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Wheat Bran and Breast Cancer : Plausibility of the Estrogen Hypothesis

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To examine the evidence that wheat bran is protective against breast cancer development and that its main mechanism of action is by modulating estrogen metabolism. This review explores the role of different experimental factors on the anticancer effects of wheat bran and the relationship of changes to estrogen metabolism by wheat bran on breast cancer risk. The timing of the experimental diets in relation to carcinogen administration, the length of feeding of the experimental diets, and the level of dietary fat had an impact on the effectiveness of different doses of wheat bran in reducing breast carcinogenesis. Wheat bran supplementation resulted in significant reductions in human plasma estrogen levels but not in that of animals tested. The change in excretory metabolism of estrogen by wheat bran feeding in animals was not related to any of the tumor indices measured. The protective effect of wheat bran in breast carcinogenesis is greatest at the promotional phase and when supplemented in a high fat diet. Doses of wheat bran in the 9-12% range in diet have been consistently protective. The inconsistency observed with higher doses of wheat bran may be dependent on the animal model used. Although wheat bran's inhibitory effects on tumor growth may involve changes to estrogen metabolism, the fiber and phytochemical components of wheat bran may also act through estrogen-independent mechanisms. For a better understanding of the effect of wheat bran on breast carcinogenesis, studies comparing the effects of different wheat bran components both alone and in combination need to be performed.

Key words : Breast cancer, dietary fiber, estrogen, lignans, phytic acid, wheat bran.

INTRODUCTION

Breast cancer is one of the most common forms of cancer in the world, representing approximately 7% of total cancer mortality.[1-3] Breast cancer incidence has been on the rise in many developing countries in South America, the Caribbean, Western Asia, and North Africa.

However, Asian and Latin American countries typically have the lowest breast cancer incidence and mortality rates worldwide,[4,5] but there are trends for increasing breast cancer incidence over time in Asian countries.[6] These variations may be partly due to differences in dietary fiber intake.

Although international comparisons have found an inverse correlation between age-adjusted mortality rates for breast cancer and cereal intake, a marker of dietary fiber consumption,[7] the role of dietary fiber in reducing breast cancer risk is not clear. Several case-control studies have suggested that consuming a diet high in dietary fiber and low in fat is protective against breast cancer development.[8-13] However, results in prospective cohort trials have been inconsistent, with protective[14] or equivocal[15-18] effects of dietary fiber on breast cancer risk. The role of dietary fiber in chronic disease in general may be complicated by the lack of a consensus on the definition of dietary fiber and consequently appropriate methodology for its measurement in foods.[19] More importantly, different fibers not only vary in their physiological effects,[20] but also contain various levels of phytochemicals with anticarcinogenic properties,[21,22] thus contributing to the inconsistency observed in the literature.

Dietary fiber consumption is thought to reduce breast cancer risk by interrupting the enterohepatic circulation of estrogen and hence lowering plasma levels.[23] Reductions in serum estrogen levels have been observed with high fiber diets in controlled metabolic studies.[24-26] The major risk factors for breast cancer - early menarche, late menopause, late first pregnancy, and nulliparity - appear to be related to the life-time exposure of less mature breast tissue to the growth-promoting effects of estrogen.[27-29] Epidemiological studies have found that women

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at high risk of breast cancer have higher circulating estrogen levels compared to women at low risk of the disease.[30-32] However, evidence from case-control studies examining the role of estrogen in increasing breast cancer risk has not been conclusive.[27,33] Nevertheless, a recent prospective cohort study of over 14,200 women found that those who eventually developed breast cancer had higher levels of estrone, total estradiol (the most potent form of estrogen), and free estradiol (the biologically available fraction).[34]

Of the various fiber sources tested, wheat bran appears to have the most consistent protective effect against colon carcinogenesis,[35] and studies in animals suggest that this is also true for mammary (breast) cancer development.[36-39] Although modulation of estrogen metabolism has been proposed as a potential mechanism of wheat bran,[40,41] evidence of this in animal models of cancer has not been supportive.[38,42] Wheat bran, in addition to having high levels of insoluble fiber, also contains phytic acid and lignans.[21]

These phytochemicals have been shown to inhibit both breast and colon cancer growth *in vitro* and *in vivo*.[43,44]

In this review, we will examine studies investigating the relationship between wheat bran and breast cancer risk. The plausibility of the "estrogen hypothesis" as a mechanism for the protective effects of wheat bran will be discussed and other potential mechanisms of action explored.

Inhibitory effects of wheat bran on mammary carcinogenesis

Studies examining the effect of wheat bran on mammary tumor development to date have been done only in murine models. In general, wheat bran significantly reduces mammary tumor formation and growth in rats and mice.[36-39] Only one study has found no effect on mammary tumorigenesis with wheat bran supplementation.[45]

The inhibitory effects of wheat bran appear to be enhanced with the addition of the soluble fiber psyllium, with maximum protection occurring with equal levels (4% in diet each) of both fibers.[42]

Despite these generally positive results with wheat bran, the dose at which wheat bran is protective has not been consistent. Cohen *et al.*[38] found that although doses of 9-12% in diet were inhibitory on mammary tumor development, supplementation with 15-18% wheat bran had no effect. In contrast, high doses (23.75-40% in diet) of wheat bran were found to be inhibitory in two other studies.[36,39] In addition, Zile and colleagues[39] found that intermediate doses of wheat bran (11.5% in diet) had similar inhibitory effects on mammary carcinogenesis as higher doses (22% or 40% in diet).

The dose-related inconsistencies in animal studies with wheat bran may be partly attributable to differences in experimental design. The strain of rat, type and dose of carcinogen used, and source of dietary fat may have affected the results. However, other differences in design, described below, would have had a much stronger influence on the outcome.

First, introduction of the experimental diets in relation to carcinogen administration varied between studies. Both Arts *et al*[36] and Vucenik *et al*[45] started feeding of the experimental diets 2-3 weeks prior to carcinogen administration and were therefore testing the effect of wheat bran on the initiation stage of carcinogenesis. In contrast, the studies by Cohen and colleagues[37,38] and Zile *et al*[39] began experimental treatments 2-3 days after giving the carcinogen dose, testing the effect of wheat bran on tumor promotion. More tumor parameters were significantly reduced when wheat bran was fed during the promotional stage of carcinogenesis.

Second, studies examining the effectiveness of different wheat bran doses were carried out for different lengths of time. In rats, the experiment by Cohen *et al*[38] was terminated at 25 weeks after carcinogen administration whereas that of Zile *et al*[39] ended in half that time at 13 weeks after the carcinogen dose. In the Cohen study, tumor incidence in the 15% and 18% wheat bran groups began to rise and separate from the 9% and 12% wheat bran groups at about 120 days (or 16-17 weeks) after injection with *N*-methyl-*N*-nitrosourea (MNU).[38] This suggests that higher doses of wheat bran may be equally protective at first but then may become increasingly ineffective with time. Nevertheless, high doses of wheat bran (22%) were found to be protective in the spontaneous and transplantable tumor models in the mouse after 10 months of feeding.[39] Thus, wheat bran may have different levels of effectiveness in different models of tumorigenesis.

Finally, the level of fat used in the diet may affect the relative anticancer effects of wheat bran. Cohen *et al*[37] tested the influence of dietary fat on the effectiveness of wheat bran by feeding MNU-treated rats high or low fat diets alone or supplemented with 10% soft white wheat bran. Although wheat bran supplementation to the high fat diet significantly reduced various tumor indices, no further inhibition in tumor development was observed with the addition of wheat bran to a low fat diet.[37] Thus, the protective effect of the low fat diet on mammary carcinogenesis was not enhanced by the addition of wheat bran. The low fat diet (5% by wt) used by Vucenik *et al*[45] may have contributed to the non-significant results found with wheat bran supplementation in their study.

The source of the wheat bran fiber used in animal carcinogenesis studies also appears to play a role in the anticancer effects observed. In the studies by Zile and colleagues,[39] different sources of wheat bran ("Minne-

sota" vs. "Michigan") were examined in both rat and mouse models of mammary tumorigenesis. Although these two wheat bran sources had similar effects in the rat models, Minnesota wheat bran, but not Michigan wheat bran, inhibited spontaneous tumor formation in mice. The opposite effect was observed in the mouse transplantable tumor model, with Michigan wheat bran having the protective effect.[39] The levels of wheat bran (22% in diet) and dietary fiber (9.6%) used were identical. The disparity in results may be due to variability in phytochemical levels, a phenomenon observed with different varieties of soybean[46] and flaxseed.[47] For example, amount of the phytochemical phytic acid found in wheat bran can vary from 3-6%.[48] In addition, wheat bran and its associated components may have different mechanisms of action in different animal models of carcinogenesis which may be dose-dependent.

Effects of wheat bran on estrogen metabolism

Human trials with wheat bran suggest that it may be protective against breast cancer development by reducing circulating estrogen levels, and hence the amount of estrogen which may potentially interact with breast tissue. Dietary supplementation of wheat bran for two months (average daily fiber intake = 30 g/day) significantly reduced serum estrogen levels in premenopausal women.[40] Consumption of either oat or corn bran had no effect on serum estrogen levels in this study. A later study by the same group found overall reductions of 10-20% in serum estrogen levels after one or two months of wheat bran supplementation at 10 or 20 g/day.[41] A reduction in serum estradiol of 17% has been suggested to decrease breast cancer risk by 4-5 fold in American women,[49] indicating that the results of Rose and colleagues[41] may be biologically significant in reducing risk. Nevertheless, because total and not free serum estrogen levels were measured, it is unknown whether significant reductions in estrogen bioavailability occurred. Only unbound estrogen, which represents 1-2% of plasma levels, is biologically available to tissues.[27]

Wheat bran may reduce serum estrogen levels in humans by directly binding estrogen. *In vitro* binding studies indicate that the determining factor for the estrogen binding capacity of a fiber is its insoluble fiber content, particularly the lignin component.[50,51] Of the total dietary fiber content of wheat bran, 98% is insoluble fiber and 3.5% of this value is lignin.[50] Wheat bran was shown to have a greater affinity for binding estrogen than corn bran, but not oat bran, in one study.[50] This was attributed to the relatively high content of lignin (3.1%) found in oat bran. In contrast, Shultz and Howie[51] showed that wheat, oat, and corn bran have similar binding capacities for estrogen *in vitro*. This suggests that the lower serum estrogen levels found with wheat bran, but not corn or oat bran, consumption in the study by Rose and colleagues[40] was not only due to the estrogen binding ability of the dietary fiber.

Another mechanism whereby wheat bran may reduce serum estrogen levels is by inhibiting the action of the enzyme beta-glucuronidase. In the liver, estrogen is conjugated with glucuronide and a large proportion of the estrogen metabolites is excreted into the intestine via the bile. Estrogen must be acted upon by beta-glucuronidase to remove the glucuronide moiety in order to be reabsorbed, and thus undergo enterohepatic circulation.[52] Wheat bran appears to have a greater inhibitory effect than either corn or oat bran on the activity of fecal beta-glucuronidase.[53] With reduced beta-glucuronidase activity, the amount of estrogen that would be deconjugated for reabsorption from the intestinal lumen would be decreased, resulting in increased fecal estrogen excretion and potentially lower blood estrogen levels. Interestingly, estrogens conjugated with glucuronide have less capacity for binding to dietary fiber,[51,54] suggesting that the estrogen binding capacity of a fiber is dependent on its ability to inhibit beta-glucuronidase.

The role of estrogen in mammary tumor development in the wheat bran studies on animals is questionable. In contrast to humans, wheat bran does not appear affect circulating estrogen levels in rats. Many different studies in rats have found no significant reduction in plasma or serum levels of estrogen after wheat bran supplementation.[36,42,55,56] Because all studies but one[56] controlled for the stage of estrous cycle, inconsistency in blood sampling does not appear to play a role in wheat bran's ineffectiveness on serum estrogen levels in rats. Although Cohen *et al*[38] found an overall reduction in serum estradiol levels after comparing all doses of wheat bran to all doses of cellulose, these reductions were not correlated with either the dose of wheat bran or the tumor yields. Furthermore, Zile *et al*[39] found that feeding 22% wheat bran (9.6% dietary fiber) to ovariectomized rats treated with carcinogen still resulted in significant reductions in tumor number, multiplicity, and incidence, suggesting that wheat bran may be acting through an estrogen-independent mechanism. This mechanism may involve the action of phytochemicals present in wheat bran, which is discussed below. Although wheat bran fiber has been shown to directly bind carcinogens *in vitro*,[57] this is not a likely mechanism in the animal studies where wheat bran is fed 2-3 days after carcinogen administration.

Another estrogen-independent mechanism of wheat bran fiber may involve the inhibition of the promoting effect of the high fat diet. In all but one of the animal studies on wheat bran, corn oil, which is high in the n-6 polyunsaturated fatty acid linoleic acid, was used as the fat source. High levels of linoleic acid has been shown

to promote on mammary tumor growth in animals and *in vitro* and is believed to be due to increased synthesis of the biologically active eicosanoids such as prostaglandin E2 and leukotriene B4.[58] Because wheat bran fiber is one of the most effective fiber sources in decreasing transit time,[59,60] wheat bran supplementation would increase the excretion of fat and thus inhibit the absorption and subsequent metabolism of linoleic acid. Increased 24 h fecal lipid levels, particularly triglycerides, have been found in rats fed 10% soft white wheat bran.[56]

Despite its ineffectiveness on circulating estrogen levels in rats, wheat bran supplementation does appear to alter fecal and urinary estrogen levels. Decreased urinary and/or increased fecal estrogen levels are observed with wheat bran supplementation[36,38,42,56] and therefore indicate a reduction in the enterohepatic circulation of estrogens. Enhanced fecal estrogen excretion may be due to the decreased intestinal transit time and increased fecal bulking of the insoluble fiber component of wheat bran.[20] Results from the Cohen study using wheat bran and psyllium[42] suggest that insoluble fiber sources (wheat bran) are more effective in increasing fecal estrogen excretion whereas soluble fiber sources (psyllium) have a greater ability to reduce beta-glucuronidase activity. Nevertheless, there is evidence that wheat bran can decrease beta-glucuronidase activity in rats[36] as has been observed in humans.[53]

Anticarcinogenic activity of phytochemicals present in wheat bran

In addition to fiber, wheat bran is a moderate source of the mammalian lignans enterodiol and enterolactone and contains high levels of inositol hexaphosphate, commonly referred to as phytic acid. Both of these phytochemicals have been shown to independently inhibit breast cancer growth in a variety of *in vitro* and animal model systems.[43,44,61]

Mammalian lignans are formed from colonic bacterial action on plant lignan precursors present in foods.[62] Wheat bran feeding to rats results in urinary lignan levels of 8 ug/g.[63] Therefore, using the estimate of 15 g as typical daily food consumption in the rat, supplementation of the highest dose of wheat bran used in animal studies (about 40%) can potentially result in lignan concentrations of 0.16 mM in the blood. Mammalian lignan concentrations in this range have been shown to compete with estradiol for binding to the rat uterine type II estrogen receptor *in vitro*.[55] However, inhibitory effects of lignans on mammary tumor growth in animals or *in vitro* have been observed with concentrations of at least three times this value.[64-68] Nevertheless, wheat bran is not the only source of fiber or lignans in human trials, and potential synergistic effects between wheat bran and dietary lignans on reducing breast cancer risk have not been explored.

Of the various phytochemicals present in wheat bran, phytic acid probably plays a large role in the anticarcinogenic effects observed. Phytic acid is a potent antioxidant[69] and its level in wheat bran is relatively high, varying from 3-6%.[48] Because phytic acid exists as a highly charged molecule in the gut, it has strong binding properties which may play a role in its anticancer effects.[43] When added to the drinking water or diets of carcinogen-treated rats, phytic acid alone has been shown to decrease proliferation and nuclear aberrations of mammary epithelial cells[70] and to inhibit mammary tumor formation and growth.[71,72] Phytic acid has also inhibited the growth and induced the differentiation of human breast cancer cells *in vitro* independent of their estrogen status,[73] suggesting that this may be a mechanism for the estrogen-independent effect observed for wheat bran by Zile *et al.*[39] Nevertheless, like wheat bran, phytic acid has been shown to reduce beta-glucuronidase activity in carcinogen-treated rats,[74] which suggests that phytic acid may also interfere with the enterohepatic circulation of estrogens. Thus, the greater inhibitory effect of wheat bran on fecal beta-glucuronidase activity compared to corn or oat bran[53] may be related to its higher phytic acid content. In addition to antioxidant activity, phytic acid appears to have an immunomodulatory effect by enhancing the activity of natural killer cells.[75]

Because phytic acid is fed as a purified compound in these studies on breast carcinogenesis, it is not known if the phytic acid present in wheat bran would exhibit the same effect. Wheat bran contains endogenous phytases which, if not deactivated by heat or processing, can hydrolyze phytic acid in the intestinal tract.[76] Although the effect of dephytinized wheat bran on mammary tumor development has not been examined to date, hydrolysis products of phytic acid have exhibited antineoplastic activity both in rats and *in vitro*.[43] The role of phytic acid in the effect of wheat bran on breast carcinogenesis would be clarified by comparing the effects of untreated wheat bran with that of dephytinized wheat bran and purified phytic acid, alone and in combination, on breast carcinogenesis.

SUMMARY

Wheat bran has an overall protective effect in mammary carcinogenesis and appears to be the dietary fiber source ingredient that shows the most consistent efficacy. Although a dose of 9-12% in diet seems to be the most efficacious, the optimal dose for the anticarcinogenic effect of wheat bran remains to be determined. Variations in the timing of the experimental diets in relation to carcinogen administration, in the length of feeding of the

experimental diets, and in the level of dietary fat used in animal studies have confounding effects. Nevertheless, wheat bran appears to be most protective at the promotional phase of carcinogenesis and when supplemented to a high fat (i.e. high risk) diet. Higher doses of wheat bran (more than 15% in diet) appear to have more variable effects, which may be dependent on the animal model being used.

Both the insoluble fiber and phytochemical components of wheat bran are postulated to play a role in its inhibitory effect on breast carcinogenesis. The insoluble fiber may modulate estrogen metabolism through direct estrogen binding and inhibition of beta-glucuronidase action, the latter of which shown to be influenced by phytic acid. Human trials indicate that wheat bran lowers total serum estrogen levels; however, the effect of wheat bran on free estrogen levels and hence bioavailability is unknown. Although animal studies indicate that wheat bran feeding changes the excretory metabolism of estrogen, these changes were not related to measured tumor indices. Thus, the anticancer effect of wheat bran may involve estrogen-independent mechanisms such as reduced absorption of fat by its fiber component, which would reduce the formation of the tumor promoting eicosanoids derived from linoleic acid, or the antioxidant, immunomodulatory, and strong binding properties of its phytic acid component. For a better understanding of the effect of wheat bran on breast carcinogenesis, studies comparing the effects of different wheat bran components both alone and in combination need to be performed.

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