Effects of flaxseed on breast cancer growth

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The use of flaxseed (linseed) to combat breast cancer has attracted increased attention since the preliminary results of a clinical study were presented in the San Antonio Breast Cancer Symposium in December 2000. One of the most often quoted implications of the study was that the anti-tumour effect of flaxseed muffin may be comparable to that of tamoxifen. However, flaxseed also contains secoisolariciresinol diglycoside (SDG), which is converted by the gut bacteria into the oestrogenic lignans, enterodiol and enterolactone. Given that other plant-derived oestrogenic substances (phyto-oestrogens) can stimulate breast cancer growth under certain circusmtances, there are concerns regarding the safety of flaxseed. The following review will look at the existing data to help clarify some of these issues. ***J Oncol Pharm Practice (2004) 10: 145–147.***

Key words: breast cancer; complementary therapies; estrogens; flax; lignans; patient education

INTRODUCTION

The use of flaxseed (linseed) to combat breast cancer has attracted increased attention since the preliminary results of a clinical study were presented in the San Antonio Breast Cancer Symposium in December 2000.[1] One of the most often quoted implications of the study was that the anti-tumour effect of flaxseed muffin may be comparable to that of tamoxifen. However, flaxseed also contains secoisolariciresinol diglycoside (SDG), which is converted by the gut bacteria into the oestrogenic lignans, enterodiol and enterolactone.[2] Given that other plant-derived oestrogenic substances (phyto-oestrogens) can stimulate breast cancer growth under certain circusmtances,[3] there are concerns regarding the safety of flaxseed.[4] The following review will look at the existing data to help clarify some of these issues.

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PRECLINICAL DATA

In vitro

The effects of enterodiol and enterolactone on oestrogen-dependent (ER+)[5–9] and oestrogen-independent (ER−) breast cancer cells[8,10] have been studied.[5–9] Enterodiol was not associated with significant effects on the growth of ER+ cells.[5–9] In contrast, enterolactone 1–10 μmol/L was generally associated with increased DNA synthesis[9] and proliferation[5–8] of ER+ cells. Enterolactone was also associated with antagonism of tamoxifen-induced inhibition of DNA synthesis.[9] However, low concentrations (~1–10 μmol/L) of enterolactone and enterodiol were also found to inhibit the metastatic processes (adhesion, invasion, migration) of ER− cells.[10] Enterolactone at higher concentrations (~50–100 μmol/L) generally inhibited proliferation of both ER+[6–8] and ER− cells.[11]

Animal studies

The effects of flaxseed were studied in 102 female rats with chemically induced breast tumours,[11] which are generally considered to be ER+.[12] Compared to basal diet, additional intake of flaxseed or flaxseed oil (but not secoisolariciresinol diglycoside (SDG)) was associated with significant reduction

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in tumour volume after seven weeks ($P < 0.04$). The effects of flaxseed were also studied in 44 female nude mice with ER − human breast cancer xenograft. Compared to basal diet, additional intake of ground flaxseed was associated with lower tumour growth after 6 weeks ($P < 0.05$)[13] and 15 weeks ($P < 0.05$).[14] Flaxseed was also associated with significant reduction in metastases ($P < 0.05$) and cell proliferation ($P < 0.05$).[14]

CLINICAL DATA

The only relevant human study on flaxseed is that presented at the San Antonio Breast Cancer Symposium.[1] In that trial, 29 postmenopausal women with newly diagnosed breast cancer were randomized to a daily placebo muffin or a muffin containing 25 g of flaxseed. Cancer cell proliferation was compared between tissues obtained at baseline and after a median of 28 days of treatment.

Amongst the women who took flaxseed muffins, cell proliferation was significantly lower after treatment ($P < 0.05$). The investigators stated that this reduction was '...not [observed] in the placebo group' and '..., was comparable to those seen with tamoxifen using similar study protocol.'

As this study was presented as an abstract, there were limited details on the methods and results. For example, concurrent therapies and ER status were not reported. More importantly, the authors did not report the actual data from the placebo group or the difference in tumour cell inhibition between the placebo and the flaxseed groups.

INTERPRETATION

Although *in vitro* data suggest that flaxseed lignans may stimulate breast cancer growth,[5–9] animal studies generally showed that dietary intake of flaxseed and flaxseed oil was associated with inhibition of breast cancer progression.[11,13,14] Similarly, preliminary results from the only clinical trial also showed favourable effects with flaxseed.[1]

Several important issues emerge from these data. For example, *in vitro* data suggest the effects of flaxseed lignans on breast cancer growth may be concentration dependent: stimulation at lower concentrations (< 10 μmol/L)[5–9] but inhibition at higher concentrations (50–100 μmol/L).[6–8] Currently, there are limited data on the correlation between the amount of flaxseed intake and the serum lignans level. However, enterolactone level in healthy women has been reported to be as low as 0.02 μmol/L.[15]

These seemingly contradictory effects of flaxseed lignans on breast cancer may be partly explained by different mechanisms involved. For example, increased tumour growth *in vitro* may be related to oestrogenic stimulation, as it was associated with enhanced ER activity,[5] reversed by tamoxifen,[6,9] and partially enhanced by coadministration of estradiol.[7,9] In contrast, tumour inhibition *in vitro* may be due to nonoestrogenic mechanisms, as it was common with ER − cells[10,11] and not reversed by tamoxifen.[10] Similarly, tumour inhibition in animal studies was observed in both ER + [11] and ER − [13,14] breast cancers. This hypothesis is further supported by the fact that tumour inhibition by flaxseed oil was associated with negligible increase in oestrogenic lignans in the urine.[11]

The anti-tumour effects of flaxseed from animal[11–14] and human data[1] need to be interpreted with careful consideration. For example, the gut microflora are needed to convert flaxseed into the oestrogenic lignans. This means that lignan levels in humans may be very different from those in animals due to interspecies difference. The implication that flaxseed may have similar anti-tumour effects on breast cancer as tamoxifen[1] means that it may have similar potential in reducing the efficacy of cytotoxic chemotherapy.[16]

CONCLUSION

Breast cancer patients should be aware that the putative beneficial anti-cancer effects of flaxseed are based on limited human and animal data, and may potentially interfere with their conventional cancer treatments. These effects also need to be balanced against *in vitro* data which suggest that some flaxseed components may stimulate oestrogen-dependent breast tumour growth. However, this is not to say that regular intake of flaxseed as part of normal diet should be avoided. The interaction of the various components of flaxseed, when taken as whole food, on the kinetics and dynamics of phytoestrogens on breast tumour growth is largely unknown. Given the marginal nature of both clinical benefit and harm, it is reasonable to expect patients and health professionals may decide to avoid or continue taking flaxseed, provided that it is made clear that such a decision is based on marginal, conflicting evidence.

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