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Efficacy of Soyfoods and Soybean Isoflavone Supplements for Alleviating Menopausal Symptoms Is Positively Related to Initial Hot Flush Frequency

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ABSTRACT

Soy has received attention as an alternative to conventional hormone replacement therapy (HRT) largely because it is a unique dietary source of isoflavones. Isoflavones are diphenolic compounds that have both hormonal and nonhormonal properties and are considered to be selective estrogen receptor modulators. The estrogen-like effects of isoflavones in combination with the low reported frequency of hot flushes in Japan has prompted investigation of the effect of soy on menopausal symptoms. The purpose of this review is to evaluate the efficacy of soyfoods and isoflavone supplements for the alleviation of hot flushes. Nineteen trials (13 using a parallel design) involving more than 1,700 women were identified. Six trials were excluded from analysis: two that involved breast cancer patients, two that reported data on severity but not hot flush frequency, one that was not blinded, and one that did not include a control group. Based on a simple regression analysis of the remaining data set (13 trials), there was a statistically significant relationship ($P = .01$) between initial hot flush frequency and treatment efficacy. Initial hot flush frequency explained about 46% of the treatment effects, and hot flush frequency decreased by about 5% (above placebo or control effects) for every additional initial hot flush per day in women whose initial hot flush frequency was five or more per day. Although conclusions based on this analysis should be considered tentative, the available data justify the recommendation that patients with frequent hot flushes consider trying soyfoods or isoflavone supplements for the alleviation of their symptoms.

INTRODUCTION

SOYFOODS HAVE PLAYED an important role in the diets of many Asian countries for centuries. But within the past 10 years, soyfoods and soybean constituents have attracted widespread research attention in the West for their purported health benefits. Many of the newly developed "Westernized" soy products specifically target women because of reports that soy may be helpful for conditions and diseases associated with the menopausal years. Soy is much discussed as a possible alternative to conventional hormone replacement therapy (HRT),[1–6] in large part because it is a unique natural dietary source of isoflavones.[7,8] This perspective may gain even further attention as a result of the recently published disappoint-

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ing findings from the Heart and Estrogen/Progestin Replacement Study (HERS) I/II[9,10] and the Women's Health Initiative.[11] Isoflavones have estrogen-like properties[12–14] and are considered by many experts to be natural dietary selective estrogen receptor modulators (SERMs).[15–17]

Traditionally, one reason, if not the primary reason, that women elected to use HRT was for relief of menopausal symptoms.[18] Because many women may now opt not to use HRT for such purposes, health professionals, especially clinicians, need accurate information about the efficacy of alternative agents and approaches to alleviating hot flushes. Soyfoods and soybean isoflavones are popular alternatives,[19] but thus far no comprehensive review on their efficacy in the alleviation of hot flushes has been published. The intent of this paper is to fill this void and to present the hypothesis that soyfoods and soybean isoflavones effectively alleviate menopausal symptoms in women who have frequent hot flushes. Trials examining the effects of isoflavones derived from red clover were not included in the statistical analysis to avoid any potential differences in efficacy stemming from the difference in isoflavone profile between soybean- and red clover-derived isoflavones. Results of several recent studies on the effects of red clover isoflavones are available elsewhere.[20–24]

BACKGROUND

Isoflavones have traditionally been considered to be weak estrogens, although it is not possible to arrive at a single estimate of potency, which varies according to tissue. In addition, it is well established that serum isoflavone levels in response to modest soyfood consumption can reach the low micromolar range, about 100 to 1,000 times that of estrogen.[25] This suggests, even assuming a relatively weak potency, that isoflavones have the potential to exert biological effects *in vivo*, and in fact they have been reported to do so in several trials that included a variety of different endpoints.[26–30]

However, it is probably more accurate to refer to isoflavones as having estrogen-like (rather than estrogenic) properties, because they behave differently from estrogen. For example, isoflavones bind with much greater affinity to estrogen receptor-β (ER-β) than to ER-α,[12,31] and they are much more potent at triggering transcriptional activity when bound to ER-β rather than ER-α.[32] Also, isoflavones have potentially important nonhormonal effects.[33]

In 1992, Adlercreutz et al.[34] first suggested that the estrogen-like properties of isoflavones might account for the low incidence of hot flushes reportedly experienced by women in Japan, a notion later popularized by Lock.[35,36] In general, the incidence of hot flushes among Asian women tends to be lower[37,38] than among Western women, although many other menopausal symptoms (e.g., shoulder aches, psychological changes) are experienced to a similar extent.[39] Consistent with these observations are recent epidemiological data indicating that American women of Chinese and Japanese ancestry are about one third less likely to report experiencing hot flushes, compared with Caucasian-American women.[40]

Obviously, there are many reasons why Asian women may experience fewer hot flushes than Western women do. For example, it could be that the lower premenopausal estrogen levels among Asian women mitigate the drop in estrogen concentration that occurs as a woman enters the menopause, and thus the trigger for the onset of hot flushes is minimized.[41] However, there exists epidemiological support, albeit limited, for the notion that soy may be a contributing factor. For example, in a small cross-sectional study involving 284 Japanese women 40–59 years of age, fermented but not total soy product intake was inversely related to hot flush severity ($P < .05$).[42] Stronger support came from a Japanese prospective epidemiological study: during 6 years of follow-up among the 101 women who experienced hot flushes, the hazard ratios were 0.42 (P for trend = .005) and 0.47 (P for trend = .002) for intake of total soy product (g/d) and isoflavones (mg/d), respectively, when comparing those in the highest and lowest tertiles of intake.[43]

Finally, in a case-control study by Somekawa et al.[44] involving 478 postmenopausal Japanese

women, the incidence of hot flushes tended to decrease as isoflavone intake increased, although this relationship was not statistically significant. Lack of statistical significance may have been partially related to the isoflavone intake cutoff values used in this study. The lowest intake quartile included women who consumed as much as 35 mg of isoflavones per day. This represents considerable soy intake and is an amount that may have exceeded the threshold isoflavone exposure necessary to experience benefit. In the prospective study by Nagata et al.[43] cited previously, the hazard ratio for hot flushes decreased from 1.00 to 0.78 between the first and second tertile of intake; the average isoflavone intakes in those two groups were 20.5 and 32.6 mg/day, respectively.[43]

One of the difficulties of conducting trials to evaluate the efficacy of agents for hot flush relief is the large placebo effect observed in most studies. According to Loprinzi et al.,[45] placebo decreases hot flushes by an average of 25% over a 3- to 4-week period, about 10% of women experience a 75% or greater reduction in hot flushes with placebo, and another 10% experience a reduction of 50% to 75%. To circumvent this problem, Pan et al.[46] examined the effects of soy on rat tail skin temperature. They found that the rise in tail skin temperature induced by ovariectomy was significantly reduced in rats fed a diet containing isoflavone-rich soy protein (soy+), compared with rats fed the control diet lacking soy ($P = .04$) or a diet containing isoflavone-poor soy protein ($P = .10$). However, the effect of soy+ was not as pronounced as the effect of estrogen. Obviously, ovariectomized rats are not little menopausal women, but at least in this model the placebo effect is eliminated.

CLINICAL TRIALS

Overall description

The first trial assessing the efficacy of soy (soyflour) for the alleviation of menopausal symptoms was published in 1995.[47] Since that time, 11 additional studies[48–58] have examined the effects of soyfoods (7 using isolated soy protein, 1 soyflour, 1 soymilk, 1 textured vegetable [soy] protein, and 1 a combination of traditional soyfoods[58]), and 7 others[59–65] have investigated the effects of isoflavone supplements, on hot flush frequency, or severity, or both (Table 1). These 19 trials were conducted in eight countries, ranged in duration from 4 weeks to 24 months (although 11 of the trials were 12 weeks in length), and exposed women to intakes of 34 to 100 mg isoflavones per day (in most cases, ≥70 mg/day). For comparison, average isoflavone intake for a Japanese adult is about 35 to 40 mg/day.[66]

Twelve of the 19 studies were randomized, double-blinded, parallel trials; 5 were randomized, double-blinded, crossover trials; 1 was a parallel trial that was not blinded; and 1 had no control group. Altogether, in the 12 soyfood trials, 467 women were given the control diet and 482 the soy diet, and in the 7 supplement trials, 323 women were given the placebo and 474 the isoflavones, for a total of 1,746 participants. (The actual number of women in these trials is slightly different, because some women participated in both the control and active arms, and, in three trials[51,52,67] there was more than one soy group but only the group fed the soy protein with the highest isoflavone content was considered for review and analysis.) Because the trial by Brzezinski et al.,[48] which found a statistically significant decrease in hot flush frequency in women fed soyfoods (and some flax) compared with the control group, was not blinded, it was excluded from the analysis, as was the trial by Albert et al.,[63] which found a statistically significant favorable response among women given an isoflavone supplement but did not include a placebo group. Elimination of these two trials brings the totals down to 431 control and 404 experimental subjects in the soyfood trials and 323 placebo and 323 experimental subjects in the isoflavone supplement trials.

Analysis

Of the 11 remaining soyfood trials, only 1 found that women in the active arm experienced a statistically significant decrease in hot flush frequency.[50] This trial is intriguing because the investigators noted that improve-

TABLE 1. FINDINGS FROM TRIALS EXAMINING THE EFFICACY OF SOYFOODS AND ISOFLAVONE SUPPLEMENTS FOR ALLEVIATING HOT FLUSHES

Author (ref. no.)	*Design*	*Duration (wk)*	*Isoflavone exposure (mg/day)*	*Age (yr)*	*Control/ Placebo (N)*	*Soyfood/ Isoflavone (N)*	*Initial hot flushes/day*[a]	*Absolute % change versus inactive arm*[b]
Trials involving soyfoods								
Albertazzi (50)	Parallel	12	76	53	39	40	11.2	↓ 12.5%
Knight (54)	Parallel	12	77	53	11	9	7.6	↓ 22.2%
Woods (58)	Crossover	12	46	45–58	85	85	6.6[c]	↑ 4.6%
Murkies (47)	Parallel	12	53	55	24	23	5.7	↓ 17%
Dalais (49)	Crossover	12	52	54	11	11	3.9[c]	↑ 29%
Washburn (51)	Crossover	6	34	51	51	51	3.7	↓ 4.7%
Burke (57,66)	Parallel	12	58	51	70	65	3.4	↓ 1.4%
St. Germain (52)	Parallel	24	80	50	24	21	2.2[c,d]	↑ 33.2%
Totals					315	305		
Trials involving isoflavone supplements								
Han (62)	Parallel	16	100	49	40	40	10.7	↓ 26.4%
Faure (64)	Parallel	16	70	54	35	38	9.8	↓ 35.8%
Upmallis (60)	Parallel	12	50	55	63	59	8.6[e]	↓ 9%
Hochanadel (65)	Crossover	12	100	45–55	11	11	4.5[c]	↑ 27.0%
Scambia (61)	Parallel	6	50	54	19	20	4.3	↓ 19.5%
Totals					168	168		
Trials excluded from regression analysis and reason for exclusion								
Quella (59)—cancer patients	Crossover	4	—	>18	155	155	7.3	↓ 1%
van Patten (55)—Cancer patients	Parallel	12	—	55	64	59	7.3	↑ 8.4%
Kotsopoulos (53)—no data on frequency	Parallel	12	—	59	40	33	NA	Decrease in severity, 3.7%
Balk (56)—no data on frequency	Parallel	24	—	57	12	7	NA	Increase in severity, 25.8%
Brzezinski (48)—not blinded	Parallel	12	—	52	36	78	NA	Improvement in hot flush score, 19%
Albert (63)—no control	Single arm	16	—	>45	0	151	7.12[c]	↓ 57.9%
Totals					307	483		

NA, not available.
[a]Represents average of control/placebo and soyfood/isoflavone supplement groups.
[b]Unless otherwise indicated, refers to changes in hot flush frequency.
[c]Data on hot flush frequency provided by authors via personal communication.
[d]Only the isoflavone-rich soy protein and the whey group were considered for analysis; results from week 12 of study.
[e]Values estimated from figure in published article.

ment in the soy group lessened as compliance worsened. One additional trial found that isolated soy protein, when consumed two times per day, significantly reduced hot flush severity (although not incidence), compared with the control diet or with consumption of the same amount of isolated soy protein but in one sitting per day.[51]

In contrast to the soyfood trials, four of the six remaining isoflavone supplement trials found that women in the active arm experienced a statistically significant decrease in hot

flush frequency; however, in one of these four studies, the results were significant at 6 weeks ($P = .0275$) but only marginally significant at 12 weeks ($P = .078$).[60] Of the two trials that did not find isoflavone supplements to be effective at any point, one involved only 11 subjects[65] and the other was a large, 4-week trial that involved breast cancer patients, two thirds of whom were taking tamoxifen.[59] This latter trial was the only study conducted for such a short duration. The U. S. Food and Drug Administration (FDA) recommends that trials evaluating the efficacy of drugs such as HRT for alleviation of menopausal symptoms be continued for at least 3 months.[68] In any case, in those trials that found soy or isoflavones to be efficacious, differences between the inactive and active arms were apparent early on, and the gap between the two typically continued to increase beyond 4 weeks.[50,60]

The supplement trial by Han et al.[62] which reported a 26% decrease in hot flush frequency in the isoflavone group (relative to placebo), is particularly interesting because the subjects were specifically instructed to consume the isoflavones three times each day. This pattern is likely to result in higher serum isoflavone levels than would have been seen with consumption of the same total amount in one or two sittings per day, given the known half-life of isoflavones (6–9 hours).[25] The dose of isoflavones used in this trial (100 mg) was also at the high end among all trials, which would further increase serum isoflavone levels. Findings from the study by Han et al.[62] are consistent with the data from Washburn et al.[51] discussed previously.

The lack of statistical significance among the soyfood trials, in and of itself, should not be taken as an indication of a lack of efficacy, because the large placebo effect makes most of these trials underpowered to detect modest effects. Therefore, it is worthwhile to consider the absolute differences between the groups. Of the nine soyfood trials in which no statistically significant effects were found, three reported percentage decreases (absolute differences relative to control) in hot flush frequency or severity (3.7%,[53] 17.0%,[47] and 22.2%[54]), and six reported percentage increases (1.4%,[67] 4.6%,[58] 8.4%,[55] 19.0%,[52] 25.8%,[56] and 29.0%[49]). Although many of the soy trials were of small size, it is apparent that there is essentially an equal chance that women in the soy group will experience an increase rather than a decrease in symptomology. On this basis, it is hard not to conclude that soyfoods lack efficacy.

If that is the case, is one to conclude that isoflavone supplements are more efficacious than soyfoods? First, it is important to acknowledge in addressing this question that the isoflavone supplement trials involved a total of only 323 women in each arm, and that the largest trial[59] ($N = 155$) did not report a statistically significant decrease in hot flush frequency (although, as noted previously, that trial involved breast cancer patients). With this small number of subjects, the favorable findings may be due to chance. Also, hot flush frequency decreased only slightly in the placebo group in two of the four supplement trials, in one[60] by less than 20%, and in another[62] by only 1%. Certainly, decreases of even 25% in the placebo group would have prevented statistically significant effects from being observed between the placebo and isoflavone groups in both trials. But these trials did involve 63[60] and 40[62] women in the placebo groups and therefore should not be dismissed.

The explanation that the results observed were due to "chance" is appealing because there is no obvious biological basis for thinking that isoflavones and soyfoods would differentially affect menopausal symptoms. Isoflavones are the only components of soy thought to be responsible for the hypothesized effects on hot flushes. Furthermore, the bioavailability of isoflavones from soyfoods is similar to that of supplements,[25] and the amount of isoflavones to which women were exposed was similar in the soyfood and the isoflavone supplement trials. Still, differences in "isoflavone delivery vehicle" cannot be completely dismissed as an explanation for the apparent discrepancy in results between the soyfood and the isoflavone supplement trials. However, there is at least one other, even more attractive explanation: that the supplement trials produced favorable findings compared with the soyfood trials because, on average, the baseline level of hot flush frequency was higher among the participants in the supplement trials.

In the four supplement trials in which statistically significant beneficial effects were observed, the number of hot flushes per day initially was 10.7,[62] 9.8,[64] 8.6,[60] and 4.3.[61] Three of these values are on the very high end among all trials conducted. Interestingly, in the three trials in which women in groups fed soyfoods reported markedly fewer hot flushes (only one of which was statistically significant), the number of initial hot flushes per day was 11.2,[50] 7.6,[54] and 5.7.[47] As with the supplement trials, these values are also on the high end.

In contrast, the number of initial hot flushes per day for women in the soyfood trials that did not report decreases was 7.3,[55] 6.6,[58] 3.9,[49] 3.7,[51] 3.4,[67] and 2.2.[52] Furthermore, of these six studies, the one with the highest initial hot flush frequency (7.3/day) involved breast cancer patients, one third of whom were taking tamoxifen.[55] Consistent with the hypothesis proposed here, that soy/isoflavones are effective in women who have more frequent hot flushes, are the results from two trials that examined only severity, neither of which reported beneficial effects of soyfoods. Women in these two trials reported initial values of 0.84[53] and 1.3[56] on a three-point severity scale (0, none; 1, mild; 2, moderate; 3, severe). Although it is not possible to directly translate degree of severity into frequency, it would appear that women in these two groups were not terribly bothered by their symptoms.

Figure 1 presents the correlation between initial frequency of hot flushes and treatment efficacy (i.e., the absolute percentage change in the soy/isoflavone group minus that in the control/placebo group). Based on a simple regression analysis of the whole (see Table 1 and text for reasons four additional trials were excluded from analysis) data set (13 trials), there was a statistically significant relationship ($P = .01$) between initial hot flush frequency and treatment efficacy. More specifically, initial hot flush frequency explained about 46% of the treatment effects, and hot flush frequency decreased about 5% (above placebo/control effects) for every additional initial hot flush per day in women whose initial hot flush frequency was ≥5. Assuming a 20% placebo effect, these findings indicate, for example, that women having approximately 10 hot flushes per day who begin to consume soy or isoflavones can

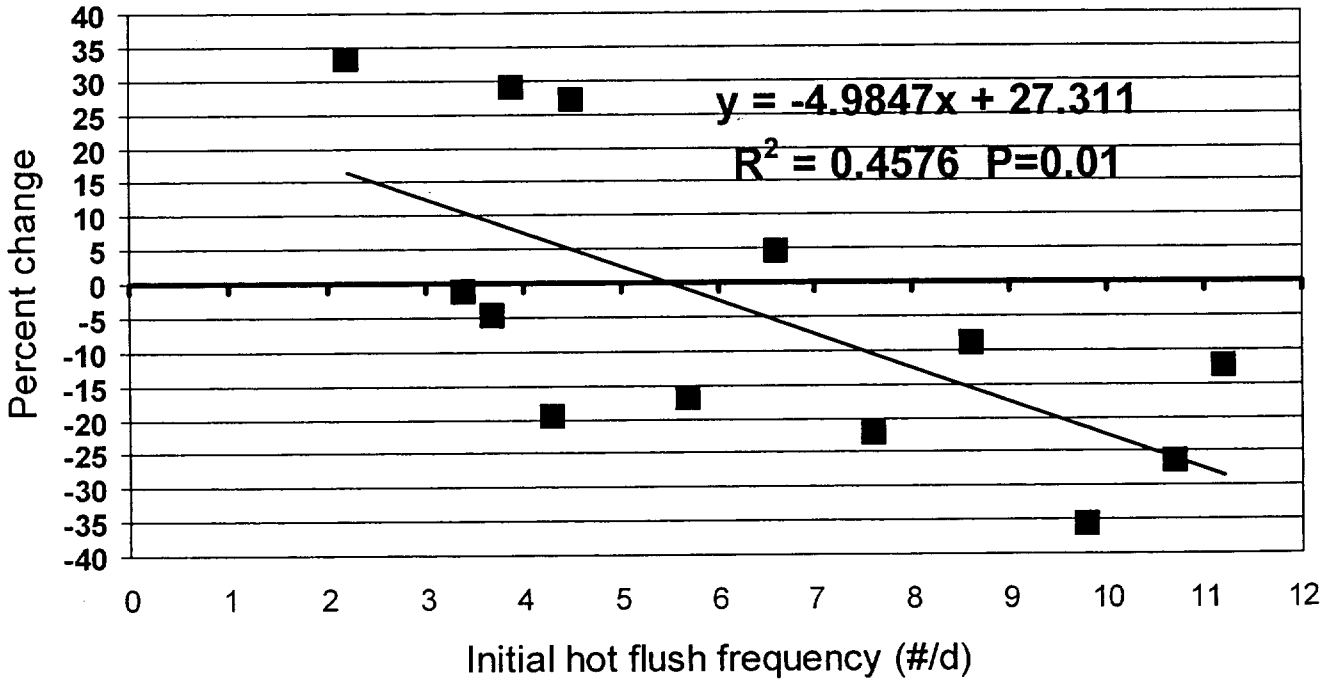

FIG. 1. Relationship between initial hot flush frequency and treatment efficacy of soyfoods and isoflavone supplements.

expect to experience a reduction of about 4.5 hot flushes per day, whereas women with an initial 7 hot flushes per day will experience a reduction of about 3 hot flushes per day. Further analysis of covariance (data not shown) suggested that treatment efficacy was greater in those trials utilizing a parallel, rather than a crossover, design. There is no obvious reason why efficacy would be greater in the parallel trials, but the observation that efficacy is greater in women with more frequent hot flushes is certainly biologically plausible if greater frequency reflects a lower estrogen status. In this type of hormonal environment, the estrogen-like properties of isoflavones may be more apparent.

Given the significant correlation between frequency and efficacy, the recommendation by the FDA that trials examining the efficacy of drugs for menopausal symptom relief include women with more than 60 moderate to severe hot flushes per week is particularly germane.[67] Trials adhering to such guidelines would obviously place them at the very highest frequency level among women in the soy/isoflavone trials included in this review. In fact, all four of the trials meeting this recommendation[50,60,62,64] found statistically significant beneficial effects of soyfoods/isoflavones. Nevertheless, at least three caveats need to be cited when evaluating the hypothesis that the efficacy of soy/isoflavones is related to initial hot flush frequency.

First and foremost, the final analysis included only 13 data points. Second, four trials that did not show efficacy were among those excluded from the correlation. Two trials involving breast cancer patients[55,59] were excluded on the premise that breast cancer patients (regardless of tamoxifen use) may respond differently to soy and isoflavones than healthy women do. Whether this is the case is a matter of debate.[69] Two trials that examined only severity were also excluded because of the lack of data.[53,56] Third, in a small subgroup analysis, Burke et al.[67] failed to find that women with four or more hot flushes per day responded differently to soy than did women with fewer hot flushes per day (the average number of hot flushes per day was 7.4 in the placebo group and 9.0 in the soy group). Among women with more frequent hot flushes, the frequency decreased by 59.5% and 62.2% in the control and soy groups, respectively.[67] However, it is clear that with a placebo effect this large, a modest effect of soy may have been obscured.

It should be noted that the correlation as calculated leaves open the possibility that soy/isoflavones could actually increase hot flushes in women with infrequent hot flushes. But this appears doubtful, and the findings from the three trials that actually reported relatively large increases relative to the control/placebo groups[49,52,65] were likely a result of chance. Two of these three trials involved only 11 subjects in each study arm.[49,65] The other trial[52] involved perimenopausal women, a difficult group to study because of fluctuating hormone levels and because perimenopausal women are reported to experience a higher placebo response than postmenopausal women.[70] Also, the primary endpoint of this particular trial was bone mineral density; the data on hot flushes were collected retrospectively.

Furthermore, it is important that all three trials that reported increases in hot flush frequency relative to placebo also noted decreases in comparison to the baseline values in the soy/isoflavone groups. In the perimenopausal trial[52] and in the trials by Dalais et al.[49] and Hochanadel et al.,[65] hot flush frequency decreased by approximately 17%, 22%, and 12%, respectively, relative to baseline values. Therefore, in contrast to other SERMs such as tamoxifen[71,72] and raloxifene,[73] there is no evidence to suggest that soyfoods or isoflavones exacerbate hot flushes.

Finally, trials examining the impact of isoflavones derived from red clover provide some support for the hypothesis that soyfoods and soybean isoflavones are effective primarily in women with frequent hot flushes. Van de Weijer et al.[20] found that Promensil® reduced hot flush frequency to a statistically significantly greater extent than did placebo. To be enrolled in this trial, women had to have at least 5 hot flushes per day. The authors suggested that the failure of previous trials to show that red clover isoflavones were efficacious may have occurred

because of the inclusion of women who were only mildly symptomatic.[22,23]

CLINICAL RELEVANCE

One might question the clinical relevance of the soy/isoflavone effect because those trials in which soy/isoflavones were effective mostly reported decreases of less than 20% compared with the inactive arm. Clearly, the effects are less than that of estrogen.[74] However, for at least three reasons this degree of improvement should not be dismissed. First, in women with severe symptoms, any improvement is likely to be welcomed. Furthermore, it is not just the soy/isoflavone effect that needs to be considered, but also a possible placebo effect accompanying the act of using soyfoods or isoflavone supplements, such that the overall improvement is likely to be as high as 50%. For women who are having ten hot flushes per day, five per day may look very appealing. Second, some women are likely to experience above-average responses; for these women, soy/isoflavones may be very effective. And third, an intriguing but still speculative body of research suggests that isoflavones and isoflavone-rich soy protein may have skeletal benefits[75–78] and may also reduce coronary heart disease risk by improving arterial compliance[26] and flow-mediated dilation.[27] Of course, soy protein also has a modest cholesterol-lowering effect.[79]

Thus, there appear to be several reasons for menopausal women to ingest isoflavones through foods or pills. Importantly, there is no reason to suspect that isoflavones pose any of the disease risks observed in the HERS I/II and WHI trials.[80] Consequently, although health professionals should take a guarded approach and emphasize that the data are inconsistent and the effects are likely to be modest, they can in good conscience recommend that their clients with frequent hot flushes try soy/isoflavones for relief of their symptoms. In respect to dose, based on the results from the hot flush trials and from studies examining other possible benefits, an initial dose of 50 mg isoflavones per day can be recommended, with an upper limit of approximately 100 mg/day.

FUTURE RESEARCH

In view of the hypothesis suggested in this paper, future trials involving soyfoods and isoflavone supplements are warranted but should focus on women who have frequent hot flushes. In addition, within a given trial, investigators should examine whether there exists a correlation between initial hot flush frequency and the extent of reduction of symptoms among trial subjects. Parenthetically, it may be possible to do this type of analysis retrospectively, using the raw data from existing trials. Although it is unlikely that any single future trial will be sufficiently large to prove or disprove the proposed hypothesis, the results from several smaller trials, even if the findings are not statistically significant, can help to establish whether initial hot flush frequency is related to efficacy.

Ideally, trials should be large enough to also consider the impact of isoflavone metabolism on efficacy. A recent Japanese cross-sectional study of 180 women given a standardized questionnaire to evaluate the severity of menopausal symptoms found that those who produced equol (from the action of intestinal bacteria on the soybean isoflavone daidzein, occurring in approximately 30% to 50% of those who consume soyfoods) recorded the least severe symptomology.[81] Therefore, investigators should establish whether efficacy differs according to equol production. Some research suggests that equol is more estrogen-like than its parent isoflavone daidzein, which could account for this observation.[82–85] There are also large variations in serum isoflavones among subjects in response to the intake of similar amounts of isoflavones.[25,86] Therefore, serum isoflavone levels or perhaps isoflavone excretion should also be considered as a possible variable affecting efficacy.

Finally, it would be interesting to determine whether isoflavones are more effective at preventing the onset of hot flushes when consumed before the menopause (rather than alleviating them once they have already begun). This might account for the very low incidence of hot flushes in Japan. Although this hypothesis would obviously be quite difficult to test clinically, additional epidemiological research could provide some insight.

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