Dr Dale ‘Buck’ Hales has shown that a diet containing flaxseed can minimise or even prevent ovarian cancer in an unusual but apposite animal model. After successful work with laying hens, he is now seeking to trial the approach in women at high risk of developing the disease.

**Overcoming ovarian cancer**

Ovarian cancer is a complex disease, and making scientific advancements requires an extensive and continuing investment in laboratory research. What is the current state of the art research in this area?

There are no biomarkers identified for early-stage disease which can easily be developed into a wide-scale screen. Moreover, treatment options for late-stage disease have not changed appreciably for the last four decades.

**Could you outline the key objectives of your current investigation?**

Our aim is to determine which biologically-active components of flaxseed cause beneficial effects, and through what mechanisms they act. The three major ‘nutriceuticals’ in flaxseed are the lignan secoisolariciresinol diglucoside and the soluble fibre in the hull, and the omega-3 fatty acids in the germ. We hypothesise that lignan and omega-3 work synergistically against the disease via separate mechanisms. Lignan is a potent phytoestrogen which targets the negative effects of oestrogen and omega-3 decreases inflammatory prostaglandins.

What have you demonstrated regarding the effect of diet on ovarian cancer?

We have shown that diets enriched with flaxseed cause a substantial decrease in both the incidence and severity of ovarian cancer, which brings new hope for prevention, intervention and treatment with simple natural products.

Flaxseed is the richest vegetable source of omega-3 fatty acids, which are potent anti-inflammatoryatories. They target the prostaglandin pathways that contribute to inflammation. Omega-3 fatty acids work similarly to aspirin and other non-steroidal anti-inflammatory drugs by inhibiting cyclooxygenase activity. The omega-3s are also cardioprotective, increase lean body weight and promote wellbeing.

**Can you comment on the similarities between the common laying hen and humans regarding ovarian cancer?**

The hen is afflicted with ovarian cancer spontaneously and presents with many of the same features as the human disease, such as profuse ascites (fluid secreted by the cancer cells that accumulates in the abdomen); extensive peritoneal dissemination of metastases; heterogeneity – all of the known human subtypes of ovarian cancer are seen in hens with the disease; and each subtype, or histotype, has a remarkably similar microscopic appearance to a human subtype.

The disease arises when the hens are about two and a half years old, with an incidence of 4 per cent. By the time they are four or five years old, incidence is about 50 per cent. So the timeframe for the progression of the disease in hens is compressed relative to women; we can explore intervention and treatment options in real-time.

**Have your efforts to date resulted in any significant findings?**

Diets enriched with flaxseed fed to old hens for one year resulted in a significant shift from late-stage (highly aggressive, poor prognosis) to early-stage disease. In a long-term study, which is now published online (http://dx.doi.org/10.1016/j.jygyno.2013.05.018), we have shown that feeding hens flaxseed for their whole reproductive life, starting when they first start to lay, results in not only a suppression, but a significant reduction in the incidence of the disease. We are still analysing these data (from a five-year-long study!).

We have determined the first identifiable cellular change common to all stages of primary ovarian cancer. This molecular marker has significant potential for development as a diagnostic marker when suspect ovarian tissues are analysed.

**How might dietary recommendations be implemented for human ovarian cancer?**

One of our funding agencies, the American Institute for Cancer Research, is the foremost proponent of healthy diets as the best way to prevent cancer, and they are very interested in our work. They have helped us to translate our hen diets into human equivalents, determining that women should consume about 10 tablespoons of flaxseed per day to achieve the same dosing level of our hens. Flaxseed oil and lignan capsules are easy-to-consume supplements that can augment whole flax in the diet.

Do you aim to prove that similar outcomes achieved with hens can be reproduced with ovarian cancer in humans?

We should like to conduct pre-clinical trials with women at high risk of ovarian cancer. Women who have a familial risk – usually due to a mutation in the BRCA gene – who elect to have protective surgery (removal of ovaries and Fallopian tubes) will be recruited to participate in a flax trial while they await surgery. We have identified many ‘surrogate endpoints’ involved in cancer, such as prostaglandin and oestrogen pathways, which can be evaluated post-operatively in the patients. We will be able to determine if whole flax, flax oil, and purified flax lignan versus controls show beneficial results in the reduction of these endpoints.
Curbing cancer naturally

Trials at the Southern Illinois University School of Medicine have not only determined a histological marker of early-stage ovarian cancer, but also proved that a dietary intervention is effective in inhibiting the severity and incidence of the disease. The team is building on this success to offer key insights into all aspects of the disease known as the ‘silent killer’ because it is often asymptomatic in its early stages and therefore difficult to detect, ovarian cancer commonly arises in the epithelial cells on the surface of the ovary. If detected at an early stage, it is treatable, with a survival rate of about 95 per cent. However, because symptoms appear to arise from gastrointestinal problems such as bloating, loss of appetite and pelvic or abdominal pain, women may put off visiting a doctor. Diagnosis of cancer can then take further time, as initial diagnoses of cysts, irritable bowel syndrome or urinary tract infection are often made.

The risk of ovarian cancer is particularly pronounced in women over middle age and those with the inherited BRCA gene mutation. Presently, there is no simple screening method; it is usually only in late-stage disease that the symptoms prompt full investigation, by which time it is too late: the cancer will have spread and so prognosis is poor.

Dr Dale Buchanan ‘Buck’ Hales is Professor of Physiology and Gynaecology/Obstetrics, and Chair of the Physiology Department at the Southern Illinois University School of Medicine. Over the last decade, he has conducted trials of an unusual intervention for ovarian cancer: flaxseed.

FLAX AND OVARIAN CANCER

Hippocrates wrote that flax would relieve abdominal pain; centuries later, Charlemagne made its consumption mandatory for all of his subjects in order to preserve their health. Flax is now regarded as a superfood, being high in omega-3 fatty acids, B vitamins and antioxidants, including phytoestrogen lignans such as secoisolariciresinol diglucoside (SDG). Lignans are known to have antiviral and anti-cancer effects and are thought to protect against oestrogen-linked conditions, such as osteoporosis, and SDG is a highly effective antioxidant that takes up free radicals in the body and so protects against tissue damage.

Hales’ thesis is that repeated ovulation during a woman’s lifetime is essentially the trigger for ovarian cancer, since with every ovulation the ovary surface epithelium ruptures, and then undergoes rapid healing: “The inflammation of ovulation creates a pro-carcinogenic environment which can lead to the initiation of cancer in both the ovarian surface and the adjacent fimbriae of the Fallopian tubes,” Hales states.

Hales has been testing the effects of diet on laying hens, whose pattern and types of ovarian cancer mirror those of humans. Their progression to disease is more rapid than in humans, which allows Hales and his group to examine in the entire progression of disease from its early stages to late-stage metastatic disease.

Hales and his group are now analysing the results of a five year study of ovarian cancer in hens and the effects of a diet rich in flaxseed, administered from six months old, on the development of the disease.

TRIALS OF FLAXSEED

In an earlier project, Hales found that a diet constituted of 10 per cent flaxseed fed to hens for a year significantly reduced the severity of cancer. From this, the researchers determined that flaxseed reduced levels of a prostaglandin, PGE2, which signified that the progression of ovarian cancer was driven by inflammation: PGE2 is a potent hormone-like molecule that activates an inflammatory programme, usually in response to particular stimuli.

A subsequent longer term study with older hens found that the incidence of spontaneous ovarian cancer was not reduced, though the severity of the disease was lowered and the hens’ overall wellbeing improved. These hens would by then have ovulated about 400 times, so Hales reasoned that the damage had already been
INTELLIGENCE

THERAPEUTIC EFFICACY OF FLAXSEED IN THE TREATMENT OF OVARIAN CANCER

OBJECTIVES

To examine the individual contribution of flax derived omega-3 fatty acids versus phytoestrogen lignans to the chemopreventative and chemo-suppressive effects of whole flaxseed in ovarian cancer. The studies examine alterations in three classes of surrogate endpoints – inflammation (prostaglandin pathways); oestrogen metabolism and signalling; and oxidative stress pathways.

KEY COLLABORATORS

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FUNDING

National Institutes of Health – National Center for Complementary and Alternative Medicine – grant no. R01AT005295 (current) and R21 AT004085 (past)
National Institutes of Health – National Cancer Institute – grant no. R03CA162511 (current) and R03 CA139195 (past)
American Institute of Cancer Research (AICR)
Department of Defense, Ovarian Cancer Research Program

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The work not only offers great hope for the disease, but has also revealed important insights into the basic biology of ovarian cancer, against three classes of surrogate endpoints: prostaglandin pathways involved in inflammation, oestrogen metabolism and signalling, and oxidative stress pathways. The lab believes that the ability of flaxseed to prevent the development of cancer is due to anti-oestrogen effects, whereas its ability to suppress its progression is due to its anti-prostaglandin actions. Results suggest that existing ovarian cancer can likely be treated via flaxseed, and prevention may in fact result from the slowing down of indolent disease to the point that it never becomes detectable. Hales hopes to soon be able to validate the effects of flaxseed in diet with women at high risk of developing the disorder.

The researchers are now examining the specific contributions of the omega-3 and lignan constituents of flaxseed to its ability to inhibit the development of ovarian cancer against three classes of surrogate endpoints: prostaglandin pathways involved in inflammation, oestrogen metabolism and signalling, and oxidative stress pathways. The lab believes that the ability of flaxseed to prevent the development of cancer is due to anti-oestrogen effects, whereas its ability to suppress its progression is due to its anti-prostaglandin actions. Results suggest that existing ovarian cancer can likely be treated via flaxseed, and prevention may in fact result from the slowing down of indolent disease to the point that it never becomes detectable. Hales hopes to soon be able to validate the effects of flaxseed in diet with women at high risk of developing the disorder.

The results of the project will be presented at cancer and medical conferences this year. However, Hales feels that it is also important to convey the results to a wider audience: “Our work really speaks to the ovarian cancer survivor network and cancer advocacy groups. Women who are affected by the disease are encouraged by the hope our work offers,” he reflects.