NATUROPATHIC TREATMENT OF OVARIAN CANCER

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ABSTRACT

This report describes a protocol, based on scientific research, for the treatment of ovarian cancer. Direct and indirect evidence has been compiled using diet alterations, nutritional supplements, quercetin, Hoxsey-like formula, paclitaxel in the form of Yew tree tea, and melatonin in the proposed protocol. Also included are 'red flags' for risks of ovarian cancer when doing a gynecological history: use of antidepressants, benzodiazepine tranquilizers, and antihistamines, Raynaud's phenomenon, tamoxifen, dermatomyositis, hair dyes, estrogen replacement therapy, ovulation induction medications and human papillomavirus.

RESEARCH REVIEW

BRIEF OVERVIEW OF OVARIAN CANCER

Due to the diversity of cell types in the ovary, about 50 different kinds of ovarian cancer can occur. There are 3 broad groups that categorize most tumors: tumors of the surface epithelium, germ cell tumors, and sex cord stromal tumors. The epithelial tumor, serous adenocarcinoma (also called serous cystadenocarcinoma) is the most common tumor. 80% of the cancers are in the outer epithelial lining of the ovary. (1,2)

In 1996 in the U.S., an estimated 14,500 women will die of ovarian cancer, producing more deaths than any other female reproductive system cancer. It is the second most common gynecological cancer with an overall 5 year survival rate of 37%. Half of the cases occur in women over 65. (3)

Diagnosis of ovarian cancer is difficult. The symptoms usually appear after the cancer has progressed and in some cases metastasized. (4) Signs and symptoms may include indigestion, abnormal vaginal bleeding, vague pelvic or abdominal discomfort, urinary frequency, abdominal swelling, or palpable abdominal mass. (5) There is no exact test to determine ovarian cancer. CA 125 SC (serum concentration) is elevated in 80-85% of patients with serous epithelial cancer and in a lower percentage in other ovarian cancers. CA 125 SC under 35U/ml and a lack of detectable color flow in the color-and-pulsed-Doppler can reliably exclude ovarian malignancy. (6,7)

Factors which appear to be protective against ovarian cancer are: pregnancy, early menopause, breast feeding, oral contraceptive use, and tubal ligation. (8,9) Factors which appear to increase the risk are: residence in North America or northern Europe, nulliparity, and having a mother or sister with ovarian cancer. Women with one first degree relative with ovarian cancer are presently the highest risk, about 9%, compared to a lifetime risk of 1.4% in women without an affected first degree relative. The three known hereditary syndromes, familial site-specific ovarian cancer syndrome, Lynch syndrome II, and breast-ovarian cancer syndrome, place a woman at exceedingly high risk for ovarian cancer if a family member has one of the hereditary syndromes. These women also have a high mortality rate. (10,11,12)

DIET ALTERATIONS

VEGETABLES AND SATURATED FATS

A study in Canada over a 3 year period was conducted on 631 confirmed malignant epithelial ovarian tumor patients and 564 randomly selected population control subjects. Average daily consumption of macro- and micro- nutrients was taken from the quantitative diet history information. It was

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concluded that for every 10 grams of saturated fat consumed per day, there was a 20% increased risk of ovarian cancer and for every 10 grams of vegetable fiber consumed per day, there was a 37% decrease in the risk. Egg consumption was also associated with an increased risk though this association is unclear. (13)

Milk

The Physicians Committee for Responsible Medicine stated that milk consumption may be linked to ovarian cancer. (14) According to Cramer et al. when the consumption of dairy products exceeds a finite amount of galactase, galactose collects in the blood and possibly affects the ovaries. Hence, women who have particularly low levels of galactase may have 3 times the risk of ovarian cancer if they consume dairy. Galactose is considered the problem, not milk fat, so non-fat dairy products cannot solve this problem. Also, the bacteria used to make yogurt and cottage cheese can produce galactose from lactose. (15)

Legumes

Over a 2 year period in Poland, analysis on 81 cases of confirmed epithelial ovarian cancer and 162 age-matched controls showed that frequent consumption of legumes was associated with a significant decrease risk of epithelial ovarian cancer. (16)

Nutritional Supplements

Eleven gynecologic tumor specimens were assayed to determine if any had high vitamin D receptor (VDR) levels. A high VDR level was demonstrated in 1 of 1 uterine sarcoma, and 3 of 6 ovarian tumors but did not appear in endometrial, cervical or Krukenberg tumors. A 3 day incubation of the ovarian carcinoma cell line NIH:OVCAR3 with 1,25 dihydroxyvitamin D3, (which possessed a high VDR level) resulted in 49% cell growth inhibition (note: 25-hydroxy-and 24,25-dihydroxy failed to effectively compete with 1,25-dihydroxy for the binding sites). (17) Saunders, Wappler et al. did another study demonstrating retinoic acid enhanced the effectiveness of 1,25 hydroxyvitamin D3 (calcitriol) against MCF-7 and NIH:OVCAR3 cells and calcitriol was also enhanced by the synergism of dexamethasone. (18) Due to the fact that ovarian cancer and mortality are more prevalent in northern than southern latitudes, an epidemiological study, from 1979-1988, was conducted in counties containing the 100 largest US cities. Considered were average annual sunlight energy and age-specific ovarian cancer mortality rates, with variables for ozone and sulphur dioxide. It was concluded that sunlight may be a protective factor for ovarian cancer mortality. (19) Retinoic acid was demonstrated to inhibit angiogenesis *in vitro*, collagen synthesis, and endothelial cell proliferation *in vitro*. It has also shown to induce both differentiation and apoptosis *in vitro*. (20)

Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) is an aglycone found in flavonoids, which are in a wide variety of vegetables like onion, asparagus, kale, brussels sprouts, bell pepper, apple, pear; spices like dill, tarragon; and plants including *Passiflora incarnata, Arctostaphylos uva-ursi, Hamamelis virginica,* and *Podophyllum peltatum.* (21) Quercetin has been shown to have an inhibitory effect on ovarian cancer cells. In OVCAR 5, quercetin inhibited 1-phosphatidylinositol 4-kinase activity by 80% and inositol 1,4,5-triphosphate (the second messenger) concentration by 65%, thus demonstrating the inhibition of the enhanced capacity for operation of signal transduction of ovarian carcinoma cells. (22) In OVCA 433 cells, quercetin displaced 1,25 1-transforming growth factor beta 1 (1,25 1-TGF beta 1) from binding to its receptor resulting in growth inhibition. (23) Type II estrogen binding sites (type II EBS) were detected in appreciable amounts in primary ovarian tumors. Quercetin competed with estradiol for type II EBS, exerting inhibition of cell proliferation. (24,25) This inhibitory mechanism of quercetin with type II EBS has been demonstrated not only in primary ovarian cancer but also in lymphoblastoid cells, breast cancer, and transitional cell carcinoma of the bladder containing type II EBS. (26,27,28)

Hoxsey-like Formula

The Hoxsey-like formula consists of *Trifolium pratense* (red clover), *Baptisia tinctoria* (wild indigo), *Arctium lappa* (burdock), *Berberis spp.* (Oregon grape), *Rhamnus purshiana* (cascara), *Rhamnus frangula* (buckthorn), *Phytolacca americana* (poke), *Stillingia sylvatica* (queen's root), *Xanthoxyllum clava herculis* (prickly ash), *Glycyrrhiza glabra* (licorice), and 3% WV potassium iodide.

Trifolium pratense (red clover) and *Baptisia tinctoria* (wild indigo) contain the isoflavones genistein, biochanin A and daidzein. (29) Research has shown genistein to induce apoptosis and inhibit mitosis *in vitro* in rat ovarian granulosa, human neuroblastoma cells, Jurkat T-leukemia, rat lymphoma, human gastric carcinoma, human myelogenous leukemia, human lymphocytic leukemia, human prostate cancer and ER-positive and ER-negative human breast cancer cell lines. Genistein and biochanin A inhibited ten human gastrointestinal cell lines. Genistein induced differentiation in 5 human melanoma cell lines, human medulloblastoma and neuroblastoma cell lines, mouse embryonal carcinoma cells, mouse leukemia cells, HL-60 and human erythroid K-562 clones. Daidzein inhibited differentiation in human leukemia HL-60 cells, B16 melanoma cells and HL-60 cells. (30)

Arctium lappa (burdock) contains several lignans, including arctigenin (31), which has potent cytotoxic effects against HL-60 human lymphocytic leukemia. The seed induced differentiation in mouse myeloid leukemia cell (32), and the root contained a tumor growth inhibiting mixture. (33) The root also contained water-soluble polysaccharides which exhibited chemotactic activity for granulocytic leukocytes and antitumor effects against solid sarcoma 37 tumor in CAFI mice. (34) A complex polymer found in burdock reduces the mutagenicity of direct and indirect mutagens. (35,36)

Berberis spp. (Oregon grape) contains berberine, an alkaloid, which has been shown to inhibit the respiration of ascites tumor by 15% (37) and *in vitro* was a potent macrophage activator for inducing cytostatic activity against tumor cells (38) and inhibited oxygen uptake by neoplastic cells. Berberine has shown to induce differentiation in human teratocarcinoma. (39)

Rhamnus purshiana (cascara) and *Rhamnus frangula* (buckthorn) both contain the anthraquinones, emodin and rhein (40), which possess cytotoxic mechanisms and inhibit protein synthesis in neoplastic cells due to decreasing cellular respiration rates and decreasing glycolysis. (41) In mice studies, the emodin in buckthorn showed significant inhibition of P-388 lymphocytic leukemia. (42)

Phytolacca americana (pokeweed) contains a series of lectins, Pa^{1} to Pa^{5}, which are mitogentic (43) for T-cells or for both T-cells and B-cells. (44) It also stimulates production of interleukin 1 and tumor necrosis factor. (45,46)

Stillingia sylvatica (queen's root) contains diterpene esters, including prostatin and gnidilatin which are irritants (47) that influence lymphatic and secretory functions. Stillingia was also shown to reduce growth of tumors in DBA mice with RC mammary carcinomas. (48)

Xanthoxyllum clava herculis (prickly ash) contains several alkaloids, including nitidine and gamma- and beta-fagarine. (49) Indenoisoquinoline analogue 9-of nitidine was found to possess significant anti cancer activity against P388 lymphocytic leukemia, L1210 lymphoid leukemia and B16 melanocarcinoma. (50) Wang et al. published results showing nitidine and fagaronine inhibited the topoisomerase I-mediated relaxation of supercoiled pSP64 plasmid DNA more effectively than the antitumor agent, camptothecin. (51)

Glycyrrhiza glabra (licorice) contains the triterpene glycyrrhizin, its aglycone glycyrrhetinic acid, phytosterols, flavonoids and isoflavoids among its many constituents. Russian researchers, Shvarev et al., concluded that licorice root inhibits the growth of sarcoma-45 and Ehrlich ascites cells. (52) Suzuki et al. reported licorice stimulates natural killer cell activity, inhibits suppressor T-lymphocyte activity, and induces interferon production. (53)

Potassium iodide is believed to encourage destructive metamorphosis and rapid elimination of morbific products and retard constructive metamorphosis. (54) It is readily eliminated through saliva, kidneys, and broncho-pulmonary glands. (55)

Although these cited studies pertain to cancers, the botanicals in the Hoxsey-like formula have many other properties that have a variety of biochemical effects on the body which appear to work synergistically with the anticancer factions. Red clover, licorice, Oregon grape, stillingia, burdock, cascara, prickly ash, and buckthorn detoxify and nurture, according to Mowrey. (56) Stillingia and licorice are "tonics" which affect multiple organ and glandular systems. (57) Cascara, stillingia, buckthorn, wild indigo (58), and licorice have laxative properties. Prickly ash, red clover, stillingia, licorice, Oregon grape, and burdock are alteratives and pokeweed is a lymphatic alterative. Other characteristics shared by some of the formula include thyroid stimulating, diuretic, estrogen inhibiting, anti-microbial, immune stimulating and diaphoretic. (59) Thus, collectively, the Hoxsey-like formula is anti-cancerous, detoxifying, eliminating, immune stimulating, anti-microbial, hormone regulating, and metabolism stimulating.

PACLITAXEL

The Pacific Yew Tree, *Taxus brevifolia*, grows in moist soils in Montana, Oregon, Washington, Alaska, California, Idaho, and British Columbia and is currently a threatened species. (60) Of the hundreds of compounds in the Pacific Yew, those that have been identified are diterpenes (taxanes), glycosides, flavonoids, lignans, benzenoids, and enzymes. (61) One of the diterpenes, paclitaxel, has been called the most promising anti-cancer agent to come along in years. (62)

Paclitaxel targets the rapidly dividing cancer cells and prevents them from replicating. It binds to the microtubules and inhibits their depolymerization into tubulin. Thus the break down of the mitotic spindle during mitosis is blocked and the cell can no longer divide into daughter cells. It also has the ability to polymerize tubulin in the absence of cofactors. (63,64) Milas et al. concluded there may also exist other mechanisms by which the anticancer activity of paclitaxel works. (65)

Leukemias, melanomas, and carcinomas of the lung, kidney, ovary, colon, central nervous system, (63) pancreas, and hepatocellular system (66) have proven to be sensitive to the action of paclitaxel. Paclitaxel is most effective against ovarian carcinomas and advanced breast carcinomas. (60,66,67,68)

MELATONIN

Kerenyi et al. hypothesized that the increase of cancer and cancer mortality, 50% of deaths in women 45-64 and 30% in men 45-64, may be due in part to an increase in light exposure, causing a reduction in melatonin production, and leading to the diminished non-specific oncostatic effects of the pineal. While sunlight in moderation is protective against a variety of cancers, the breakdown of the ozone layer has increased the number of hours of sunlight in a day, thus the cycle for melatonin production is altered and its tumoricidal effect compromised. (69)

Experimental pinealectomy induces a state of immunodepression which is reversed with administration of melatonin. Apparently the immunoenhancing action of melatonin is mediated by T-helper cell-derived opioid peptides, lymphokines, and perhaps by pituitary hormones. One of the main targets of melatonin is the thymus. (70) Moss discusses a German study of 25 patients with cervical, uterine and ovarian cancer, noting all patients showed a deficiency of thymus-mediated immunity. (71) Estrogen-responsive MCF-7 human breast cancer cells were exposed to melatonin (dose not given) for 4 days. The MCF-7 cells showed significantly smaller cell and nuclear sizes than the controls and estradiol-treated cells. Also the melatonin treated MCF-7 cells displayed mitochondrial swelling and disruption of cristae, nuclear chromatin disgregation, cytoplasmic vacuolation and cell lysis. It was concluded that melatonin had an antitumor effect through cell-cycle specific mechanism delaying mitosis of MCF-7 cells, although melatonin's antitumor effect was counteracted by the addition of estrogens.

Interestingly these effects by melatonin were counteracted by estradiol. (72) In a preliminary study, 14 metastatic solid tumor patients, who had no effective standard of antitumor therapy, were randomly placed in either a group receiving human tumor necrosis factor-alpha (TNF) or a group receiving a concomitant treatment with TNF and melatonin. TNF was given at a daily dose of 0.75 mg IV for 5 consecutive days. Melatonin was given orally at a daily dose of 40 mg, starting 7 days before TNF. It was noted the lymphocyte mean number was higher in the TNF and melatonin group than in the TNF group after treatment. Asthenia and hypotension were also less frequent in the TNF with melatonin group. (73)

Melatonin may inhibit cancer by augmentation of interleukin-2 (IL-2). In several studies, melatonin and IL-2 used concomitantly had a positive effect on 17 of 24 patients with a variety of advanced solid tumors, 14 of 20 patients with non-small cell lung cancer, 11 of 14 patients with

hepatocellular carcinoma, 9 of 14 patients with metastatic gastric cancer, 16 of 22 patients with progressing renal cell carcinoma, and 9 of 14 patients with advanced solid tumors, either by complete remission, partial remission, or stabilization. (74)

'Red Flags' in the Gynecological History

Use of Antidepressants, Benzodiazepine Tranquilizers and Antihistamines

A study done by Harlow and Cramer on women of the Boston, MA area, between November 1978 through September 1981, and July 1984 through September 1987, showed that a self-reported history of use of antidepressants or benzodiazepine tranquilizers, exceeding 1 to 6 months, whose first use was before age 50, increased the risk for ovarian cancer. (75)

The senior investigator and medical oncologist at the Manitoba Cancer Treatment and Research Foundation in Winnipeg, Lorne Brandes, conducted tests on rodents deliberately given cancer. He injected the rodents with human equivalent doses of Prozac® or Elavil® and sacrificed them after a few weeks. The induced tumors were 2 to 3 times heavier than tumors in the rodents who did not receive the antidepressant drugs. He also noted that low and medium sized human equivalent doses produced the heaviest tumors while high doses did not promote tumor growth. This work was published in the Cancer Research in July 1992. In the journal, Carcinogenesis, in September 1993, Japanese researchers published similar findings about Elavil® promoting colon cancer growth. German scientists published similar findings in the International Journal of Oncology in April 1994 about desipramine enhancing the growth of melanoma in rodents. In the Federation of American Societies for Experimental Biology in June 1994, Susan Wright, senior scientist with the Palo Alto Institute of Molecular Medicine, concluded that 10 suspected tumor promoters including Prozac® and Elavil® interfered with apoptosis, thus encouraging tumor growth by not letting the cancerous cells die.

Brandes also tested various antihistamines in the same manner as he tested antidepressants and got similar results. Doses of Claritin®, Hismanal® and Atarax® accelerated the growth of the tumors implanted in rodents. These findings were published in the Journal of National Cancer Institute in May 1994.

The common denominator of the antihistamines, Claritin®, Hismanal® and Atarax®, and the antidepressants, Prozac® and Elavil®, is the similarity of their molecular structure and that all had an effect on histamine. Frank LaBella, professor of pharmacology at the University of Manitoba, reported in the British Journal of Pharmacology in 1992 that inside the body's cells, histamine binds to an enzyme involved in cell growth mediation, cytochrome P450. LaBell and Brandes thought that some antihistamines and antidepressants bind to the cytochrome P450 instead of the histamines, upsetting the level of histamine influence on the cells. (76)

Raynaud's Phenomenon

Kohli and Bennett report a case of a 53 year old woman with a sudden onset of severe Raynaud's phenomenon as the presenting sign of ovarian adenocarcinoma. After removal of the adenocarcinoma and chemotherapy, the Raynaud's regressed. This is the second reported case. (77)

Tamoxifen

175 menopausal breast cancer patients treated with tamoxifen were studied from September 1989 to November 1994. Ten of the 175 (5.7%) had ovarian tumors. In 5 of these patients, the findings were bilateral. The authors conclude there are 2 possibilities: (1) regardless of tamoxifen treatment, breast cancer patients are more prone to develop ovarian tumors and (2) tamoxifen may stimulate growth of such tumors and may even cause them. (78) Tamoxifen additionally has a well-established side-effect of creating endometrial neoplasia.

Dermatomyositis

Four of 15 women with dermatomyositis were subsequently diagnosed with metastatic papillary serous ovarian carcinoma. Another patient developed metastatic pelvic papillary adenocarcinoma, believed to have begun in the ovary. All 5 of these women presented similarly with dermatomyositis. The 4 patients that survived the postoperative period showed either improvement or resolution of their dermatomyositis. It was concluded that women with dermatomyositis have an increased incidence of ovarian cancer, which is usually detected months to a few years after diagnosis of dermatomyositis. (79)

Hair Dyes

Between 1989-1991 in Athens, a study was conducted with 189 women with confirmed malignant epithelial tumors of the ovary compared to 200 controls. The data were collected through interviews. There was a statistically significant and a dose-dependent association between hair dying and risk of ovarian cancer. Women who dyed their hair at least 4 times a year had a relative risk of 1.75 and women who dyed their hair 5 times or more a year had a relative risk of 2.16 compared to women who did not dye their hair at all. (80)

Estrogen Replacement Therapy

Rodriguez et al. of Emory University did a 7 year follow-up study of 240,073 peri- and postmenopausal women, who had no prior history of cancer, hysterectomy, or ovarian surgery. 436 deaths occurred from ovarian cancer during the 7 years. Estrogen replacement therapy (ERT) was associated with a rate ratio for fatal ovarian cancer of 1.15. Duration of ERT prior to the study increased the mortality rate ratio to 1.40 with a 6-10 year use (a 40% increase in mortality) and to 1.71 with an 11 year or greater use (a 70% increase in mortality). (81)

Ovulation Induction Drugs

There are 2 groups of ovulation induction medications: 1) clomiphene citrate (Clomid® and Serophene®) which stimulates the pituitary gland to secrete LH and FSH. It is not a natural compound, and is a relative of tamoxifen and DES; and 2) naturally occurring, normal body compounds, human menopausal gonadotropins (Pergonal® and Metrodin®) and GnRH (Factrel® and LutrePulse®). GnRH, like clomiphene citrate, stimulates the pituitary gland to secrete LH and FSH. Human menopausal gonadotropins directly stimulate the ovary. In December of 1992, Whittmore et al. published a study which compared infertile women who had taken ovulation induction drugs to infertile women who had taken nothing. It was concluded that the women who had taken the drugs had a 2.7 times increased relative risk of developing ovarian cancer. Rossing et al. published a study on women who had attended an infertility clinic in

the Seattle area. It was noted that women who had used clomiphene citrate (Clomid® and Serophene®) were 3.1 times more likely to develop ovarian cancer than women who had not taken these drugs. This increased risk with clomiphene citrate was associated with 12 cycle usage. (82) Shushan et al. did a similar study and concluded that ovulation induction drugs, particularly human menopausal gonadotropin, may increase the risk of epithelial ovarian tumors. (83)

HUMAN PAPILLOMAVIRUS

Lai et al. tested benign and malignant ovarian and endometrial tissues for human papillomavirus (HPV). DNA of HPV types 16 and 18 were detected in both benign (50% ovarian, 70% endometrial) and malignant (27.2% in ovarian and 37.5% in endometrial) tissues. (84)

OVARIAN CANCER TREATMENT PROTOCOL:

(In composing this protocol, it is assumed the patient is following general guidelines to maximize cancer prevention: taking a good multivitamin/mineral supplement with antioxidants, exercising, meditating, avoiding tobacco, alcohol and sugar, and reducing environmental toxins.)

NUTRITION:

Eat fresh vegetables and fruits
Eat legumes
Avoid animal fats
Avoid dairy products

SUPPLEMENTS:[1]

Calcitriol
Vitamin A
Quercetin
Melatonin
Paclitaxel (Yew tree tea)[2]
Hoxsey-like formula

RED FLAGS IN GYNECOLOGICAL HISTORY:[3]

Use of antidepressants, especially Prozac and Elavil
Use of benzodiazepine tranquilizers
Use of antihistamines, especially Atarax, Claritin and Hismanal
Sudden onset of Raynaud's phenomenon
Tamoxifen
Dermatomyositis
Hair dyes
Estrogen replacement therapy
Ovulation induction medications
Human papillomavirus

FOOTNOTES

[1] Current research does not focus on clinically effective dosages for the treatment of ovarian cancer.

[2] Yew tree tea is used because it contains not only paclitaxel but also hundreds of compounds including diterpenes (taxanes), glycosides, flavonoids, lignans, benzenoids, and enzymes, many of which also exert anticancer properties.

[3] If several of these red flags are present, the physician should consider a recto-vaginal examination, CA 125, and color-and-pulsed-Doppler.

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