or GL in **upper digestive tract cancers** (oral and pharyngeal cancer, squamous cell esophageal cancer and laryngeal cancer) has only been assessed in a case controlled studies in Italy. Data from these studies suggest increased risk with diets high in GI and GL. (39) These data show the risk is greater for women and those with high BMIs. Overall, there is too little data to determine the impact of either GI or GL on these cancers.
In terms of risk for prostate cancer, there was a dose-related association between GI and GL and risk in an Italian case-control study with 1,204 cases and matched controls. The odds ratio (OR) for the highest versus the lowest quintile of intake of GI was 1.57 and GL was 1.41. (40) An intervention study with prostate cancer patients suggests that a low-fat/low-GL diet, which also resulted in weight loss, was associated with significant gene expression changes in human prostate epithelium. Some of these could affect tissue proliferation through mechanisms such as increasing IGF-1 receptor cells or binding. Other changes can alter metabolic pathways and redox potential. (41)

Ovarian Cancer – Long-term consumption of a high GI or GL diet may elevate circulating insulin. This is thought to be a potential risk factor for many cancers including ovarian cancer. Currently there are only two studies – one case-control study and one prospective study – assessing the association between GI, GL and ovarian cancer. In the case-control study of women from four Italian regions with over 1,000 cases and twice as many controls, high GI or GL increased ovarian cancer risk by 70%. (42) These associations were observed in both pre- and postmenopausal women. A more recent prospective study on 49,613 women enrolled in the Canadian National Breast Screening Study (NBSS), GI and total carbohydrate and sugar intakes were not associated with ovarian cancer risk. (43) GL was positively associated with a 72% increase in risk of ovarian cancer for the entire population. (43) The risk was even slightly greater for postmenopausal women.

GI, GL and Endometrial Cancer and Fibroids – The relationship of dietary GI or GL and endometrial cancer risk also yielded contradictory findings. For example, there was no significant association between dietary GL and GI and endometrial cancer risk in the 288,428 women in the European Prospective Investigation into Cancer and Nutrition cohort (1992-2004). (44) However, segmentation of the data indicates there could be a modest positive association with total CHOs, total sugars, and dietary GL – especially among those who have never used hormones. In the Swedish Mammography Cohort (n=61,226), there was no overall association between CHO intake, GI or GL and the incidence of endometrial cancer in the population as a whole. (45) However, for overweight women (BMI ≥25) who were also sedentary, both CHO intake and GL were positively related to endometrial cancer risk. In a prospective study of 49,613 Canadians aged between 40 and 59, both GI and GL were associated with increased risk. (46) The hazard ratios (HRs) for the highest versus the lowest quartile level of overall glycemic index and glycemic load were 1.47 and 1.36, respectively. The HR increased to 1.88 for obese women (BMIs ≥30). Risks also went up for pre- and postmenopausal women using hormone replacement therapy. A case-control study from Italy and Switzerland (410 cases) showed that those in the quintile ingesting the highest GI and GL were associated with a two-to-three fold increased risk compared to those in the quintile ingesting the lowest GI or GL. (47) The associations were stronger in older women, those with higher BMI and users of hormone replacement therapy.

Abnormal, albeit usually benign, growth of the uterine tissue was assessed in a large prospective cohort, the Black Women’s Health Study (n = 21,861). (48) GL was associated with fibroids in women under 35 years old. GI was very weakly related to fibroids in the cohort overall. (48)
Summary for GI and GL for all Cancers

The case that GI and GL increase the risk for most cancer types is weak or inconclusive. For many types of cancer, an association found in case-control studies may fail to show significance in pooled cohort studies.

For breast and colorectal cancer, the bulk of the evidence shows a lack of association between dietary GI or GL and either cancer. Parsing and reanalyzing the data by BMI, gender, estrogen responsiveness of the tumor, menopausal status or other factors may show associations between GI and/or GL and cancer risk. However, the consistency of effect of these factors across studies is wanting because there is significant between-study heterogeneity for colorectal cancer risk. (49) Taking into account publication bias, a purported association weakens for both colon cancer and breast cancer and the role of GI/GL. (49)

No significant associations emerged between pancreatic, gastric or other digestive tract cancers. For these cancers, as well as prostate and ovarian cancer, there is too little evidence or too few studies to make firm conclusions about the impact of GI or GL on risk. (27) For endometrial cancer, GI and/or GL may increase risk.

Despite mostly negative findings relating GI and GL to cancers, it is possible that high dietary GI and GL may promote tumor growth through mechanisms such as increases in IGF-I and IGF-binding protein-1 or other receptors and metabolic changes. Increases in IGF-1 are known to stimulate cell proliferation and differentiation, inhibit apoptosis, and promote tumor angiogenesis. Increases in expression of proteins involved in glucose transport and breakdown may promote tumor cell survival.

The variability of GI and GL is due to many factors, but perhaps most importantly dietary composition may explain some of the seemingly contradictory studies. Diets that are low GI or GL may inherently be high in fruits, vegetables, fibers, nuts, legumes and whole grains and may be nutrient and antioxidant rich. Or diets may be low GI simply because they contain little CHO. Either of these dietary patterns may have the same blood glucose impact, but have very different nutrient delivery to the body, and can have profound impacts on cancer risk.
References


