Cancer Is a Preventable Disease That Requires Major Changes in Life Style

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Indian American Cancer Network (IACAN)
Role of Diet and Complementary Medicine in Cancer
Beverly Gor, EdD, RD, LD, CDE; Neeta Pahwa, MS, RD, LD, CNSD
Bharat Aggarwal, Ph.D., P. G. Parameswaran, M.D.
Sunday, May 23 Time: 3 – 5 PM
India House; 8888 West Belfort, Houston, TX 77031
“I will ask for an appropriation of an extra $100 million to launch an extensive campaign to find a cure for cancer. Let us make a total national commitment to conquer this dread disease. America has long been the wealthiest nation in the world. Now it is time we became the healthiest nation in the world”.

--President Richard Nixon, 1971
State of the Union address
Change in the US Death Rates* by Cause, 1950 & 2002

* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
“Forty-one percent of Americans will develop cancer, which means, with very few exceptions, every family will be touched by this disease. The need is urgent,” said John Mendelsohn, M.D., president of M. D. Anderson.

“But the time is optimal because we have more knowledge than ever before about cancer and we have new research tools that position M. D. Anderson to speed progress against this disease.

January, 2010
Projection for Cancer Incidence and cancer deaths

<table>
<thead>
<tr>
<th>Year</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>2020</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>2030</td>
<td>20</td>
<td>14</td>
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</table>

Millions
Where is the problem?

FDA Approves Avastin for Renal Cell Carcinoma, although there was no improvement in OVERALL SURVIVAL. Median OS = 23 months in the Avastin plus IFN-a2a arm and 21 months in the IFN-a2a plus placebo arm.

With colon cancer, Avastin treatment costs about $50,000/year, can reach $100,000 a year, and adds four months of life.

Herceptin sells for $40,000 a year.
Cancer Is a Preventable Disease That Requires Major Changes in Life Style

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
Hippocrates proclaimed ~2500 years ago

“Let food be thy medicine and medicine be thy food”
National Cancer Institute

Eat 8 servings of fruits and vegetables every day!
“You are what you eat”
Diet (Fruits & Vegetables) and Cancer

Consumption of vegetables and fruit and the risk of bladder cancer in the European Prospective Investigation into Cancer and Nutrition.

Greater vegetable and fruit intake is associated with a lower risk of breast cancer among Chinese women.

Fruit and vegetable consumption and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition,

Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: The JPHC study.

No association between fruit, vegetables, antioxidant nutrients and risk of renal cell carcinoma,

Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study,

Fruit and vegetable intake and esophageal cancer in a large prospective cohort study,
Diet (Fruits & Vegetables) and Cancer

No association between fruit, vegetables, antioxidant nutrients and risk of renal cell carcinoma,
International Journal of Cancer, 2010, Bertoia M et al,

Antioxidant intake from fruits, vegetables and other sources and risk of non-Hodgkin's lymphoma: the Iowa Women’s Health Study,

Vegetable and fruit consumption and cancer risk,

Food-group consumption and colon cancer in the adelaide case-control study. I. Vegetables and fruit

Lung cancer risks in relation to vegetable and fruit consumption and smoking,

Vegetable and fruit consumption and risk of renal cell carcinoma: Results from the Netherlands cohort study,

The role of vegetable and fruit consumption in the aetiology of squamous cell carcinoma of the oesophagus: A case-control study in Uruguay,
Diet (Fruits & Vegetables) and Cancer


*Vegetable, fruit and meat consumption and potential risk modifying genes in relation to colorectal cancer.*

*Fat, fiber, fruits, vegetables, and risk of colorectal adenomas,*

*Fruits, vegetables and lung cancer: A pooled analysis of cohort studies,*

*Intake of fruits, vegetables and selected micronutrients in relation to the risk of breast cancer,*

*Vegetables, fruit and risk of gastric cancer in Japan: A 10-year follow-up of the JPHC study Cohort I.*

*Cohort analysis of fruit and vegetable consumption and lung cancer mortality in European men,*
Diet (Fruits & Vegetables) and Cancer

**Bladder-cancer incidence in relation to vegetable and fruit consumption:**
A prospective study of atomic-bomb survivors,

**Vegetables and fruit and human cancer: Update of an Italian study,**

**Protective effect of fruits and vegetables on stomach cancer in a cohort of Swedish twins,**
Cancer incidence is less in spice consuming countries

Figure 1. Relationship between production of spices and cancer incidence. Data is modified from 2000 faostat.fao.org (http://www.foodmarketexchange.com/datacenter/product/herb/herb/detail/dc_pi_hs_herb0406.htm) and cancer data from the World Health Organization GLOBOCAN 2002. A color version of the figure is available in the online journal.
THE SECRET KILLER

- The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER’S and other diseases
- What you can do to fight it
The FIRES Within

Inflammation is the body’s first defense against infection, but when it goes awry, it can lead to heart attacks, colon cancer, Alzheimer’s and a host of other diseases.

Illustration for TIME by Brian Stauffer

By CHRISTINE GORMAN and ALICE PARK

What does a stubbed toe or a splinter in a finger have to do with your risk of developing Alzheimer’s disease, suffering a heart attack or succumbing to colon cancer? More than you might think. As scientists delve deeper into the fundamental causes of those and other illnesses, they are starting to see links to an age-old immunological defense mechanism called inflammation—the same biological process that turns the tissue around a splinter red and causes swelling in an injured toe. If they are right—and the evidence is starting to look pretty good—it could radically change doctors’ concept of what makes us sick. It could also prove a bonanza to pharmaceutical companies looking for new ways to keep us well.

Most of the time, inflammation is a lifesaver that enables our bodies to fend off various disease-causing bacteria, viruses and parasites. (Yes, even in the industrialized world, we are constantly bombarded by pathogens.) The instant any of these potentially deadly microbes slips into the body, inflammation marshals a defensive attack that lays waste to both invader and any tissue it may have infected. Then just as quickly, the process subsides and healing begins.

Every once in a while, however, the whole inflammatory production doesn’t shut down. Sometimes the problem is a genetic predisposition; other times something like smoking or high blood pressure keeps the process going. In any event, inflammation becomes chronic rather than transitory. When that occurs, the body turns on itself—like an army child who can’t resist picking a scab—with aftereffects that seem to underline a wide variety of diseases.

Suddenly, inflammation has become one of the hottest areas of medical research.
What is Inflammation?

Cornelius Celsus, a physician in first century Rome:

Heat (*calor*)

Pain (*dolor*)

Redness (*rubor*)

Swelling (*tumour*)
Inflammation and cancer

Redness, swelling, heat and pain

Rudolf Virchow
(1821-1902; in 1850)

His Pathology laboratory in Wurzburg, Germany

Linked Inflammation with atherosclerosis, rheumatoid arthritis, multiple sclerosis, cancer, asthma, Alzheimer’s

From Heidland A et al, History of Nephrology, 2006
Inflammation is “itis”

Arthritis is inflammation of the joints
Bronchitis .................................. Bronchus
Sinusitis .................................... Sinus
Gastritis ...................................... Stomach
Esophagitis .................................. Esophagus
Pancreatitis .................................. Pancreas
Meningitis ..................................... Brain
Rhinitis ....................................... Rhina
Gingivitis .................................... Gum
## Inflammation as a risk factor for most cancers

<table>
<thead>
<tr>
<th>Inducer</th>
<th>Inflammation</th>
<th>Cancers</th>
<th>% predisposed that progress to cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoke</td>
<td>Bronchitis</td>
<td>Lung Cancer</td>
<td>11-24</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>Gastritis</td>
<td>Gastric Cancer</td>
<td>1</td>
</tr>
<tr>
<td>- 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>Cervicitis</td>
<td>Cervical cancer</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hepatitis B &amp; C virus</td>
<td>Hepatitis</td>
<td>HCC</td>
<td>10</td>
</tr>
<tr>
<td>Bacteria, GBS</td>
<td>Cholecystitis</td>
<td>Gall bladder cancer</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>Gram- uropathogens</td>
<td>Cystitis</td>
<td>Bladder cancer</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tobacco, genetics</td>
<td>Panreatitis</td>
<td>Pancreatic cancer</td>
<td>≤10%</td>
</tr>
<tr>
<td>GA, alcohol, tobacco</td>
<td>Esophagitis</td>
<td>Esophageal cancer</td>
<td>15</td>
</tr>
<tr>
<td>Asbestos fibers</td>
<td>Asbestosis</td>
<td>Mesothelioma</td>
<td>10–15</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Mononucleosis</td>
<td>Burkitt’s lymphoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gut pathogens</td>
<td>IBD</td>
<td>Colorectal cancer</td>
<td>1*</td>
</tr>
<tr>
<td>Ultraviolet light</td>
<td>Sunburn</td>
<td>Melanoma</td>
<td>≤9%</td>
</tr>
</tbody>
</table>

**Infections, STD**

GA, gastric acid; GBS, gall bladder stones; HCC, hepatocellular carcinoma; STD, sexually transmitted diseases; PIA, prostate inflammatory atrophy.

Hypothesis!

NF-κB activation is a major mediator of inflammation in most **chronic diseases** & inhibition of NF-κB can prevent/delay the onset of the **chronic disease**
NF-κB activation has been linked to most major diseases

Role of inflammation in tumorigenesis

- NF-κB
- DNA damage
- Oncogenes
- Bcl-xl
- Bcl-2
- Survivin
- C-FLIP
- cIAP-1
- cIAP-2
- XIAP
- Cyclin D1
- C-myc
- TNF
- IL-1
- IL-6
- COX2
- MMP-9
- uPA
- ICAM-1
- ELAM-1
- VCAM-1
- VEGF
- CXCR4
- TWIST

- Notch-1
- PPAR-γ
- STAT3
- β-catenin
- p53
- AP-1

- 10-20 Years
- 10 Years

Normal cell
- Transformation
- Survival
- Proliferation
- Invasion
- Angiogenesis
- Metastasis

Inflammation
Constitutive activation of NF-κB has been linked with most cancers

Carcinogens → NF-κB → Carcinogens

Tobacco-linked cancers:
- Esophageal cancer
- Laryngeal cancer
- Pharyngeal cancer
- Pancreatic cancer
- Renal carcinoma
- Colon cancer
- Head and neck SCC
- Lung cancer
- Bladder cancer

Viral cancers:
- Acute lymphoblastic leukemia
- Adult T cell leukemia
- Cervical cancer
- Nasopharyngeal carcinoma

UV light:
- Melanoma

Carcinogens linked to tobacco:
- Esophageal cancer
- Laryngeal cancer
- Pharyngeal cancer
- Pancreatic cancer
- Renal carcinoma

Shishodia and Aggarwal, *Biochemical Pharmacology*, 2004
Working Hypothesis

- Stress
- NF-kappaB
- Inflammation
- Cancer
How to suppress NF-κB activation safely!
To treat/prevent most chronic diseases, we need to “dial down” but not “turn off” of “multiple”, not “single” gene
FDA approved chemopreventive agents!

Tamoxifen
Raloxifene
Celebrex
Finesteride
Among 1,000 women, 19 would be expected to develop breast cancer over the next five years but if those women all took tamoxifen, however, 9 of those women would avoid breast cancer.

Tamoxifen is expected to cause 21 additional cases of endometrial cancer, a cancer of the uterine lining that is typically treatable when caught early.

An additional 21 would develop blood clots, 31 would develop cataracts and 12 would develop sexual problems.

More than half of the 1,000 women would naturally develop hormonal symptoms like hot flashes, changes in vaginal discharge or irregular periods, tamoxifen would cause those symptoms in about an additional 120 women.

Raloxifene, which has been shown to significantly reduce breast cancer risk but with fewer side effects. Although the data has not yet been published, she said the findings appeared to be similar.
Identification of inhibitors of NF-κB from natural sources
Drug Development

High Throughput Screen vs. Reverse Pharmacology
Traditional Knowledge
(Traditional Chinese Medicine
Ayurvedic Medicine
Egyptian Medicine
Kampo)

Modern Technology

Modern Knowledge
(Allopathic Medicine)

Ayurveda (Sushruta Samhita)

- Ayurveda means “science of long life”.

- This is an ancient medical system primarily practiced in India for over 6000 years.
From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer


Therapeutic Uses of Ayurvedic plants

- **Guggul**
  Commiphora mukul

- **Salai Guggul**
  Boswellia Serrata

- **Ashwagandha**
  Withania Somnifera

- **Amla**
  Emblica Officinalis

- **Grapes**
  Vitis Vinifera

- **Pipalli**
  Piper Longum

- **Bala**
  Sida cordifolia

- **Guduchi**
  Tinospora cardifolia

- **Hareetaki**
  Terminalia-chebula

- **Bhumiyamalaki**
  Phyllantus amarus

- **Shilajit**
  Asphaltum

- **Isabgol**
  Plantago Ovata

- **Punarnava**
  Spreading Hogweed

- **Basil**
  Ocimum sanctum

- **Vanshalochan**
  Bamboosa arundinacea

- **Dalchini**
  Cinnamomum zeylanicum
Therapeutic Uses of Ayurvedic plants

- **Jeevanti**: Leptadenia reticulata
- **Kachur**: Curcuma zedoary
- **Karkatakashringi**: Pistacia integerrima
- **Laghu Kantakari**: Solanum xanthocarpum
- **Mustaka**: Cyprus rotundus
- **Patala**: Sterospermum suaveolens
- **Kushta**: Saussurea lappa
- **Kokum**: Garcinia indica
- **Clove**: Syzygium aromaticum
- **Ashok**: Saraca indica
- **Yastimadhu**: Glycyrrhiza glabra
- **Saunf**: Foeniculum vulgare
- **Neem**: Azadirachta indica
- **Bakul**: Erythrina Indica
Identification of inhibitors of NF-κB from natural sources
Sloan School of Management at M.I.T. and the Harvard Business School has created *Pharmer’s* Market, however, we need a *Farmer’s* Market.

*New York Times, November, 2009*
Inhibitors of NF-κB from our lab
Spices can block NF-κB activation
Curcumin: Getting Back to Our Roots!
Structure of Curcumin
From turmeric (curry powder)

Diferuloylmethane

Turmeric in India

Pharmacological basis for the role of curcumin in chronic diseases: an age old spice with modern targets

Aggarwal BB & Sung B.

Curcumin

Chemopreventive skin, liver, colon, stomach

Diabetes

Cardiovascular diseases
Cholesterol, platelet aggregation, inhibition of smooth muscle cell proliferation

Alzheimer disease

Antioxidant

Nephrotoxicity

Chemotherapeutic
Chemopreventive Skin, liver, colon, stomach

Antiangiogenic

Antiflammatory

Arthritis

Lung fibrosis

Wound healing

HIV replication

Cardiotoxicity

Cataract formation

Gall-stones formation

Multiple sclerosis

Turmeric in India

Activation of transcription factor Nuclear Factor-kappa B is suppressed by curcumin

Singh S, and Aggarwal BB.

Curcumin Downregulates Expression of Cell Proliferation, Antiapoptotic and Metastatic Gene Products Through Suppression of \( \text{I} \kappa \text{B} \alpha \) Kinase and AKT Activation

Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB.

Molecular Pharmacology
[2006 Jan;69(1):195-206]
Curcumin & cancer
**Different stages of cancer progression and its suppression by curcumin**

**Constitutive activation of transcription factors**
- AP-1 & NF-κB
- Tumor Suppressor genes

**Overexpression of**
- Oncogenes
- HER2
- Growth factors (e.g., EGF, PDGF, FGF)
- Growth factor receptors
- Survival factors (e.g., Survivin, Bcl-2 and Bcl-xl)
- Cyclin D1
- Decoy receptor

**Overexpression of**
- Matrix metalloproteases
- Cyclooxygenase-2
- Adhesion molecules
- Chemokine
- TNF

**Transformation**
- Normal cells
- Tumor cells

**Proliferation**
- Tumor cells
- Tumor growth

**Invasion**
- Tumor growth
- Tumor Metastasis

*curcumin*

*From Aggarwal B et al, Anticancer Research 23, 2003, 363-398*
Curcumin in cell culture models!
Preclinical data with curcumin against various cancers

- Gynecologic cancers (Cervix, Ovary, Uterus)
- Thoracic/ H&N Cancers (Lung, Oral, Thymus)
- Gastrointestinal cancers (Esophagus, Intestine, Liver, Stomach, Pancreas, Colorectal)
- Hematological cancers (Leukemia, Lymphoma, Multiple myeloma)
- Bone cancer
- Melanoma
- Breast cancer
- Brain tumors
- Gynecologic cancers (Cervix, Ovary, Uterus)

Both curcumin and piperine inhibited mammosphere formation, serial passaging, and percent of ALDH+ cells by 50% at 5 uM and completely at 10 muM concentration in normal and malignant breast cells.

There was no effect on cellular differentiation.

Wnt signaling was inhibited by both curcumin and piperine by 50% at 5 uM and completely at 10 uM.

Curcumin and piperine separately, and in combination, inhibit breast stem cell self-renewal but do not cause toxicity to differentiated cells.
Curcumin in animal models!
## Cancer prevention by curcumin in animals

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Carcinogen</th>
<th>Animal</th>
<th>Dose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal cancers:</strong></td>
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<tr>
<td>ACF</td>
<td>AOM</td>
<td>Rat</td>
<td>2000 ppm</td>
<td>Rao et al, 1993</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Mice</td>
<td>0.5 to 0.2 % w/w</td>
<td>Huang et al, 1994</td>
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<td>Colon cancer</td>
<td>DMH</td>
<td>Mice</td>
<td>0.5%</td>
<td>Kim et al, 1998</td>
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<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>2000 ppm</td>
<td>Rao et al, 1995</td>
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<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>0.2 or 0.6% w/w</td>
<td>Kawamori et al, 1999</td>
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<tr>
<td>Colon cancer</td>
<td>PhIP</td>
<td>Apc mice</td>
<td>2000 ppm</td>
<td>Collett et al, 2001</td>
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<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>1 or 2% w/w</td>
<td>Pereira et al, 1996</td>
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<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>0.6% w/w</td>
<td>Kwon et al, 2004</td>
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<tr>
<td>Colon cancer</td>
<td>DMH</td>
<td>Rat</td>
<td>0.6%</td>
<td>Shiptz B, 2006</td>
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<tr>
<td>Colitis</td>
<td>TNBS</td>
<td>Mice</td>
<td>0.5-5%, diet</td>
<td>Sugimoto K, 2002</td>
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<td>Colitis</td>
<td>DNB</td>
<td>Mice</td>
<td>0.25%; diet</td>
<td>Salh B, 2003</td>
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<tr>
<td>Colitis</td>
<td>TNBS</td>
<td>Mice</td>
<td>50mg/kg</td>
<td>Ukil A, 2003</td>
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<tr>
<td>Ulcerative colitis</td>
<td>TNCB</td>
<td>Rat</td>
<td>30-60 mg/kg</td>
<td>Jung H, 2006</td>
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<tr>
<td>Ulcerative colitis</td>
<td>DNCB</td>
<td>Rat</td>
<td>25-100 mg/kg</td>
<td>Venkatarangana MV, 2007</td>
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<td>Duodenal tumor</td>
<td>MNNG</td>
<td>Mice</td>
<td>0.5 to 2.0% w/w</td>
<td>Huang et al, 1994</td>
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<tr>
<td>Esophageal cancer</td>
<td>NMBA</td>
<td>Rat</td>
<td>500 ppm</td>
<td>Usida et al, 2000</td>
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<tr>
<td>FAD*</td>
<td>AOM</td>
<td>Mice</td>
<td>2%</td>
<td>Huang et al, 1992</td>
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<tr>
<td>FAP*</td>
<td>---</td>
<td>Min/+ mice</td>
<td>0.1, 0.2 or 0.5% w/w</td>
<td>Perkins et al, 2002</td>
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<td>Forestomach neoplasia</td>
<td>B[a]P</td>
<td>Mice</td>
<td>2% w/w</td>
<td>Azuine et al, 1992</td>
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<tr>
<td>Forestomach tumor</td>
<td>B[a]P</td>
<td>Mouse</td>
<td>2% w/w</td>
<td>Singh et al, 1998</td>
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<td>Forestomach neoplasia</td>
<td>B[a]P</td>
<td>Mice</td>
<td>2% w/w</td>
<td>Nagabhushan et al, 1992</td>
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<tr>
<td>Stomach cancer</td>
<td>MNNG</td>
<td>Rat</td>
<td>0.05% w/w</td>
<td>Ikezaki et al, 2010</td>
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<td><strong>Liver cancers:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hepatic hyperplasia</td>
<td>DNM</td>
<td>Rat</td>
<td>200 or 600 mg/kg</td>
<td>Chuang et al, 2000</td>
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<td>DNM</td>
<td>Mice</td>
<td>0.2% w/w</td>
<td>Chuang et al, 2000</td>
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<td><strong>Lung cancers:</strong></td>
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<td></td>
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<td><strong>Blood cancers:</strong></td>
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<td>Lymphoma/leukemia</td>
<td>DMBA</td>
<td>Sencar mice</td>
<td>2% w/w</td>
<td>Huang et al, 1998</td>
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</table>

*Goel et al, Biochem. Pharm., 2007*
# Cancer prevention by curcumin in animals

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<td><strong>Breast cancers:</strong></td>
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<tr>
<td>Mammary tumor</td>
<td>DMBA</td>
<td>Rat</td>
<td>0.8 to 1.6% w/w</td>
<td>Pereira et al, 1996</td>
</tr>
<tr>
<td>Mammary tumor</td>
<td>DMBA</td>
<td>Rat</td>
<td>50 to 200 mg/kg</td>
<td>Singletary et al, 1996</td>
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<tr>
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<td>DMBA</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Deshpande et al, 1998</td>
</tr>
<tr>
<td>Mammary tumor</td>
<td>DMBA</td>
<td>Sencar mice</td>
<td>2% w/w</td>
<td>Huang et al, 1998</td>
</tr>
<tr>
<td>Mammary tumor</td>
<td>γ-radiation</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Inano et al, 1999</td>
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<td>Mammary tumor</td>
<td>γ-radiation</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Inano et al, 2002</td>
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<tr>
<td>Mammary tumor</td>
<td>DMBA</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Lin et al, 2001</td>
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<tr>
<td>Mammary tumor</td>
<td>DMBA</td>
<td>Sencar mice</td>
<td>2% w/w</td>
<td>Lin et al, 2001</td>
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<tr>
<td>Mammary tumor</td>
<td>γ-radiation</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Inano et al, 2002</td>
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<td><strong>Oral cancers:</strong></td>
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<tr>
<td>Oral cancer</td>
<td>MNA</td>
<td>Hamster</td>
<td>500 ppm</td>
<td>Azuine et al, 1992</td>
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<tr>
<td>Oral cancer</td>
<td>NQO</td>
<td>Rat</td>
<td>500 ppm</td>
<td>Tanaka et al, 1994</td>
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<td><strong>Prostate cancers:</strong></td>
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<td>Prostate cancer</td>
<td>DMAB &amp; Phen</td>
<td>Rat</td>
<td>15 to 500 ppm</td>
<td>Imaida et al, 2001</td>
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<td><strong>Skin cancers:</strong></td>
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<tr>
<td>Dermatitis</td>
<td>TPA + UV-A</td>
<td>Mice</td>
<td></td>
<td>Ishizaki et al, 1996</td>
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<tr>
<td>Skin tumor</td>
<td>TPA</td>
<td>Mice</td>
<td></td>
<td>Huang et al, 1988</td>
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<td>DMBA</td>
<td>Mice</td>
<td></td>
<td>Azuine et al, 1992</td>
</tr>
<tr>
<td>Skin tumors</td>
<td>TPA</td>
<td>Mice</td>
<td>10 &amp; 30 mmol</td>
<td>Lu et al, 1993</td>
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<td>Skin tumor</td>
<td>TPA</td>
<td>Mice</td>
<td></td>
<td>Huang et al, 1995</td>
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<tr>
<td>Skin tumor</td>
<td>TPA</td>
<td>Mice</td>
<td>1, 10, 100 or 3000 nmol</td>
<td>Huang et al, 1997</td>
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<td>Mice</td>
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<td></td>
<td>Soudamini, 1989</td>
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<td>DMBA</td>
<td>Mice</td>
<td></td>
<td>Nagabhushan et al, 1992</td>
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<td>Skin tumor</td>
<td>B[a]P and DMBA</td>
<td>Mice</td>
<td></td>
<td>Huang et al, 1992</td>
</tr>
<tr>
<td><strong>Other cancers:</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-organ cancer</td>
<td>DHPN, EHEN</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Takaba et al, 1997</td>
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</tbody>
</table>

## Treatment of cancer by curcumin in animals

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Route</th>
<th>Dose</th>
<th>Model</th>
<th>References</th>
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<tbody>
<tr>
<td>Ascites²</td>
<td>IP</td>
<td>50 mg/kg</td>
<td>Ascites</td>
<td>Kuttan et al, 1985</td>
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<tr>
<td>Ascites</td>
<td>IP</td>
<td>50 mg/kg</td>
<td>Ascites</td>
<td>Ruby et al, 1995</td>
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<tr>
<td>Breast¹</td>
<td>Diet</td>
<td>2% w/w</td>
<td>Orthotopic</td>
<td>Aggarwal et al, 2006</td>
</tr>
<tr>
<td>Breast¹</td>
<td>Diet</td>
<td>1% w/w</td>
<td>Orthotopic</td>
<td>Bachmeier et al, 2007</td>
</tr>
<tr>
<td>Colon²</td>
<td>IV</td>
<td>40 mg/kg</td>
<td>Orthotopic</td>
<td>Li et al, 2007</td>
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<tr>
<td>Gastric cancer</td>
<td>Oral</td>
<td>50-200 mg/kg</td>
<td>Xenograft</td>
<td>Cui et al, 2006</td>
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<tr>
<td>Glioblastoma</td>
<td>IT</td>
<td>10 mg/kg</td>
<td>Orthotopic</td>
<td>Aoki et al, 2007</td>
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<td>HCC³</td>
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<td>100-200 mg/kg</td>
<td>Orthotopic</td>
<td>Ohashi et al, 2003</td>
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<tr>
<td>Hepatoma</td>
<td>Oral</td>
<td>50-200 mg/kg</td>
<td>Xenograft</td>
<td>Cui et al, 2006</td>
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<tr>
<td>HNSCC</td>
<td>Sub cut</td>
<td>50-250µmol/L</td>
<td>Xenograft</td>
<td>LoTempio et al, 2005</td>
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<tr>
<td>Leukemia</td>
<td>Oral</td>
<td>50-200 mg/kg</td>
<td>Xenograft</td>
<td>Cui et al, 2006</td>
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<tr>
<td>Melanoma</td>
<td>IP</td>
<td>25 mg/kg</td>
<td>Xenograft</td>
<td>Odot et al, 2004</td>
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<td>Ovarian</td>
<td>IP</td>
<td>500 mg/kg</td>
<td>Orthotopic</td>
<td>Lin et al, 2007</td>
</tr>
<tr>
<td>Pancreas</td>
<td>IV</td>
<td>40 mg/kg</td>
<td>Xenograft</td>
<td>Li et al, 2005</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Gavage</td>
<td>1 gm/kg</td>
<td>Orthotopic</td>
<td>Kunnumakkara et al, 2007</td>
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<tr>
<td>Prostate</td>
<td>Diet</td>
<td>2% w/w</td>
<td>Xenograft</td>
<td>Dorai et al, 2001</td>
</tr>
<tr>
<td>Prostate</td>
<td>Gavage</td>
<td>5 mg/kg</td>
<td>Orthotopic</td>
<td>Hong et al, 2006</td>
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<tr>
<td>Prostate</td>
<td>Gavage</td>
<td>5 mg/day</td>
<td>Xenograft</td>
<td>Li et al, 2007</td>
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<tr>
<td>Colorectal cancer</td>
<td>Gavage</td>
<td>1 gm/kg</td>
<td>Orthotopic</td>
<td>Kunnumakkara et al, 2008</td>
</tr>
</tbody>
</table>

1. Lung metastases; 2. Liposomal curcumin; 3. Intrahepatic metastasis; IP, intraperitoneal; IT- intratumoral; IV- intravenous

Goel et al, Biochem. Pharm., 2007
Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of NF-κB-regulated gene products.

Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB.

Curcumin Suppresses the Paclitaxel-induced NF-κB Pathway in Breast Cancer Cells and Inhibits Lung Metastasis of Human Breast Cancer in Nude Mice


Clinical Cancer Research
Curcumin potentiates the effect of paclitaxel by suppressing the metastasis of the human breast cancer to the lung in mouse xenograft model.
Curcumin Inhibits RANKL-Induced NF-κB Activation in Osteoclast Precursors and Suppresses Osteoclastogenesis

A.C. Bharti, Y. Takada, and B. B. Aggarwal

Journal of Immunology;
172, 5940-5947, 2004
Medium RANKL + Curcumin (10 μM)

RANKL + Curcumin (5 μM)

RANKL + Curcumin (10 μM)

Bharti et al, JI, 2004
Curcumin

Molecular targets downregulated
- Bcl-xL
- Hsp-70
- DEF-40
- Cyclin D1
- ICAM-1
- VCAM-1
- ELAM-1
- IAP-1
- MDRP
- ER-α
- Fas R
- EPCR
- EGFR
- DR-5
- CXCR4
- AHR
- ITR
- AR
- TF
- NGF
- TGF-β1
- EGF
- VEGF
- uPA
- uPA
- Bcl-2
- Hsp-70
- p53
- AP-1
- CREB-BP
- Notch-1
- Nrf-2
- NF-κB
- EGR-1
- WT-1
- β-catenin
- STAT-1
- STAT-3
- STAT-4
- STAT-5
- PPAR-γ
- HIF-1
- ERE
- NF-κB

Molecular targets upregulated
- IL-1
- IL-2
- IL-5
- MCP
- MIP
- IL-6
- IL-8
- IL-12
- AATF-1
- ATPase
- COX-2
- 5-LOX
- Desaturase
- GCL
- GST
- iNOS
- MMP
- NQO-1
- ODC
- TMMP-3
- PhD
- AHR
- CXCR4
- EPCR
- ER-α
- Fas
- H2R
- HER-2
- IL-8 R
- ITR
- IR
- LDLR
- DR-5
- ELAM-1
- ICAM-1
- VCAM-1

Transcriptional factors
- AP-1
- CREB-BP
- Notch-1
- Nrf-2
- NF-κB
- EGR-1
- WT-1
- β-catenin
- STAT-1
- STAT-3
- STAT-4
- STAT-5
- PPAR-γ
- HIF-1
- ERE
- NF-κB

Inflammatory cytokines
- IL-1
- IL-2
- IL-5
- MCP
- MIP
- IL-6
- IL-8
- IL-12

Kinases
- FAK
- EGFR-K
- MAPK
- JNK
- JAK
- PAK
- PKA
- PKB
- PTK
- PTP
- Src-2
- DNA pol
- TMMP-3

Enzymes
- GCL
- GST
- iNOS
- COX-2
- 5-LOX
- ATPase
- Desaturase
- GCL

Growth factors
- HGF
- CTGF
- FGF
- NGF
- PDGF
- TGF-β1
- EGF
- VEGF

Receptors
- EPCR
- ER-α
- Fas R
- H2R
- HER-2
- IL-8 R
- ITR
- IR
- LDLR

Others
- NF-κB
- uPA
- uPA
- Bcl-2
- Hsp-70
- p53
- AP-1
- CREB-BP
- Notch-1
- Nrf-2
- NF-κB
- EGR-1
- WT-1
- β-catenin
- STAT-1
- STAT-3
- STAT-4
- STAT-5
- PPAR-γ
- HIF-1
- ERE
- NF-κB

Anand et al, CL, 2008
Kunnumakkara et al, CL, 2008
Curcumin Targets

Multi-targeted

Inflammatory cytokines
IL-1, IL-2, IL-5, IL-6, IL-8, IL-12, IL-8, MCP-1, MIP-1, MaIP

Enzymes
ATFase, ATPase, Desaturase, FPTase, GST, GCL, HO-1, iNOS, MMPs, NQO-1, ODC, PhPD, TIMP-3, 5-LOX, Telomerase

Growth factors
TGF β, FGF, HGF, PDGF, TF

Receptors
AR, AHR, CXCR4, DR, EGFR, ER-α, FasR, H2R, IL-8R, ITPR, IR, LD-R

Adhesion molecules
ELAM-1, ICAM-1, VCAM-1

Anti-apototic proteins
Bcl-2, BclxL, IAP-1

Protein Kinases
IKK, AAPK, Ca2+ PK, EGFR, ERK, FAK, IL-1 RAK, JAK, JNK, MAPK, Phk, PK, PKA, PKB, PKC, pp60c-src tk, PTK

Transcriptional factors
AP-1, β-Catenin, CBP, ERG-1, ERE, HIF-1, Notch-1, Nrf-2, NF-κB, PPAR-γ, STAT-1, STAT-3, STAT-4, STAT-5, WTG-1

Others
Cyclin D1, Cyclin E, HsP 70, MDR

Mono-targeted

COX-2
Celecoxib

EGFR
Erbitux

TNF
Remicade, Humira, Enbrel

HER-2
Herceptin

Bcr-Abl
Gleevec

VEGF
Avastin

Tubulin
Paclitaxel

Topoisomerase
Camptothecin

Kunnumakkara et al, CL, 2008
Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo

Anand P, Nair HB, Sung B., Kunnumakkara AB, Yadav VR., Tekmal RR and Aggarwal BB; Biochemical Pharmacology, 2009
Curcumin at MD Anderson

Bharat B. Aggarwal, Ph.D.
Bokyung Sung,
Vivek R. Yadav,
KB Harikumar,
Simone P. Reuter,
MK Pandey,
Byoungduck Park,
AB Kunnunakkara
P Anand,

Razelle Kurzrock, M.D.
L. Li
DR Siwak
FS Braiteh
B. Ahmed
M. Sun
Coombes KR
Harris DH
Dhillon R
Angelo LS
Newman RA
Mach CM
Mathew L
Mosley SA
Smith JA

Anil Sood, M.D.
Lin YG
Kamat AA
Merritt WM
Gershenson DM
Spannuth WA

Ashish Kamat, M.D.
Tharakan ST
Inamoto T

Burton Dickey, M.D.
Moghaddam SJ
Barta P
Mirabolfathinejad SG
Ammar-Aouchiche Z
Garza NT
Vo TT
Evans CM
Tuvim MJ

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Madeline Duvic
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X. Zhang
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H Kadara
DJ Yoon
JW Shay

John Mendelsohn, M.D.
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Gamsa hamnida!
Namaste! Merci! Thank you! Terima Kasih! Kiitos! Gracias! Shalom! Arigato! Shei-shei! Do Jeh! Danke!