Dietary glycemic index, glycemic load, and cancer risk: results from the EPIC-Italy study

S. Sieri1, C. Agnoli2, V. Pala1, S. Grioni1, F. Brighenti2, G. Masala3, D. Palli3, A. Mattiello4, S. Panico4, F. Ricceri5,6, F. Fasanelli7, G. Frasca8, R. Tumino8 & V. Krogh1

Factors linked to glucose metabolism are involved in the etiology of several cancers. High glycemic index (GI) or high glycemic load (GL) diets, which chronically raise postprandial blood glucose, may increase cancer risk by affecting insulin-like growth factor. We prospectively investigated cancer risk and dietary GI/GL in the EPIC-Italy cohort. After a median 14.9 years, 5112 incident cancers and 2460 deaths were identified among 45,148 recruited adults. High GI was associated with increased risk of colon and bladder cancer. High GL was associated with: increased risk of colon cancer; increased risk of diabetes-related cancers; and decreased risk of rectal cancer. High intake of carbohydrate from high GI foods was significantly associated with increased risk of colon and diabetes-related cancers, but decreased risk of stomach cancer; whereas high intake of carbohydrates from low GI foods was associated with reduced colon cancer risk. In a Mediterranean population with high and varied carbohydrate intake, carbohydrates that strongly raise postprandial blood glucose may increase colon and bladder cancer risk, while the quantity of carbohydrate consumed may be involved in diabetes-related cancers. Further studies are needed to confirm the opposing effects of high dietary GL on risks of colon and rectal cancers.

Factors linked to glucose metabolism seem to be involved in the etiology of several cancers1–4. Consumption of most carbohydrates increases blood glucose and blood insulin, but to varying extents, depending on carbohydrate type and processing, amount consumed, and presence of other nutrients. These variations are captured by the glycemic index (GI)5, which ranks carbohydrate foods according to their ability to raise blood glucose levels. High GI foods, like white bread, are rapidly digested and cause a rapid peak in blood glucose. Low GI foods like pulses and pasta, are digested more slowly, prompting a more gradual rise in blood glucose. Glycemic load (GL), the product of a food’s GI and its available carbohydrate content, was introduced to incorporate the effect of the total amount of carbohydrate consumed: it is a measure of total glycemic effect, and is hence an indicator of the insulin demand of the diet.

Several observational studies have investigated associations between dietary GI/GL and risk of different types of cancer, but have produced mixed results. Three meta-analyses – one that investigated only cohort studies6, and others that considered both case-control and cohort studies7, 8 – found that high GI was associated with increased risk of colorectal cancer. Meta-analyses also found that high GI and GL were weakly associated with increased risk of breast cancer9 and diabetes-related cancers10, while high GL was associated with increased risk of endometrial cancer9. The risks of developing other cancers do not appear to be influenced by dietary GI or GL6, 7, 10, 11.

Associations of dietary GI/GL with colorectal and breast cancer have been investigated previously in persons recruited to the Italian section of the European Prospective Investigation into Cancer and Nutrition (EPIC-Italy)12, 13. It was found that high GI was significantly associated with increased risk of colorectal cancer12, and high dietary GL was significantly associated with increased risk of breast cancer13. In the present study we
updated the follow-up of the EPIC-Italy cohort in order to assess associations of dietary GI and GL with various types of cancer.

Results

Characteristics of participants in the upper and lower quintiles of GI and GL are shown in Table 1. Mean dietary GI ranged from 50.0 in the lowest to 57.4 in the highest quintile. GI ranged from 86 g in the lowest to 235 g (glucose equivalents) in the highest. Participants in the highest GI quintile consumed more carbohydrate, especially more carbohydrate from high GI foods, more fiber, and more alcohol, but less fat especially saturated and monounsaturated fat, than those in the lowest GI quintile. Participants in the highest GL quintile consumed more carbohydrate, fiber, fat, alcohol, and energy than those in the lowest quintile. Those in the highest GI and GL quintiles smoked more, and those in the highest GI quintile had a slightly higher BMI than those in the lowest. Participants in the highest GL quintile were younger and more educated than those in the lowest.

Dietary GI (Table 2) was not associated with risk of all cancers combined, but high GI was associated with increased risk of colon cancer (HR 1.48, 95%CI 1.09–2.01 highest vs. lowest quintile; \( P \) trend 0.027) and bladder cancer (HR 1.51, 95%CI 1.01–2.25 highest vs. lowest quintile; \( P \) trend 0.042). GI was not associated with any other cancer.

Dietary GL (Table 3) was not associated with increased risk of all cancers combined, but high GL was associated with increased risk of colon cancer (HR 1.80, 95%CI 1.18–2.67 highest vs. lowest quintile; \( P \) trend 0.010), and increased risk of DRCs (HR 1.23, 95% CI 1.03–1.48 highest vs. lowest quintile; \( P \) trend 0.015), as well as decreased risk of rectal cancer (HR 0.42, 95%CI 0.18–0.98 highest vs. lowest quintile; \( P \) trend 0.047).

Table 1. Characteristics of study participants in the lower and upper quintiles of energy-adjusted* glycemic index and glycemic load. *Table entries are means, except where indicated. *Energy adjustment by residual method. Figures in brackets are standard errors.

| Glycemic index      | Glycemic load      |
|---------------------|-------------------|
| Quintile 1          | Quintile 5        | Quintile 1          | Quintile 5        |
| N                   | 9,089             | 9,089               | 9,089             | 9,089             |
| Glycemic index      | 50.0 (0.01)       | 57.4 (0.02)         | 52.5 (0.03)       | 54.4 (0.03)       |
| Glycemic load       | 132.6 (0.51)      | 167.8 (0.63)        | 86.0 (0.17)       | 235.2 (0.38)      |
| High GI (g/day)     | 90.0 (0.41)       | 186.5 (0.81)        | 72.2 (0.24)       | 231.2 (0.65)      |
| Low GI (g/day)      | 171.7 (0.70)      | 106.0 (0.43)        | 91.7 (0.30)       | 202.0 (0.68)      |
| Total carbohydrate  | 266.9 (1.02)      | 292.5 (1.10)        | 163.9 (3.32)      | 433.2 (0.69)      |
| Fiber (g/day)       | 22.3 (0.09)       | 26.4 (0.14)         | 15.9 (0.05)       | 34.7 (0.14)       |
| Total fat (g/day)   | 92.3 (0.32)       | 82.1 (0.29)         | 66.9 (0.21)       | 112.2 (0.32)      |
| Saturated fat (g/day)| 32.5 (0.13)      | 28.1 (0.11)         | 23.0 (0.08)       | 39.5 (0.13)       |
| Monounsaturated fat (g/day)| 44.0 (0.16) | 38.8 (0.14)       | 32.2 (0.11)       | 52.4 (0.16)       |
| Polysaturated fat (g/day)| 10.6 (0.04) | 10.5 (0.04)       | 7.95 (0.03)       | 13.8 (0.05)       |
| Alcohol (g/day)     | 11.3 (0.16)       | 13.7 (0.19)         | 10.5 (0.16)       | 14.9 (0.20)       |
| Energy (kcal/day)   | 2287.0 (7.42)     | 2299.6 (7.28)       | 1568.2 (5.38)     | 3244.4 (5.81)     |
| Age (years)         | 50.7 (0.08)       | 50.8 (0.08)         | 52.4 (0.08)       | 48.9 (0.08)       |
| Body mass index (kg/m^2) | 25.9 (0.04) | 26.2 (0.04)       | 26.1 (0.04)       | 26.1 (0.04)       |
| Physical activity  | 1.54 (0.001)     | 1.53 (0.001)        | 1.53 (0.001)      | 1.55 (0.001)      |
| Education (% over 8 years) | 50 | 51 | 46 | 53 |
| Smoking (% smokers) | 24 | 31 | 24 | 31 |

When participants being treated for diabetes, or diagnosed with cancer during the first 6 months of follow-up were excluded, the results did not differ from those cited above and all significant associations remained significant or nearly so. When participants who reported they were dieting were excluded, high dietary GL became associated with increased risk of breast cancer (HR 1.34, 95%CI 1.02–1.76 highest vs. lowest quintile; \( P \) trend 0.049; data not shown).

When the analyses on GL/GI and risk of colon cancer were stratified by subsite (proximal and distal), GI was significantly associated with distal colon cancer (HR 2.23, 95%CI 1.33–3.74 highest vs. lowest quintile; \( P \) trend 0.011). The results for GI and low GI carbohydrate did not differ between proximal and distal sites. (data not shown in Tables).
### Table 2. Hazard ratios (HR) of cancer and mortality in the EPIC-Italy cohort in relation to quintiles of energy-adjusted dietary glycemic index (GI). (5112 cancers, 2460 deaths, median follow-up 14.9 years). *Stratified by food frequency questionnaire and adjusted for sex, education, smoking status, BMI, alcohol intake, fibre intake, saturated fat intake, non-alcohol energy intake and physical activity. **Tests for linear trend were calculated after assigning an ordinal number to each quintile. †Diabetes-related cancers.

| Cancer        | N cases | 1 HR (95% CI) | 2 HR (95% CI) | 3 HR (95% CI) | 4 HR (95% CI) | 5 HR (95% CI) | P trend |
|---------------|---------|--------------|--------------|--------------|--------------|--------------|---------|
| Tongue        | 76      | 1.06 (0.34–1.36) | 0.86 (0.45–1.64) | 0.54 (0.25–1.13) | 0.69 (0.35–1.39) | 0.230       |
| Stomach       | 146     | 1.07 (0.44–1.17) | 0.90 (0.56–1.43) | 0.52 (0.30–0.91) | 0.66 (0.40–1.21) | 0.065       |
| Colon         | 441     | 1.21 (0.89–1.66) | 1.18 (0.86–1.62) | 1.18 (0.86–1.62) | 1.48 (1.09–2.01) | 0.027       |
| Rectum        | 102     | 1.58 (0.87–2.86) | 1.18 (0.62–2.22) | 1.08 (0.56–2.09) | 0.90 (0.45–1.79) | 0.413       |
| Liver         | 70      | 1.21 (0.36–1.58) | 1.17 (0.60–2.28) | 0.71 (0.33–1.52) | 0.57 (0.26–1.29) | 0.221       |
| Pancreas      | 117     | 0.84 (0.48–1.46) | 0.70 (0.38–1.25) | 1.06 (0.62–1.83) | 0.85 (0.48–1.52) | 0.893       |
| Lung          | 307     | 0.95 (0.65–1.38) | 1.10 (0.75–1.62) | 0.82 (0.53–1.27) | 0.88 (0.53–1.46) | 0.486       |
| Melanoma      | 194     | 1.68 (1.05–2.69) | 1.68 (1.05–2.71) | 1.39 (0.84–2.30) | 1.51 (0.91–2.48) | 0.312       |
| Breast        | 1362    | 1.02 (0.68–1.23) | 1.10 (0.83–1.46) | 1.08 (0.81–1.43) | 1.13 (0.84–1.51) | 0.235       |
| Kidney        | 136     | 1.16 (0.66–1.72) | 0.62 (0.35–1.10) | 0.58 (0.32–1.05) | 1.19 (0.72–1.96) | 0.759       |
| Meninges      | 75      | 0.78 (0.34–1.76) | 1.37 (0.67–2.81) | 1.47 (0.71–3.03) | 1.45 (0.69–3.02) | 0.125       |
| Brain         | 95      | 1.33 (0.69–2.57) | 1.40 (0.73–2.70) | 1.57 (0.82–3.01) | 0.99 (0.48–2.04) | 0.805       |
| Thyroid       | 132     | 1.21 (0.72–2.04) | 0.65 (0.35–1.21) | 1.24 (0.73–2.11) | 0.90 (0.50–1.60) | 0.783       |
| Lymphomas     | 106     | 1.13 (0.64–1.98) | 0.78 (0.41–1.45) | 0.90 (0.49–1.66) | 0.92 (0.50–1.70) | 0.565       |
| Myeloma       | 72      | 1.16 (0.56–2.38) | 0.85 (0.39–1.86) | 0.54 (0.22–1.03) | 1.37 (0.68–2.78) | 0.829       |
| All cancers combined | 5112 | 1.06 (0.97–1.15) | 1.04 (0.95–1.14) | 1.04 (0.95–1.14) | 1.06 (0.97–1.16) | 0.332       |
| DRC*         | 2449    | 1.01 (0.89–1.15) | 1.02 (0.90–1.16) | 1.04 (0.92–1.19) | 1.10 (0.96–1.25) | 0.141       |
| Mortality     | 2460    | 1.07 (0.94–1.22) | 1.07 (0.94–1.22) | 1.10 (0.97–1.25) | 1.06 (0.93–1.20) | 0.350       |

### Discussion

The main findings of our study are that high dietary GI was significantly associated with increased risk of colon and bladder cancer; whereas high dietary GI was significantly associated with increased risk of colon cancer and DRCs (which include colon cancer), but decreased risk of rectal cancer. Furthermore, high carbohydrate intake from high GI foods was significantly associated with increased risk of colon cancer and DRCs, but decreased risk of stomach cancer, whereas high carbohydrate intake from low GI foods was significantly associated with decreased risk of colon cancer.

Our finding that high dietary GI, high dietary GL, and high carbohydrate intake from high GI foods, are associated with increased colon cancer risk is in line with the previous EPIC-Italy study, which found that high dietary GI (but not GL) and high consumption of carbohydrates from high GI foods, were associated with significantly increased colon cancer risk. Like the present study, which considered 122 more colon cancer cases than the previous study, our previous study also found that high consumption of carbohydrates from low GI foods was associated with lowered colon cancer risk: thus taken together the results of both studies suggest that colon cancer risk depends more on the ability of the carbohydrate foods consumed to raise postprandial blood glucose than the overall quantity of carbohydrate consumed.

An alternative interpretation would be that high consumption of highly refined carbohydrates reduces consumption of carbohydrates from low GI foods and hence also reduces consumption of polyphenols and other antioxidants which may protect against colon cancer.

Several cohort studies have examined associations between dietary GI/GL and risk of colon or colorectal cancer. Most found no association, however two are in broad agreement with our findings: the George et al. study found that high dietary GI was associated with modestly increased risk of colorectal cancer in men but not women; the Women’s Health Study found that colorectal cancer risk in women was significantly associated with high GI, while the increased risk associated with high GI was not significant. As regards meta-analyses, one published in 2009 (case-control and cohort studies) and another in 2012 (cohort studies) found no evidence of links between dietary GI/GL and colorectal cancer. However other meta-analyses of cohort and case-control and cohort studies found that high GI, but not GL, was associated with increased risk of colorectal or colon cancer. By contrast, we found that colon cancer risk significantly increased with increasing GL (as well as GI) in agreement with a single meta-analysis published in 2008.

We expected that high dietary GI would increase the risk of both colon and rectal cancer (both are DRCs), but instead found that high GI was associated with significantly lowered risk of rectal cancer. It is known that etiologic factors for the two cancers differ; that colon and rectum derive from different segments of embryonic...
As regards DRCs, we found that high dietary GL was significantly associated with increased risk of developing DRCs. Although we found no association between DRCs and dietary GI, we did find that high carbohydrate intake from high GI foods was significantly associated with increased risk of DRCs. Taken together these findings suggest that increased risk of DRCs may be conferred by dietary GI and GL.

As regards bladder cancer, we found that high dietary GI was associated with increased risk of this disease. This is consistent with the finding of a 2013 case-control study that the highest quartile of dietary GI was associated with significantly increased bladder cancer risk. However, although a meta-analysis found that risk of DRCs was increased in those with high GI (but not GL), when bladder cancer was considered separately, risk was unaffected by GI. Furthermore, a 2009 cohort study found no association of dietary GL/GI with bladder cancer risk.

Unexpectedly, we found that high carbohydrate from high GI foods was associated with significantly lowered risk of stomach cancer. This result is not inconsistent with the findings of a cohort study and a case-control study, both of which found that risk of stomach cancer reduced slightly (not significant) as dietary GI and GL increased. Nevertheless a 2016 meta-analysis that analyzed 2 cohort and 4 case-control studies found no significant association between dietary GI/GL and stomach cancer. It is possible that many people who eventually develop stomach cancer have problems digesting foods years before diagnosis and change their diet to mitigate these problems, thus masking any association between carbohydrate intake and this cancer. Stomach cancer risk has been found to be inversely related to socioeconomic status which could confound the association with high GI foods. However when we adjusted for a proxy of socioeconomic status, results did not change.

As regards DRCs, we found that high dietary GI was significantly associated with increased risk of developing these cancers. This is broadly consistent the results of a meta-analysis that evaluated 60 811 patients considered to have a DRC from 36 prospective cohort studies. The study found a ‘modest-to-weak’ (significant) association between dietary GI/GL and stomach cancer. It is possible that many people who eventually develop stomach cancer have problems digesting foods years before diagnosis and change their diet to mitigate these problems, thus masking any association between carbohydrate intake and this cancer. Stomach cancer risk has been found to be inversely related to socioeconomic status which could confound the association with high GI foods. However when we adjusted for a proxy of socioeconomic status, results did not change.

As regards DRCs, we found that high dietary GI was significantly associated with increased risk of developing these cancers. This is broadly consistent the results of a meta-analysis that evaluated 60 811 patients considered to have a DRC from 36 prospective cohort studies. The study found a ‘modest-to-weak’ (significant) association between dietary GI (but not GL) and risk of developing a DRC. Although we found no association between DRCs and dietary GI, we did find that high carbohydrate intake from high GI foods was significantly associated with increased risk of DRCs. Taken together these findings suggest that increased risk of DRCs may be conferred not by a carbohydrate-rich diet, but by one rich in rapidly-absorbed carbohydrate.

As regards overall cancer risk, our data indicate no association with dietary GI/GL. As far as we are aware just one cohort study has examined associations between GI/GL and overall cancer risk. This study found that high GI was associated with increased risk of total cancer in men but not women, while high GL was associated with reduced overall cancer risk in both men and women.
| Cancer      | N cases | Carbo-hydrate | 1      | 2       | 3      | 4       | 5      | P trend  |
|------------|---------|--------------|--------|--------|--------|--------|--------|---------|
| Tongue     | 76      | High GI      | 0.75   | 0.81   | 0.66   | 0.59   | 0.218  |
|            |         | Low GI       | 1.59   | 1.26   | 0.99   | 1.60   | 0.585  |
| Stomach    | 146     | High GI      | 0.63   | 0.68   | 0.61   | 0.51   | 0.045  |
|            |         | Low GI       | 1.18   | 1.21   | 0.77   | 0.75   | 0.395  |
| Colon      | 441     | High GI      | 1.02   | 1.29   | 1.18   | 1.71   | 0.004  |
|            |         | Low GI       | 0.94   | 0.86   | 0.77   | 0.75   | 0.032  |
| Rectum     | 102     | High GI      | 1.27   | 0.70   | 0.84   | 0.66   | 0.141  |
|            |         | Low GI       | 1.38   | 1.37   | 1.13   | 0.98   | 0.774  |
| Liver      | 70      | High GI      | 0.72   | 0.88   | 0.84   | 1.43   | 0.441  |
|            |         | Low GI       | 1.09   | 1.43   | 1.40   | 1.41   | 0.326  |
| Pancreas   | 117     | High GI      | 0.83   | 0.60   | 0.96   | 0.75   | 0.582  |
|            |         | Low GI       | 1.86   | 1.67   | 0.88   | 1.33   | 0.732  |
| Lung       | 307     | High GI      | 0.90   | 0.80   | 0.82   | 0.82   | 0.304  |
|            |         | Low GI       | 0.89   | 0.86   | 0.84   | 0.80   | 0.830  |
| Melanoma   | 194     | High GI      | 1.56   | 1.46   | 1.48   | 1.63   | 0.171  |
|            |         | Low GI       | 0.79   | 0.83   | 0.91   | 0.79   | 0.118  |
| Breast     | 1362    | High GI      | 1.05   | 1.08   | 1.05   | 1.19   | 0.381  |
|            |         | Low GI       | 1.04   | 1.07   | 1.05   | 1.09   | 0.401  |
| Cervix     | 53      | High GI      | 0.90   | 0.85   | 1.26   | 1.01   | 0.720  |
|            |         | Low GI       | 0.79   | 1.10   | 0.89   | 0.60   | 0.421  |
| Endometrium| 203     | High GI      | 0.96   | 1.11   | 0.93   | 0.98   | 0.935  |
|            |         | Low GI       | 1.33   | 1.49   | 1.15   | 1.36   | 0.471  |
| Ovary      | 135     | High GI      | 0.88   | 0.68   | 0.82   | 0.81   | 0.252  |
|            |         | Low GI       | 1.83   | 1.49   | 1.45   | 1.59   | 0.402  |
| Prostate   | 481     | High GI      | 1.00   | 0.97   | 1.17   | 1.07   | 0.431  |
|            |         | Low GI       | 1.08   | 0.90   | 0.93   | 1.00   | 0.638  |
| Bladder    | 251     | High GI      | 1.35   | 1.27   | 1.51   | 1.44   | 0.124  |
|            |         | Low GI       | 0.88   | 0.91   | 0.87   | 0.67   | 0.112  |
| Kidney     | 136     | High GI      | 1.10   | 0.92   | 0.61   | 1.02   | 0.391  |
|            |         | Low GI       | 0.91   | 1.11   | 0.93   | 0.74   | 0.418  |
| Meninges   | 75      | High GI      | 0.97   | 0.88   | 1.21   | 1.53   | 0.322  |
|            |         | Low GI       | 0.67   | 0.89   | 0.54   | 0.56   | 0.137  |
| Brain      | 95      | High GI      | 1.10   | 1.07   | 1.66   | 0.85   | 0.654  |
|            |         | Low GI       | 1.49   | 1.42   | 1.42   | 1.05   | 0.972  |
| Thyroid    | 132     | High GI      | 0.96   | 0.99   | 0.72   | 0.91   | 0.526  |
|            |         | Low GI       | 1.14   | 1.19   | 1.37   | 1.06   | 0.651  |
| Lymphomas  | 106     | High GI      | 0.78   | 0.93   | 0.62   | 0.97   | 0.656  |
|            |         | Low GI       | 1.12   | 0.84   | 0.97   | 0.79   | 0.538  |
| Myeloma    | 72      | High GI      | 0.81   | 0.87   | 1.14   | 1.13   | 0.541  |
|            |         | Low GI       | 1.18   | 1.19   | 1.10   | 0.90   | 0.926  |
| All cancers combined | 5112 | High GI | 1.07   | 1.02   | 1.03   | 1.09   | 0.338  |
|            |         | Low GI       | 1.01   | 1.02   | 0.96   | 0.98   | 0.399  |
| DRCs*      | 2449    | High GI      | 1.05   | 1.11   | 1.12   | 1.23   | 0.011  |
|            |         | Low GI       | 0.98   | 1.02   | 0.95   | 0.96   | 0.517  |
| Mortality  | 2460    | High GI      | 1.02   | 0.89   | 1.03   | 1.04   | 0.651  |
|            |         | Low GI       | 1.01   | 0.97   | 0.87   | 0.91   | 0.029  |

Table 4. Hazard ratios (HR) of cancer and mortality in the EPIC-Italy cohort in relation to quintiles of intake of high GI carbohydrate and low GI carbohydrate. (5112 cancers, 2460 deaths, median follow up 14.9 years).

1Stratified by food frequency questionnaire and adjusted for sex, education, smoking status, BMI, alcohol intake, fibre intake, saturated fat intake, non-alcohol energy intake and physical activity; §Tests for linear trend were assessed after assigning an ordinal number to each quintile. *Diabetes-related cancers.

For breast cancer, we found that neither GI nor GL had any significant association with the risk of this disease. However a subgroup analysis that excluded participants who reported they were dieting at recruitment found that high GL was significantly associated increased breast cancer risk (HR 1.34, 95%CI 1.02–1.76 highest vs. lowest quintile; P trend 0.049). This result is fully consistent with our previous analysis of breast cancer in EPIC-Italy."
This study, which ab initio excluded all those who were dieting, also found that high GL was significantly associated with increased risk. The present subgroup analysis involved 507 more breast cancer cases and had approximately three more years of follow-up than our original study. A 2016 meta-analysis of 12 cohort studies found that both high GI and GL were significantly associated with modestly increased risk of breast cancer.

Regarding endometrial cancer, all published meta-analyses report a direct significant association between dietary GI and risk of endometrial cancer. However we found that although the risk of this cancer increased with increasing GL quintiles, the increases were never significant and P trend was 0.176. We only had 203 cases, so the lack of a significant association could be due to insufficient power.

Although several etiological hypotheses have been put forward, chronically high blood glucose giving rise to hyperinsulinemia, insulin resistance, and enhanced bioactivity of the IGF axis (and in particular of the potent mitogen IGF-1) is the most commonly-invoked mechanism to account for associations of a high GI/GL diet with increased cancer risk. Insulin may also influence cancer development by altering sex hormone metabolism. The differing associations of dietary GI and GL with different cancers probably reflect the fact that dietary GI is a measure of glucose availability and is independent of quantity, while dietary GL is a measure of the total glycemic effect, and is hence an indicator of the insulin demand of the diet. Thus, since a high GI diet is more likely than a high GI diet to produce chronically elevated blood glucose and insulin, cancer should depend more on dietary GL than dietary GI. Our findings for DRCs fit this scenario: DRC risk was significantly related to high dietary GI and high carbohydrate intake from high GI foods, but not to high dietary GI. Similarly colon cancer risk was significantly associated with high GI and high carbohydrate intake from high GI foods, but also a high GI diet; by contrast high carbohydrate intake from low GI foods was associated with decreased colon cancer risk.

Strengths of our study are its large sample size, prospective design and complete follow-up. It is also notable for the fact that, compared to previous cohort studies, GI values were determined specifically on local foods and are likely to be more accurate than values estimated from international food tables. Study limitations are first that the FFQs were not specifically designed to furnish dietary GI and GL, although they were designed to provide estimates of total carbohydrate and total energy intake. Second, we only have one dietary measurement and are unable to estimate long-term dietary intake, giving rise to some misclassification of exposure that would be expected to weaken associations between carbohydrate intake and cancer. Third, GI and GL estimates derived from FFQs may not take account of effects due to consuming mixed dishes, varying meal frequency, varying cooking methods, or chewing habits that can all influence the postprandial glycemic response. Strong correlations between observed and calculated GI values for component foods in mixed meals were found in one study; however another study found that predicted GIs were 22–50% larger than directly measured GIs suggesting that dietary GIs estimated from FFQs may be overestimates.

Fourth, although we adjusted for several dietary and lifestyle factors that could confound the association between dietary GI/GL and cancer, residual confounding remains a possibility. It is also possible that unmeasured or unknown factors may have caused confounding. Fifth, because of multiple comparisons, chance might have played a role in our findings although they are consistent with the findings of previous studies on the same cohort. Finally, we have no information on Helicobacter pylori infection and were thus unable to examine whether H. pylori influenced associations between stomach cancer and dietary GI/GL; furthermore, the analyses for stomach cancer could not be stratified by subsite or histologic type because of the small numbers of cases.

To conclude, this Italian study on a Mediterranean population characterized by traditionally high and varied carbohydrate intake suggests that a high GI diet may increase risk of colon and bladder cancer, while a high GI diet may increase risk colon cancer and DRCs in general, but reduce risk of rectal cancer. Further prospective studies are needed to confirm the opposing effects of high dietary GL on risks of colon and rectal cancer.

Materials and Methods

Study population. EPIC is a large European study on diet and cancer. EPIC-Italy enrolled 47,749 adult volunteers (men and women) at five centers: Varese and Turin in northern Italy, Florence in central Italy, and Naples and Ragusa in southern Italy. The design, population, and baseline data collection methods of EPIC-Italy are described elsewhere. Participants completed a food-frequency questionnaire (FFQ) and a lifestyle questionnaire after signing an informed consent form. The lifestyle questionnaire solicited information on education, socioeconomic status, occupation, history of previous illnesses and surgery, lifetime tobacco and alcohol use, and physical activity.

Participants lost to follow-up at baseline (n = 206) or who emigrated (n = 840) (zero follow-up); with missing information on diet (n = 874), anthropometry (n = 355) or lifestyle (n = 16); and with ratio of total energy intake (determined from the questionnaire) to basal metabolic rate at either extreme of the distribution (cut-offs first and last half-percentiles, n = 449) were excluded. Persons lost to baseline/emigrated had similar baseline characteristics to study participants with full follow-up (data not shown). After a median follow-up of 14.9 years, 5112 incident cancers and 2460 deaths were identified among study participants.

Ethics Statement. The study protocol was approved by the ethics committee at the Azienda Ospedaliera di Firenze (Italy). At baseline, participants signed a written informed consent to use clinical data for research. Consent forms were stored with barcode ID for subject identification. The ethics committee approved this consent procedure. The study protocol and informed consent procedure met the requirements of Italian legislation and the Declaration of Helsinki of 1975, as revised in 2008.

Dietary assessment. Dietary intake during the year before recruitment was assessed by validated FFQs (separate ones for Naples, Ragusa, and Varese-Turin-Florence) designed to capture local eating habits. Detailed descriptions of the questionnaires are available elsewhere. Nutrient values for all food items in the FFQs were
obtained from Italian food composition tables. GIs for about 150 commercially available Italian foods and prepared foods were obtained from published data, while GIs from other foods are available from unpublished data (Brighenti F, University of Parma). If there was no analyzed food item sufficiently similar to a consumed item, GIs published elsewhere (International GI Tables and www.glycemicindex.com) were used. Detailed descriptions of the procedure for linking FFQ responses to GIs are given elsewhere. The average dietary GI of each participant was calculated as the sum of the GIs of each food item consumed, multiplied by the average daily amount consumed and the carbohydrate content (percentage), all divided by the total daily carbohydrate intake. Dietary GL was calculated similarly except that there was no division by total carbohydrate intake. Each unit of GL is equivalent to the blood glucose-raising effect of consuming 1 g of glucose.

We divided carbohydrate intake into that from high GI foods and that from low GI foods, adopting GI 57 as cut-off, such that high and low GI foods each contributed 50% of mean total carbohydrate intake in the EPIC-Italy cohort. The main sources of carbohydrate from high GI foods were bread, sugar/honey and jam, pizza, and refined rice; the main sources of carbohydrate from low GI foods were pasta and fruit.

Follow-up. In Varese, Turin, Florence and Ragusa, incident cancer cases were identified by linkage to regional cancer registries. In Naples, incident cases were identified through linkage to the regional archive of hospital discharges, and by telephone enquiry where necessary. Participants were followed from study entry until first cancer diagnosis (except non-melanoma skin cancer), death, emigration, or end of follow-up, whichever occurred first. Follow-up ended December 31, 2010, in Florence, Turin, Ragusa and Naples; and December 31, 2009, in Varese. This difference was due to the fact that cancer registry and hospital discharge file availability for updating varied with recruitment center. Cancer cases were identified from the codes of the second edition of the International Classification of Diseases for Oncology. Only cancers with over 50 cases were included in cancer site-specific analyses for statistical power reasons. Diabetes-related cancers (DRCs) are cancers of bladder, breast, colon, rectum, endometrium, liver, pancreas and prostate, as identified in the consensus report of the American Diabetes Association and the American Cancer Society. Diabetes is associated with reduced risk of prostate cancer and increased risk of the other diabetes-related cancers. We assessed associations of dietary carbohydrate with DRCs excluding prostate cancer. Data on vital status, cause and date of death were obtained from mortality databases. Causes of death were coded according to the International Classification of Diseases, 10th Revision.

Statistical methods. Hazard ratios (HRs) of developing cancer in relation to quintiles of carbohydrate from high GI foods, carbohydrate from low GI foods, dietary GI and dietary GL were estimated by Cox multivariate models stratified by FFQ (north-central Italy, Naples and Ragusa) to control for differences in questionnaire design. The quintiles were defined on the whole cohort and the variables were adjusted for total energy intake using the residual method. In all models, age was the primary time variable. Sex, non-alcohol energy intake, smoking (never smoker/former smoker/current smoker), education (years of schooling), alcohol intake ( abstainer, <12 g/day, ≥12 g/day and ≥24 g/day), BMI (<25, ≥25 & <30, ≥30), fiber intake (tertiles), saturated fat intake (g/day) and physical activity (quartiles of MET-hours) were included in the models as confounders.

The significance of linear trends was assessed by treating each quintile as a continuous variable in the model and performing the Wald test. Sensitivity analyses were carried out, first by excluding persons diagnosed during the first six months of follow-up, second by excluding those with diabetes, and finally by excluding those who reported they were dieting. The analyses were performed with STATA (version 14.0; Stata Corp, TX, USA).

References

1. Giovannucci, E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 131, 31095–3120S (2001).
2. Giovannucci, E. & Michaud, D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 132, 2208–2225 (2007).
3. Kaaks, R. Nutrition, energy balance and colon cancer risk: the role of insulin and insulin-like growth factor-I. IARC Sci Publ. 156, 289–293 (2002).
4. Sieri, S. et al. Prospective study on the role of glucose metabolism in breast cancer occurrence. Int J Cancer 130, 921–929 (2012).
5. Jenkins, D. J. et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am. J. Clin. Nutr. 34, 362–366 (1981).
6. Choi, Y., Giovannucci, E. & Lee, J. E. Glycemic index and glycemic load in relation to risk of diabetes-related cancers: a meta-analysis. Br. J Nutr. 108, 1934–1947 (2012).
7. Turati, F. et al. High glycemic index and glycemic load are associated with moderately increased cancer risk. Mol Nutr. Food Res 59, 1384–1394 (2015).
8. Galeone, C., Pelucchi, C. & La, V. C. Added sugar, glycemic index and load in colon cancer risk. Curr. Opin. Clin Nutr. Metab Care 15, 368–373 (2012).
9. Mullie, P. et al. Relation between Breast Cancer and High Glycemic Index or Glycemic Load: A Meta-analysis of Prospective Cohort Studies. Crit Rev Food Sci Nutr. 56, 152–159 (2016).
10. Wang, R., Tang, J. E., Chen, Y. & Gao, J. Dietary fiber, whole grains, carbohydrate, glycemic index, and glycemic load in relation to risk of prostate cancer. Oncol. Targets. Ther. 8, 2415–2426 (2015).
11. Ye, Y. et al. Association between dietary carbohydrate intake, glycemic index and glycemic load, and risk of gastric cancer. Eur. J Nutr. (2016).
12. Sieri, S. et al. Dietary glycemic index and glycemic load and risk of colorectal cancer: results from the EPIC-Italy study. Int J Cancer 136, 2923–2931 (2015).
13. Sieri, S. et al. High glycemic diet and breast cancer occurrence in the Italian EPIC cohort. Nutr. Metab. Cardiovasc. Dis. 23, 628–634 (2013).
14. Williams, C. D. Antioxidants and prevention of gastrointestinal cancers. Curr. Opin. Gastroenterol. 29, 195–200 (2013).
15. George, S. M. et al. Dietary glycemic index, glycemic load, and risk of cancer: a prospective cohort study. Am. J Epidemiol. 169, 462–472 (2009).
16. Higginbotham, S. et al. Dietary glycemic load and risk of colorectal cancer in the Women’s Health Study. J Natl. Cancer Inst. 96, 229–233 (2004).
17. Mulholland, H. G., Murray, L. J., Cardwell, C. R. & Cantwell, M. M. Glycemic index, glycemic load, and risk of digestive tract neoplasms: a systematic review and meta-analysis. *Am J Clin Nutr.* **89**, 568–576 (2009).

18. Aune, D. *et al.* Carbohydrates, glycemic index, glycemic load, and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. *Cancer Causes Control.* **23**, 521–535 (2012).

19. Gnagnarella, P., Gandini, S., La, V. C. & Maisonneuve, P. Glycemic index, glycemic load, and cancer risk; a meta-analysis. *Am. J Clin Nutr.* **87**, 1793–1801 (2008).

20. Giovannucci, E. *et al.* Diabetes and cancer: a consensus report. *CA Cancer J Clin.* **60**, 207–221 (2010).

21. Iacopetta, B. Are there two sides to colorectal cancer? *Int. J Cancer* **101**, 403–408 (2002).

22. Wei, E. K. *et al.* Comparison of risk factors for colon and rectal cancer. *Int. J. Cancer* **108**, 433–442 (2004).

23. Hjartaker, A. *et al.* Subsite-specific dietary risk factors for colorectal cancer: a review of cohort studies. *J. Oncol.* **2013**, 703854 (2013).

24. McBain, A. J. & Macfarlane, G. T. Ecological and physiological studies on large intestinal bacteria in relation to production of hydrolytic and reductive enzymes involved in formation of genotoxic metabolites. *J. Med. Microbiol.* **47**, 407–416 (1998).

25. Vece, M. M. *et al.* Dietary Total Antioxidant Capacity and Colorectal Cancer in the Italian EPIC cohort. *PLoS One* **10**, e0142995 (2015).

26. Agnoli, C. *et al.* Italian Mediterranean Index and risk of colorectal cancer in the Italian section of the EPIC cohort. *Int J Cancer* **132**, 1404–1411 (2013).

27. Zhu, Y. *et al.* Increased number of chews during a fixed-amount meal suppresses postprandial appetite and modulates glycemic response in older males. *Physiol Behav.* **133**, 136–140 (2014).

28. Wolfe, T. M. *et al.* Food glycemic index, as given in glycemic index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. *Am. J Nutr.* **83**, 1306–1312 (2006).

29. Dodd, H., Williams, S., Brown, R. & Venn, B. Calculating meal glycemic index by using measured and published food values compared with directly measured meal glycemic index. *Am J Clin Nutr.* **94**, 992–996 (2011).

30. Battaglia, A. *et al.* A molecular epidemiology project on diet and cancer: the EPIC-Italian Prospective Study. Design and baseline characteristics of participants. *Tumori* **89**, 586–593 (2003).

31. Pisanu, P. *et al.* Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC cohorts. *Int J Epidemiol.* **26**(Suppl 1), S152–S160 (1997).

32. Pala, V. *et al.* Diet in the Italian EPIC cohorts: presentation of data and methodological issues. *Tumori* **89**, 594–607 (2003).

33. Salini, S. *et al.* Banca dati di composizione degli alimenti per studi epidemiologici in ItaliaMilano, 1998).

34. Scorzetti, F. *et al.* Glycemic index and glycemic load of Italian foods. *Nutr. Metab Cardiovasc. Dis.* **26**, 419–429 (2016).

35. Ascari, G., Foster-Powell, K. & Brand-Miller, J. C. Glycemic load and chronic disease. *Nutr. Rev.* **61**, 549–553 (2003).

36. Zhu, Y., Hsu, W. H. & Hollis, J. H. Increased number of chews during a fixed-amout meal suppresses postprandial appetite and modulates glycemic response in older males. *Physiol Behav.* **133**, 136–140 (2014).

37. Wolfe, T. M. *et al.* Food glycemic index, as given in glycemic index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. *Am. J Clin Nutr.* **83**, 1306–1312 (2006).

38. Dodd, H., Williams, S., Brown, R. & Venn, B. Calculating meal glycemic index by using measured and published food values compared with directly measured meal glycemic index. *Am J Clin Nutr.* **94**, 992–996 (2011).

39. Battaglia, A. *et al.* A molecular epidemiology project on diet and cancer: the EPIC-Italian Prospective Study. Design and baseline characteristics of participants. *Tumori* **89**, 586–593 (2003).

40. Pisanu, P. *et al.* Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC cohorts. *Int J Epidemiol.* **26**(Suppl 1), S152–S160 (1997).

41. Pala, V. *et al.* Diet in the Italian EPIC cohorts: presentation of data and methodological issues. *Tumori* **89**, 594–607 (2003).

42. Salini, S. *et al.* Banca dati di composizione degli alimenti per studi epidemiologici in ItaliaMilano, 1998).

43. Scorzetti, F. *et al.* Glycemic index and glycemic load of commercial Italian foods. *Nutr. Metab Cardiovasc. Dis.* **26**, 419–429 (2016).

44. Ascari, G., Foster-Powell, K. & Brand-Miller, J. C. Glycemic load and chronic disease. *Nutr. Rev.* **61**, 549–553 (2003).

45. Zhu, Y., Hsu, W. H. & Hollis, J. H. Increased number of chews during a fixed-amout meal suppresses postprandial appetite and modulates glycemic response in older males. *Physiol Behav.* **133**, 136–140 (2014).

46. Wolfe, T. M. *et al.* Food glycemic index, as given in glycemic index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. *Am. J Clin Nutr.* **83**, 1306–1312 (2006).

47. Willett, W. & Stampfer, M. J. Total energy intake: implications for epidemiologic analyses. *Am. J. Epidemiol.* **124**, 17–27 (1986).

Acknowledgements
The authors thank all participants in the Italian section of the EPIC study and Don Ward for help with the English. The Italian Ministry of Health and the Italian Association for Cancer Research (AIRC) provided financial support for EPIC Italy.

Author Contributions
Conceived and designed the experiments: S.S., V.K., D.P., G.M., S.P., R.T. Performed the experiments: S.S., V.K., S.P., A.M., S.G., C.A., V.P., F.R., E.B., N.P., G.F., F.E. Contributed analysis tools: V.K., C.A., F.R., F.F. Wrote the paper: S.S., V.K., A., V.P. All authors reviewed the manuscript.

Additional Information
Competing Interests: The authors declare that they have no competing interests.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.