

Health impact of childhood and adolescent soy consumption

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Soyfoods have been intensely researched, primarily because they provide such abundant amounts of isoflavones. Isoflavones are classified as both plant estrogens and selective estrogen receptor modulators. Evidence suggests that these soybean constituents are protective against a number of chronic diseases, but they are not without controversy. In fact, because soyfoods contain such large amounts of isoflavones, concerns have arisen that these foods may cause untoward effects in some individuals. There is particular interest in understanding the effects of isoflavones in young people. Relatively few studies involving children have been conducted, and many of those that have are small in size. While the data are limited, evidence suggests that soy does not exert adverse hormonal effects in children or affect pubertal development. On the other hand, there is intriguing evidence indicating that when soy is consumed during childhood and/or adolescence, risk of developing breast cancer is markedly reduced. Relatively few children are allergic to soy protein, and most of those who initially are outgrow their soy allergy by 10 years of age. The totality of the available evidence indicates that soyfoods can be healthful additions to the diets of children, but more research is required to allow definitive conclusions to be made.

INTRODUCTION

Soyfoods play an important role in the cuisines of many Asian countries and have done so for centuries. The variety of foods made from soybeans makes it relatively easy to incorporate soy into the diet. Traditional Asian soyfoods include fermented versions such as miso, natto, and tempeh and unfermented versions such as edamame (green soybeans), tofu, and soymilk.

The availability and consumption of soyfoods has markedly increased in the United States as well as in many other Western countries over the past 25 years. In many Western countries, in addition to traditional Asian soyfoods, there exists a large variety of soy products that use whole soybeans or soy protein products such as isolated soy protein (ISP), soy protein

concentrate, or soy flour/textured vegetable protein as a base to mimic more traditional foods, such as soy-based meat and dairy analogues. These soy protein products are approximately 90%, 70%, and 50% protein, respectively.

Several factors account for the increased popularity of soyfoods. One is dietary recommendations calling for a shift toward more plant-based diets.¹ Another is the increased consumer interest in protein and the recognition that soyfoods are good sources of high-quality protein.² A third reason is that many consumers are aware of research suggesting that soyfoods may exert a number of health benefits.

Over the past 25 years, the health effects of soyfoods have been rigorously investigated. Much of this research is aimed at understanding the effects of

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soyfoods and soybean components, such as isoflavones, on chronic disease risk. Isoflavones have long been classified as phytoestrogens but, more recently, have come to be viewed as selective estrogen receptor (ER) modulators (SERMs).³ Isoflavones may also have effects independent of their interaction with ERs.⁴ Proposed benefits of soyfoods include protection against coronary heart disease,⁵ breast⁶ and prostate⁷ cancer, and osteoporosis⁸ and alleviation of menopausal symptoms.⁹

However, soyfoods are not without controversy. The presence of isoflavones in soybeans has raised concern, based mostly on studies in animals, that in some subpopulations, such as women with estrogen-sensitive breast cancer, soyfoods may exert untoward effects.¹⁰ However, extensive clinical research has consistently shown that isoflavones do not negatively affect markers of breast cancer risk,¹¹ and prospective epidemiologic studies have shown that postdiagnosis soy consumption by breast cancer patients is associated with reduced recurrence and improved survival.¹²

The contrast between the animal and human data is not surprising, as animal studies often poorly predict effects in humans.¹³ Furthermore, rodents metabolize isoflavones very differently than humans.¹⁴ Nevertheless, questions have arisen about the possibility that soy adversely affects development. Most attention in this regard has been directed toward infants consuming soy-based infant formula (SIF),¹⁵ but concerns about the impact of childhood soyfood consumption on development also exist.¹⁶ Not unexpectedly, in comparison with research involving adults, relatively little soy-related research involving children has been conducted, and much of the research that has been conducted has involved malnourished individuals.¹⁷

For several reasons, it is critical to establish whether soyfood consumption early in life is safe and potentially beneficial. Because childhood eating habits track into adulthood,¹⁸ young soy consumers will be more likely to consume soy during adulthood and, therefore, to possibly reap the proposed benefits of soy consumption as adults. Also, evidence suggests that lifestyle and, in particular, diet early in life affect the likelihood of developing a number of chronic diseases.^{19,20} Existing data, discussed below, show this is the case for soy and epidemiologic studies indicate soy consumption early in life is associated with a lower risk of breast cancer.²¹ Finally, there is the possibility that soy could exert immediate benefits on long-term outcomes when consumed early in life because, in some cases, chronic diseases begin to develop during adolescence.²² Research shows that soyfoods are generally well accepted by children, so there is an opportunity for these foods to become part of the diets of young people.^{23,24}

Many reviews addressing the short-term health consequences of SIF have been published, but no reviews were identified that specifically evaluated soyfood consumption by children and adolescents.²⁵ This omission is especially glaring given evidence that isoflavone bioavailability appears to be higher in children than adults.²⁶ Therefore, this review focuses on the health consequences of childhood and adolescent soy consumption, considering both short-term and long-term effects. Before discussing this relationship, background information on the nutrient content of soyfoods, isoflavones, and Asian soyfood intake is provided. To identify relevant research, PubMed was searched using the search terms “soy” or “soya” or “isoflavones” and “children.” Each of the identified studies was evaluated to determine relevance. In addition, references were searched within relevant papers for possible inclusion.

NUTRIENT CONTENT OF SOY

In comparison with other legumes, the macronutrient composition of the soybean is quite different. It is much higher in fat, much lower in carbohydrates, and moderately higher in protein.²⁷ However, the nutrient content of specific types of soyfoods and soy products can vary quite markedly from the bean according to the manufacturing processes used to produce them. In general, the nutrient content of soyfoods has been shown to help children meet US dietary guidelines.^{28,29}

The quality of plant proteins is considered inferior to animal proteins; however, this is not the case for soy protein. The protein digestibility–corrected amino-acid score for soy protein ranges from approximately 0.9 to 1.0 depending upon the source from which the protein is derived.² Most research on soy protein quality has focused on modern soy products such as ISP and soy protein concentrate, but the limited evidence indicates that the protein from traditional Asian soyfoods is also very well digested.^{30,31}

Because higher protein diets may aid in body-weight management³² and research shows consuming protein in excess of the US recommended daily allowance may augment the impact of physical activity on bone mineral density,³³ it is important for children to have access to healthful protein sources. Furthermore, the current recommended daily allowance may significantly underestimate the protein needs of children.³⁴

One possible advantage of traditional Asian soyfoods for people with diabetes is their low carbohydrate content.³⁵ Furthermore, much of the carbohydrate is comprised of oligosaccharides (predominately stachyose),³⁶ which, because they are poorly digested by intestinal enzymes, stimulate the growth of colonic bacteria considered to be advantageous to the host. For this

reason, soybean oligosaccharides are classified as prebiotics.³⁷ However, as a result of processing, many soy products, including tempeh,³⁸ tofu,³⁸ and ISP³⁹, lack significant oligosaccharide content.

Of the approximate 40% of the calories in soybeans comprised of fat, approximately 12% is saturated, 29% is monounsaturated, and 59% is polyunsaturated, although these figures vary according to soybean variety.⁴⁰ The fatty-acid composition of soybean oil is especially noteworthy because it contains ample amounts of the essential fatty acids linoleic acid and α -linolenic acid in a ratio of approximately 8:1, although this ratio varies among soybean varieties.⁴⁰ Because it is used so widely, soybean oil accounts for >40% of the US intake of both linoleic acid and α -linolenic acid.⁴¹

Like many legumes, the soybean provides significant amounts of a number of vitamins and minerals; most notable in this regard are folate and other B vitamins and potassium.²⁷ The latter is especially important because the mineral has been identified as a problem nutrient in the United States, in that its intake falls substantially below recommendations.⁴² Also noteworthy is that natto, a traditional Japanese soyfood produced by fermentation, is an extremely rich source of vitamin K.⁴³

Soybeans are relatively high in iron,²⁷ which is not surprising because many plant foods are actually rich in this mineral.^{44,45} However, discussions of the impact of soyfood intake on mineral status focus more on bio-availability than content. The absorption of calcium and iron from soy is an important consideration because soyfoods often replace foods that are high in these 2 nutrients.

Unexpectedly, even though soybeans and soyfoods contain ample amounts of both phytate and oxalate, calcium absorption from soybeans is quite good.⁴⁶ In fact, fractional calcium absorption from calcium-fortified soymilk^{47,48} and tofu made by coagulating soymilk with a calcium salt⁴⁹ is similar to the absorption of calcium from cow's milk. Many children often fail to consume sufficient calcium,⁵⁰ the consequences of which will be low bone mineral density and an increased risk of bone fracture during adulthood.⁵¹ Therefore, for many children, especially those who do not regularly consume dairy products, calcium-fortified soy products represent important options for meeting calcium needs. It is notable in this regard that a Japanese observational study that involved 262 girls and 286 boys aged 10–15 years found that an increased intake of soy products was positively associated with the annual increase in the stiffness index (a measurement reflecting bone mineral density) in girls but not boys.⁵²

The long-held view that the iron in soyfoods is poorly absorbed is contradicted by newer research showing that iron absorption from soy is quite good.

This appears to be the case because much of the iron in soy is in the form of ferritin, a form of iron thought not to be affected by inhibitors of iron absorption such as phytate.^{53,54} Furthermore, in contrast with older understanding,⁵⁵ research indicates that chronic consumption of a high-phytate diet causes a lessening of the effects of phytate on iron absorption.⁵⁶ Consequently, acute studies likely have underestimated the absorption of minerals from soy.

Finally, zinc absorption from soy is lower than from animal products but only moderately so.⁵⁷ Nevertheless, soy is not a particularly good source of this mineral because, unlike iron, the zinc content of soybeans is relatively low.⁵⁸ It is difficult to assess zinc status,⁵⁹ so individuals consuming little in the way of animal products should consider using zinc-fortified foods and/or taking a zinc supplement.⁶⁰

ISOFLAVONES

Among commonly consumed foods, soyfoods are uniquely rich sources of isoflavones. This point is illustrated by the mean daily isoflavone intake of 30–50 mg among older individuals in Japan,⁶¹ whereas in the United States⁶² and Europe,⁶³ daily per capita intake is <3 mg. Isoflavones are diphenolic molecules that bind to both ERs. Consequently, they can act as ER agonists (Figure 1). However, as already noted, isoflavones are classified as SERMs in addition to phytoestrogens.³ As the name implies, SERMs have tissue-selective effects. The ability of isoflavones to function as SERMs almost certainly is because they preferentially bind to and activate ER β in comparison with ER α .³

The 2 ERs have different tissue distributions and often perform divergent and, at times, opposing functions in the body when activated. For example, in breast tissue, ER β activation appears to oppose the proliferative effects of ER α activation.⁶⁴ The clinical literature is replete with examples of isoflavones exerting ER-agonist effects in some tissues⁹ but having no such effects in others.⁶⁵ On the other hand, there are relatively few clinical examples of isoflavones acting as true ER antagonists.^{66–68}

The isoflavones in soybeans and unfermented soyfoods are present primarily as glycosides (the sugar accounts for approximately 40% of the total molecular weight); fermentation converts the glycosides to aglycones to varying degrees.⁶⁹ Some studies show the aglycone form of isoflavones is absorbed faster and to a greater extent than the glycoside form.^{70–72} However, data are conflicting on this point because studies also show that, although aglycones are absorbed more quickly than glycosides, total absorption is similar or even reduced in comparison with aglycones.^{73–75}

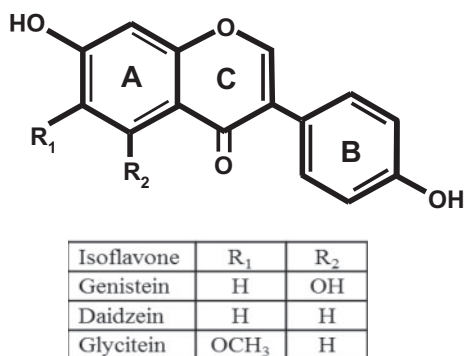


Figure 1 Aglycone structure of soybean isoflavones.

The recommended approach and the approach used in this article when referring to an amount of isoflavones is to refer to the aglycone equivalent weight.

There is considerable variation in isoflavone metabolism among individuals, but the one difference that is potentially most relevant from a physiological perspective is that only approximately 25% of non-Asians are considered equol producers, whereas this is true for approximately 50% of Asians. In 2002, Setchell et al.⁷⁶ proposed that individuals who host the types of intestinal bacteria that are able to convert daidzein into equol are more likely to benefit from soyfood consumption. One study reported that equol production is developmentally regulated and initially related to diet composition. More specifically, at birth, infants are unable to produce equol, but by age 3, 25% and 50% of breast-fed and formula-fed infants produce equol, respectively.⁷⁷ Also, a child's equol production is associated with the mother's equol producer status.⁷⁸

In soybeans, the 3 isoflavones (genistein, daidzein, and glycitein) and their respective glycosides account for approximately 50%, 40%, and 10%, respectively, of the total isoflavone content.⁶⁹ Each of the 3 soybean isoflavones is a distinct chemical entity with different binding affinities for ERs, but for most endpoints, genistein is considered to be the most potent isoflavone.^{9,79}

Finally, traditional soyfoods contain approximately 3.5 mg of isoflavones per gram of protein,^{61,80} whereas more refined soy products can lose as much as 80% of their isoflavone content during processing.⁶⁹ On average, traditional soyfoods contain 20–30 mg of isoflavones per serving (eg, 250 mL of soymilk made from whole soybeans or 100 g of tofu).⁶¹

CHILDHOOD SOY INTAKE IN ASIAN POPULATIONS

Among ethnic Chinese, nearly all soy consumed is in unfermented form,^{5,81,82} whereas in Japan, approximately

equal amounts come from unfermented (primarily tofu) and fermented foods (primarily miso and natto).^{83,84} In 2006, a review by Messina et al.⁶¹ reported that adult mean soy protein and isoflavone intakes in Japan and Shanghai range approximately 7–12 g/d and 30–50 mg/d, respectively. Shanghai is a high-soy-consuming region within China.⁸⁵ Soy intake in Japan and Shanghai is roughly twice that in Hong Kong⁸⁶ and Singapore,⁸⁷ whereas the intake in Taiwan⁸⁸ and Korea⁸⁹ falls in between these 2 extremes.

In comparison with adults, relatively little information is available on soy consumption by children. However, it is evident that in Asian populations soy is consumed at very early ages (Table 1). According to Nagata,⁹⁰ Japanese infants begin to consume soy products such as tofu and miso soup, which are common baby foods, between 6 and 12 months of age.

The regular consumption of soyfoods at early ages is evidenced by a survey of >400 Japanese boys and girls aged 3–6 years.⁹¹ Hsiao and Lyons-Wall⁹² noted that in their study of 66 Taiwanese boys and girls, soy products were introduced at a mean age of 1.9 years, primarily as soymilk (40%), tofu (40%), soybean curd jelly (9%), and other products (11%). A study of healthy children in Singapore aged <10 years found that 70% had consumed soy products, and of those that had, >95% had done so before the age of 18 months.⁹³ According to the authors, whether children were breast- or bottle-fed, they were introduced to rice and tofu at approximately 4 months of age.

More limited data are available from China, although a survey of almost 200 12-year-olds in Beijing found 41% normally included soymilk or tofu at breakfast.⁹⁴ Finally, a survey of 400 boys and 400 girls attending 4th and 5th grades in Daejeon, Korea, found that 62% liked (13% disliked) hard-boiled tofu and 67% liked (9% disliked) soft tofu soup, whereas only 42% liked (30% disliked) fermented soybean soup.⁹⁵

Information on childhood isoflavone intake is quite sparse (Table 1). Hsiao and Lyons-Wall⁹² reported a mean daily isoflavone intake of 36.6 mg among 8–9-year-old boys and girls in Taiwan, which is surprisingly high considering that Tai et al.⁸⁸ reported an isoflavone intake of 23–25 mg/d for middle-aged Taiwanese women. Having said this, Lee et al.⁹⁶ reported a mean daily isoflavone intake of 28.1 mg for 714 Korean middle-age and high-school students. This figure is similar to the 30.3 mg/d reported for 2–18-year-old participants in the 2008 Korea National Health and Nutrition Examination Survey who consumed the recommended intake of fruits and vegetables (n = 512), but it was much higher than the intake of the participants who did not meet this recommendation (n = 1716; 4.9 mg/d).⁹⁷ Park et al.⁹⁸ reported a mean daily isoflavone intake of only approximately 8 mg for 8-year-old children in

Table 1 Estimated adolescent soyfood and isoflavone intake for select countries

Reference	Location	Participants	Age, y ^a	Intake ^b	
				Soyfoods, g/d	Isoflavones, mg/d
Messina et al. (2006) ⁶¹	Japan	Boys and girls (combined in 2 age groups)	1–6 7–14	~38 ~61	~14 ~20
Wada et al. (2011) ⁹¹	Japan	230 boys 198 girls	5.12 ± 0.89 5.14 ± 0.90 Range, 3–6	24.4 (21.7–27.4) 22.8 (20.0–26.0)	12.2 (11–13.6) 11.4 (10.2–12.8)
Lee et al. (2004) ⁹⁶	Korea	714 boys and girls	Middle and high school students	Not reported	28.1 19.7 (median)
Park et al. (2007) ⁹⁸	Korea	426 boys 365 girls	9.8	Not reported	8.3 7.2
Kim et al. (2010) ⁹⁹	Korea	12 girls (first quartile intake) 12 girls (fourth quartile intake)	10.3 ± 0.5 10.2 ± 0.7	Not reported	3.0 ± 0.9 13.3 ± 3.4
Lee et al. (2013) ⁹⁷	Korea	512 boys and girls 1716 boys and girls	2–18 2–18	Not reported	30.3 ± 4.8 (meet fruit and vegetable intake recommendations) 4.9 ± 0.6 (do not meet fruit and vegetable intake recommendations)
Hu et al. (2014) ¹⁰⁰	China	174 (87 boys and 87 girls)	1–14	Not reported	531.7 ± 343.8 µg/kg body weight 75th percentile, 726 µg/kg body weight
Hsiao and Lyons-Wall (2000) ⁹²	Taiwan	66 boys and girls	8–9	150.1	36.6 mg
Leung et al. (2001) ¹⁰¹	Hong Kong	24 boys, 27 girls	4–14	Soymilk ~40 g/d (only food listed)	10 meals/wk

^aData are mean, mean ± standard deviation, and/or range.

^bData are mean, mean (95% confidence interval), or mean + standard deviation.

Korea, which is similar to what Kim et al.⁹⁹ found in a small study.

Wada et al.⁹¹ reported a mean intake of approximately 12 mg/d for 5-year-old Japanese boys and girls, which is similar to the estimate of 14 mg/d for children ranging in age from 1 to 6 years based on data from the Japanese National Nutrition Survey.⁶¹ Only 1 study that reported isoflavone intake for Chinese children was identified. This study found that for children ranging in age from 1 to 14 years, mean isoflavone intake was a little greater than 500 µg/kg body weight.¹⁰⁰ In Hong Kong, although data on isoflavone intake were not available, Leung et al.¹⁰¹ reported that young boys consumed approximately 10 soy-containing meals per week. Finally, Nagata⁹⁰ estimated that 6-month-old Japanese infants consume approximately 3.1 mg of isoflavones per day.

SOY AND CHILDREN: HEALTH EFFECTS

As noted, Asian children have historically consumed soy beginning at very early ages. However, in the United States, a large percentage of infants are exposed to soy soon after birth because of the widespread use of

SIF.^{102,103} There is general agreement that during the first year of life there are no obvious or significant growth differences between infants fed SIF and those fed cow's milk formula.^{25,102,104} Nevertheless, the resulting high isoflavone exposure in infants has led to interest in studying the health effects of SIF in greater depth.^{105,106}

A thorough discussion of SIF specifically is outside the scope of this review, so only a few general comments are made, primarily to draw a distinction between SIF use by infants and soyfood consumption by children. A recent US survey found that among the 81% of infants who were fed formula or regular milk, 11.6% consumed SIF.¹⁰³ In infants fed SIF, isoflavone exposure, depending upon the age, ranges approximately 4.5–8.0 mg/kg because there are approximately 40 µg of isoflavones per milliliter of finished product.¹⁰⁵ Not surprisingly, because soyfoods comprise only a part of the childhood diet, intake on a body weight basis is much lower in children consuming 1 or 2 servings of soyfoods daily. Furthermore, it is recognized that the very earliest (first few months) developmental stages of life are most susceptible to endocrine disruption.^{107–110}

In any event, in 2009, the US National Toxicology Program Center for the Evaluation of Risks to Human

Reproduction evaluated the safety of SIF (they also did so in 2006 and, although their initial conclusions supported the safety of SIF, no final report was issued^{109,110}). The conclusion of the 14-member panel of independent scientists was that there was “minimal concern” about the safety of SIF, although there was recognition of the need for long-term data.¹¹¹ In response to the National Toxicology Program report, the American Academy of Pediatrics (AAP) opined that in their view there was negligible concern.

Hormone levels

Two clinical studies and one epidemiologic study that examined the impact of soy intake on reproductive hormone levels in children were identified. A Japanese cross-sectional study that involved 230 boys and 198 girls aged 3–6 years found that, after multiple adjustments, soy intake was significantly inversely related to urinary estrone and estradiol in boys and positively related to urinary testosterone and androstenediol in girls.⁹¹ Similar findings were reported for isoflavone intake. Fourth quartile median isoflavone intake in boys and girls was 26.5 and 24.0 mg/d, respectively. The clinical implications of the findings from this study, if any, are unclear.

In contrast with this cross-sectional study, no effects of isoflavone exposure were noted in the 2 clinical studies, although both involved small numbers of participants. In 1, Maskarinec et al.¹¹² enrolled US girls aged 8–14 years for 8 weeks during which time they were instructed to consume 1 daily serving of soy that provided approximately 30 mg of isoflavones. Of the 17 (average age = 10.7 ± 2.0 y) of 20 girls who completed the study, average isoflavone intake was approximately 27 mg/d. After the intervention, none of the changes in hormone levels were statistically significant, except for a small increase in dehydroepiandrosterone levels ($P = 0.007$). The increase in estrone excretion was close to statistical significance ($P = 0.09$), although this was not true for estradiol ($P = 0.36$). The authors noted that in their study, because sex steroid levels were associated with pubertal development based on Tanner stages, their results support the validity of the sex steroid measurements.¹¹²

The second intervention was a small 8-week cross-over study that involved 12 hypercholesterolemic Israeli children (8 females) aged 5.3–11.2 years, who received in random order a placebo or 16 or 48 mg/d of isoflavones in tablet form.¹¹³ There was a 2-week washout between treatments. Despite the high dose of isoflavones, there were no effects on serum levels of estradiol (measured in girls only), testosterone (measured in boys only), follicle stimulating hormone, luteinizing

hormone, thyroid stimulating hormone, free thyroxine (T4), and total triiodothyronine (T3).¹¹³ Limitations of this study are the small sample size and that the data were not presented separately for boys and girls.

More data on thyroid function come from a study that involved 139 girls and 129 boys aged 8–15 years from the Czech Republic, which found a very modest association between circulating isoflavone levels and measurements of thyroid function.¹¹⁴ However, when children were divided into 2 groups (soyfood eaten within the past 24 hours, yes or no) thyroid stimulating hormone and free T3 levels did not differ between groups, although free T4 levels were higher in the soyfood consumers. An Iranian case-control study of nearly 600 children aged 6–12 years also assessed thyroid function but only by determining whether risk of goiter was impacted by soy intake, which it was not.¹¹⁵ Although the findings from these 2 epidemiologic studies are mentioned here, they are likely of limited utility because appreciable amounts of soy are not consumed in either the Czech Republic or Iran. As first argued more than a decade ago, epidemiologic studies conducted outside of Asia that involve the general population are of questionable value for providing insight into the health effects of soy because intake is so low.¹¹⁶

Finally, it is worth noting that there is a wealth of clinical evidence showing neither soy nor isoflavones affect thyroid function in euthyroid adults,^{61,117} a conclusion recently reached by the European Food Safety Authority after it conducted an extensive review of the literature.¹¹⁸ Similarly, the lack of effect of isoflavones on reproductive hormone levels in the 2 previously cited clinical trials that involved children^{112,113} is consistent with clinical research in adults showing that isoflavone exposure from soyfoods or supplements has no effects on circulating testosterone in men¹¹⁹ or estrogen levels in men¹²⁰ or women.¹²¹ A study in infants fed SIF also found no correlation between blood isoflavone levels and concentrations of estrone, estradiol, testosterone, luteinizing hormone, and follicle stimulating hormone.¹²²

Puberty

Soyfoods support the normal growth and development of children¹²³ and improve growth of malnourished preschoolers.^{124,125} Nevertheless, there is increasing interest in understanding the impact of soy on development because pubertal characteristics are occurring at an earlier age in children throughout the world, as evidenced by a number of changes, including earlier onset of menarche (Table 2).^{126–136} Earlier menarche has been implicated in the etiology of breast and ovarian cancer, so these trends are of concern.^{137,138}

Table 2 Trends in estimated average age of menarche over time in select countries

Reference	Country	Period of study	Average age, y	
			Start of study	End of study
Junqueira et al. (2003) ¹²⁸	Brazil	1932–1977		
		— Girls with <8 y of education	13.4	11.7
		— Girls with >8 y of education	12.4	12.2
Harris et al. (2008) ¹²⁹	Canada	1933–1988	13.2	12.5
Hosokawa et al. (2008) ¹³⁰	Japan	1930–1985	13.8	12.6
Cho et al. (2010) ¹³¹	Korea	1920–1985	16.9	13.8
Morris et al. (2011) ¹³²	United Kingdom	1908–1993	13.5	12.3
Cabanes et al. (2009) ¹³³	Spain	1925–1962	13.7	12.8
Talma et al. (2013) ¹³⁶	The Netherlands	1955–2009	13.7	13.1
Himes (2006) ¹³⁵	United States	1948–(1988–1994) ^a	12.9	12.6

^aEnd range of 1988–1994 reflects the period of the National Health and Nutrition Examination Survey III from which the final average was collected.

Many factors potentially contribute to this trend, such as increasing adiposity¹³⁹ and even possibly xenoestrogen exposure.^{140,141} Diet may also play a role: epidemiologic studies have found that both total protein and animal protein intake is associated with earlier menarche and earlier development of pubertal characteristics.^{142,143}

There has been only limited investigation of the effects of soy on pubertal development. This issue received some attention as the result of a case report from Brazil describing a nearly 5-year-old girl who presented with premature thelarche that was attributed to an intake of approximately 40 mg/d of isoflavones from soyfoods.¹⁴⁴ Blood isoflavone levels were not determined, however. The parents were advised to limit their daughter's soy consumption to once per week. Although this case report is certainly intriguing, because no follow up examination was described until the patient was almost 9 years of age, when it was said that the patient was at the same stage of pubertal development as her peers and had maintained the growth rate and bone development compatible with her chronological age, insight gained from this report is limited.

Two Korean case-control studies found that urinary isoflavones in girls with precocious puberty were higher than in children serving as controls.^{145,146} In 1 of the studies, 108 girls (aged 8.6 ± 0.8 y) with central precocious puberty were compared with 91 age-matched controls (aged 8.5 ± 0.8 y).¹⁴⁵ Serum concentrations of total isoflavones were significantly greater in the central precocious puberty group compared with the control children (77.9 ± 57.2 nmol/L vs 62.9 ± 40.2 nmol/L; $P = 0.0009$), although there was a large overlap in values between groups as evidenced by the standard deviations. Nevertheless, the prevalence of precocious puberty was significantly higher in children with a serum isoflavone level ≥ 30 nmol/L (a cutoff arbitrarily chosen by the authors) than it was for those with a serum level < 30 nmol/L ($P = 0.0008$). However, when assessing

risk of central precocious puberty associated with serum isoflavones, the only factors adjusted for were age, height, and body weight.

The second Korean study involved 150 girls (aged 8.91 ± 1.40 y) with precocious puberty and 90 control subjects (aged 8.50 ± 1.68 y).¹⁴⁶ The plasma genistein concentration was significantly higher in the girls with precocious puberty than in the control girls (8.12 ± 12.71 ng/mL vs 3.04 ± 4.21 ng/mL; $P = 0.0008$), but there were no differences between groups for daidzein or equol. As noted previously, equol is an intestinal bacterially derived metabolite of daidzein.¹⁴⁷ Further, it appears that no statistical adjustments were made for potentially confounding variables when comparing groups.

In Korea, there has been an ongoing trend for girls to begin menstruating at younger ages,¹³¹ as is true in many regions of the world. One analysis identified many lifestyle factors that appear to influence age of menses (AOM) among girls in Korea.¹³¹ Furthermore, because there is no evidence that soy consumption has increased over the past several decades in Korea, it would appear that soy intake is not contributing to the observed trend in the earlier AOM. It should be emphasized that AOM is also trending earlier in countries where soyfoods are not consumed.

In contrast with the 2 Korean studies,^{145,146} a prospective study that involved 1239 girls living in the United States who were aged 6–8 years and were followed for 7 years found no relationship between pubertal development and urinary isoflavone excretion.¹⁴⁸ In fact, another US study found isoflavone exposure was associated with delayed breast development, although this cross-sectional study was quite small in size.¹⁴⁹ Nevertheless, this finding agrees with the results of a German longitudinal study.¹⁵⁰ However, as pointed out previously, non-Asian epidemiologic studies involving the general population are of questionable value for understanding the health effects of soy.¹¹⁶

One US cross-sectional study that does provide meaningful insight into the issue of whether soy intake impacts development involved Seventh-day Adventist (SDA) girls ($n=327$; age range = 12–18 y; mean age = 15 y).¹⁵¹ Approximately 40% of SDAs practice some form of vegetarianism,¹⁵² so their soy consumption is much higher than that of the general US population.⁴⁴ The authors of this study used current soy intake as a measure of intake earlier in life. There is research justifying this approach.¹⁵³

The mean number of servings of soyfoods among the adolescent girls was 12.9 per week, and 21.1% of the girls consumed soyfoods ≥ 4 times per day. These findings confirm the higher soy intake among SDAs compared with the general US population. The mean AOM of all girls in the study was 12.5 years. The results showed that the consumption of total soyfoods ($P=0.77$) and the intake of 3 specific types of soyfoods (meat alternatives, tofu/traditional soy, and soy beverages; $P=0.84, 0.40, 0.76$, respectively) was not significantly associated with AOM nor was total soy intake significantly associated with the odds of early (<12 y of age) or late (≥ 14 y of age) AOM.¹⁵¹

Finally, no studies examining the impact of soy intake on pubertal development were identified in boys. However, a 6-week Australian study evaluated the impact of isoflavones (50 mg/d) on high-density lipoprotein cholesterol (HDL-C) levels in male teenagers.¹⁵⁴ The authors undertook this study because HDL-C levels decrease as boys enter puberty, whereas no corresponding decrease occurs in girls; a difference they reasoned could be due to the higher estrogen levels in the latter. It was therefore hypothesized that isoflavone exposure would raise HDL-C levels in boys. The lack of effect on HDL-C levels suggests that, for at least this 1 endpoint, soy was not exerting an estrogen-like effect. A limitation of this study is that the boys were aged 16–18 years. On the other hand, the previously cited intervention study by Zung et al.¹⁵⁴ that involved young Israeli children also found no effect of isoflavones on HDL-C levels.

Breast cancer

Evidence suggesting that soy consumption early in life reduces breast cancer risk argues against soy advancing puberty because, as noted previously, earlier menarche is associated with an increased breast cancer risk.^{137,138} The “early soy intake” hypothesis was first proposed >2 decades ago.¹⁵⁵ As summarized by Lamartiniere et al.,¹⁵⁶ rats administered genistein for just a few weeks early in life who were then put on a typical soy-free laboratory diet and given a mammary carcinogen developed 50% fewer mammary tumors than rats not given

this isoflavone. Interestingly, if these rats were also given genistein as adults, tumor number was further reduced, even though genistein exposure only during adulthood was not protective. Other researchers have also shown early genistein exposure reduces chemically induced mammary cancer.¹⁵⁷

These observations in rats are consistent with an increasing amount of data that the first 2 decades of life are particularly influential on risk of developing breast cancer.^{158,159} In fact, early life events may affect risk of a number of cancers.¹⁶⁰

Epidemiologic evidence provides support for the early soy intake hypothesis. Four studies that evaluated the impact of adolescent soy intake on the risk of developing breast cancer are listed in Table 3.^{161–164} Two of these were conducted in China,^{161,164} and 2 were conducted in the United States,^{162,163} but all 4 involved women of Asian ethnicity. A fifth study that involved 3024 cases and 3420 controls from Canada found adolescent isoflavone intake was protective against breast cancer (odds ratio [OR] = 0.81; 95% confidence interval [CI] = 0.71–0.94) but is not included in Table 3 because of the extremely low isoflavone intake of this population.¹⁶⁵

Of the 4 studies in Table 3, 3 found adolescent soy intake was associated with a statistically significant reduction in breast cancer risk.^{161–163} In the fourth study, by Baglia et al.,¹⁶⁴ the odds ratio associated with the soy protein intake pattern of high adolescent intake and low adult intake for premenopausal breast cancer was very low (0.56) but was not quite statistically significant (95% CI = 0.31–1.00). High soy protein intake during both adolescence and adulthood was associated with a statistically significant reduction in premenopausal breast cancer (OR = 0.53; 95% CI = 0.32–0.88), although as can be seen, the odds ratio was almost the same as that associated with high soy protein intake during adolescence only.

This study by Baglia et al.¹⁶⁴ is especially interesting because high adolescent intake was not protective against postmenopausal breast cancer, whereas high adult soy intake was (OR = 0.63; 95% CI = 0.43–0.91) but only when adolescent intake was low. The authors suggested these findings indicate that the protective effects of high adolescent soy intake will be completely manifested during the premenopausal period. Although epidemiologic studies generally show adult soy intake is protective against breast cancer, the data are not totally consistent.⁶ This inconsistency could be due in part to the influence of adolescent soy intake, which is generally not considered in case-control and prospective studies.

Interestingly, Korde et al.¹⁶³ found childhood (ages 5–11 y) soy intake was considerably more protective

Table 3 Risk of breast cancer according to childhood and/or adolescent soy intake

Reference	Location	Menopausal status	Intake metric	Intake period, y	No. of cases	No. of controls	Odds ratio or relative risk ^a (95% CI)	Statistical adjustments
Shu et al. (2001) ¹⁶¹	China	Pre	Soyfoods	13–15	952	990	0.53 (0.39–0.72)	Intake level of rice and wheat products, age, education, family history of breast cancer, history of breast fibroadenoma, waist: height ratio, age at menarche, physical activity, ever had live birth, menopausal status, and age at menopause
		Post	Soyfoods		501	562	0.49 (0.33–0.74)	
Wu et al. (2009) ¹⁶²	United States	Post	Soyfoods	12–18	175	170	0.72 ^b (0.54–0.96)	Asian ethnicity, education, birthplace, years of residence in the United States, years of physical activity, marital status, parity, age at menarche, type of menopause, age at menopause, recent body mass index (in quartiles), waist:hip ratio, intake of tea (never, green tea only, black tea only, and green and black tea), and history of diabetes
					423	486	0.62 ^c (0.48–0.82)	
Korde et al. (2009) ¹⁶³	United States	Pre (73%)	Soyfoods	5–11	99	156	0.36 ^b (0.15–0.86)	Parity/age at first live birth, menopausal status at diagnosis, age at menarche, family history of breast cancer, and personal history of benign breast disease
		Post (27%)		12–19			0.80 (0.59–1.08)	
Baglia et al. (2016) ¹⁶⁴	China	Pre	Soy protein	13–15 ^b	273	36 024	0.56 (0.31–1.00)	Age, body mass index, age at first live birth, physical activity, education, family history of breast cancer, season of recruitment, total adult energy, total juvenile rice intake, and menopause (time-varying)
				13–15 ^c			0.53 (0.32–0.88)	
				13–15 ^b	761	33 520	0.94 (0.67–1.32)	
		Post		13–15 ^d			0.63 (0.43–0.91)	

Abbreviation: CI, confidence interval.

^aComparisons are between the highest and lowest intake groups.^bRepresents high soy intake during adolescence and low intake during adulthood.^cRepresents high soy intake during both adolescence and adulthood.^dRepresents low soy intake during adolescence and high soy intake during adulthood.

than adolescent (ages 12–19 y) intake (Table 3). The other 3 studies in Table 3 evaluated intake during the teenage years only; therefore, it is possible that the protective effects of early soy intake have been underestimated. However, only 16 cases and 37 controls were in the “high childhood, low adulthood soyfood” intake category, so, although these subfindings are intriguing, they should be viewed with considerable caution. Having said this, extremely preliminary data suggest that use of SIF may be protective against breast cancer.¹⁶⁶

With respect to mechanisms, isoflavone exposure early in life appears to cause breast cells in the developing breast to become permanently less likely to be transformed into cancer cells.²¹ The effect of isoflavones may be similar to that of early pregnancy, which also reduces breast cancer risk.¹⁵⁸ Proposed mechanisms for protective effect of isoflavones include an increase in cell differentiation^{158,167} and an increase in *BRCA1* gene expression¹⁶⁸ and ER β levels.¹⁶⁹ Thus far, no clinical studies have evaluated the early intake hypothesis, which is not surprising given the difficulty of doing so. However, a recently published cross-sectional study by Wang et al.¹⁷⁰ may provide the basis for an intervention.

Finally, although the early intake hypothesis remains speculative, it is not unreasonable on the basis of the existing evidence to recommend that girls consume 1 serving of soyfoods per day, the approximate amount associated with protective effects against breast cancer in the previously discussed observational studies. This amount is easily incorporated into the diet and can contribute to meeting nutrient needs.

Cholesterol levels

Clinical studies that show soy protein lowers cholesterol were first conducted 40 years ago.¹⁷¹ This benefit of soy protein was formally recognized by the US Food and Drug Administration (FDA) in 1999.¹⁷² At that time, the consumption of 25 g/d of soy protein was set as the amount needed for lowering cholesterol. More than 10 countries¹⁷³ have approved similar claims, including Canada, which did so in 2014.¹⁷⁴

Meta-analyses of the clinical data published over the past decade or so indicate that soy protein directly lowers low-density lipoprotein cholesterol (LDL-C) levels by approximately 4%–6%^{174–177} and that the effect is greater in hypercholesterolemic versus normocholesterolemic individuals.^{176–178} Nevertheless, the health claim has become controversial because the results of several studies have failed to support the hypocholesterolemic effect of soy protein,¹⁷⁹ which is not surprising given the small sample size of many studies. The FDA is currently evaluating the level of support for the claim and

is soon expected to announce whether any modification to the existing claim is necessary.

As with adults, clinical research in children shows that soy protein favorably affects lipid levels, although the data are very limited.^{180–184} As can be seen from Table 4, 6 studies that ranged in length from 4 weeks to approximately 1.5 years and that evaluated the effects of soy protein on LDL-C in very hypercholesterolemic children have been published. In all cases, children were already consuming diets designed to lower cholesterol. In 4 of the 6 studies marked decreases in LDL-C were found in comparison with baseline and/or the control group,^{180,182,184,185} whereas in 2 studies LDL-C was not statistically significantly reduced but the LDL-C/HDL-C ratio was.

However, there are a number of important limitations to this research, such as, most notably, the small number of study participants. Also, several of the studies failed to describe in sufficient detail the background diet and the soy intervention product used. Nevertheless, although much more data are needed, the existing evidence suggests that soy protein used in combination with other dietary therapies can help to reduce cholesterol levels to target goals,¹⁸⁶ including in children taking cholesterol-lowering medication.¹⁸⁷

Kawasaki disease

Kawasaki disease (KD) is an acute, self-limited vasculitis that affects small- and medium-sized vessels, can lead to severe cardiac complications,¹⁸⁸ and is responsible for more cases of acquired heart disease among children than any other condition.¹⁸⁹ Kawasaki disease most commonly affects children aged 6 months–5 years (peak incidence occurs between the ages of 6 and 11 months).¹⁹⁰ There are approximately 6000 new cases of KD each year in the United States.¹⁹¹ Asian ethnicity appears to be an important risk factor for KD,¹⁹⁰ and genetic studies have indicated a major role for Fc γ receptors (FcGRs) in KD pathogenesis.^{192,193}

Based on the knowledge that in vitro genistein inhibits FcGR function,¹⁹⁴ that the prevalence of KD in Japan and Asia is elevated relative to Western countries,¹⁹⁵ and that soy is a commonly consumed food among the Japanese population, Portman et al.¹⁹⁶ hypothesized that soy consumption increases KD risk. To experimentally examine this hypothesis, Portman et al.¹⁹⁷ evaluated soyfood intake and isoflavone consumption in nearly 200 cases of KD and 200 age-matched controls in the United States using a food frequency questionnaire for children and their mothers. Maternal soy intake during pregnancy and nursing had no significant effect on isoflavone consumption between groups. In contrast, KD risk in children relative to total isoflavone intake increased approximately 2-fold (OR = 2.33; 95% CI = 1.37–3.96) when comparing high

Table 4 Summary of clinical studies evaluating cholesterol-lowering effects of soy protein in children

Reference	Country/study type	Duration, Wk	Product/dose	Total no. (no. by sex)	Age, y	Initial vs final levels, mg/dL			
						TC	LDL-C ^a	HDL-C ^b	LDL-C:HDL-C
Gaddi et al. (1987) ¹⁸²	Italy/O	18	TVP (~90% total protein from soy)	16 (9 M, 7 F)	3–12	360 vs 292 ($P < 0.001$)	302 vs 230 ($P < 0.01$)	35.6 vs 36.8	8.5 vs 6.3
Blumenschein et al. (1991) ¹⁸³	United States/P	NR	TVP (1/g kg bw)	20 (NI)	5–12	~247 vs 234	NR vs 163	NR vs 51 ($P < 0.05$)	NR vs 3.5 ($P < 0.05$)
Laurin et al. (1991) ¹⁸⁰	Canada/XO	4	Wheat (control) ISP	10 (6 M, 4 F)	6–12	~247 vs 227 7.93 vs 7.89	NR vs 164 6.34 vs 6.33	NR vs 42 1.15 vs 1.20 ($P < 0.05$ vs control)	NR vs 4.2 5.5 vs 5.3
Widhalm et al. (1993) ¹⁸¹	Austria/XO	8	Cow's milk (control) ~28 g from test protein Soy flour (15–20 g/d)	23 (12 M, 11 F)	9.3 ± 4.5	7.62 vs 7.89	6.08 vs 6.29	1.11 vs 1.15	5.5 vs 5.5
Weghuber and Widhalm (2008) ¹⁸⁴	Austria/O	12	Standard AHA diet (control) Soy (milk alternatives) 0.25–0.5 g protein/kg bw	16 (10 M, 6 F)	8.8 ± 4.2	229 vs 190 ($P < 0.05$) 215 vs 195 267 vs 247 ($P < 0.01$)	173 vs 132 ($P < 0.01$) 160 vs 144 190 vs 178 ($P < 0.02$)	48 vs 45 47 vs 45 54 vs 53	3.6 vs 2.9 3.4 vs 3.2 4.9 vs 4.7
Kreissl and Widhalm (2010) ¹⁸⁵	Austria/O	~88	Soy (dairy alternatives)/– 0.5 g protein/kg bw	10 (5 M, 5 F)	10.1 ± 4.8	–38.7 (16%; $P < 0.003$)	–34.5 (19%; $P < 0.002$)	Not significant	Not specified

Abbreviations: AHA, American Heart Association; bw, body weight; F, female; HDL-C, high-density lipoprotein cholesterol; ISP, isolated soy protein; LDL-C, low-density lipoprotein cholesterol; M, male; NR, not reported; O, open label (no control); P, parallel; TC, total cholesterol; TVP, textured vegetable protein (Cholsoy; Pro-Gen, Bologna, Italy); XO, cross-over.

Table 5 Prevalence of common food allergies among US children

Age group	All allergens (N = 3339)	Peanut (N = 767)	Milk (N = 702)	Shellfish (N = 509)	Tree nut (N = 430)	Egg (N = 304)	Fin fish (N = 188)	Strawberry (N = 189)	Wheat (N = 170)	Soy (N = 162)
Prevalence (%) among all children (N = 38 480)										
All ages	8.0	2.0	1.7	1.4	1.0	0.8	0.5	0.4	0.4	0.4
3–5 y	9.2	2.8	2.0	1.2	1.3	1.3	0.5	0.5	0.5	0.5
Prevalence (%) among children with at least one diagnosed food allergy (N = 3339)										
All ages	...	25.2	21.1	17.2	13.1	9.8	6.2	5.3	5.0	4.6
3–5 y	...	30.3	22.1	12.9	14.3	13.7	5.7	5.5	5.0	5.1

Data from Gupta et al. (2011).²⁰⁰

soy consumers versus nonconsumers of soy. However, when the data were subanalyzed, the increased risk associated with higher isoflavone intake was primarily found in Asian children. Risk among Asian American children with the highest intake was increased nearly 7-fold (OR = 7.29; 95% CI = 1.73–30.75), whereas among white children risk was not significantly increased (OR = 1.61; 95% CI = 0.86–3.01).

Although these findings are certainly intriguing and warrant additional research, it is important to recognize that this study included only 51 Asian children. In addition, the low isoflavone intake even among the individuals with KD raises doubt about the biological plausibility of the findings. For example, among Asian children who consumed, on average, approximately 0.5 mg of genistein per day, risk was increased 4-fold. Genistein would not be expected to affect FcGRs at that level of exposure.

SOY PROTEIN ALLERGY

In the United States, soy protein is 1 of the 8 food proteins responsible for approximately 90% of all food allergic reactions. Nevertheless, relatively few adults are allergic to soy protein. To this point, a telephone survey conducted by the FDA in 2007 found approximately 1 in 2000 and 1 in 2500 US adults reported a self-described and doctor-diagnosed allergy to soy protein, respectively. In this survey, cow's milk allergy was 40-fold more common than allergy to soy protein.¹⁹⁸

Not surprisingly, soy protein allergy is more common among children than adults, as is true for essentially all food protein-induced allergic reactions.¹⁹⁹ A US survey conducted by Gupta et al.²⁰⁰ that involved 38 480 individuals aged <18 years found the prevalence of overall food allergy was 8.0% (Table 5). The prevalence of soy protein allergy among all children was 0.4%, which was slightly higher than the prevalence among children (0.3%) up to 2 years of age. Allergy to milk and peanut was 4- and 5-fold more common, respectively, than allergy to soy protein (Table 5). The estimates of the prevalence of soy allergy reported by Gupta et al.²⁰⁰ are similar to those reported for soy allergy in Europe²⁰¹ and the conclusion of a recent systematic

review that found that, even among infants and children, the prevalence of soy allergies among the general population is ≤0.5%.²⁰² Importantly, although estimates vary, recent evidence indicates that 70% of children outgrow their soy allergies by the age of 10 years,^{199,203–205} which suggests that by that age the prevalence of soy allergy among children is estimated to be only 0.1%.

Finally, there is evidence that SIF is hypoallergenic relative to cow's milk formulas.²⁰⁶ However, because some infants who are allergic to cow's milk formula are also allergic to SIF, the AAP recommends that infants with documented cow's milk protein allergy be switched directly to a hydrolyzed protein formula.¹⁰² In contrast with the position of the AAP, Australian experts concluded that SIF is an appropriate alternative for infants aged >6 months who demonstrate immediate food allergy to cow's milk.²⁰⁷ The French Society of Pediatrics holds a similar position but recommends that tolerance to soy protein be established by clinical challenge.²⁰⁸ Interestingly, there are data that show SIF is actually less allergenic than hydrolyzed formula²⁰⁹ and has advantages over it.²¹⁰

CONCLUSION

The role of soyfoods in the prevention of chronic disease has been rigorously investigated over the past 30 years. Much of this research has been undertaken because soybeans are uniquely rich in isoflavones. Isoflavones are purported to exert a number of health benefits. However, their isoflavone content has also given rise to concerns that soyfoods could have unwanted effects in some individuals. These concerns are based almost exclusively on animal studies.

The available evidence indicates that, with the exception of those who are allergic to soy protein, which is relatively uncommon, soyfoods can be safely incorporated into the diets of children and teens. There is little evidence that soy exerts adverse hormonal effects in children, but data are very limited.

Soyfoods have a desirable nutrient profile, particularly as a source of high-quality protein and essential fatty acids. Soy protein can be a valuable approach to the management of hypercholesterolemia in young

people. When consumed early in life, these foods may also help reduce breast cancer risk.

Regardless of the nutritional and health attributes of any single food, the basic principles of variety and moderation should always be followed. Based on the results of the clinical and epidemiologic research discussed in this review, data on soy intake in Asian populations, and basic dietetic principles, a reasonable intake recommendation for preschoolers and school-aged children is 5–10 g/d of soy protein which equates to approximately 1 serving of a traditional soyfood. This recommendation is meant to serve only as a general guideline and one that is adaptable to the dietary needs of individual children.

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