Invited Review

Can rye intake decrease risk of human breast cancer?

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Abstract

Background: Rye contains more fibre and bioactive compounds than other cereals used for bread production. The fibre and compounds of the fibre complex could provide protection against breast cancer (BC).
Objective: To review the evidence and theoretical background for a role of rye and some of its components in the prevention of BC.
Design: A short review based to a great extent on the work by scientists in the Nordic countries.
Results: Some of the possible mechanisms by which the fibre complex could reduce BC risk are presented. The fibre through its effect on fermentation increases esterification of bile acids reducing toxicity of the free bile acids and is involved in the production of butyrate with potential anticancer effects including BC. The fibre reduces the enterohepatic circulation of the oestrogens leading to lower plasma oestrogen concentrations. The fibre complex contains bioactive compounds such as lignans and alkylresorcinols that are antioxidative and potentially anticarcinogenic. In addition, vitamins, minerals, and phytic acid in rye may provide protection against BC.
Conclusion: Rye products made from wholegrain rye flour are likely to contribute to reduced BC risk.

Keywords: *wholegrain*; *lignans*; *fibre*; *oestrogens*; *alkylresorcinols*

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Many risk factors for breast cancer (BC) have been identified, one of the more important being diet. However, it has been difficult to identify dietary components involved and mechanisms of action. The results are still controversial. In this short review the possible BC preventive role of wholegrain rye products, commonly consumed in all Nordic countries and the Baltic countries, Poland and Russia, will be discussed.

Wholegrain and breast cancer (BC)

In 1984 we proposed that a fibre-rich food containing lignan precursors like wholegrain rye and wheat bread could protect against both breast and colon cancer (1). Epidemiological studies have supported that wholegrain intake may protect against breast and colorectal cancer as well as diabetes, obesity, and cardiovascular disease (CVD) (2).

Searching literature for 'wholegrain and breast cancer' from Pub Med revealed 39 references, but few of them relate to wholegrain rye intake. However, in some pig experiments rye products were separately fed to pigs and the differences of metabolic effects between wheat and rye could be studied (3, 4).

Two studies throw some light on the problem of comparing intake of wholegrain products by dietary records and assay of plasma enterolactone (ENL), a metabolite of lignans. It was found in a very large prospective study comprising 978 cases of BC that there is no association between wholegrain intake and BC risk (5). In this study food frequency forms were used. However, in an earlier study by the same group, measuring ENL in plasma, a clear tendency towards a lower risk for BC with higher ENL concentration was found, particularly for BC with the genotype Erα (6). Because 40–50% of ENL is formed from lignans in wholegrain products (7), these two results are contradictory. In the study by Chatenoud et al. (8), wholegrain intake was associated with lower cancer risk for all cancers except thyroid cancer.

Mediterranean diet including wholegrain products also seems protective (9). However, in a large study in USA, both refined and unrefined grain intake were unrelated to BC risk (10). Two reviews by Slavin (11, 12) try to explain the mechanisms of the wholegrain effect but nothing

seem to explain the discrepancies between results. In this short review with emphasis on rye and BC, some possible mechanisms of protective wholegrain effects will be discussed.

Oestrogens important risk factors for breast cancer (BC) and role of fibre intake in oestrogen metabolism

Oestradiol, the main female sex hormone is produced almost exclusively in the ovaries in premenopausal women, but in postmenopausal women the oestrogens derive from conversion of male sex hormones (androgens) by aromatisation in various tissues like fat and muscle tissue. Abundance of fat tissue as in obese subjects leads to increased production of oestrogens, mainly oestrone, the oxidation product and primary metabolite of oestradiol. Oestrone can be converted back to oestradiol but the main metabolic pathways lead to 2-hydroxylated cathecol oestrogens and 16α-hydroxyoestrone and oestriol. The 2- and 4-hydroxylated catechol oestrogens and 16α-hydroxyoestrone have been regarded as carcinogens, but the opinions are very controversial. Oestrogens stimulate BC cell growth of oestrogen receptor positive BCs and are regarded as a risk factor for this disease (13). Fibre can reduce oestrogen activity by binding and/or fermentation (see below).

Because oestrogens participate in the so-called enterohepatic circulation (14), diet, particularly fat and fibre, influence significantly oestrogen disposition and level in the body. The mechanism is as follows: the liver takes up the oestrogens produced in the body and 50% is excreted in the bile in the conjugated form coupled mainly to glucuronic acid and to a small extent to sulphate (15). The glucuronic acid and the sulphate groups are removed by hydrolysis in the colon. The free oestrogens are then absorbed but immediately re-conjugated with glucuronic acid in the mucosal cells lining the colon and transported to the liver in the portal vein. A small part enters the portal vein in the free form. Some oestrogens are passing through the liver to the blood (hepatic vein) and some again into the bile. The whole circulation takes about 6 h (14).

Because of increasing faecal volumes, a fibre-rich diet dilutes the content of the intestine reducing concentrations of enzymes responsible for the hydrolysis of the oestrogen conjugates. Since the oestrogens cannot be reabsorbed from the intestine in the conjugated form, the fibre reduces oestrogen plasma levels. Fat intake increases absorption of oestrogens in the colon and a high fat/low fibre diet leads to high oestrogen levels in the urine and blood, and low concentration in the stools (16–18). Women consuming a low fibre diet usually also consume a high fat diet increasing in this way the oestrogen levels and BC risk.

Rye bread and other rye foods, compared to other cereal products, are particularly rich in fibre and certain phytochemicals like lignans (19) and alkylresorcinols (ARs) (20). Rye contains about 15–17% fibre of its dry matter, of which 3–4% or 20% of total fibre is soluble fibre and the main part is insoluble fibre. Cellulose and lignin are important components of the insoluble fibre. The soluble fibre is mainly arabinoxylans and β-glucans. By consuming at least 150–200 g/day of wholegrain rye bread and other rye products (see also http://rye.vtt.fi/) we obtain a considerable part of the daily recommended intake of vitamins such as vitamin E, thiamin, riboflavin, niacin, and folate as well as the minerals like zinc, iron, manganese and magnesium, and some selenium. The aleurone layer of the kernel contains the main part of these compounds.

Health effect of rye intake may be related to its fibre content but also to various bioactive compounds in the 'fibre complex', such as lignans, ARs, phytic acid, and other phenolic compounds. From the point of view of BC prevention lignans have got much attention in recent years.

Lignans

The mammalian lignans (nowadays called enterolignans), ENL and enterodiol (END), are intestinal bacterial metabolites of plant lignans. Rye has the highest concentration of lignans compared to other cereals used for bread dough production. The enterolignans are included in the group of phyto-oestrogens because they are weakly oestrogenic (21) as demonstrated *in vivo* in the mouse, and also seem to stimulate production of sex hormone-binding globulin (SHBG) (22). An increase in SHBG results in more oestradiol being bound to this protein reducing the biological activity of oestradiol. Furthermore, the conversion of androgens to oestrogens in fat and muscle tissue (called aromatisation) is inhibited by phyto-oestrogens (23), including lignans.

The lignans were first detected in the urine of human subjects and monkeys (24–26). ENL occurs in nanomolar to micromolar concentrations in body fluids and in lower amounts in tissues. Unchanged plant lignans have also been found and measured in urine (27). The lignans have numerous biological effects and plants containing lignans have been used extensively in popular medicine. The precursors in plants are considered antirheumatic, anti-inflammatory, antiallergic, antihypertensive, and syringaresinol (SYR), particularly abundant in rye, enhances endurance in rats (28, 29).

High concentrations of lignans occur particularly in flax and sesame seed, and wholegrain cereals (Table 1 in Ref. (30)) but also in some vegetables and berries (19, 31). Vegetarians have the highest urinary excretion and plasma values of lignans (32). Two plant lignans and precursors of ENL, matairesinol (MAT), and secoisolariciresinol (SECO), have been known for more than 25 years (33, 34) and their occurrence in food has been studied (31, 35, 36). It has been well known for a long time that there must be other quantitatively more important precursors of

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enterolignans in cereals than SECO and MAT, and relatively recently this area of research has provided important new results (19, 30, 36, 37) showing that there exists many other precursors for the enterolignans. These precursors are pinoresinol (PIN), lariciresinol (LAR), medioresinol (MED), SYR, and 7-hydroxymatairesinol (HMR) in addition to SECO and MAT. When these compounds were incubated with human faecal flora ENL was produced (37). Also sesamin and lignin can serve as a precursor for ENL (38, 39).

Originally we suggested that ENL, the main enterolignan, is a good biomarker of wholegrain intake, particularly rye consumption. This was due to the large consumption of rye bread in Finland. However, later studies in other than Finnish populations with higher vegetable and fruit intake and low intake of wholegrain products showed that ENL did not correlate with wholegrain intake and sometimes not even with total fibre intake. This is due to the fact that, in addition to fruits and vegetables, also wine, tea, coffee, and fruit juice contain plant lignans (40). Furthermore, it was found that smoking and obesity (41) decrease plasma ENL and that antibiotics destroy the bacteria responsible for the formation of ENL in the colon (42). The effects of antibiotics on the colonic microflora may last up to 12–14 months and considerably reduces the formation of ENL and other metabolites. In Finland three studies dealing with BC and coronary heart disease (CHD) (43–45) show that when rye intake is significant and correlates with plasma ENL levels, the plasma ENL concentration is negatively associated with this disease.

Role of intestinal microflora and fermentation

Faecal bacteria have been identified converting plant lignan precursors to END and ENL (46, 47). This occurs in the upper part of the large intestine.

The effect of cereal fibre and fat on oestrogen metabolism (48, 49) is mediated by the intestinal microflora, particularly in the colon. In both rats and human subjects an increase in dietary fat decreases the urinary excretion of lignans despite identical grain fibre intake (40, 50). Obesity is negatively associated with plasma ENL in women (41). Thus, if high ENL lowers BC risk, the effect of fat intake may be an indirect one via reduction of the production of enterolignans. The intake of wholegrain rye stimulates the formation of butyrate, a short-chain fatty acid, in the gut. Simultaneously ENL production increases, but these are independent phenomena (51). Butyric acid has anticancer activity and may contribute to an anticancer effect of the cereal (rye) fibre complex. We may conclude that fat intake reduces ENL formation and fibre intake increases it, provided that the intestinal microflora is normal and not changed by intake of antibiotics.

Breast cancer (BC) studies in rodents fed flaxseed and pure lignans

Flaxseed contains very high amounts of secoisolariciresinol diglucoside (SDG), which is converted in the gut to END and ENL. Flaxseed and particularly the purified SDG seem to inhibit the growth of mammary tumours in experimental rat studies both in the initiation and promotional phase of the disease. Both tumour size and multiplicity were influenced. Also the oil component of flaxseed containing unsaturated fatty acids contributed to the effect. The results have been reviewed and discussed by Thompson (52, 53).

Some results in rodents suggest that flaxseed or purified lignans may have the same effect on the mammary gland as isoflavones from soy when administered prepubertally by enhancing differentiation of highly proliferative terminal end bud structures (53). As for isoflavones, intake of lignans before puberty may be beneficial, because the increase of differentiation observed in rats seems to reduce BC risk (54–57).

This is in agreement with the results of a recent Canadian human study in adolescent girls (58). More than 3,000 cases and the same number of controls were studied. High lignan or isoflavones, or total phyto-oestrogen intake during adolescence was highly protective, particularly for the lignans (trend significant, $p < 0.0001$). The odds ratio (OR) for the highest quartile of intake compared to the lowest was 0.74 for lignans and 0.81 for isoflavones. For total phyto-oestrogens it was 0.71 (trend significant, $p < 0.0001$).

Pure HMR isolated from Norway spruce and fed to rats is converted to ENL in the large bowel and inhibits, in physiological concentrations, mammary carcinogenesis induced with a carcinogen (59). Other important work with flaxseed and BC is cited in Ref. (30).

Human studies on lignans and breast cancer (BC)

In the beginning of the 1980s we got an opportunity to measure urinary ENL in 72-h urine samples during four seasons in small groups of postmenopausal omnivorous (consume all foods) and vegetarian Boston women as well as in healthy BC patients after surgical removal of small breast tumours (60). The diet of the subjects was carefully recorded using balances. The urinary ENL values in the BC patients were significantly lower than those of the control omnivores but particularly lower than those of the vegetarians. Later three additional groups of young Finnish women were included into the study including omnivores, vegetarians, and BC patients (61). In these Finnish women there was a highly significant correlation between urinary ENL and grain fibre as well as grain calorie intake, but we did not separate fibre from wheat and rye. The mean intake of cereal fibre was only 3.5 g/day in the postmenopausal BC subjects living in Boston (60) more than 40 years ago. The low urinary excretion of

ENL in BC was confirmed in an Australian material (62), a country also consuming wholegrain products. These observations paved the way for research on lignans and cancer. It was suggested that both fibre and lignans may be involved in reducing breast and colon cancer risk, and presented as an extension of the Burkitts original fibre hypothesis (1, 63).

Many prospective and case-control epidemiological studies on ENL and BC have been identified and reviewed (30). No prospective studies show overall association between lignan intake and plasma ENL with risk, but in some investigations certain groups of women seemed to benefit from high levels of ENL (see below). Most of the case-control studies show a negative association between plasma concentration of ENL and BC risk, but all results are not significant. The reasons for the variable results are many. The establishment of a persons ENL level needs three different blood samples or 24-h urine collections (30), but in most cases only one single value has been obtained. In addition to the numerous factors affecting ENL production in the gut or its plasma concentration (antibiotics, smoking, obesity, fat intake, constipation) the dietary source of the enterolignan precursors in plants may play an important role as it is likely that fibre, other phytochemicals, vitamins, and minerals in the food are also playing a role in cancer prevention. In several studies the lignan intake is calculated from databases with values only for SECO and MAT. Even if we would know the content of plant lignans in all foods we do not know exactly how effective formation of enterolignans is from certain foods and from which food source they derive in a particular subject. If the food source of lignans does not contain any or very little fibre like wine, orange juice, coffee, and tea the protective effect may be smaller. According to our original hypothesis (1, 48) when consuming a non-supplemented diet, it is the fibre or perhaps mainly the cereal fibre (now cereal fibre complex), including the associated lignans and other compounds which are cancer and CHD protective in human subjects. The positive results obtained in Eastern Finland in a region with high cereal (rye) fibre intake regarding CHD (44), and BC risk (43) support the view that lignans from rye combined with a fibre effect may be protective.

The controversial results obtained in prospective and case control studies have been discussed previously (30). The observation that women with urinary and other infections treated with antibiotics may have higher risk for BC is an indication of a possibly important role of the intestinal microflora in this disease (64). That intake of antibiotics may increase BC risk was confirmed in one (65), but not in two other epidemiological studies (66, 67). We suggested that the increase of risk could be in part due to reduced ENL levels in the body. However, the two cohort studies by Horn-Ross (68, 69) finding no association with lignan intake represent the largest studies with highest number of cases, but they were carried out at a time when all the new lignans in foods were not known and consequently only 10% or less of the lignans consumed were quantified by calculation of lignan content of the food.

In a much smaller Finnish case-control study comprising 194 BC cases and 208 community-based controls the mean serum ENL concentration was 20 nmol/l for the healthy BC subjects and 26 nmol/l for the controls. The OR in the highest quintile of ENL values compared to the lowest quintile adjusted for all the known risk factors for BC was 0.38 (43, 70). Low risk was associated with high intake of rye products, fibre, tea, and vitamin E. Rye contains high amounts of fibre and lignan precursors and also vitamin E (http://www.rye.vtt.fi). Tea is also rich in lignans (71). Judged from these studies a plasma level of about 20–60 nmol/l of ENL may reduce risk of BC (70, 72). The minimum ENL level indicating a relatively healthy lifestyle has been estimated to 15–20 nmol/l, but the optimum level is likely to be higher than 30 nmol/l. In one prospective study on BC (73) both the median values for cases and controls were below 15 nmol/l. This study belongs to the few in which subjects were excluded if they had taken antibiotics within 4 weeks before the sampling, but this is a too short time to wait and the low values suggest that most subjects were at risk.

In many studies food records were used and from them the intake of SECO and MAT was calculated based on published values or the production of ENL and END (74) from various plant lignans. In only one study four lignans were investigated because at that time food lignan values for PIN and LAR were also available (75, 76).

The most recent epidemiological publications are summarised in Table 1 (77–81). In the studies using FFQ four lignan precursors were calculated. Of the three prospective studies one was negative. In one case-control study (77) only one group of young premenopausal obese women, after stratification by BMI, showed an increased risk when lignan intake was low, and in a Mexican study (79) consumption of the two plant precursors LAR and PIN was negatively associated with BC risk.

Effect of lignans on breast cancer (BC) risk combined with polymorphisms of metabolic enzyme genes or with BC receptors on human BC risk

In two case-control studies the women who had a genotype with one A2 allele of CYP 17, that may result in higher androgen and oestrogen levels, high lignan levels were associated with a highly significant risk reduction for BC (82). This is in accordance with the

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Table 1. Studies during 2008–2010 on association between plasma levels of enterolactone (ENL) or lignan consumption with breast cancer

Cotterchio et al. (77)	Brief food frequency questionnaire (FFQ) $n=3063$ with BC, controls =3,430; Canadian women 25–74 years old. Lignans calculated from databases	Reduced breast cancer risk among premenopausal women. Following stratification by BMI, the risk reduction was confined to obese women
Sonestedt et al. (78)	ENL in plasma by TR-FIA[a] (prospective) BC cases (age 45–73 years, controls (age 46–81). After excluding some subjects due to insufficient data 366 cases and 733 controls remained	Reduced BC risk for ERα(+) and ERβ(−) tumours. Dietary fibre, fruits, and berries and *high-fibre bread* showed statistically significant negative association with plasma ENL. Values of ENL above 16 nmol/l were associated with reduced BC risk. Reduced risk was only found for ERα(+) and ERβ(−) cancer
Torres-Sanchez et al. (79)	FFQ 141 cases with BC, 141 hospital controls. Aged 21–79 years, which had been living in Mexico City at least 20 years. Published values for phytoestrogens in Mexican food were used	Consumption of lariciresinol and pinoresinol was negatively associated with BC risk
Sonestedt et al. (80)	ENL by TR-FIA (prospective) 365 cases and 728 hospital controls with various diseases	BC risk was not significantly associated with any of the selected polymorphisms. There was a tendency for an interaction between a polymorphism of intron 3 of ERα (rs2347867) and ENL concentration ($P=0.07$). An inverse association among carriers of the minor allele (G) ($P=0.007$) was found. Conclusion: The protective association of ENL is reasonably robust across the investigated genotypes
Ward et al. (81)	(Prospective) 244 BC cases and 941 controls aged 40 to 79 years (EPIC–Norfolk). Seven days dietary records Method: [a]TR-FIA =time-resolved fluoroimmunoassay	No association between lignan intake and breast cancer risk

Earlier studies have been summarised in Tables 3 and 4 in Ref. (30).
[a]TR-FIA, time-resolved fluoroimmunoassay.

protective effect of high ENL levels in postmenopausal woman on HRT (83). A German group found that in premenopausal women high intake of MAT and also high calculated production of ENL and END were associated with less risk of BC (84). MAT is with few exceptions found in significant amounts only in rye and oat products. Later, this observation was confirmed by the same group measuring plasma ENL (85). An American study (86) found that high lignan intake was associated with lower risk of BC and concluded that 'dietary lignans may be important in the etiology of BC, particularly among premenopausal women'.

Studies in both Denmark and USA found a lower risk with higher levels of ENL mainly for ERα-negative BC (6, 87). This could be an explanation for the controversial results obtained in BC studies. Oestrogen receptor negative BC is likely to be stimulated by growth factors and there are indications that in such situations ENL may be protective (88–90). In a Swedish study (78) the reduced risk was seen only for ERα(+) and ERβ(−) tumours with significantly different risk for ERβ(−) and ERβ(+) tumors. It therefore, seems that certain groups of women are particularly receptive to the protective effect of ENL. The protective association was most evident in tumours that expressed ERα, but not ERβ.

The perfect epidemiological study has still to be carried out separating rye and wheat foods. High levels of ENL cannot be achieved without consuming wholegrain bread, particularly rye bread, or by adding linseed or sesame seeds to the diet. A better biomarker than ENL for cereal fibre intake such as AR metabolites (91) should be used. An adequate intake of fibre also seems necessary, in addition to the lignans, because of its effect on oestrogen metabolism. Negative association between plasma ENL or lignan intake and risk seem to be found mainly in regions with moderate to high intake of wholegrain cereals in Finland (43), Sweden (92), Denmark (6), Germany (84, 85), and Australia (93) with relatively high consumption of rye, but the results are negative or controversial in countries where wine, juice, tea, and coffee are the main source of lignans (94–97).

Alkylresorcinols (ARs)

Of the common cereals rye has also the highest amounts of antioxidative and potentially anticarcinogenic ARs (20, 98), but nothing is known about their relation to BC.

However, recently we found that the metabolites of ARs are low in healthy Finnish women with operated BC indicating low consumption of wholegrain products including rye bread (99). Studies on ARs and cancer will continue to obtain larger materials.

Conclusion

The results indicate that the association of wholegrain products and lignans with BC is very complex. However, the original hypothesis (1) that fibre, with associated lignans, may be protective with regard to BC has been at least partly supported.

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