Effects of dietary supplements in young and aged rats

Drs. Magnuson and Malik
University of Maryland
Drs. Franke-Carroll, Hines & Alam
FDA
Background

- Estimated that 40% of US population uses dietary supplements often
- Over 80% have tried at least 1 of 29,000 supplements on the market
- Safety concerns for special populations
  - Children, elderly
  - Pregnant women, health compromised
- Evaluated curcumin and soy isoflavones
Curcumin

- Claims include:
  - Anti-inflammatory
  - Antioxidant
  - Anticarcinogenic
  - Anti-aging

![Curcumin Bottle](image1.png)

![Curcumin Label](image2.png)
Curcumin

- Colorectal cancer prevention in rodent studies with young rats

- Phase 1 Clinical trials in humans
  - no toxic effect in humans consuming 8 gm/d for 3 mo
  - 5 other studies lower doses
Project Objectives

• What effect does curcumin have on the development of age-related pathological changes in rats?
• Does age affect prevention of early stage colorectal cancer by curcumin?
Experimental Design

- F344 male rats:
  - 6 week-, 12 month-, and 22 month-old
- Six rats of each age group
  - randomly assigned to either 0.6% curcumin or control diet
- One week after starting experiment diet, all the rats were treated with a colon carcinogen
- Rats were fed experimental diets for 12 wks
- Tissues were obtained and evaluated.
Common age-related changes in rats were not affected by curcumin

- **Kidney damage**
  - chronic progressive nephropathy
  - degree of severity *increased with age*
  - dietary curcumin did not affect

- **Heart damage**
  - chronic cardiomyopathy
  - the degree of severity *increased with age*
  - dietary Curcumin effect was not observed.
Curcumin-fed rats had higher incidence of some lesions

- Lung, heart and liver lesions
  - Pulmonary microgranulomas
  - Myxomatous degeneration of heart valves
  - Liver microgranulomas

- Gastrointestinal tract
  - Lymphoplasmocytic infiltrates in stomach, duodenum and colon

At this time, the significance of these finding is not clear due to the small number of animals
Old Curcumin-fed had lower incidence of all neoplastic lesions

- Malignant (aggressive) lesions found only in control diet rats
  - Lung carcinoma, histiocytic sarcoma of spleen, C-cell carcinoma in thyroid, tumors in adrenals
  - Pancreatic islet cell adenoma, testicular adenoma, pituitary adenoma, skin fibroadenoma
Curcumin reduces early stage colon cancer in young & old, but not Mature rats

(mean ± SE, n=6 rats/group).
Curcumin Study Conclusions

- No support for anti-aging claims
- Support for anti-cancer claims in old group
- Lack of effect in middle-aged group raises questions about testing in only young for preclinical testing
Soy Isoflavones

- Prevention of
  - breast cancer
  - Heart disease
  - prostate cancer
  - symptoms of menopause

- also colon cancer, but only done in males
Project Objectives

- Is soy isoflavone effective in females?
- Does age affect prevention of early stage colorectal cancer by soy isoflavones?
- Similar experiment – used Novasoy as source of isoflavones (0.4% of diet)
Surprising Results

- **No inhibition** of colon cancer lesions by soy
- Old female rats fed soy were **VERY ill**
  - 4/7 died before the end of the experiment
- Mature female rats fed soy also ill
- Young – no adverse effect
- Soy isoflavones acted like estrogen in older groups
Serum Estradiol

<table>
<thead>
<tr>
<th>Group</th>
<th>Estradiol (pmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YC</td>
<td>ab</td>
</tr>
<tr>
<td>MC</td>
<td>bc</td>
</tr>
<tr>
<td>OC</td>
<td>c</td>
</tr>
<tr>
<td>YS</td>
<td>ab</td>
</tr>
<tr>
<td>MS</td>
<td>a</td>
</tr>
<tr>
<td>OS</td>
<td>a</td>
</tr>
</tbody>
</table>
Uterine/Body weight

Uterine (mg)/body wt (g)

YC, MC, OC, YS, MS, OS
Soy Study Conclusions

- In combination with another drug, soy isoflavones were toxic to older female rats
- Is this a drug/diet interaction?
- Soy isoflavones affected estrogen and estrogen-responsive tissues in older rats
- May have adverse effects on hormone-dependent cancers
So what?

- Use of Supplements by aging consumers
  - Safety?
  - Efficacy?
Acknowledgements

UM students
– Youngjoo Kwon
– James Montgomery
– Kathleen Daly
– Amy Tracy

• JIFSAN Grant support
• American Institute for Cancer Research