Title
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Permalink
https://escholarship.org/uc/item/7768m4jb

Journal
Essays in biochemistry, 46

ISSN
0071-1365

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Publication Date
2009-11-04

DOI
10.1042/bse0460008

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Polyamines as mediators of APC-dependent intestinal carcinogenesis and cancer chemoprevention

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Abstract

Combination chemoprevention for cancer was proposed a quarter of a century ago, but has not been implemented in standard medical practice owing to limited efficacy and toxicity. Recent trials have targeted inflammation and polyamine biosynthesis, both of which are increased in carcinogenesis. Preclinical studies have demonstrated that DFMO (difluoromethylornithine), an irreversible inhibitor of ODC (ornithine decarboxylase) which is the first enzyme in polyamine biosynthesis, combined with NSAIDs (non-steroidal anti-inflammatory drugs) suppresses colorectal carcinogenesis in murine models. The preclinical rationale for combination chemoprevention with DFMO and the NSAID sulindac, was strengthened by the observation that a SNP (single nucleotide polymorphism) in the ODC promoter was prognostic for adenoma recurrence in patients with prior sporadic colon polyps and predicted reduced risk of adenoma in those patients taking aspirin. Recent results from a phase III clinical trial showed a dramatic reduction in metachronous adenoma number, size and grade. Combination chemoprevention with DFMO and sulindac was not associated with any serious toxicity. A non-significant trend in subclinical ototoxicity was detected by quantitative audiology in a subset of patients identified by a genetic marker. These preclinical, translational and clinical data provide compelling evidence for the efficacy of combination chemoprevention. DFMO and sulindac is a rational strategy for the prevention of metachronous adenomas, especially in patients with significant risk for colorectal cancer. Toxicities from this combination may be limited to subsets of patients identified by either past medical history or clinical tests.

Introduction

Increased concentrations of polyamines are found in cancerous tissue [1]. Polyamines are influenced by factors such as import, export, biosynthesis and catabolism. ODC (ornithine decarboxylase) is a rationale target in several cancers, with the goal to decrease cellular polyamine pools. ODC inhibition may not be sufficient therapy in situations where polyamine synthesis is not the rate-limiting step regulating polyamine pool sizes.
The  ODC  gene  is  regulated  by  the  Wnt  signalling  cascade  [2].  Activated  WNT  signalling  up-regulates  MYC  [3],  a  transcriptional  activator  of  ODC  [4].  The  WNT  cascade  is  silenced  in  the  majority  of  adult  intestinal  tissues,  but  can  be  dysregulated  through  mutations.  The  APC  (adenomatous  polyposis  coli)  tumour  suppressor  gene  is  a  component  of  the  WNT  cascade  and  has  been  identified  as  the  germ-line  mutation  in  FAP  (familial  adenomatous  polyposis)  [5].  Over  80%  of  sporadic  colorectal  cancers  also  carry  mutations  in  APC.  APC  mutations  and  WNT  signalling  lead  to  up-regulation  of  MYC  activity  and  increased  expression  of  ODC,  and  increased  polyamine  pools.  Other  genetic  influences  of  CRC  (colorectal  cancer)  are  mutant  K-RAS,  a  proto-oncogene  that  also  activates  ODC.

Colorectal  carcinogenesis  is  also  influenced  by  high-fat  diet  and  sedentary  lifestyle.  Long-term  use  of  aspirin  and  the  reduction  of  CRC  mortality  led  to  the  COX  (cyclo-oxygenase)-based  hypothesis  [6].  These  environmental  risk  factors  influence  an  individual's  genetic  susceptibility  and  produce  a  risk  profile  for  cancer.  A  mechanism  for  CRC  involves  mutated-APC  and  K-RAS  in  combination  with  environmental  risk  factors  that  elevate  polyamines  and  inflammation.  A  rationale  strategy  for  cancer  chemoprevention  would  be  the  combination  of  inhibitors  of  polyamine  biosynthesis  and  inflammation.

Pre-clinical  data

Cancer  burden

In  the  United  States,  cancer  is  the  leading  cause  of  death  in  people  under  the  age  of  85  years  [7].  There  were  an  estimated  1437180  new  cases  and  565650  deaths  attributed  to  cancer  in  2008,  whereas  10.8  million  Americans  are  living  with  a  history  of  cancer.  Cancer  therapeutics  are  most  effective  in  the  early  stages  of  disease,  but  are  less  effective  in  treating  advanced  cancers.  This  point  underscores  the  need  for  prevention,  early  detection  and  effective  treatment.

The  vast  majority  of  US  cancer  incidence  and  mortality  are  epithelial-derived  cancers  of  the  lung,  colon,  breast  and  prostate.  Epithelia  provide  a  protective  barrier  while  also  importing  nutrients  and  exporting  waste,  especially  the  colon.  The  ACS  (American  Cancer  Society)  estimated  that  there  were  148810  new  cases  of  colorectal  cancer  in  2008,  with  a  mortality  of  49960  deaths.

APC:  the  genetic  risk  factor  for  CRC

Carcinogenesis  occurs  by  inactivation  of  a  tumour  suppressor  gene  or  activation  of  an  oncogene.  Inherited  loss  of  a  single  allele  in  the  APC  gene  increases  an  individual's  risk  of  a  hereditary  carcinogenesis,  known  as  FAP  [5].  FAP  is  characterized  by  an  increase  in  adenomatous  polyps  of  the  colon  with  advancing  age.  The  risk  is  malignant  transformation  of  the  polyps  and  treatment  is  colectomy.  Greater  than  80%  of  sporadic  CRCs  also  have  mutations  in  the  APC  gene.  Shown  in  Figure  1  is  a  representation  of  the  WNT  pathway  in  normal  tissue  and  in  carcinogenesis.

The  APC  protein  interacts  with  GSK-3β  (glycogen  synthase  kinase-3β)  and  β-catenin.  This  interaction  allows  GSK-3β  to  phosphorylate  β-catenin  and  marks  it  for  proteosomal  degradation.  In  carcinogenic  tissue,  GSK-3β  and  β-catenin  are  disrupted  by  mutant-APC.  As  a  result  GSK-3β  can  no  longer  phosphorylate  β-catenin.  β-Catenin  accumulates  in  the  cytoplasm  and  then  translocates  to  the  nucleus  forming  a  heterodimer  with  its  cognate  binding  partner,  TCF/LEF  (T-cell  factor/lymphoid-enhancing  factor).  The  heterodimer  binds  to  promoter  regions  of  genes  and  alters  expression  [2].  Dysregulation  of  WNT  signalling  leads  to  changes  in  c-MYC  gene  expression.  MYC  activation  occurs  in  neuroblastoma,  breast  and  prostate  cancers,  but  its  dysregulation  in  CRC  is  unique  given  mutations  in  the  upstream  APC  gene  and  rapid  cellular  turnover.

Essays Biochem. Author manuscript; available in PMC 2013 February 17.
In APC-dependent carcinogenesis c-MYC activation affects transcription of ODC through binding regions in the promoter. An SNP (single nucleotide polymorphism) occurs in ODC between two MYC-binding regions. Differential repression of ODC occurs by MAD1 binding at the SNP sequence to the A-allele, not the G-allele. In a population-based study of humans with prior colonic adenomas, aspirin use was associated with a 90% reduction in relative risk for development of metachronous adenomas among individuals homozygous for the minor ODC A-allele compared with the non-aspirin users homozygous for the major ODC G-allele [8]. This ODC polymorphism appears to be a genetic marker for CRC risk. Our group has sought to test features of the hypothesis depicted in Figure 1. We have developed a transgenic mouse expressing a mutant Apc and conditional deletion of the c-Myc alleles in the intestinal and colonic mucosa. Conditional suppression of Myc in the intestinal tract was associated with reduced intestinal tumour number, compared with these same Apc<sup>Min/+</sup> mice expressing intestinal Myc [9]. Treatment with DFMO (difluoromethylornithine) also suppresses intestinal tumorigenesis in Apc<sup>Min/+</sup> mice [10]. These results implicate both Myc and Odc as downstream mediators of APC-dependent intestinal carcinogenesis.

The MYC protein can act as a transcription factor activator when bound to MAX. The MYC–MAX heterodimer can activate the expression of genes through binding on consensus sequences (enhancer box sequences or E-boxes), as well as recruiting HATs (histone acetyltransferases). In contrast, when MAX is bound to MAD1, transcription is repressed. In the presence of normal APC, C-MYC was suppressed whereas MAD1 was elevated. In the presence of mutant-APC, C-MYC was elevated whereas MAD1 was suppressed [2]. This interaction is shown in Figure 2.

Mutant-APC led to elevations in c-MYC that increased expression of ODC [2]. The results indicated that ODC was a modifier of APC-dependent signalling in models of CRC. Mouse models were employed to determine whether mutant-APC led to elevated polyamines in vivo. Murine models recapitulate this finding, with elevated polyamines found in the small intestine of Apc<sup>Min/+</sup> mice [10].

**Polyamine-dependent regulation and colon carcinogenesis**

Arginine is a component of the urea cycle which converts nitrogenous waste for excretion [11]. Elevated dietary arginine can also increase polyamine levels through its conversion into ornithine in the urea cycle. Apc<sup>Min/+</sup> mice fed a diet of elevated arginine had an elevated tumour burden [12]. In patients with CRC, increased meat consumption was a surrogate for arginine and was associated with decreased overall survival [13]. Polyamines are exported, as depicted in Figure 3, via a mechanism which involves an arginine transporter [14].

K-RAS mutation is another significant risk factor for CRC. The RAS-family of proteins is a mediator of extracellular signals through the cytoplasm and eventually into the nucleus; the effect of which is to alter gene expression and enhance proliferation. In cell culture models, mutant K-RAS increases ODC transcription and decreases transcription of SAT1 (spermidine/spermine acetyltransferase; also referred to as SSAT in other chapters in this volume), an enzyme important in the catabolism of polyamines. Mutant K-RAS increases polyamine biosynthesis via ODC activation and decreases acetylation of polyamines.

**Polyamine pool limitation**

One strategy to inhibit polyamine levels is to decrease biosynthesis. Selective inhibition of ODC by the suicide-inhibitor, α-DFMO, was developed at the Merrell Dow Research Center in Strasbourg, France [11]. Although α-DFMO showed promise in cell culture
models, compensatory polyamine import limited the success of DFMO in early murine models.

SAT1 is an important factor in polyamine export. As shown in Figure 3, SAT1 can acetylate both spermidine and spermine, targeting them for export. SAT1 can be induced by NSAIDs (non-steroidal anti-inflammatory drugs), including aspirin, sulindac, ibuprofen and indomethacin [15]. SAT1 induction can lead to apoptosis in CRC cell lines [16]. Sulindac induced Sat1, decreased intestinal levels of monoacetylspermidine, spermidine and spermine, and reduced tumour number in the small intestine of mouse models [17]. Dietary putrescine restored tissue polyamine content and partially abrogated the antitumour effects of sulindac, indicating that sulindac was acting via a polyamine-dependent mechanism.

Inflammation and colorectal carcinogenesis

In 1863 Virchow hypothesized a causal interaction between chronic inflammation and cancer mediated via the tumour microenvironment [18]. Within the microenvironment of carcinogenesis both intrinsic and extrinsic cellular factors contribute to a pro-inflammatory state. The intrinsic pro-inflammatory factor NF-κB (nuclear factor κB) is activated by many signals. Activation of NF-κB up-regulates target genes facilitating cancer growth by initiation, promotion and progression. One of the target genes of NF-κB is the enzyme COX. COX-1 is a constitutive gene that mediates homoeostatic functions, whereas inducible COX-2 is associated with inflammation. PGE₂ (prostaglandin E₂) is downstream of COX-2 and is associated with tumorigenesis (Figure 4). In cell culture models the NSAID sulindac decreased both COX-2- and PGE₂ synthase-mediated inflammation. While NSAIDs block COX-2, they also inhibit production of NO (nitric oxide) via inhibition of NOS-2 (inducible nitric oxide synthase). NO is a known activator of inflammation. As shown in Figure 4, arginine can be converted into NO, leading to increased inflammation.

Clinical data with DFMO

Cancer therapeutic experience

DFMO has been evaluated as a cancer therapeutic agent. It was not especially active as a single agent and its use was associated with ototoxicity at high doses [11,19]. Based on mouse model studies, DFMO was subsequently evaluated as a potential cancer chemopreventive agent [11].

Clinical trials of DFMO for colon cancer prevention

Early studies have confirmed that ODC and polyamine contents were elevated in human colon cancer tissue compared with adjacent normal colorectal mucosa [20]. Measurements of colorectal tissue polyamine contents were subsequently validated as measures of DFMO effects in patients. Validation of these markers allowed for the conduct of clinical trials to assess efficacy of DFMO dose, oral dose delivery and frequency of dosing. Consequently, we were able to conduct a dose de-escalation trial to determine the lowest DFMO dose capable of suppressing colorectal polyamine contents while minimizing toxicities, including ototoxicity [21]. A subsequent trial built on these findings evaluated three oral doses of DFMO given daily for 1 year. Patients were randomized to a control or treatment group with three separate doses of DFMO: 0.075, 0.2 and 0.4 g/m² per day [22]. The end of trial analysis showed that the 0.2 g/m² per day dose had similar biological effects compared with the 0.4 g/m² per day dose, with a decreased report of toxic side effects and decreased drop-out rate. The implications were that a low dose of DFMO inhibited colorectal polyamine content in rectal mucosa while demonstrating a safe toxicity profile.
Sulindac

While a phase IIb/III trial was being considered with DFMO, strong and extensive epidemiological evidence accumulated suggesting that aspirin and other NSAIDs might be effective as colon cancer prevention agents. Sulindac decreased polyp formation in high-risk patients with FAP [23]. It was hypothesized that sulindac and DFMO in combination would have a greater effect than either agent alone on the development of colon polyps, and this point was established in preclinical models [24]. As shown in Figure 5, NSAIDs and DFMO affect multiple targets related to inflammation.

Phase IIb and III DFMO and sulindac trials in non-cancerous patients

Cell culture models indicated that DFMO and sulindac could act at least additively to suppress growth and cell survival [24]. With mounting cell culture, murine model, clinical and epidemiological data, a prospective, randomized, placebo-controlled, phase IIb trial, with the combination of DFMO and sulindac, for 3 years was initiated in patients with prior sporadic colon polyps. The study used 0.2 g of DFMO/m² per day and was converted from a liquid oral dose into an oral pill form. A dose of 500 mg/day closely approximated the 0.2 g/m² per day liquid form. The study also used 150 mg of sulindac, 50% of the conventional dose [23]. In addition to the need for efficacy, a major intent was to evaluate potential toxicity. The phase IIb trial of DFMO and sulindac, with biochemical markers as primary endpoints, was subsequently modified and converted into a phase III trial with metachronous adenomas as the primary endpoint of the study.

Baseline and serial audiological tests were performed to assess potential long-term ototoxicity. Participants with greater than 20 dB uncorrectable hearing loss above the age-adjusted norms were ineligible for the phase III trial. The eligible patients were randomized to receive placebo or 500 mg of DFMO plus 150 mg of sulindac. Patients were stratified according to two parameters: the seven clinical sites and low-dose aspirin use (either 81 mg/day or less than 325 mg twice weekly). Safety evaluations of the patients occurred after the 1 month run-in as well as at 3, 6 and 9 months, and every 6 months for the remainder of the phase III trial. Evaluations included physical examination and laboratory evaluations. Pure-tone audiograms were performed at 0, 18 and 36 months. Adenomas removed during any part of the phase III trial were submitted to a central pathology facility with standardized diagnostic objectives. The colorectal polyps were counted, measured and graded according to predetermined criteria. Safety analysis included investigator-reported adverse events and were coded according to the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) Body System [25]. An independent DSMB (Data and Safety Monitoring Board) reviewed the safety and efficacy of the data twice yearly. The investigators were blinded to the results of the DSMB’s findings throughout the phase IIb and phase III trials. A pre-specified early stopping point was made based on potential efficacious or futile results. Interim analysis was planned at approx. 60% and 80% of the total accrual of patient information.

Based on the primary and secondary endpoints of the phase III trial, as well as oversight by the DSMB, the blind study was broken at the second interim analysis. The phase III trial intervention of combination DFMO and sulindac was found to be significantly effective. The combination of 500 mg of DFMO and 150 mg of sulindac decreased the number and severity of adenoma recurrence without significant toxicity [25]. The results are presented in Table 1 and summarized here. There was a 70% reduction in metachronous adenomas for those in the treatment arm. In addition, there was a 92% reduction in advanced adenomas and a 95% decrease in the recurrence of multiple adenomas in patients in the treatment arm compared with those in the placebo arm. Sporn and Hong [26] wrote an accompanying
editorial with this publication and stated that “the clinical results represent a landmark advance to [reduce the number] of cancer deaths”.

**Toxicity**

An adjusted, non-significant, mean decrease in hearing threshold of 1.08 dB was detected in the treatment arm compared with placebo [27]. There was no difference in the clinical audiotoxicity between the two arms. Cardiotoxicity was also evaluated in this study. Patients were stratified into low-, moderate- and high-CV (cardiovascular) risk factors. Among high-risk patients, the number of CV events was higher in the treatment than the placebo arm. Excluding the high-risk CV patients, the numbers of CV events were similar between treatment and placebo arms [28].

These clinical results from a phase III trial proved to be consistent with preclinical studies in mouse models. Combination DFMO and sulindac was effective in reducing tumour number by more than 80% when compared with the untreated controls in the ApcMin/+ mouse model ($P < 0.0001$) [29]. Combination sulindac–DFMO was effective in reducing the number of high-grade adenomas when compared with the sulindac alone ($P = 0.003$). The clinical implications are twofold: (i) first DFMO is effective in the reduction of adenomatous polyps and (ii) secondly, the combination of DFMO and sulindac can further reduce the risk of CRC through the reduction in the number of high-grade intestinal adenomas. These high-grade adenomas are those lesions most likely to progress to colon cancer.

**Phase III DFMO and sulindac in patients with cancer**

Although the phase III trial with DFMO and sulindac provided strong evidence for preventing disease recurrence in patients with prior adenomas, the chemoprevention has not been evaluated in higher risk populations. Even after surgical resection and optimal treatment with chemotherapy (when indicated), stage I–III colon cancer patients remain at considerable risk for distant recurrence, secondary colonic tumour formation and subsequent mortality. A phase III trial of these key compounds among surgically resected colon cancer patients is in the planning stages.

**Future**

**Clinical practice**

Approx. 30 million patients over the age of 50 years will develop adenomatous polyps each year in the United States. A proportionally similar number will develop these lesions in Western Europe. Approx. 10% will progress to advanced polyps or frank cancer. Genetically at-risk patients along with those with a history of CRC [sporadic, FAP, HNPCC (hereditary nonpolyposis colorectal cancer) or prior CRC] are the target population for chemoprevention. Current techniques for CRC screening include endoscopy at regular intervals with polyps removed. There is a significant risk reduction for CRC through endoscopy and polypectomy, but barriers of cost, preparation and the procedure translates into approx. 50% screening of eligible populations.

Endoscopy is also a poor screening method for right-sided cancers, as well as flat or depressed lesions. Further complicating the role of endoscopy is the frequent overuse by patients with previously diagnosed disease. The resultant gaps in screening with overuse by others necessitate another disease prevention strategy. Chemoprevention clearly has the potential to reduce disease burden.

The results from the phase III trials potentially affect the surveillance of higher risk populations. As previously stated, approx. 50% of CRC patients with Stage I, II or III...
disease recur. Patients’ and physicians’ anxieties may decrease with combination therapy and lessen the overutilization of endoscopic procedures in patients with a moderate risk of colon cancer. Combination chemoprevention may also have applications in high-risk populations such as those with FAP. The positive results of this combination in the \( Apc^{Min/+} \) model of FAP may lead to trials in this high-risk group. Positive results of such trials could increase the time to surgery in patients with FAP.

**Dietary sources of polyamines**

A database has been developed to assess dietary polyamine content [30]. It is hypothesized that a reduction in total-body polyamine pools may reduce carcinogenesis. Table 2 presents some of the foods for which the polyamine content has been determined. The intention for the database is to quantify dietary polyamines and qualify them as a risk factor for carcinogenesis.

**Conclusions**

Epithelia provide a protective barrier from the external environment. It is a mediator of transport. In the process, epithelia are exposed to harmful substances and harbour genetic mutations. In this context, cells are transformed from normal to neoplastic and the carcinogenic process is initiated. For the past several decades, collaborative efforts of scientific research have led to a new paradigm in cancer management: chemoprevention. Chemoprevention is an approach that is not applicable to everyone. It should target people with elevated risks of cancer. The caveat for chemoprevention is that target populations are still relatively healthy compared with patients who currently have cancer. Therefore chemoprevention must have a clear benefit that exceeds the risk of treatment. The development of DFMO and sulindac underscore this sentiment.

**Summary**

- Polyamine pools are elevated in cancerous tissue.
- ODC is a committed step, converting ornithine into putrescine.
- DFMO is an irreversible, competitive inhibitor of ODC.
- In CRC cell culture models, DFMO decreased polyamine levels.
- Murine models of CRC with mutant-Apc have increased Myc and Odc activation.
- DFMO alone had limited efficacy in therapeutic clinical trials.
- NSAIDs decrease COX activity.
- NSAIDs can activate polyamine export pathways.
- Polyamine pools are dynamically regulated by anabolism, catabolism, import and export.
- Low-dose DFMO was evaluated as a chemopreventative agent for CRC by biomarker assays, efficacy, safety, toxicity and dose de-escalation before large clinical trials.
- Combination DFMO and sulindac was evaluated in a large, randomized, prospective, multi-centre, double-blind clinical trial.
- Combination DFMO and sulindac was effective in reducing adenoma recurrence by number, size and grade.
- Ototoxicity was measured in the treatment arm, but without clinical significance.
• Patients with baseline high-CV risk had a higher number of CV events.

References


Figure 1. The WNT pathway in normal and carcinogenic cells

The WNT pathway in a normal, adult, colonic epithelial cell is depicted on the left-hand side of the Figure. On the basolateral portion of the cell the WNT receptor is activated and transmits the signal intracellularly to the APC, GSK-3β and β-catenin complex. GSK-3β phosphorylates β-catenin, marking it for proteosomal degradation. The WNT pathway in carcinogenesis is depicted on the right-hand side of the Figure. The WNT receptor may be activated and transmission of the signal intracellularly may occur, but inactivation of β-catenin by GSK-3β does not. Cytoplasmic accumulation of β-catenin leads to its nuclear translocation and binding with its cognate partner TCF/LEF. This heterodimerization regulates genes through transcription, notably of MYC.
Figure 2. ODC regulation occurs through both positive and negative mechanisms
ODC is suppressed by MAD. Transcriptional activation of ODC can occur through MYC, RAS or both. Upstream activation of c-myc may occur via mutant APC. Pharmacogenetic manipulation of ODC occurs through identification of SNP status. The combination of these factors may increase individual risk stratification.
Figure 3. Polyamine transport is shown schematically via import, export, anabolism and catabolism
Arginine is imported into the cell and then converted into ornithine which contributes to the polyamine pools. Polyamine pools may be further increased by import or decreased by catabolism and export.
Inflammation within a colonic epithelial cell may occur through multiple mechanisms. Imported dietary arginine may either be converted into NO or processed in the polyamine pathway. NSAIDs can disrupt these and other pathways via inhibition of NOS-2, up-regulation of polyamine export or inhibition of COX-2. External sources of polyamines and bile acids may also contribute to inflammation.
Figure 5. The interaction among mutant-APC, polyamines and inflammation is depicted in a colonic epithelial cell
Mutant-APC and activated K-RAS lead to increased MYC production and up-regulate ODC which increases the polyamine concentration. Elevated dietary arginine can also contribute to increased polyamine pools. NSAIDs and DFMO can inhibit multiple targets in both the polyamine and inflammatory pathways.
### Table 1

**Adenoma recurrence as a function of intervention**

The adenomas and pathologies are shown on the left-hand side, while intervention number and type are shown along the top. The risk ratio for development of adenomatous lesions based on intervention strategy is quantified and statistical significance is shown. Data taken from [25].

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Placebo (n = 129)</th>
<th>DFMO+sulindac (n = 138)</th>
<th>Risk ratio</th>
<th>95% Confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adenoma</td>
<td>53</td>
<td>17</td>
<td>0.30</td>
<td>0.18–0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Advanced adenoma</td>
<td>11</td>
<td>1</td>
<td>0.085</td>
<td>0.011–0.65</td>
<td>0.001</td>
</tr>
<tr>
<td>Large (≥1 cm) advanced adenoma</td>
<td>9</td>
<td>1</td>
<td>0.10</td>
<td>0.013–0.81</td>
<td>0.004</td>
</tr>
<tr>
<td>Multiple adenomas</td>
<td>17</td>
<td>1</td>
<td>0.055</td>
<td>0.0074–0.41</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 2

Polyamine content in food

The three polyamines: putrescine, spermidine and spermine are listed. The amount of polyamines, in nmol/day, is given for multiple food items. Data taken from [30].

<table>
<thead>
<tr>
<th>Polyamine</th>
<th>Food item</th>
<th>Amount (nmol/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putrescine</td>
<td>Orange juice and grapefruit juice</td>
<td>44441</td>
</tr>
<tr>
<td></td>
<td>Oranges, grapefruit and tangerines (excluding juice)</td>
<td>17613</td>
</tr>
<tr>
<td></td>
<td>Fresh tomatoes</td>
<td>10042</td>
</tr>
<tr>
<td></td>
<td>Bananas</td>
<td>7344</td>
</tr>
<tr>
<td></td>
<td>Beer (all types)</td>
<td>6374</td>
</tr>
<tr>
<td>Spermidine</td>
<td>Green peas</td>
<td>3283</td>
</tr>
<tr>
<td></td>
<td>Cheese, such as American and cheddar</td>
<td>3124</td>
</tr>
<tr>
<td></td>
<td>Lasagne and pasta with meat sauce</td>
<td>2900</td>
</tr>
<tr>
<td></td>
<td>Potatoes (boiled, baked and mashed)</td>
<td>2388</td>
</tr>
<tr>
<td></td>
<td>Burritos, tacos, tostadas and quesadillas</td>
<td>1890</td>
</tr>
<tr>
<td>Spermine</td>
<td>Ground meat</td>
<td>2186</td>
</tr>
<tr>
<td></td>
<td>Lunch meats (e.g., ham, turkey, bologna and salami)</td>
<td>1977</td>
</tr>
<tr>
<td></td>
<td>Green peas</td>
<td>1905</td>
</tr>
<tr>
<td></td>
<td>Lasagne and pasta with meat sauce</td>
<td>1443</td>
</tr>
<tr>
<td></td>
<td>Peanut butter, peanuts and other nuts and seeds</td>
<td>1237</td>
</tr>
</tbody>
</table>