Glutathione S-Transferase Activity and Glutathione S-Transferase \( \mu \) Expression in Subjects with Risk for Colorectal Cancer\(^1 \)

Christine E. Szarka,\(^2 \) Gordon R. Pfeiffer, Susan T. Hum, Lynette C. Everley, Andrew M. Balshem, Dirk F. Moore, Samuel Litwin, Eric B. Goosenberg, Harold Frucht, Paul F. Engstrom, and Margie L. Clapper


ABSTRACT

The glutathione S-transferases (\( \alpha, \mu, \) and \( \pi \)), a family of Phase II detoxication enzymes, play a critical role in protecting the colon mucosa by catalyzing the conjugation of dietary carcinogens with glutathione. We investigated the efficacy of using the glutathione S-transferase (GST) activity of blood lymphocytes and GST-\( \mu \) expression as biomarkers of risk for colorectal cancer. GST activity was measured in the blood lymphocytes of control individuals (\( n = 67 \)) and in the blood lymphocytes (\( n = 60 \)) and colon tissue (\( n = 34 \)) of individuals at increased risk for colon cancer. Total GST activity was determined spectrophotometrically with the use of 1-chloro-2,4-dinitrobenzene as a substrate. The ability to express the \( \mu \) subclass of GST was determined with the use of an ELISA. Although interindividual variability in the GST activity of blood lymphocytes was greater than 8-fold (range, 167.6-146.8 mmol/min/mg), the GST activity of blood lymphocytes and colon tissue within an individual was constant over time and was unrelated to sex, age, or race. The GST activity of blood lymphocytes from high-risk individuals was significantly lower than that of blood lymphocytes from control individuals (\( P \leq 0.004 \)). No association was observed between the frequency of GST-\( \mu \) phenotype and risk for colorectal cancer. Blood lymphocytes from high-risk individuals unable to express GST-\( \mu \) had lower levels of GST activity than did those from control subjects with the GST-\( \mu \) null phenotype; however, this difference was significant in male subjects only (\( P \leq 0.066 \)). Analysis of paired samples of blood lymphocytes and colon tissue indicated a strong correlation between the GST activity of the two tissue types (Spearman’s rank correlation, \( r = 0.87; P \leq 0.0001 \)). The GST activity of blood lymphocytes may be used to identify high-risk individuals with decreased protection from this Phase II detoxication enzyme who may benefit from clinical trials evaluating GST modulators as chemopreventive agents for colorectal cancer. The GST activity of blood lymphocytes may also be used in colorectal cancer chemoprevention trials to monitor the responsiveness of colon tissue to regimens that modify Phase II detoxification enzymes.

INTRODUCTION

Each year, approximately 155,000 individuals in the United States are diagnosed with colorectal cancer, and more than 50,000 deaths are attributed to this disease (1). Unfortunately, a significant number of individuals with colorectal cancer are identified at an advanced stage, making them ineligible for curative treatments. Protection from colorectal cancer requires the establishment of additional methods to identify high-risk individuals who are asymptomatic, as well as the development and implementation of effective preventive regimens.

Traditionally, the definitive end point for cancer prevention trials has been defined as a decreased cancer incidence in a designated population. Investigating the ability of potential chemopreventive agents to lower cancer incidence requires the enrollment and follow-up of large numbers of patients for many years, thus resulting in substantial costs. If the field of cancer prevention is to advance more rapidly and with cost effectiveness, validated intermediate endpoints or biomarkers of risk assessment and intervention efficacy are needed (2).

Phase II detoxication enzymes play a critical role in protecting tissues from xenobiotics and carcinogens through a variety of reactions and are being investigated currently as biomarkers of risk for various cancers, including colorectal cancer. One such family of enzymes, the glutathione S-transferases (\( \alpha, \mu, \) and \( \pi \)), catalyze the conjugation of electrophilic compounds with glutathione, resulting in soluble complexes that are generally more hydrophilic and less cytotoxic (3-6). The association between the expression of the \( \mu \) subclass (present in 40-60% of the general population) and cancer susceptibility has been investigated (7-9). Several studies have suggested that cigarette smokers deficient in the expression of GST-\( \mu \) are at increased risk for lung (10), bladder (11, 12), and larynx (11) cancer. The contribution of the GST-\( \mu \) null phenotype to risk for colorectal cancer remains equivocal.

We have investigated the feasibility of using GST as a biomarker of risk for colorectal carcinogenesis. To accurately address this issue, it was important to first measure the inherent inter- and intra-individual variability in the GST activity of blood lymphocytes and colon tissue over time. We have characterized the total GST activity of blood lymphocytes and colon mucosa, as well as the expression of GST-\( \mu \), in individuals at increased risk for colorectal cancer and compared these findings with those in normal individuals. The feasibility of using the GST activity of blood lymphocytes as a surrogate biomarker of the detoxification potential of colon mucosa also has been ascertained.

MATERIALS AND METHODS

Study Population. Eligible individuals at increased risk for colorectal carcinoma included men and women over age 18 with a family history of colorectal cancer, a personal history of colon polyps, or a personal history of colorectal cancer (>2 years from definitive treatment). Individuals were deemed ineligible if they had: (a) a known untreated primary or metastatic carcinoma; (b) hereditary nonpolyposis colorectal carcinoma; (c) familial adenomatous polyposis; (d) a history of colitis (inflammatory, radiation induced, or Crohn’s disease); or (e) significant medical or psychiatric problems that would make them poor protocol candidates. Eligible high-risk individuals were recruited from the community via newspaper advertisements, as well as from the Medical Oncology clinics and the Gastrointestinal Tumor Risk Assessment Program at the Fox Chase Cancer Center. Enrolled high-risk subjects possessed a WBC count ≥4000/mm\(^3\), a platelet count ≥100,000/mm\(^3\), a hemoglobin level ≥11 g/dl, and results of renal and liver function studies within two times the upper limit of normal institutional values. Control subjects were without active medical problems and included hospital personnel and residents from a local retirement community.

Tissue Collection and Processing. After informed consent was given, blood samples (20 ml) were obtained by venipuncture and immediately transported to the laboratory at room temperature. An aliquot of whole blood was stored at −80°C for GST-\( \mu \) phenotyping. Blood lymphocytes were

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3 The abbreviation used is: GST, glutathione S-transferase.
isolated from the remaining sample with the use of Lymphocyte Separation Medium (Organon Teknika Corp., Durham, NC) according to the manufacturer’s instructions and were stored at −80°C.

Multiple tissue biopsies (n = 5; ~100 mg each) were obtained from the sigmoid colon (~20 cm from the anal verge) by flexible sigmoidoscopy or at the time of colonoscopy, immediately frozen in liquid nitrogen, and stored at −80°C.

Tissue Analysis. At the time of analysis, blood lymphocytes and colon biopsies were each suspended in 1 ml of 10 mM Tris-HCl (pH 7.8). Blood lymphocytes were lysed by pulsed sonication for 30 s (Fisher 550 sonic dismembrator; Fisher Scientific Co., Pittsburgh, PA) while colon biopsies were homogenized (Omni 1000 homogenizer; Waterbury, CT). All samples were centrifuged at 10,000 rpm for 15 min at 4°C. The protein concentration of the supernatant was determined with the use of the Bio-Rad microassay (Bio-Rad, Hercules, CA).

Total GST activity was determined spectrophotometrically according to the method of Habig et al. (13) with the use of 1-chloro-2,4-dinitrobenzene as a substrate. Glutathione conjugates formed in the presence of the enzyme were quantified spectrophotometrically, and specific activity was expressed as nmol/min/mg of protein.

The presence of GST-μ in whole blood (100 μl) was determined with the use of an ELISA kit supplied by Biotrin International (Dublin, Ireland). Assays were performed in duplicate according to the manufacturer’s instructions, and known GST-μ-positive and GST-μ-negative controls were evaluated simultaneously.

Statistical Analysis. The Kruskal-Wallis and Wilcoxon two-sample tests were applied to the analysis of the relation of GST levels to discrete levels of the several factors studied (race, sex, history of polyps, etc). Multiple linear regression was used to model GST level as a function of more than one covariate. GST activity values are cited as mean ± SE. Differences were considered significant at P ≤ 0.05. The significance of the correlations was judged with the use of Spearman’s test of rank correlation. The reported P values are two sided.

RESULTS

Enrolled subjects ranged in age from 22 to 91 years and included 60 individuals at increased risk for colorectal cancer and 67 healthy individuals. The high-risk population included a higher proportion of older individuals and males. An attempt was made to recruit age- and sex-matched control individuals from a local retirement community. However, because the average life span of females exceeds that of males, the majority of the enrolled control individuals were females. Racial representation for both groups was similar. The majority of the registered high-risk individuals had only one risk factor for colorectal cancer (Table 1).

The intrapatient variability of GST activity was determined by analyzing multiple blood and colon tissue samples from the same individual. The combined technical variability in sample analysis and inherent variability of the GST activity was evaluated by analyzing three separate samples of blood and colon mucosa obtained at a single time point from 10 and 7 individuals, respectively (Fig. 1). The variance of GST activity within a tissue type was found to be consistent for all patients. The mean GST activity of all blood lymphocytes was 65.9 nmol/min/mg, with a SD of 6 within an individual. Evaluation of the colon tissues demonstrated a mean GST activity of 67.4 with a SD of 6 within an individual. Repeated sampling of blood lymphocytes over a 2- or 4-week time interval indicated that GST activity was constant over time with a mean GST level of 72.2 nmol/min/mg for the blood lymphocytes of 11 individuals and a SD of 3 within an individual (Fig. 2). Evaluation of colon tissue over a 2-week interval from 10 subjects revealed a mean GST activity of 74.9 nmol/min/mg and a SD of 6 within an individual.

As shown in Table 2, interpatient variability in the GST activity of blood lymphocytes of the study population was greater than 8-fold, and total GST levels ranged from 16.7 to 146.8 nmol/min/mg. The total GST activity (nmol/min/mg; mean ± SE) of blood lymphocytes from high-risk individuals (62.7 ± 3) was significantly lower than that of control individuals (75.3 ± 3; P ≤ 0.004). A significant decrease in GST activity was seen, even when only a single risk factor was present. Individuals with a family history of colorectal cancer or a history of colon polyps had significantly lower levels of GST activity. Although these data suggest that the GST activity of blood lymphocytes is decreased with increased numbers of risk factors, a larger study population with two or more risk factors will be required.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Subject characteristics</th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
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<tr>
<td></td>
<td>Sample size</td>
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<tr>
<td>Age (yrs)</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
</tr>
<tr>
<td></td>
<td>African-American</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Personal history of colon cancer</td>
</tr>
<tr>
<td></td>
<td>Family history of colon cancer</td>
</tr>
<tr>
<td></td>
<td>Personal history of colon polyps</td>
</tr>
<tr>
<td></td>
<td>1 risk factor for colon cancer</td>
</tr>
<tr>
<td></td>
<td>2 risk factors for colon cancer</td>
</tr>
<tr>
<td></td>
<td>3 risk factors for colon cancer</td>
</tr>
</tbody>
</table>
A more refined understanding of the data emerges when males and females are considered separately. In Table 3, all of the factors are considered separately by sex; it can be seen that GST-μ expression is statistically significant only for males and that history of risk factors is statistically significant only for females. There was a significant decrease in the GST activity of blood lymphocytes from males (healthy and high-risk) who were unable to express GST-μ compared with those male subjects who possessed the GST-μ protein \( (P \leq 0.006) \). Female subjects with risk factors for colorectal cancer had significantly lower levels of GST activity than did female subjects without risk factors \( (P \leq 0.016) \). Age was not statistically significant for either sex.

A total of 26 of 63 control individuals (41%) and 18 of 49 high-risk individuals (37%) were found to possess the GST-μ null phenotype. Although there was not a notable difference between the frequency of GST-μ expression in these two populations, those individuals who were at increased risk for colorectal cancer and were unable to express GST-μ were found to have lower levels of GST activity than were null controls. However, this was significant in males only \( (P \leq 0.018; \) Table 5). A larger study population is needed to confirm this observation and to further clarify the significance in females.

Paired samples of blood and colon mucosa were obtained from 34 high-risk individuals during their scheduled surveillance colonoscopy or flexible sigmoidoscopy. A strong correlation was observed between the GST activity of the blood lymphocytes and colon mucosa of each individual (Spearman’s rank correlation, \( r = 0.87; \) \( P \leq 0.0001 \); Fig. 3).

Table 2. Comparison of the GST activity of blood lymphocytes from normal and high-risk individuals

<table>
<thead>
<tr>
<th>GST activity ( \text{nmol/min/mg} ) (( \text{nmol/min/mg} ))</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (GST range, 25.8—138.7)</td>
<td>75.3 ± 3 (67)</td>
</tr>
<tr>
<td>High risk (GST range, 16.7—146.8)</td>
<td>62.7 ± 3 (60)</td>
</tr>
<tr>
<td>Control</td>
<td>75.3 ± 3 (67)</td>
</tr>
<tr>
<td>High risk</td>
<td>61.3 ± 5 (33)</td>
</tr>
<tr>
<td>2 risk factors</td>
<td>66.8 ± 3 (38)</td>
</tr>
<tr>
<td>3 risk factors</td>
<td>51.0 ± 4 (4)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>64.9 ± 4 (34)</td>
</tr>
<tr>
<td>Personal history of colon cancer</td>
<td>71.0 ± 3 (93)</td>
</tr>
<tr>
<td>Family history of colon cancer</td>
<td>63.6 ± 4 (31)</td>
</tr>
<tr>
<td>No history of colon polyps</td>
<td>58.9 ± 4 (26)</td>
</tr>
<tr>
<td>No history of colon polyps</td>
<td>72.1 ± 3 (101)</td>
</tr>
</tbody>
</table>

* Activity is shown in \( \text{nmol/min/mg} \); data are mean ± SE.
* Wilcoxon’s two-sample test.
* Kruskal-Wallis test.

Table 3. GST activity of various populations

<table>
<thead>
<tr>
<th>GST activity ( \text{nmol/min/mg} ) (( \text{nmol/min/mg} ))</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male( ^b )</td>
<td>64.3 ± 3 (60)</td>
</tr>
<tr>
<td>Female( ^b )</td>
<td>76.8 ± 4 (42)</td>
</tr>
<tr>
<td>Male( ^b )</td>
<td>68.3 ± 4 (22)</td>
</tr>
<tr>
<td>Female( ^b )</td>
<td>64.9 ± 3 (34)</td>
</tr>
<tr>
<td>Male( ^b )</td>
<td>71.0 ± 3 (93)</td>
</tr>
<tr>
<td>Female( ^b )</td>
<td>63.6 ± 4 (31)</td>
</tr>
<tr>
<td>Male( ^b )</td>
<td>71.3 ± 3 (96)</td>
</tr>
<tr>
<td>Female( ^b )</td>
<td>58.9 ± 4 (26)</td>
</tr>
<tr>
<td>Male( ^b )</td>
<td>72.1 ± 3 (101)</td>
</tr>
</tbody>
</table>

\( ^a \) Activity expressed as \( \text{nmol/min/mg} \) protein.
\( ^b \) Data are expressed as means ± SE.
\( ^c \) Wilcoxon’s two-sample test.
**DISCUSSION**

Recent advances in the identification and development of novel chemopreventive agents have created a critical need for biological markers of cancer susceptibility and chemopreventive effect. Numerous cellular and molecular events have been associated with tumor formation and currently are being evaluated as intermediate biomarkers of cancer (14–17). Many of these biomarkers may be identifiable only when cells are irreversibly committed to tumorigenesis and unresponsive to chemopreventive strategies. It is, therefore, important to find biomarkers of cancer risk that (a) are associated with the preneoplastic phases of the tumorigenic process, (b) are reversible, (c) are stable over time, and (d) have easy, inexpensive methods of detection.

The ability of the GSTs to provide cellular protection against a wide variety of xenobiotics makes this enzyme family an attractive candidate biomarker of both cancer susceptibility and chemopreventive activity. Significant increases in the GST activity of both human cultured cells (18, 19) and human tumors (20, 21) resistant to chemotherapeutic alkylating agents have been observed repeatedly. Highly reactive epoxides of numerous compounds, including benzo(a)pyrene, are substrates for the \( \mu \) class of human GST (22). Inhibition of chemically induced organ damage or tumors in animal models by chemopreventive agents such as oltipraz has been accompanied by increases in GST activity (23, 24).

Although the interindividual variability in the GST activity of normal colon mucosa (37.5–118 nmol/min/mg) and blood lymphocytes (16.7–146.8 nmol/min/mg) was comparable with that reported by others (4, 21, 25), the degree of intraindividual variability in GST activity had not been established previously. Blood lymphocytes and colon mucosa were best suited for such an investigation because of their accessibility for repetitive sampling. Minimal variability in the GST of subjects over a 2–4-week interval suggests that enzyme levels are reproducible and only minimally affected by recent diet and immediate environmental conditions. Since completion of this study, subsequent blood lymphocyte samples have been taken at time points up to 1 year from a small subset of subjects. The GST activity in blood lymphocytes continues to demonstrate stability within an individual over a 1-year time period. Although GST activity was unrelated to sex or age, the effect of race or smoking status on this measurement remains less clear. Additional minority participants are needed to evaluate the variability in GST activity among different racial groups.

Investigation of the contribution of the GST-\( \mu \) null phenotype to cancer susceptibility has produced varied results (3, 5, 7–12). No correlation was observed between the frequency of the GST-\( \mu \) null phenotype and increased risk for colorectal cancer in this study. This observation is in agreement with results generated previously with the use of distinct methodologies (3, 8). Using starch gel zymograms, Strange et al. (3) found that 67% of individuals with adenocarcinoma of the stomach and colon (\( n = 45 \)) did not express GST-\( \mu \) and concluded that individuals possessing the null phenotype had a ~3-fold increased risk for these cancers. However, independent evaluations of only those individuals with colon cancer reveal that 61% possess the GST-\( \mu \) null phenotype, a proportion that does not differ significantly from the number of individuals expressing the null phenotype in the general population (40–60%) (7–9). Comparison of the GST-\( \mu \) phenotype of control individuals (\( n = 64 \)) with that of individuals with colon carcinoma (\( n = 50 \)) by Peters et al. (8) revealed no association between the lack of GST-\( \mu \) expression, as detected by mAb, and increased susceptibility to colon cancer. In all, 66% of the high-risk group and 62.5% of the controls possessed the null phenotype.

The observed decreases in the level of GST activity within blood lymphocytes of individuals at increased risk for colorectal cancer have not been noted previously and suggest that these subjects are deficient in the cellular protection afforded by GST. It would be interesting to see whether this correlation holds true in the colon mucosa of high-risk individuals as well. This could be performed by comparing the GST activity of colon mucosa from high-risk individuals in this study with that of colon mucosa from individuals without risk factors for colorectal cancer who are undergoing a colonoscopy/flexible sigmoidoscopy for screening purposes based on age. This correlation was not investigated in this study because of the absence of subjects without cancer risk undergoing routine screening endoscopy at the Fox Chase Cancer Center.

An association between the GST-\( \mu \) null phenotype and a decrease in total GST activity was observed in 41% of the GST-\( \mu \) null subjects identified. The GST activity of blood lymphocytes from male high-risk individuals with the null phenotype was significantly less than that of blood lymphocytes from null control individuals. Although high-risk females with the GST-\( \mu \) null phenotype had lower levels of GST activity, a larger study population is needed to clarify the significance. These findings are in agreement with those of Heckbert

**Table 4 Model of GST activity (both sexes) after forward stepwise linear regression**

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Estimate</th>
<th>SE</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>70.2</td>
<td>4.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Risk factors</td>
<td>-14.5</td>
<td>4.0</td>
<td>0.001</td>
</tr>
<tr>
<td>GST-( \mu ) expression</td>
<td>10.6</td>
<td>4.7</td>
<td>0.026</td>
</tr>
</tbody>
</table>

**Table 5 Relationship between risk for colorectal cancer, GST-\( \mu \) expression, and total GST activity**

<table>
<thead>
<tr>
<th>GST-( \mu ) expression</th>
<th>Females (( n ))</th>
<th>( P ) value</th>
<th>Males (( n ))</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null (13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>80.0 ± 7</td>
<td>0.089</td>
<td>62.5 ± 6</td>
<td>0.012</td>
</tr>
<tr>
<td>High risk</td>
<td>78.9 ± 5 (31)</td>
<td>0.131</td>
<td>67.1 ± 10 (11)</td>
<td></td>
</tr>
<tr>
<td>Expression (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>66.3 ± 8</td>
<td>0.018</td>
<td>41.3 ± 5</td>
<td>0.196</td>
</tr>
<tr>
<td>High risk</td>
<td>79.2 ± 9 (66)</td>
<td></td>
<td>67.1 ± 4 (20)</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Activity expressed as nmol/min/mg protein.
\( ^b \) Data are expressed as means ± SE.
\( ^c \) Wilcoxon's two-sample test.

**Fig. 3.** The correlation between the GST activity of blood lymphocytes and colon mucosa from the same individual (\( n = 34 \)). Peripheral blood cells and colon biopsies were obtained from subjects at the time of endoscopy. Total GST activity of each tissue was measured with the use of 1-chloro-2,4-dinitrobenzene as the substrate (Spearman's rank correlation coefficient, \( r = 0.87, P \leq 0.0001 \)).
et al. (4), who examined GST and GST-µ activity in leukocytes and found a direct association between the two in a subset of their subjects who were GST-µ null. They suggested that the isozyme responsible for the glutathione conjugation of trans-stilbene oxide (GST-µ) also plays a role in the glutathione conjugation of 1-chloro-2,4-dinitrobenzene in leukocytes. Coordinate regulation of the GST classes (α, μ, and π) has been reported (26). Therefore, deletion of the GST-µ gene may be accompanied by decreased expression of the other isoenzyme classes.

In the majority of GST-µ null subjects, total GST activity was unaffected by the GST-µ null phenotype. In contrast with the work of Heckbert et al. (4), Seidegard et al. (27) have reported no apparent correlation between the activities of GST toward trans-stilbene oxide and 1-chloro-2,4-dinitrobenzene. Perhaps there is an increase in the α and π classes of GST in these individuals to compensate for the loss of protective effect from GST-µ. Clearly, the molecular basis for the levels of total GST in individuals who are unable to express GST-µ and are at increased risk for colorectal cancer must be investigated further.

The GST activity of blood lymphocytes represents a noninvasive biomarker of the cellular protection present in colon mucosa. The strong correlation between the GST activities of blood lymphocytes and colon mucosa supports this finding. Obtaining colon biopsies for enzyme analysis in chemoprevention trials via endoscopy is invasive, time consuming, and costly and requires bowel-preparative regimens. More convenient sampling procedures with minimal risk for complications (such as phlebotomy) are required for evaluating enzymatic response to chemopreventive agents and may encourage more individuals to enroll in chemopreventive trials. The potential of using the GST activity of blood lymphocytes to monitor the responsiveness of colon mucosa to chemopreventive regimens is being evaluated currently in two Phase I chemoprevention trials.

In summary, the association of individuals at increased risk for colorectal cancer with low levels of GST activity indicates that additional evaluation of GST activity as a biomarker of cancer susceptibility is warranted. Identification of a subgroup of high-risk individuals with low GST activity suggests that these individuals could benefit from chemopreventive strategies that modulate the protective Phase II detoxication enzymes in an attempt to reduce colon cancer incidence. Decreased levels of GST activity in blood lymphocytes of individuals at increased risk for colon cancer has been determined to be a good potential biomarker of risk because it is stable and reproducible over time, is easily and inexpensively detected, and correlates with the levels of activity in the colon mucosa. Our results suggest that the GST activity of blood lymphocytes may be used in future chemoprevention trials to monitor the responsiveness of colon tissue to chemopreventive regimens that modify Phase II detoxication enzymes.

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REFERENCES


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