

Breast Cancer and Curcumin

Breast cancer doesn't typically become a deadly disease until it metastasizes. Tumors that remain confined to the breast tissue can usually be treated with relative ease by surgery, radiation, and/or anticancer drugs. But once cancer cells metastasize, or spread, to other parts of the body—forming satellite tumors in places like the lymph nodes, bones, liver, lungs, and brain—tracking down and destroying every errant malignant cell may be near impossible ... and the chances of survival worsen considerably. No known pharmaceutical drug effectively prevents breast cancer metastasis. However, new research from the M.D. Anderson Cancer Center at the University of Texas in Houston suggests that consuming adequate amounts of the common spice curcumin may halt the spread of breast cancer in its tracks.¹

Curcumin is the primary ingredient in turmeric (*Curcuma longa*), the spice that gives curry its trademark yellow color and unique flavor. Turmeric has been used for millennia all over South Asia, not just for flavoring foods but also for its medicinal properties. Perhaps not coincidentally, epidemiologic data also suggest a relatively low rate of colon cancer and other serious chronic diseases in South Asian countries.²

The new findings on breast cancer metastasis come from a study in mice with breast tumors that were allowed to grow to about 10 mm in diameter (about the size of a pea) before being surgically removed. Most such tumors will have metastasized by the time of the surgery. The mice were then started on a standard diet (control), or one of three experimental diets that included either 1) powdered curcumin; 2) Taxol[®] (paclitaxel), a common breast cancer chemotherapy drug; or 3) curcumin + Taxol. Although Taxol (like other conventional chemotherapy agents) normally suppresses breast cancer growth in the short term, extended use can paradoxically increase the risk of metastasis.

Breast cancer in mice typically spreads to the lungs. As shown in Figure 1, the researchers later noted metastases visible to the naked eye in 96% of the mice on the control diet, while Taxol alone produced only a modest reduction in lung metastases. By contrast, in the mice treated with curcumin and especially curcumin + Taxol, the incidence and number of visible lung metastases was significantly reduced.

While it might be easy to dismiss this admittedly early finding as merely suggestive and not necessarily clinically important (Of course, clinical confirmation would certainly be extremely valuable!), many other studies, both in the laboratory and the clinic, have convincingly demonstrated that curcumin has important and wide-ranging anticancer benefits. For example, curcumin has been shown to suppress the growth of cancer of the colon and rectum,²⁻⁶ prostate,⁷⁻¹⁵ breast,^{1, 16-20} lung,²¹⁻²⁴ liver,^{25, 26} stomach,^{27, 28} bladder,²⁹ and ovary.³⁰ Thus, we have every reason to believe that these significant results, though reported only so far in mice, would likely translate to a comparable benefit in humans. ?

% of Mice with Breast Cancer Metastases to Lung

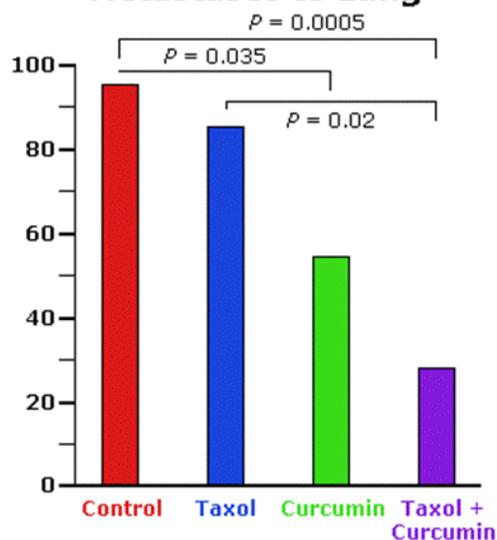


Figure 1. Curcumin, Taxol, and the combination of both inhibit breast cancer metastasis to the lungs in mice. Inhibition of metastasis was statistically significant for both curcumin and Taxol vs. control; inhibition of metastasis was also significantly greater for curcumin + Taxol vs. Taxol alone. Adapted from Aggarwal et al, 2005

Multidimensional Anticancer Activities

Unlike most conventional chemotherapy agents, including Taxol, curcumin's anticancer actions appear to be multidimensional. Curcumin has well known anti-inflammatory and antioxidant actions, both of which come into play when facing a cancer. Curcumin's inhibition of breast cancer metastasis in the new mouse study appears to rest on its ability to suppress a substance called nuclear factor kappa B (NF- κ B), which mediates cancer cell survival, proliferation, invasion, and metastasis: the higher the level of NF- κ B, the greater the risk of tumor growth and metastasis. Most chemotherapeutic agents, including Taxol, activate NF- κ B, which can actually make them procarcinogenic in the long run. On the other hand, curcumin suppresses NF- κ B activity.¹ In the animals treated with Taxol, curcumin also suppressed several procarcinogenic enzymes, which are increased by this chemotherapeutic agent: cyclo-oxygenase 2 (COX 2), an enzyme associated with inflammation and cancer cell proliferation; and matrix metalloproteinase-9, which is thought to facilitate metastasis. Curcumin also fights cancer by inhibiting cytochrome P450 activity and increasing levels of glutathione-S-transferase.²

In addition to suppressing these enzymes, other studies have demonstrated a wide variety of anticancer actions of curcumin. These include: Promotion of apoptosis. Apoptosis is a kind of cellular suicide that occurs normally in order to make way for new cells and also to remove cells whose DNA has been damaged to the

point at which cancerous change is liable to occur. Anything that suppresses apoptosis – like NF- κ B activity triggered by Taxol and other agents – can promote cancer growth and metastasis. By inducing apoptosis, curcumin prevents cancer growth and spread.^{8, 10, 16, 19, 23, 27, 31-33}

Potentiating the effects of other forms of chemotherapy. By blocking many of the procarcinogenic effects of conventional chemo- and radiation therapy, curcumin helps reduce some of the dose-limiting adverse effects of these agents, thus permitting higher doses to be used. This can result in a synergistic effect of the combination of curcumin and conventional chemotherapy. Combining curcumin and other natural therapies, such as the soy isoflavones genistein and daidzein, also appears to have synergistic effects.^{1, 6, 7, 13, 20}

Inhibiting angiogenesis. In order for tumors to thrive, blood vessels must grow to support them, a process called angiogenesis. Curcumin has been shown to inhibit angiogenesis, thus starving cancer cells of the vital nutrients they need to survive.^{10, 12, 34-36}

Inhibiting acquisition of "bone-like" properties. Prostate cancer has a propensity to spread to bone, thanks at least in part to the ability of malignant prostate cells to morph into bone-like cells. This osteomimetic ability, which allows these cells to thrive in the bony microenvironment, is blocked by curcumin.⁹

Disruption of cellular reproduction. At its basic level, cancer is a disease of cellular reproduction (mitosis). Studies indicate that curcumin interferes with mitosis and DNA expression in cancer cells in a variety of ways, thus arresting the proliferation of malignant cells.^{12, 17, 37}

How Much Curcumin Is Enough?

Although the vast majority of studies assessing the anticancer properties of curcumin have been done in vitro (test tube) or in vivo (lab animals), there is little doubt that most of these actions should work in humans as well. The question is, how much do you have to ingest to produce a clinical effect? Only a couple of trials have attempted to answer this question. In one study, patients with colorectal cancer ingested curcumin capsules containing from 450 mg to 3,600 mg (3.6 g) per day for 7 days.³ The results suggested that the 3.6-g dose produced levels in the colorectum that were considered high enough to provide a therapeutic effect.

In another well-controlled clinical trial,³⁸ patients with various high-risk premalignant lesions took curcumin for 3 months at daily doses ranging from 1 g to 12 g. Improvement in the lesions was noted in one of two patients with recently resected bladder cancer; two of seven patients with oral leukoplakia (a precancerous condition of the mouth commonly seen in long-time smokers); one of six patients with intestinal metaplasia of the stomach (a precancerous condition of the stomach lining); one of four patients with uterine cervical intraepithelial neoplasm, CIN, (a precancerous condition of the uterine cervix); and two of six patients with Bowen's disease (a form of skin cancer caused by exposure to arsenic compounds). Most important, there was absolutely no toxicity in these patients at doses up to 8 g per day. While the 12-g dose was also nontoxic, it was deemed unacceptable because the volume of curcumin was so large.

While the preliminary findings are extremely promising, clearly much more needs to be done before we have a really clear understanding of the value and optimal use of curcumin for treating or preventing cancer. Nevertheless, as noted earlier, people in South Asia, who safely consume large amounts of turmeric-containing curry dishes, have a low incidence of certain cancers (as well as Alzheimer's disease).

(Ivanhoe Newswire) ~ In a Danish Cancer Society analysis of more than 500,000 breast cancer patients, results show women with breast cancer have a 25-percent increase in the risk of developing another form of the disease.

The excess of cancer after a breast cancer diagnosis may be explained by treatment for breast cancer and by shared genetic or environmental risk factors. Researchers say there is a six-fold increase in the risk of cancer in connective tissue of the thorax and upper limbs. This could indicate radiation therapy is a factor in developing a second cancer in organs close to the breast. The study also shows an increased risk of myeloid leukemia, possibly brought about by chemotherapy treatment.

An increased risk of eudiometrical cancer could suggest the drug tamoxifen as a factor; however, researchers do not believe this is the case, because the increased risk exists within one year of breast cancer diagnosis ~ too soon to be a result of the drug. Further, the risk has existed since before 1975, when tamoxifen was rarely used.

Colorectal, kidney and postmenopausal breast cancer appear to share obesity as a risk factor, while ovarian cancer and breast cancer seem to have a genetic predisposition in common. The study shows an excess of ovarian cancer within one year of breast cancer diagnosis, along with an increased risk of breast cancer after ovarian cancer.

The overall impression from this very large study is that a breast cancer diagnosis has an effect on subsequent cancer risk in general. The authors say the known effects of treatment and common risk factors do not seem to fully explain the excess of cancer sites.

SOURCE: International Journal of Cancer, 2005;118:0001-0008

Breast Cancer Prevention through Lifestyle

(Ivanhoe Newswire) ~ A new study confirms what doctors and dieticians have long said ~ exercise and a healthy weight can significantly improve your life and even reduce the early onset of cancer. In the study, physicians from the University of Washington in Seattle report cancer can be prevented in women with genes that put them at the greatest risk.

Women who carry the genes BRCA1 or BRCA2 have a lifetime risk of breast cancer of more than 80 percent. They also have an increased risk for ovarian cancer. The new study findings indicate even among this group of women, exercise and a healthy weight as an adolescent led to delayed onset of cancer.

According to researchers, women with the BRCA1 or BRCA2 mutation have a 20 percent chance of developing breast cancer by age 40, a 55 percent chance by age 60, and more than 80 percent by the time they reach 80. The authors of this study say women who exercised during their teenage years were more likely to develop cancer later in life than women who did not exercise. The same was true for weight. If women were average weight during their teenage years, they delayed the onset of cancer.

More than 1,000 women with invasive breast cancer were enrolled in the study. It is believed to be the first study to show exercise and weight control can influence the onset of cancer in women who are predisposed to cancer. Only about 100 of the 1,000 women had the mutated BRCA1 and BRCA2 genes.

Interestingly, the authors point out some of those women had no family history of breast or ovarian cancer because the genes were passed through the father. Therefore, they stress that women should get to know their family's medical history in great detail from both the mother's and the father's side of the family.

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SOURCE: Science, 2003;302:643-645

1. Aggarwal BB, Shishodia S, Takada Y, et al. Curcumin suppresses the paclitaxel-induced nuclear factor- κ B pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. *Clin Cancer Res.* 2005;11:7490-7498.
2. Chauhan DP. Chemotherapeutic potential of curcumin for colorectal cancer. *Curr Pharm Des.* 2002;8:1695-1706.
3. Garcea G, Berry DP, Jones DJ, et al. Consumption of the putative chemopreventive agent curcumin by cancer patients: Assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. *Cancer Epidemiol Biomarkers Prev.* 2005;14:120-125.
4. Kawamori T, Lubet R, Steele VE, et al. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. *Cancer Res.* 1999;59:597-601.
5. Kim KH, Park HY, Nam JH, et al. [the inhibitory effect of curcumin on the growth of human colon cancer cells (HT-29, WiDr) in vitro]. *Korean J Gastroenterol.* 2005;45:277-284.
6. Narayan S. Curcumin, a multi-functional chemopreventive agent, blocks growth of colon cancer cells by targeting beta-catenin-mediated transactivation and cell-cell adhesion pathways. *J Mol Histol.* 2004;35:301-307.
7. Chendil D, Ranga RS, Meigooni D, Sathishkumar S, Ahmed MM. Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. *Oncogene.* 2004;23:1599-1607.
8. Deeb D, Jiang H, Gao X, et al. Curcumin sensitizes prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L by inhibiting nuclear factor- κ B through suppression of IkappaBalpha phosphorylation. *Mol Cancer Ther.* 2004;3:803-812.
9. Dorai T, Gehani N, Katz A. Therapeutic potential of curcumin in human prostate cancer. II. Curcumin inhibits tyrosine kinase activity of epidermal growth factor receptor and depletes the protein. *Mol Urol.* 2000;4:1-6.
10. Dorai T, Cao YC, Dorai B, Buttyan R, Katz AE. Therapeutic potential of curcumin in human prostate cancer. III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. *Prostate.* 2001;47:293-303.
11. Dorai T, Dutcher JP, Dempster DW, Wiernik PH. Therapeutic potential of curcumin in prostate cancer V. Interference with the osteomimetic properties of hormone refractory C4-2B prostate cancer cells. *Prostate.* 2004;60:1-17.
12. Holy J. Curcumin inhibits cell motility and alters microfilament organization and function in prostate cancer cells. *Cell Motil Cytoskeleton.* 2004;58:253-268.
13. Hour TC, Chen J, Huang CY, Guan JY, Lu SH, Pu YS. Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing p21(WAF1/CIP1) and C/EBPbeta expressions and suppressing NF- κ B activation. *Prostate.* 2002;51:211-218.
14. Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P, Aggarwal BB. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. *Oncogene.* 2001;20:7597-7609.
15. Nakamura K, Yasunaga Y, Segawa T, et al. Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines. *Int J Oncol.* 2002;21:825-830.
16. Choudhuri T, Pal S, Aggarwal ML, Das T, Sa G. Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction. *FEBS Lett.* 2002;512:334-340.
17. Holy JM. Curcumin disrupts mitotic spindle structure and induces micronucleation in MCF-7 breast cancer cells. *Mutat Res.* 2002;518:71-84.
18. Ramachandran C, Fonseca HB, Jhabvala P, Escalon EA, Melnick SJ. Curcumin inhibits telomerase activity through human telomerase reverse transcriptase in MCF-7 breast cancer cell line. *Cancer Lett.* 2002;184:1-6.

19. Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, Orłowski RZ. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. *Cancer Res.* 2002;62:3868-3875.
20. Verma SP, Salamone E, Goldin B. Curcumin and genistein, plant natural products, show synergistic inhibitory effects on the growth of human breast cancer MCF-7 cells induced by estrogenic pesticides. *Biochem Biophys Res Commun.* 1997;233:692-696.
21. Chen YS, Ho CC, Cheng KC, et al. Curcumin inhibited the arylamines n-acetyltransferase activity, gene expression and DNA adduct formation in human lung cancer cells (A549). *Toxicol In Vitro.* 2003;17:323-333.
22. Chen HW, Yu SL, Chen JJ, et al. Anti-invasive gene expression profile of curcumin in lung adenocarcinoma based on a high throughput microarray analysis. *Mol Pharmacol.* 2004;65:99-110.
23. Radhakrishna Pillai G, Srivastava AS, Hassanein TI, Chauhan DP, Carrier E. Induction of apoptosis in human lung cancer cells by curcumin. *Cancer Lett.* 2004;208:163-170.
24. Zhang J, Qi H, Wu C. [research of anti-proliferation of curcumin on a549 human lung cancer cells and its mechanism]. *Zhong Yao Cai.* 2004;27:923-927.
25. Chuang SE, Cheng AL, Lin JK, Kuo ML. Inhibition by curcumin of diethylnitrosamine-induced hepatic hyperplasia, inflammation, cellular gene products and cell-cycle-related proteins in rats. *Food Chem Toxicol.* 2000;38:991-995.
26. Notarbartolo M, Poma P, Perri D, Dusonchet L, Cervello M, D'Alessandro N. Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in NF- κ B activation levels and in IAP gene expression. *Cancer Lett.* 2005;224:53-65.
27. Moragoda L, Jaszewski R, Majumdar AP. Curcumin induced modulation of cell cycle and apoptosis in gastric and colon cancer cells. *Anticancer Res.* 2001;21:873-878.
28. Swarnakar S, Ganguly K, Kundu P, Banerjee A, Maity P, Sharma AV. Curcumin regulates expression and activity of matrix metalloproteinases-9 and -2 during prevention and healing of indomethacin-induced gastric ulcer. *J Biol Chem.* 2004.
29. Sun M, Yang Y, Li H, et al. [the effect of curcumin on bladder cancer cell line EJ in vitro]. *Zhong Yao Cai.* 2004;27:848-850.
30. Zheng L, Tong Q, Wu C. Growth-inhibitory effects of curcumin on ovary cancer cells and its mechanisms. *J Huazhong Univ Sci Technolog Med Sci.* 2004;24:55-58.
31. Jiang MC, Yang-Yen HF, Yen JJ, Lin JK. Curcumin induces apoptosis in immortalized NIH 3T3 and malignant cancer cell lines. *Nutr Cancer.* 1996;26:111-120.
32. Karunakaran D, Rashmi R, Kumar TR. Induction of apoptosis by curcumin and its implications for cancer therapy. *Curr Cancer Drug Targets.* 2005;5:117-129.
33. Rashmi R, Santhosh Kumar TR, Karunakaran D. Human colon cancer cells differ in their sensitivity to curcumin-induced apoptosis and heat shock protects them by inhibiting the release of apoptosis-inducing factor and caspases. *FEBS Lett.* 2003;538:19-24.
34. Adams BK, Ferstl EM, Davis MC, et al. Synthesis and biological evaluation of novel curcumin analogs as anti-cancer and anti-angiogenesis agents. *Bioorg Med Chem.* 2004;12:3871-3883.
35. Gao C, Ding Z, Liang B, Chen N, Cheng D. [study on the effects of curcumin on angiogenesis]. *Zhong Yao Cai.* 2003;26:499-502.
36. Hahm ER, Gho YS, Park S, Park C, Kim KW, Yang CH. Synthetic curcumin analogs inhibit activator protein-1 transcription and tumor-induced angiogenesis. *Biochem Biophys Res Commun.* 2004;321:337-344.
37. Lin JK. Suppression of protein kinase c and nuclear oncogene expression as possible action mechanisms of cancer chemoprevention by curcumin. *Arch Pharm Res.* 2004;27:683-692.
38. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.* 2001;21:2895-2900.

Breast Cancer may Indicate More Cancer to Come