Gastrointestinal Tissue Polyamine Contents of Patients with Barrett’s Esophagus Treated with α-Difluoromethylornithine

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Abstract
α-Difluoromethylornithine (DFMO), an investigational chemopreventive agent, suppresses polyamine contents and decreases epithelial carcinogenesis in experimental models. The ability of this drug to decrease polyamine contents in human esophageal tissues has not yet been determined. Eight patients with Barrett’s esophagus were treated with DFMO at a dose of 1.5 g/m²/day for 12 weeks. Four sites (Barrett’s lesion, adjacent normal squamous esophagus, gastric tissue, and small bowel) were biopsied in each patient before, during, and after DFMO treatment in order to assess the effects of this drug on tissue polyamine levels. Ornithine decarboxylase activities and polyamine contents varied in each site analyzed. The rank orders were Barrett’s > small bowel ≈ normal esophagus > gastric tissue for ODC activities, and small bowel ≥ Barrett’s = normal esophagus > gastric tissue for putrescine contents. Spermidine, but not spermine, contents in the Barrett’s lesions and normal squamous esophageal tissue were suppressed by systemic DFMO treatment and recovered to untreated control values when DFMO therapy was discontinued. Systemic DFMO treatment did not affect the levels of either of these two amines in gastric tissue and small bowel. Since DFMO can suppress polyamine contents in several gastrointestinal tissues, including Barrett’s mucosa, we conclude that it is an effective agent with which to test the hypothesis that depletion of spermidine contents may prevent the development of adenocarcinoma of the esophagus in this specific patient group.

Introduction
Cancers of the esophagus have a poor prognosis worldwide (1). Epidemiological studies have identified alcohol and tobacco as significant risk factors, along with dietary factors in certain patient groups (2). Thus, smoking cessation, restriction of alcohol consumption, and dietary interventions are logical strategies for reducing mortality from esophageal cancers in specific patient populations.

Esophageal tumors are predominantly squamous cell carcinomas, probably deriving from normal squamous esophageal tissue (3). In a small subset of patients whose esophagus is lined with metaplastic columnar epithelium, adenocarcinoma of the esophagus may develop. This aberrant columnar epithelium in the esophagus is termed “Barrett’s esophagus,” and is associated with a 30–40-fold increase in the risk of adenocarcinoma development (4). Recent studies suggest that the incidence of adenocarcinoma of the esophagus is increasing (1, 5). Barrett’s esophagus is thought to develop as a consequence of chronic gastric reflux (6). However, antireflux therapies generally have little effect on the premalignant Barrett’s lesion (7). DFMO3 is an enzyme-activated, irreversible inhibitor of ODC, the first enzyme in polyamine synthesis (8). DFMO is a potent inhibitor of carcinogen-induced cancers in a number of experimental models of epithelial carcinogenesis (9). This drug is currently being tested as a chemopreventive agent for specific human cancers by us (10) and others (11–13). We have previously reported that ODC activity is elevated in Barrett’s lesions compared to adjacent normal squamous esophageal and gastric or small bowel tissue (14, 15). We have also found that ODC activity is highest in Barrett’s lesions that display the greatest degree of dysplasia (14). Degree of dysplasia correlates positively with adenocarcinoma incidence in Barrett’s patients (16).

Thus, ODC and polyamine metabolism appear to be involved in the premalignant stages of the development of adenocarcinoma of the esophagus. This interpretation suggests that the suppression of elevated ODC in Barrett’s lesions may be an effective method of chemoprevention of esophageal adenocarcinomas. As a first step in testing this hypothesis, we treated eight patients with Barrett’s esophagus with DFMO and measured tissue polyamine contents as an indicator of DFMO action in Barrett’s lesions and other GI tissues. We chose tissue polyamine contents as our endpoint for DFMO action, because experimental studies have demonstrated that the biological effects of DFMO are a consequence of putrescine and spermidine depletion caused by this agent (17).

Materials and Methods
Patient Data. Eleven male subjects agreed to participate in this study. Three of these individuals discontinued DFMO therapy during the course of the trial because of adverse side effects (nausea and/or dizziness). Eight subjects completed the 12 weeks of treatment. As shown in

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1 The abbreviations used are: DFMO, α-difluoromethylornithine; ODC, ornithine decarboxylase; GI, gastrointestinal.
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (completing treatment)</th>
<th>Median age (range)</th>
<th>Median length (cm) of Barrett’s lesion (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 (8)</td>
<td>63 (53-76)</td>
<td>4.5 (3-7)</td>
</tr>
</tbody>
</table>

Table 1, the median age of the subjects completing the trial was 63. The median length of the Barrett’s lesion was 4.5 cm. All of the patients had specialized columnar epithelium in the esophagus, but no patient had a Barrett’s lesion characterized by definite dysplasia.

Study Protocol. After obtaining written informed consent, each patient underwent upper endoscopy. The extent of Barrett’s mucosa was assessed, and adjacent pairs of biopsies were obtained from (a) normal squamous esophageal mucosa proximal to the Barrett’s lesion, (b) Barrett’s mucosa, (c) normal gastric tissue, and (d) normal small bowel mucosa from the duodenum. One biopsy was routinely processed for histological verification, whereas the other was stored frozen at -70°C until biochemical analysis. DFMO was given p.o. as a liquid in divided doses of 0.5 g/m² three times a day for a total of dose of 1.5 g/m² daily. Treatment was continued for 12 weeks. After 6 and 12 weeks of DFMO therapy, and 1–3 months after cessation of treatment, an upper endoscopy was again performed with lesions measured and biopsies collected as before treatment initiation.

Biochemical Analyses. Tissue polyamine contents were determined as described previously for other GI biopsies (10). Briefly, tissue samples were frozen in liquid nitrogen immediately after collection. For processing, samples were coded with regard to site and patient treatment status. This information was decoded only after all lab results were obtained. Samples were minced; disrupted in 50 mM sodium-potassium phosphate buffer, pH 7.2, containing 20 µM pyridoxal phosphate, 0.1 mM EDTA, and 1 mM 1,4-dithiothreitol; and clarified by centrifugation at 2000 x g for 5 min. The soluble fraction was adjusted to 0.2 N HClO₄ and stored overnight at 4°C. After centrifugation at 12,000 x g for 5 min, acid-soluble and acid-insoluble fractions were separated. Polyamine contents in the acid-soluble fraction were determined using reverse-phase, ion-paired high performance liquid chromatography techniques as described by Seiler and Knodgen (18). Amines were resolved on a C₁₈ μBondapak column, derivatized after separation with o-phthaldehyde, and detected at 750 nm. ODC activity was measured by collecting [¹⁴C]ornithine, as described previously by us in these tissues (14, 15). Protein contents in the acid-insoluble fraction were determined using the method of Bradford (19). Polyamine contents and ODC activities in each tissue sample were then normalized to the protein content in the same sample.

Statistical Methods. To determine the differences in ODC activity and polyamine content among the four tissues prior to DFMO treatment, a repeated measures analysis of variance was performed separately for ODC activity and each of the four different measures of polyamine content. These measures were putrescine, spermidine, spermine, and the spermidine/spermine ratio. For the latter measure, analyses were performed using a logarithmic transformation to obtain better numerical stability. When indicated by a significant F test from the analysis of variance, differences between the means for pairs of tissues were tested using a paired t test. Adjustment was made for the 6 paired comparisons using a Bonferroni correction. Such an adjustment multiplies each P value by 6 in order to guarantee that the overall level of significance does not exceed the nominal level.

To determine the effect of DFMO on ODC activities and polyamine contents, data were analyzed by paired t tests, where the measurement for each patient at each of the follow-up times was compared to the corresponding patient’s pretreatment measurement. Since such an analysis again entails multiple comparisons, a Bonferroni adjustment was made for the three tests performed for each polyamine value. No further adjustments were made to these tests.

Results

Polyamine contents and ODC activities varied in the four GI tissues evaluated, as shown in Tables 2 and 3. ODC activity was significantly higher (P < 0.0001) in Barrett’s lesions (0.248 ± 0.137 units/mg protein), compared to the other normal tissues evaluated (0.056 ± 0.117 units/mg for normal esophagus, 0.003 ± 0.004 for gastric tissue, and 0.081 ± 0.166 for small bowel). Putrescine contents in normal squamous esophageal tissue (0.15 ± 0.28 nmol/mg protein) and the Barrett’s lesions (0.17 ± 0.17 nmol/mg protein) were similar and intermediate to those found in gastric (0.02 ± 0.05 nmol/mg protein) and small bowel tissue (0.48 ± 0.24 nmol/mg protein). Differences in the putrescine content of these latter two tissues were statistically significant.

Although gastric tissue had the lowest putrescine content, it contained the highest spermine levels (see Table 2), Sperrmine contents in the other three tissues were similar (1.74 ± 0.95 in Barrett’s, 2.02 ± 1.03 in normal esophagus, and 1.87 ± 0.98 in small bowel) and lower, in a statistically significant manner, than those found in gastric tissue (mean value, 4.17 ± 1.76 nmol/mg protein).

Spermidine (which is derived from putrescine and is the precursor of spermine) levels were not statistically different in any of the four tissues (see Table 2). However, the spermidine/spermine ratio, which has been correlated with increased polyamine metabolic activity (20), was statistically lower in gastric tissue (geometric mean value, 0.23) compared to the other three tissues evaluated (geometric mean values, 0.65 for small bowel; 0.92 for normal esophagus; and 0.74 for Barrett’s lesions).

We were unable to detect any statistically significant effect of DFMO on ODC activities in any of the four tissues measured (Table 3). However, we were able to detect tissue-specific changes in some polyamine parameters after DFMO treatment. Table 4 shows mean differences (with SDs and P values for the difference) in spermidine contents and spermidine/spermine ratios, comparing values obtained after 6 or 12 weeks of drug therapy, or after cessation of therapy, to those obtained prior to the initiation of DFMO treatment. Spermidine contents in both Barrett’s lesions (1.21 ± 0.51 nmol/mg protein) and normal squamous esophageal tissue (1.73 ± 0.69 nmol/mg protein) were reduced in a statistically significant manner by 0.60 ± 0.47 (P = 0.03) and 1.25 ± 0.83 (P = 0.02), respectively, (nmol/mg protein) after 6 weeks of DFMO treatment, and by 0.48 ± 0.43 (P = 0.05) and 1.14 ± 0.76 (P = 0.01),
Table 2  Polyamine contents in various GI tissues obtained from patients with Barrett’s esophagus

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Polyamine content (nmol/mg)</th>
<th>log (Spd/Spm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Putrescine</td>
<td>Spermidine</td>
</tr>
<tr>
<td>Barrett’s lesion</td>
<td>0.17 ( \pm ) 0.17</td>
<td>1.21 ( \pm ) 0.51</td>
</tr>
<tr>
<td>Normal esophagus</td>
<td>0.15 ( \pm ) 0.28</td>
<td>1.73 ( \pm ) 0.69</td>
</tr>
<tr>
<td>Gastric mucosa</td>
<td>0.02 ( \pm ) 0.05</td>
<td>1.05 ( \pm ) 0.61</td>
</tr>
<tr>
<td>Small bowel</td>
<td>0.48 ( \pm ) 0.24</td>
<td>1.14 ( \pm ) 0.42</td>
</tr>
</tbody>
</table>

\( ^a \) Values shown are means of individual biopsy determination from all patients prior to commencing DFMO treatment ± SD.
\( ^b \) Spd, spermidine; Spm, spermine; values in parentheses, geometric means.

Table 3  ODC activities in various GI tissues obtained from patients with Barrett’s esophagus before, during, and after treatment with DFMO

<table>
<thead>
<tr>
<th>Duration of DFMO treatment</th>
<th>Barrett’s</th>
<th>Gastric</th>
<th>Small bowel</th>
<th>Esophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (before rx)(^a)</td>
<td>0.248 ( \pm ) 0.137</td>
<td>0.003 ( \pm ) 0.004</td>
<td>0.081 ( \pm ) 0.166</td>
<td>0.056 ( \pm ) 0.117</td>
</tr>
<tr>
<td>6 weeks</td>
<td>0.301 ( \pm ) 0.444</td>
<td>0.093 ( \pm ) 0.120</td>
<td>0.169 ( \pm ) 0.140</td>
<td>0.176 ( \pm ) 0.214</td>
</tr>
<tr>
<td>12 weeks</td>
<td>0.324 ( \pm ) 0.261</td>
<td>0.176 ( \pm ) 0.327</td>
<td>0.132 ( \pm ) 0.116</td>
<td>0.116 ( \pm ) 0.142</td>
</tr>
<tr>
<td>Off rx(^b)</td>
<td>0.397 ( \pm ) 0.237</td>
<td>0.071 ( \pm ) 0.126</td>
<td>0.034 ( \pm ) 0.053</td>
<td>0.081 ( \pm ) 0.067</td>
</tr>
<tr>
<td>( P ) value(^d)</td>
<td>0.35</td>
<td>0.25</td>
<td>0.07</td>
<td>0.31</td>
</tr>
</tbody>
</table>

\( ^a \) ODC activity (mean values determined from triplicate determinations from a single biopsy in each patient ± SD) is defined as 1 nmol \(^{14}\)CO\(_2\) released from radiolabeled ornithine.
\( ^b \) Before rx, before treatment.
\( ^c \) Off rx, biopsies were obtained from patients 1–3 months after they had completed 12 weeks of DFMO treatment.
\( ^d \) For the difference between the first number in each row or column and the remaining values in that row or column.

Table 4  Mean differences from pretreatment spermidine contents and spermidine/spermine ratios in GI tissues from patients with Barrett’s esophagus treated with DFMO

<table>
<thead>
<tr>
<th>Rx(^e) group</th>
<th>Mean polyamine content difference(^a)</th>
<th>Barrett’s lesion</th>
<th>Normal esophagus</th>
<th>Gastric tissue</th>
<th>Small bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spermidine</td>
<td>(-0.60 (0.47; 0.03))</td>
<td>(-1.25 (0.83; 0.02))</td>
<td>(-0.55 (0.60; 0.10))</td>
<td>(-0.29 (0.40; 0.31))</td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>(-0.48 (0.45; 0.05))</td>
<td>(-1.14 (0.76; 0.01))</td>
<td>(-0.24 (0.87; &gt;0.5))</td>
<td>(-0.10 (0.79; &gt;0.5))</td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>(-0.01 (0.99; &gt;0.5))</td>
<td>(-0.01 (1.30; &gt;0.5))</td>
<td>(-0.23 (0.47; &gt;0.5))</td>
<td>(-0.05 (0.81; &gt;0.5))</td>
<td></td>
</tr>
<tr>
<td>Off rx(^c)</td>
<td>(-0.83 (1.01; 0.16))</td>
<td>(-1.35 (0.83; 0.02))</td>
<td>(-0.70 (1.01; 0.35))</td>
<td>(-0.81 (0.85; 0.14))</td>
<td></td>
</tr>
<tr>
<td>log (Spermidine/Spermine)</td>
<td>(-0.69 (0.63; 0.05))</td>
<td>(-1.06 (0.89; 0.03))</td>
<td>(-0.11 (0.81; &gt;0.5))</td>
<td>(-0.70 (0.48; 0.01))</td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>(-0.60 (0.47; 0.03))</td>
<td>(-1.25 (0.83; 0.02))</td>
<td>(-0.55 (0.60; 0.10))</td>
<td>(-0.29 (0.40; 0.31))</td>
<td></td>
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<td>12 weeks</td>
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<td>(-0.24 (0.87; &gt;0.5))</td>
<td>(-0.10 (0.79; &gt;0.5))</td>
<td></td>
</tr>
<tr>
<td>Off rx(^c)</td>
<td>(-0.01 (0.99; &gt;0.5))</td>
<td>(-0.01 (1.30; &gt;0.5))</td>
<td>(-0.23 (0.47; &gt;0.5))</td>
<td>(-0.05 (0.81; &gt;0.5))</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) Mean differences (SD in nmol/mg; \( P \) value for the difference) of single biopsy determinations from each patient and for each interval after initiation of DFMO treatment.
\( ^b \) Rx, treatment.
\( ^c \) Off rx, biopsies were obtained from patients 1–3 months after they had completed 12 weeks of DFMO treatment.

respectively, (nmol/mg protein) after 12 weeks of DFMO therapy. These reduced values returned to normal when DFMO treatment was discontinued. DFMO treatment did not affect spermidine contents in either gastric tissue or small bowel. Differences in spermidine/spermine ratios followed the same pattern of change as those for spermidine, except for the values after 6 weeks in the Barrett’s lesion and 12 weeks in small bowel.

Fig. 1 presents these and other data graphically, with 95% confidence limits for the changes in values after DFMO therapy commenced, compared to those measured in each tissue prior to initiation of treatment. The tissue-specific effects of DFMO on the various polyamine parameters and the recovery of spermidine and spermidine/spermine ratios after cessation of therapy to pretreatment levels in affected tissues are especially apparent in this figure. Note that putrescine contents were generally less than 10% of spermidine and spermine values (Table 2), and were near our limit of detection (~0.01 nmol/mg protein). Consequently, our ability to measure accurately a difference in putrescine contents was less than that for the more prevalent amines spermidine and spermine. Putrescine contents were highest in the small bowel (0.48 ± 0.24 nmol/mg protein). DFMO caused a nonsignificant reduction in putrescine contents of 0.17 ± 0.29 (\( P = 0.49 \)) and 0.23 ± 0.32 (\( P = 0.26 \)) (nmol/mg protein) in this tissue after 6 and 12 weeks of therapy, respectively.

Spermidine contents in tissues were not decreased after DFMO treatment, compared to pretreatment values, except in gastric tissue after the cessation of DFMO therapy (Fig. 1). Spermidine/spermine ratios were decreased as a consequence of DFMO treatment in small bowel tissue, but this decrease was primarily due to an increase in spermine contents, and not the decrease in spermidine levels as was the case in Barrett’s lesions and normal esophageal tissue.
Fig. 1. Confidence intervals (95%) for the change in polyamine contents from pre-DFMO treatment values. Changes in putrescine, spermidine, spermine, and spermidine/spermine ratio (expressed here as the logarithm of this ratio) are shown for each of the four tissues biopsied in this study.

Discussion
DFMO is under study as a possible chemopreventive agent in selected human populations due to its potent anticancer activity in a number of experimental animal models of epithelial carcinogenesis (21–23). A major limitation to the possible use of DFMO as a cancer chemopreventive agent is its ototoxicity, a high pitch hearing loss, associated with high doses of the drug or extended periods of exposure to moderate doses of this agent (24). The biological consequences of DFMO, including its anticarcinogenic activity, appear to be strictly related to the ability of the drug to suppress cellular contents of the polyamines putrescine and spermidine (17). Thus, it is important to determine whether DFMO doses can be identified that suppress target tissue (e.g., GI mucosal tissues in GI cancer chemoprevention studies) and polyamine contents but do not induce the ototoxicity that has required treatment interruption in previous clinical trials.

The efficacy of a given DFMO treatment to suppress specific human tissue polyamine contents has been documented in only one previous situation. We showed that a DFMO dose of 3 g/m²/day for 1 month was sufficient to suppress putrescine and spermidine contents in rectal mucosal biopsies (10). Other groups have indirectly evaluated the efficacy of this drug. Haegele et al. (25) correlated the urinary excretion of decarboxylated S-adenosylmethionine, which accumulates when putrescine and spermidine contents are suppressed, with the DFMO dose. The pharmacokinetics of this drug in plasma have been measured, along with its effects on polyamine contents in urine and circulating erythrocytes (12).

In this report, we evaluated the ability of DFMO at a daily dose of 1.5 g/m² for up to 12 weeks to suppress ODC activity and polyamine contents in a variety of tissues in the GI tract. Patients treated with this dose of DFMO did not suffer any clinically apparent ototoxicity during the course of our studies, a result confirmed by others investigating this dose of DFMO for treatment periods up to 6 months (11). Therapy was discontinued in 3 of 11 patients in this trial due to nausea or dizziness.

DFMO was able to suppress polyamine contents in GI tissues but the suppression was tissue specific. DFMO had little effect on polyamine contents in apparently normal gastric tissue distal to esophageal lesions in patients with Barrett’s esophagus. This result is consistent with our observation that putrescine contents were least, and spermidine/spermine ratios were lowest, in this tissue compared to other GI tissues. These two parameters (putrescine content
and spermidine/spermine ratio) are generally increased as a consequence of ODC expression (20). The lack of an effect of DFMO in this tissue is consistent with our observation that ODC activity is especially low in gastric tissue compared to other GI tissues. Thus, ODC is not a target for DFMO action in this tissue.

Results presented here confirm our previous findings of elevated ODC activity in Barrett’s mucosa versus normal upper GI tissues (14, 15). Surprisingly, we were unable to document a statistically significant effect of systemic DFMO therapy on ODC activities in any of these tissues, whereas we did find statistically significant changes in certain polyamine parameters in some tissues in response to DFMO therapy. We do not know the reason(s) for these observations.

However, it is well known that ODC activity is highly regulated (26). Its synthesis is induced by a number of hormones and growth factors (27) and the enzyme protein is rapidly turned over in proliferating cells and tissues (28, 29). In contrast, the polyamine products of ornithine decarboxylation are very stable (30). This difference in stability between the enzyme protein ODC and its secondary product spermidine may account for our ability to measure changes in spermidine and spermidine/spermine ratios, but not ODC activities, in response to DFMO treatment. Measurements of ODC activities in tissue samples are affected by a number of experimental errors, as well as biological heterogeneity. The quantitative variability in polyamine contents in some GI tissues, like colorectal mucosa, is less than that for ODC activity values (31). Because of this lesser degree of variability, and since cellular putrescine and spermidine contents are the causative effectors of DFMO action (17, 26), we conclude that target tissue polyamine contents, and not ODC activities, are the optimal parameters to measure in order to assess DFMO effects, at least for gastrointestinal tissues.

This conclusion is consistent with results from studies on experimental animal models of carcinogenesis. In the 4-nitroquinoline 1-oxide model of tongue carcinogenesis in rats, control and carcinogen-induced levels of putrescine are substantially less than levels of the longer chain amines (32). These relative levels are similar to those observed here for gastrointestinal tissues. Because of the low levels of putrescine, these authors did not find a statistically significant effect of DFMO on putrescine contents, but they did find statistically significant effects (decreases) on longer chain amine contents. DFMO has also been shown to decrease polyamine contents in models of urinary bladder (33) and skin (34) carcinogenesis.

DFMO did significantly suppress spermidine contents and spermidine/spermine ratios in the precancerous Barrett’s lesions. Both spermidine content and spermidine/spermine ratios returned to pretreatment levels on cessation of drug therapy. This observation establishes DFMO, at this dose, as a candidate inhibitor of ODC which could adequately test the hypothesis that depletion of polyamines in Barrett’s lesions could suppress adenocarcinoma of the esophagus development in these patients. DFMO also reduced spermidine and spermidine/spermine ratios in normal esophagus. The consequence of this observation is unclear. Studies to date demonstrate that DFMO administered at doses similar to those used here causes minimal toxicities, and no specific esophageal effects have been reported. Together with the experimental animal results discussed above, our data suggest that DFMO-induced polyamine depletion is of little consequence to proliferating normal tissues like the normal esophagus. However, polyamines might be necessary for the selective growth of neoplastic cells in these sites.

Our studies do not address the question of the degree of polyamine suppression necessary for the inhibition of carcinogenesis in specific human populations. Future clinical studies employing randomization techniques with placebo control groups must address this issue. However, cell studies show that growth inhibition induced as a consequence of ODC inhibitor treatment does not depend on the total depletion of intracellular putrescine and spermidine contents (35).

In summary, this study shows that DFMO can suppress spermidine contents in precancerous Barrett’s lesions. These data provide evidence that DFMO could be used to test the hypothesis that polyamine depletion would inhibit the development of esophageal adenocarcinoma in humans with Barrett’s esophagus.

Acknowledgments

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