Review Article

Can breast cancer patients use soyafoods to help reduce risk of CHD?

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Abstract

Over the past 20 years, the popularity of soyafoods has increased in part because of research suggesting that these foods convey health benefits independent of their nutrient content. For example, in 1999, the US Food and Drug Administration approved a health-claim for soyafoods and CHD based on the hypocholesterolaemic effects of soya protein. However, soyafoods have become controversial in recent years because of concerns that their uniquely rich phyto-oestrogen (isoflavone) content may cause untoward effects in some individuals. Most notable in this regard is the concern that soyafoods are contraindicated for breast cancer patients and women at high risk of developing this disease. Furthermore, the hypocholesterolaemic effects of soya protein have been challenged. However, the results of recently published meta-analyses indicate that soya protein directly lowers circulating LDL-cholesterol levels by approximately 4 %. There is also intriguing evidence that soyafoods reduce CHD risk independent of their effects on lipid levels. In regard to the breast cancer controversy, recently published clinical and epidemiological data do not support observations in rodents that soyabean isoflavones increase breast cancer risk. In postmenopausal women, isoflavone exposure does not adversely affect breast tissue density or breast cell proliferation. Furthermore, both US and Chinese prospective epidemiological studies show that post-diagnosis soya consumption is associated with an improved prognosis. Therefore, soyafoods should be considered by women as healthy foods to include in diets aimed at reducing the risk of CHD regardless of their breast cancer status.

Key words: Soya: Isoflavones: Breast cancer: Heart disease: Phyto-oestrogens

Foods made from soyabeans have been consumed in Asia for centuries beginning first with China and then spreading to Japan and other nearby countries. In Asian cuisine, the soyabean is prized in particular for its versatility. Over the past two decades, the popularity of soyafoods has increased markedly in the USA and other Western countries. Soyafoods provide ample amounts of high-quality protein[1,2] and have a healthy fatty acid profile[3]. However, the increased popularity has occurred largely because of research suggesting that independent of nutrient content soyafoods confer health benefits, especially related to the prevention of chronic disease[4–8]. There is evidence that soya intake reduces the risk of osteoporosis[7,8], certain forms of cancer[5,9,10] and CHD[11,12]. In regard to the latter, the US Food and Drug Administration (FDA)

approved a health claim for soyafoods and CHD in 1999 based on the cholesterol-lowering effects of soya protein[13]. There are also data indicating that soyafoods reduce CHD risk independent of their effects on lipid levels[14,15].

However, over the past decade, evidence in support of some of the proposed benefits of soyafoods has been less consistent than anticipated[16]. Even the heart-health claim has recently been challenged[17]. Furthermore, there are concerns that soyafoods may adversely affect certain individuals. Many of the proposed benefits and most of the concerns[18,19] about soyafoods are attributed to their uniquely rich isoflavone content[20]. These diphenolic molecules are classified as phyto-oestrogens and in traditional soyafoods each gram of protein is associated with approximately 3·5 mg isoflavones

(expressed in aglycone equivalents); consequently, one serving of a traditional soyafood contains about 25 mg isoflavones.

Most notable among the concerns is the fear that because of the oestrogen-like effects of isoflavones[21,22], soyafoods may be harmful to women with a history of breast cancer and women at high risk of developing this disease[23]. Consequently, many health professionals, uncertain about the benefits and concerned about the detrimental effects, are unsure how best to advise their female patients about the role of soyafoods in heart-healthy diets. Therefore, the purpose of this review is to critically evaluate the proposed coronary effects of soyafoods and to address concerns that soyafoods adversely affect breast tissue.

Effects of soya on circulating LDL-cholesterol levels

Direct effects

The cholesterol-lowering effect of soya protein was first demonstrated clinically in 1967[24], but not until 1995 did the hypocholesterolaemic effects of soya protein receive widespread recognition. In that year, a meta-analysis of the clinical data by Anderson et al.[25], which included thirty-four trials and thirty-eight different comparisons, found that soya protein lowered LDL-cholesterol (LDL-C) by 12·9 %. The reduction in LDL-C was attributed to the protein or components (isoflavones) associated with soya protein and not to the low saturated fat content of the soyabean, since in nineteen trials the fatty acid content of the soya and control diets was similar. And 4 years later, on the basis of their own analysis, the US FDA approved a health claim for soyafoods and CHD[13]. In the subsequent year, the American Heart Association (AHA) recognised the ability of soya protein to lower cholesterol and endorsed the use of soyafoods for people with elevated cholesterol levels[26].

However, only 2 years following approval of the health claim, the US Adult Treatment Panel III of the National Cholesterol Education Program chose not to endorse the hypocholesterolaemic effects of soya protein, citing inconsistent data and the lack of dose–response information[27]. Of greater significance, in their 2006 position paper, the AHA, while continuing to endorse the use of soyafoods for heart-healthy diets because of their 'high content of polyunsaturated fats, fibre,

vitamins and minerals, and low content of saturated fat … ' concluded that earlier research indicating that 'soya protein has clinically important favourable effects as compared to other proteins has not been confirmed'[17]. Furthermore, the FDA announced in December 2007 their intention to re-evaluate the evidence in support of the health claim, although there is no indication that this re-evaluation has been undertaken because the data are no longer supportive of the claim.

Given the gravitas of the AHA, and their pronounced change in sentiment about the efficacy of soya protein, it is instructive to consider the evidence upon which their reversal is based. Briefly, in an analysis of twenty-two studies, the AHA estimated that soya protein lowered LDL-C only by approximately 3 %[17]. In their view, this degree of reduction was insufficient to warrant a health claim. However, the AHA did not actually conduct a formal statistical meta-analysis of the data. When this was recently done, Jenkins et al.[6] found that the AHA had underestimated the hypocholesterolaemic effects of soya protein. Rather than lowering LDL-C by approximately 3 %, Jenkins et al.[6] estimated that soya protein lowered LDL-C by 4·3 %. Furthermore, when the analysis was limited to eleven of the twenty-two studies which provided evidence that the control and soya-containing diets were nutritionally matched, soya protein was found to lower LDL-C by 5·2 %. This estimate is in line with the results of other recently published meta-analyses[28–32] (Table 1) and is similar to the cholesterol-lowering effects of soluble fibre, which also has an FDA health claim[33]. Although the consensus estimate (4–6 %) of the magnitude of the hypocholesterolaemic effect of soya protein is much more modest than that initially reported by Anderson et al.[25], the decrease is still relevant at both population and patient levels.

The FDA established 25 g/d soya protein as the threshold intake required to lower LDL-C because most trials used at least this much protein, not because lower amounts were shown not to be efficacious. There is, in fact, evidence suggesting that fewer than 25 g/d soya protein is needed to lower cholesterol[29,34]. Whether exceeding 25 g/d produces larger decreases in LDL-C is unclear. In the overall statistical model in the initial meta-analysis by Anderson et al.[25], the amount of soya protein did not make an impact on cholesterol reduction although when adjusted for baseline cholesterol, it was estimated that 25 and 50 g/d soya protein decreased serum cholesterol concentrations by 89 and 174 mg/l, respectively.

Table 1. Change (%) in circulating lipid levels in response to soya protein: results from recently published meta-analyses

First author/reference	Year published	Trials	n*	↓ LDL-C (%)	↑ HDL-C (%)	↓ TAG (%)
Anderson[32]	2011	20†	1946	5·5	3·2	10·7
Jenkins[6]	2010	22	757	4·2	NR	NR
Harland[29]	2008	10	2913	6·0	4·6	5·3
Reynolds[30]	2006	36	1387	4·0	NR‡	NR§
Zhan[28]	2005	33	1749	5·3	3·0	7·3
Weggemans[31]	2003	21	959	4·0	3·0	NR

↓, Decrease; LDL-C, LDL-cholesterol; ↑, increase; HDL-C, HDL-cholesterol; NR, not reported.
* Refers to subject numbers for LDL-C measurements.
† Refers to parallel studies only.
‡ 7·70 mg/l increase.
§ 62·60 mg/l decrease.

Zhan & Ho reported that LDL-C decreased to a larger extent in response to soya protein providing ≥80 mg/d isoflavones[28]. In agreement, Reynolds *et al*.[30] found significant correlations between the reduction in LDL-C and soya protein (r −0·57, $P < 0·001$) and isoflavone (r −0·48, $P < 0·01$) intake. However, Weggemans & Trautwein[31] found that there was no dose–response relationship between soya-associated isoflavones and changes in LDL-C. Furthermore, in the meta-regression analysis by Harland & Haffner[29], no dose–response relationship between soya protein intake in the range of 15–40 g/d and LDL-C reduction was observed. This finding is particularly noteworthy because this range of soya protein intake more closely reflects the amounts likely to be consumed by free-living populations than the ranges in the other meta-analyses (Table 1). In support of Weggemans & Trautwein[31] and Harland & Haffner[29], the results of the recent meta-analysis by Anderson & Bush[32] also support the notion that neither dose of soya protein (range, 15–50 g/d) nor isoflavones (range, 22–185 mg/d) affect the LDL-C-lowering response.

Participants in the studies in the meta-analyses listed in Table 1 were roughly equally divided between men and women; however, there is some evidence indicating that there are sex differences in the response to soya protein. For example, Zhan & Ho[28] found that LDL-C reductions in response to soya protein for men and women were −0·30 and −0·14 mmol/l, respectively, although it is not clear whether their analysis controlled for potentially confounding variables such as baseline cholesterol levels. Nevertheless, in agreement, Harland & Haffner[29] found greater LDL-C reductions in men than in women.

Indirect effects

In addition to the direct hypocholesterolaemic effect of soya protein, as a result of differences in fatty acid content, Jenkins *et al*.[6] using US National Health and Nutrition Examination Survey III population survey data, estimated that when soya-foods replace commonly consumed sources of animal protein in the diet, LDL-C is reduced by 3–6%. There was a 4% reduction in LDL-C when 24 g soya protein – an amount similar to the 25 g/d established by FDA as the threshold intake for cholesterol reduction – replaced a comparable amount of animal protein. Obviously, the displacement effect can vary greatly, as it depends entirely on the types of soyafoods consumed and the types of foods that are replaced.

As an oil seed, soyabeans derive approximately 40% of their energy from fat, which is much higher than that for other legumes[35] with the exception of peanuts, another oil seed legume. The predominant fatty acid in soya oil, as in many vegetable oils, is the essential *n*-6 PUFA linoleic acid, which accounts for about 55% of the total fat content[3,36]. The soyabean has a moderate amount of oleic acid (approximately 29%) and a low amount of saturated fat (approximately 12%). Importantly, unlike many other vegetable oils, soya oil is comprised of approximately 6% α-linolenic acid, the essential *n*-3 fatty acid[3,36].

Although conventional thinking has been that replacing cholesterol-raising saturated fats with *n*-6 PUFA will lower cholesterol and CHD risk[37], a recent comprehensive analysis of the clinical data found that to lower CHD, saturated fat needs to be replaced with a mix of *n*-6 and *n*-3 PUFA[38]. In fact, according to Ramsden *et al*.[38], replacement of saturated fat with *n*-6 PUFA increases risk[38]. Replacing saturated fat with refined carbohydrate also increases risk, whereas the effect of replacement with monounsaturated fat is unclear[38–41]. Therefore, the fatty acid profile of soyabeans would appear to be ideally suited for lowering blood cholesterol. On the other hand, the high *n*-6:*n*-3 fatty acid ratio (approximately 9:1) has led to concern that soyafoods might elicit a pro-inflammatory response. However, this fear does not appear to be justified[42].

Linoleic acid is converted *in vivo* to arachidonic acid, the fatty acid from which pro-inflammatory eicosanoids are produced; however, plasma and tissue levels of arachidonic acid are very tightly regulated[43]. Further, it is now recognised that some eicosanoids produced from arachidonic acid are anti-inflammatory and possess other desirable attributes[44]. To this point, in a cross-sectional study of 915 men aged 40–49 years, both serum linoleic acid and arachidonic acid were found to be inversely related to plasma levels of plasminogen activator inhibitor-1. Because plasminogen activator inhibitor-1 is a primary inhibitor of plasminogen activators, it has an anti-fibrinolytic function.

Finally, given the desirable fatty acid profile of and high-quality protein[1,2] provided by soyafoods, it is not surprising that in research diets shown to dramatically lower blood LDL-C levels, soyafoods have played an important role[45,46]. If one assumes that there is a 4% reduction in LDL-C resulting from a direct effect of consuming 25 g/d soya protein and a 4% reduction due to displacement effects, in theory, CHD risk will be reduced by 8–16% when soyafoods replace conventional sources of protein in Western diets[47,48]. Obviously, only long-term clinical trials can definitively show that incorporating soyafoods into the diet reduces coronary events.

Beyond effects on LDL-cholesterol levels

In addition to the effects on LDL-C, meta-analyses have found that soya protein modestly increases (1–3%) fasting HDL-cholesterol and decreases (5–11%) TAG levels (Table 1). Each 1% or 1 mg increase in HDL-cholesterol lowers CHD risk by 2–3%[49–51]. Although there is debate about whether an elevated TAG level is an independent predictor of CHD risk[52], evidence suggests that the role of fasting TAG levels in the aetiology of CHD may be underestimated[53,54]. Furthermore, new research suggests that soya protein decreases postprandial TAG levels, elevated levels of which are increasingly viewed as an important CHD risk factor[55].

There is also clinical evidence that soyafoods exert coronary benefits independent of their effect on lipid levels. For example, four meta-analyses have found that soya lowers blood pressure[14,56–58]. The most recently published and comprehensive of these, which included twenty-seven studies, reported that soya lowered systolic and diastolic blood pressure by 2·2 and 1·3 mmHg, respectively[14]. Decreases in blood pressure of this magnitude can be estimated to reduce risk of stroke, CHD and overall mortality by approximately

10, 5 and 4%, respectively[59]. There are suggestive data that the hypotensive effects are more pronounced in women than in men[56] and that traditional soyafoods have a greater impact than isolated soya protein (ISP, which by definition is ≥90% protein)[57]. However, until the blood pressure-lowering effects of soya are demonstrated in more trials whose primary health outcome is a change in blood pressure, the hypotensive effects of soya should be considered speculative. Work identifying the component(s) responsible for the proposed hypotensive effects is also needed; evidence suggests that both the protein (via peptides formed upon digestion)[60,61] and isoflavone content[62,63] of soya may be contributing factors.

Other biological processes and measures related to heart disease that may be favourably affected by various soya components include endothelial function, systematic arterial compliance[64], arterial stiffness[65], LDL-C oxidation[66] and LDL particle size[67,68]. However, because of the inconsistent and/or limited data, no conclusions can be made about the effects of soya on these CHD markers except for endothelial function. Endothelial cells in the intima layer of blood vessels are thought to play a central role in inhibiting the development of arteriosclerosis and its thrombotic consequences. For this reason, endothelial function has been referred to as a global indicator of CHD risk[69]. The health of the endothelium and factors affecting it can be non-invasively assessed by measuring flow-mediated dilatation (FMD), using ultrasound imaging of the brachial artery.

A recent meta-analysis by Li et al.[15] that included nine studies and 525 postmenopausal women found that soyabean isoflavones favourably improved endothelial function. However, when the data were sub-analysed, the improvement was seen only in those women with impaired endothelial function at baseline. More specifically, in women with an age-adjusted baseline FMD value < 5·2%, isoflavone administration resulted in a significant increase (weighted mean difference, 2·22; $P=0.0001$) in FMD, whereas in women with a baseline FMD ≥ 5·2%, there was no benefit (weighted mean difference, 0·24, $P=0.87$). A second review of the clinical data also found that isoflavones improve endothelial function[70]. Experimental studies indicate that isoflavones can stimulate the production of NO via oestrogen receptor (ER)−mediated activation of endothelial NO synthase[71]. However, it may also be that in the long term, isoflavones improve endothelial function by increasing the circulating levels of endothelial progenitor cells, which replace damaged endothelial cells[72].

Lack of correction for baseline FMD provides an explanation for the lack of consistency in the literature in this area. Also, although the meta-analysis by Li et al.[15] showing that isoflavones improve FMD included only studies involving postmenopausal women, there is evidence, albeit limited, suggesting that isoflavones benefit premenopausal women. For example, recently, Hoshida et al.[73] found that isoflavones (50 mg/d) increased FMD in both pre- ($P=0.004$) and postmenopausal ($P=0.019$) non-smokers. Furthermore, isoflavones reduced arterial wall stiffness in both premenopausal smokers

($P=0.027$) and non-smokers ($P=0.013$), while having no effect on postmenopausal women.

Finally, Hodis et al.[74] recently examined the effects of isoflavone-rich ISP on the progression of carotid intima-media thickness (CIMT) in postmenopausal women over a 3-year period. Participants consumed either 25 g/d ISP containing 99 mg isoflavones (n 163) or 25 g milk protein (n 162). At the end of the study, although CIMT progression was 16% lower in the soya group, the difference was not statistically significant ($P=0.35$). Nevertheless, if progression reflects future risk of coronary events, this potential reduction should not be dismissed, especially because the results showed that differences between groups increased with time, suggesting that longer exposure to soya would result in an increased benefit. Furthermore, when the data were sub-analysed, it was found that in comparison to the control, progression was reduced among women in the soya group who were < 5, 5–10, and > 10 years post-menopause by 68% ($P=0.05$), 17% ($P=0.51$) and 9% ($P=0.77$), respectively. That the greatest reduction or benefit was seen in early postmenopausal women is consistent with the oestrogen window or timing hypothesis, which maintains that exposure to oestrogen-like compounds early but not late in menopause produces coronary and cognitive benefits[75,76]. Given that the women in the soya group were exposed to high amounts of isoflavones, the oestrogen-timing hypothesis provides a biological basis for such pronounced benefits being observed in early postmenopausal women.

The breast cancer controversy

Introduction

Concerns that soyafoods are contraindicated for women with a history of breast cancer and women at high risk of developing this disease (see Table 2 for a summary of this controversy) are based on the oestrogen-like effects (see next section) of

Table 2. Summary of key findings relevant to the soya and breast cancer controversy*

Genistein stimulates the growth MCF-7 cell (ER+ human breast cancer cells) in vitro at physiologically relevant concentrations

In athymic ovariectomised mice implanted with MCF-7 cells, dietary genistein and isoflavone-containing products stimulate the growth of existing tumours and inhibit the efficacy of tamoxifen and letrozole

Dietary genistein does not stimulate tumour growth in athymic ovariectomised mice implanted with MCF-7 cells cultured in an oestrogen-free media

Differences in isoflavone metabolism between athymic mice and humans suggest that the former are not a good model for studying the effects of isoflavones in the latter

Results from the Women's Health Initiative Trial indicate that oestrogen therapy does not increase breast cancer risk in hysterectomised women

Isoflavone exposure does not adversely affect markers of breast cancer risk, including breast tissue density and breast cell proliferation, in postmenopausal women

Epidemiological studies from China and the USA indicate that post-diagnosis soya intake is associated with an improved prognosis

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ER, oestrogen receptor.
* See text for references and study details.

isoflavones and a series of studies conducted primarily by the laboratory of William Helferich at the University of Illinois, which show that isoflavones and isoflavone-containing soya products stimulate the growth of existing mammary tumours in athymic ovariectomised mice implanted with MCF7 cells[23]. These cells are derived from a human oestrogen-sensitive breast cancer cell line[23]. Data from this model also show that it is the isoflavone genistein that is responsible for tumour stimulation[77] and that this isoflavone inhibits the efficacy of tamoxifen[78] and the aromatase inhibitor letrozole[79]. However, a recently published study by Onoda *et al.*[80] failed to confirm the tumour-stimulatory effect of genistein despite the use of an almost identical model. Onoda *et al.*[80] noted that in their study before implantation, the MCF-7 cells were cultured in an oestrogen-free environment, whereas in the studies in which tumour stimulation occurred, the cells were exposed to a high concentration of oestrogen (1 nM) before implantation. According to Onoda *et al.*[80], this high oestrogen concentration is unphysiological and makes the cells hypersensitive to oestrogenic stimuli. In any event, recent work by Setchell *et al.*[81] suggests that because of differences in isoflavone metabolism between nude mice and humans, the former may not be an appropriate model for predicting effects in the latter.

Brief overview of isoflavones

The three soyabean isoflavones, genistein, daidzein and glycitein, and their respective glycosides account for approximately 50, 40 and 10 %, respectively, of total soyabean isoflavone content[82]. In Japan, mean isoflavone intake ranges from about 30 to 50 mg/d (expressed as aglycone equivalents)[83]. In considering their possible impact on breast tissue, it is important to recognise that although isoflavones are classified as phyto-oestrogens, they are more accurately classified as selective ER modulators (SERM), a group which includes the breast cancer drug tamoxifen and the osteoporosis drug raloxifene[84]. SERM have tissue-selective effects; depending upon the tissue in question, SERM can have oestrogenic effects, anti-oestrogenic effects or no effects at all on tissues affected by oestrogen. This will depend on the types and ratios of ER, the shape of the ligand–receptor complex and the types of co-activators and co-repressors in cells in a particular tissue[85]. The tissue selectivity of isoflavones probably derives from their preferential binding to and transactivation of ERβ in comparison to the ERα[84,86]. These two receptors have different tissue distributions in the body and different functions. This is particularly evident in the breast where the activation of ERβ is thought to inhibit the stimulatory and proliferative effects of ERα activation[87].

Although limited, there is considerable evidence supporting the classification of isoflavones as SERM. For example, Carmignani *et al.*[88] found that the vasomotor symptom score of postmenopausal women was decreased over a 16-week period by approximately 33, 54 and 55 % in response to a placebo, soya protein containing 53 mg isoflavones, and hormone therapy (HT, oestrogen plus progestin), respectively. However, only HT increased the vaginal maturation index

($<$0·01), a measure of the extent to which the vaginal tissue has been exposed to oestrogenic molecules. Thus, the oestrogen-like effects of isoflavones were apparently sufficient to alleviate menopausal symptoms in a manner similar to HT but unlike HT, isoflavones did not exert an oestrogenic effect on the vagina.

Isoflavones, oestrogen and breast cancer: clinical evidence

It has been postulated that in the high-oestrogen environment of premenopausal women, isoflavones function as oestrogen antagonists and potentially decrease breast cancer risk, whereas in the low-oestrogen environment of postmenopausal women, they function as oestrogen agonists, and increase risk[89,90]. However, although circulating oestradiol levels are 4-fold higher in pre- compared to postmenopausal women, breast tissue oestrogen concentrations are similar[91,92] because of the uptake of oestrogen by the breast from the circulation[93]. Thus, the notion that the effect of isoflavones on breast tissue differs according to the oestrogenic environment may not be physiologically relevant. Furthermore, in the Women's Health Initiative trial, although oestrogen-plus-progestin use increased breast cancer incidence[94] and mortality[95], in hysterectomised women, oestrogen-only use actually decreased risk[96,97] and the protective effects were maintained for several years after cessation of therapy[98]. One caveat, however, is that the most recent analysis from the Women's Health Initiative trial suggests that the protective effects of oestrogen may not apply to women at increased risk of breast cancer[99].

These findings from the Women's Health Initiative trial are generally supported by the existing epidemiological[100–104] and clinical data[105–108]. Granted, the extent to which the findings in women without a uterus can be applied to intact women is unclear; however, there is no reason why women without a uterus should be more or less sensitive to oestrogens. It is true that hysterectomy, even if the ovaries are not removed, may be associated with an earlier endocrine menopause. Such women are therefore more likely to resemble the postmenopausal state and yet are protected by oestrogen therapy.

Clinical studies in which the effects of isoflavone exposure on markers of breast cancer risk have been evaluated are supportive of safety regardless of whether isoflavones are derived from soyafoods or supplements[109]. Higher circulating oestrogen levels, greater breast tissue density and greater *in vivo* breast cell proliferation, are seen as reflecting an increased cancer risk. To this point, tamoxifen decreases cell proliferation and breast tissue density and breast cancer risk, whereas HT increases these markers and breast cancer risk[107,108,110–112]. In contrast to the effects of HT, isoflavones generally have no effect on any of these previously referred to markers[113,114]. One exception is a recently published 6-month study that found in response to very high-dose isoflavone supplementation (154 mg/d genistein), breast cell proliferation increased slightly in premenopausal women, although there were no effects on cell cytology and no effects at all in postmenopausal women, the latter group according to theory, being most vulnerable to isoflavones[115]. Further, the approximate 27 % increase in proliferation observed in

premenopausal women is more than an order of magnitude less than the approximately 4- to 10-fold increased breast cell proliferation that occurs in response to HT[108,116].

Finally, it is worth noting that the clinical findings discussed previously, although supportive of safety, also argue against adult soya intake reducing breast cancer risk as was first proposed more than 20 years ago[117–119], even though epidemiological data show that among Asian women soya intake is associated with protection against breast cancer[4]. Compelling, but still speculative, evidence indicates that to derive protection against breast cancer, soya intake must occur during childhood and/or adolescence[9,10].

Soya intake and the prognosis of breast cancer patients: epidemiology

Despite the lack of effect of isoflavone exposure on breast tissue, recent epidemiological evidence indicates that soya intake benefits breast cancer patients. Over the past 6 years, six prospective epidemiological studies, three from China[120–122], two from the USA[123,124] and one from Korea[125], have evaluated the impact of soya consumption on the prognosis of breast cancer patients. One of these showed there to be no relationship between soya intake and disease-free survival[120], four showed that soya intake improved prognosis[121,123,124,126], whereas the Korean study found that the impact of soya depended upon the type of breast cancer in question[125]. That study[125] and the largest and longest Chinese[121] and US[124] studies are briefly described next. When considering the Asian studies, it is worth noting that an argument has been made on the basis of animal studies, that breast tumours that develop in women who consumed soya when young may be different from and respond differently to tamoxifen, than breast tumours in women who did not consume soya early in life[127].

The Shanghai Breast Cancer Survival Study is a population-based cohort study that includes more than 5000 breast cancer survivors[121]. During the median follow-up period of approximately 3·9 years, the hazard ratio (HR) plus 95 % CI associated with the highest soya protein intake quartile was 0·71 (95 % CI 0·54, 0·92) for total mortality and 0·68 (95 % CI 0·54, 0·87) for recurrence compared with the lowest intake quartile. Similar protective effects were associated with isoflavone intake. Soya intake was assessed at 6, 18, 36 and 60 months post enrolment and the fourth quartile intake cut-offs for soya protein and isoflavones were >15·31 g/d and >62·68 mg/d, respectively. Soya intake was protective in both pre- and postmenopausal women.

The US study by Caan et al.[124] involved 2736 breast cancer survivors diagnosed between 1991 and 2000 with early-stage breast cancer, who were participants in the Women's Healthy Eating and Living study. During the median 7·3 years follow-up period, there were 448 new breast cancer events and 271 deaths. The results showed that as isoflavone intake increased, risk of death decreased. Women in the highest isoflavone intake category (cut-off, >16·3 mg/d; median 26·7 mg/d) had a 54 % reduction in risk of death (HR 0·46; 95 % CI 0·2, 1·05; P for trend=0·02). The benefits of isoflavone intake were most obvious in tamoxifen users (HR 0·26; 95 % CI 0·0, 1·08; P for trend=0·05). This finding is consistent with the observation that in the prospective Chinese epidemiological study by Kang et al.[126], soya intake improved the efficacy of the aromatase inhibitor anastrozole. The tamoxifen and anastrozole findings are especially noteworthy not only because of the possible implications for breast cancer patients on treatment, but because in ovariectomised athymic mice, genistein was shown to inhibit the efficacy of these drugs[78,79]. Furthermore, both Chinese and US prospective studies show benefits to breast cancer patients of post-diagnosis soya intake, including those treated with tamoxifen. These findings help to address the concern that women who consume soya early in life develop tumours that differ from those who do not.

Finally, in a Korean prospective study by Woo et al.[125], among the 339 women aged 25–77 years, during the median follow-up period of 32·6 months (range 1·3–52·4 months), there were twenty-five recurrences. The adjusted HR for women in the third isoflavone intake tertile (cut-off, ≥14·6 mg/d) was 0·23 (P for trend, 0·01) for women with epidermal growth factor receptor-2 negative (HER2−) breast cancer, whereas for women with HER2+ breast cancer the adjusted HR (cut-off, ≥15·2 mg/d) was 3·85 (P for trend, 0·17). Only approximately 25 % of breast cancers are HER2+, but this type of breast cancer is more aggressive and is associated with a worse prognosis[128]. Although these findings raise a cautionary note, no conclusions can be made on the basis of this study because of its limited size, as there were only eight recurrences among the eighty-three HER2+ breast cancer patients. The impact of post-diagnosis soya intake in HER2+ breast cancer patients in a much larger cohort is currently being evaluated.

Summary and conclusions

Soyafoods hold the potential to reduce risk of CHD through multiple mechanisms. Soya protein modestly lowers blood LDL-C[6,28–32] and the isoflavones associated with soya protein improve endothelial function in postmenopausal women[15]. In addition, soyafoods provide high-quality protein[1,2] and have a very favourable fatty acid profile[3]; consequently, they can be used to displace conventional sources of protein in Western diets which tend to be high-cholesterol and high-saturated-fat animal products[6]. As a result, blood lipid levels will be favourably affected. There is also intriguing evidence that soyafoods modestly lower blood pressure[129] and favourably affect other CHD risk factors. Recent 3-year data suggest that in postmenopausal women, and especially women early in menopause, soya, probably because it contains isoflavones, may slow down the progression of CIMT[130]. Nevertheless, soyafoods are controversial because of concerns that the oestrogen-like effects of isoflavones may harm women with a history of breast cancer and women at high risk of developing this disease. However, in contrast to some animal data, clinical evidence indicates that isoflavone exposure does not adversely affect the markers of breast cancer risk, including breast tissue density and breast cell proliferation[113,114], and both Chinese and US prospective epidemiological studies indicate
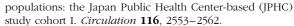
that post-diagnosis soyafood consumption improves the prognosis of breast cancer patients[120,121,123,126,131]. In the light of these findings, there is no reason to advise health professionals against recommending soyafoods to their patients as part of heart-healthy diets with or without a history of breast cancer. Women with a history of breast cancer will live for many years without succumbing to their disease; and so it is imperative that they recognise the need to adhere to dietary patterns that are protective against a variety of chronic diseases. The consumption of two-to-four servings of soyafoods daily provides the amounts of soya protein and isoflavones associated with the proposed benefits discussed in this review.

Acknowledgements

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