Danny Lennon:

Hello, you are listening to Sigma Nutrition Radio. This is episode 430 of the podcasts. My name is Danny Lennon, I am here with Alan Flanagan and today we're going to be talking about soy. Are you excited for our discussion, Alan?

Alan Flanagan:

I am. It's a topic dear to my heart. Always interested whenever a food or food group becomes part of the culture wars. It's really bringing nutrition up a level, it's raising the profile. So yeah, obviously soy has a fairly unique place in the polarization of American political life.

Danny Lennon:

So have you been called as soy boy on internet forums and in comment threads?

Alan Flanagan:

I probably have at some point. Dropping in hints as to my vegan-ness or magnitude of my vegan-ness.

Danny Lennon:

Your half vegan nature.

Alan Flanagan:

Yeah, exactly. No doubt. The juxtaposition to soy boy is, of course, liver king. So yes, these two diametrically opposed conceptions of what it means to be a man in 2022 America.

Danny Lennon:

And then this is something that will raise its head in a part of our discussion a bit later on, both in a funny, and then there's also maybe some actual serious hypotheses to be taken in stock of. So maybe as a place to set some sage or run through some basics in regards to what we're talking about. So of course with soy or people may see it written as soja if they're in the UK or in other European countries, this is basically just the same thing, we can use that interchangeably. Obviously something that is increasing in prevalence of how often soy foods are used around the world right now.

Danny Lennon:

And traditionally, obviously would've been used in a lot of Asian dishes, as I think we'll mention, but now has been used quite a lot as a dairy alternative, whether that's in replacement of dairy milks, where you can use a soy milk or an alternative for yogurts and cheeses and so on. But even more so now for people looking to reduce meat intake, it's been used in a variety of dishes that are going to be meat free. So whether that is actually a meat alternative product that has been developed used soy or using something like tofu in place of where meat may typically have gone in a traditional dish, that has been used for people reducing meat intake.

Danny Lennon:

So what are we talking about? Well, soy beans are a legume from Asian origin. And one of the interesting things, I guess, when we look at their nutrient profile is that they're maybe quite different to a number of other types of beans and other legumes, in that they tend to have a much lower carbohydrate content, but have a higher protein content as well as a higher protein quality in the sense of, if we look at their amino acid profile, they contain all nine essential amino acids, and the profile looks more similar to some of the animal based proteins that are typically considered high quality, particularly in terms of their anabolic effect or impacts on muscle recovery, muscle growth that we can maybe mention a bit later on.

Danny Lennon:

One of the other things that we'll probably come back to is the fat content of soybeans, and they are significantly higher in fat than maybe some other beans. Most of this is just going to be polyunsaturated fat, the very low unsaturated fat, which is another consideration we may circle back to in relation to if this is being substituted in, in place of, let's say, meat based products with saturated fat or high saturated fat content. The other thing maybe to note is that we have a variety or different varieties of soybeans based on color. So you have these yellow soybeans that would be the primary type used in soy milk, tofu, tempeh, soy flour, and so on. You can then have green soybeans, and particularly young green soybeans people will be familiar with as edamame, eaten as appetizer or in salads. And then many Asian cuisines will use black soybeans or fermented black soybeans in many dishes.

Danny Lennon:

We can also maybe mention that there's these unfermented soy foods, whether that's soy milk alternatives, tofu, or soy meat replacements. And then you have fermented soy foods, which are again common in these various Asian and particularly Japanese dishes where that's natto, miso, tempeh, cetera. Now, one of the things that I wanted to focus on in relation to the nutrient profile, like we said, this is a particularly good source of protein, and particularly when we're looking at plant-based proteins. Things like soy milk have much more protein than other forms of milk alternatives, like a nut milk or an oat milk, for example, so they're much closer to traditional dairy milks in that sense. And then you have products like tofu, which is very high end protein, and why it's often used by people as a meat substitute

if they're trying to keep their protein intake high. There's also a number of micronutrients folate vitamin C that we can maybe mention.

Danny Lennon:

But probably the best place to start where I want to bring you in a is that soybeans are this main dietary source of isoflavones. So these compounds that we've maybe mentioned on a couple of episodes on polyphenols in the past, but these are a particular class of flavanoids that are very interesting and what make maybe soy quite unique and why a lot of the conversation topics we're going to get into today come up, is in relation to this compound and some of their effects. So I'm just wondering maybe as a start point for people who are maybe not so familiar with this compound, can you introduce what we're talking about in relation to these isoflavones, where they sit, and how we should think of them as a a nutrient and then some of the metabolism of them and the effects then in the body that are going to be important to tee up the rest of our discussion?

Alan Flanagan:

Yeah, so they they're probably... Although like you've outlined, the macronutrient and micronutrient content of soy overall gives it quite an interesting and the profile. Part of the interest, certainly the main interest, as far as some of the purported health benefits, particularly in relation to cardiovascular disease potentially, then also in relation to hormone dependent cancers like breast and prostate, and some other health outcomes, relates to their content of isoflavones. So first I think we will position where isoflavones sit in the overall picture of nutrients and non-nutritive bioactive food components, and they fit in the latter. So they're within the overall polyphenol group, polyphenols being bioactive component from plant foods that are called such because they have a particular chemical structure. Not all of them are polyphenols. Some of them may have a single phenolic ring, but polyphenols generally is the term that represents the entire family.

Alan Flanagan:

And within the group of polyphenols, you have various sub-classifications, but the most abundant source of polyphenols in the human diet are a family of compounds known as flavanoids, which we've discussed extensively on some previous episodes where we focused primarily on flavanoids from foods like dark skinned berries, and other common flavanoid rich foods. Cacao we also discussed in relation to an episode on cardiovascular disease. So isoflavones are, if you can tell by just moving the iso out of it, they are a certain type of flavanoid right? So they are within that overall group of flavanoids, but they're a flavanoids sub-class, a specific flavanoid sub-class, and we can subdivide flavanoids themselves. So we've got polyphenols as this overall umbrella term, flavanoids as the main source of polyphenols in the human diet, and then flavanoids themselves can be broken down into, for example, anthocyanins, flavanols, flavones, and in this case isoflavones.

Alan Flanagan:

So there's three main isoflavones that we derive from soy, and they're genistein, daidzein, and glycitein, and they account for, respectively, 50, 40, and 10% of the total isoflavone content in soy. Now, they're a particularly interesting group of compounds for a couple of reasons. One is that, and it's important just to clarify that each flavanoid subclass is structurally different, which is why they all have different names. And in relation to soy isoflavones, these would be recognized as what we would term phytoestrogens. And the reason that we would consider them phytoestrogens, phyto, obviously they're derived from plants, in this case soy, but they're structurally similar to 17-beta estradiol, which is an

estrogen, a sex steroid hormone that physiologically would be produced by the ovaries, particularly during the reproductive phase of the lifespan, and then over menopause and into the postmenopausal period, this production would shift away from ovarian production.

Alan Flanagan:

So these estrogens can act by binding to estrogen receptors in the body, and they can then have potentially either pro estrogenic effects or antiestrogenic effects. Now, with these compounds, it's quite important to distinguish the potential action of both genistein and daidzein. We can kind of leave glycitein out of it for now because our main focus will be on these two compounds. So genistein itself has very strong antiestrogenic effects in truth, because it's mildly estrogenic. Its ability to bind to estrogen receptors... Experimentally, genistein has been shown to have greater affinity for binding to an estrogen receptor than Tamoxifen, which is a pharmaceutical compound. So genistein can be metabolized, but it does appear to act as the compound itself in terms of... They're all metabolized by the gut bacteria, but genistein seems to retain more of its parent compound structure.

Alan Flanagan:

But daidzein is interesting because this undergoes pretty substantial metabolism by the gut bacteria, and this is really important because we've discussed this previously in relation to flavanoids, that often it's not necessarily the parent compound that has biological activity, but the actual metabolites produced by gut bacteria acting on these compounds in the gut producing these metabolites, which are then absorbed. And one of the most important compounds that we'll mention a couple of times that is metabolized from daidzein by these gut bacteria is known as S-equol. So S-equol is exclusively a product of bacterial metabolism. It doesn't appear in urinary excretion unless you actually consume soy foods in the diet. It's a non-steroidal estrogen, so these are compounds that occur naturally, or they could be drugs potentially. And what's interesting is that the affinity for binding to the estrogen receptor is much greater for the equol metabolite than it is for the parent compounds themselves.

Alan Flanagan:

So this is a particularly important aspect to the metabolism and potential biological activity of these soy isoflavones. And it's also a really important concept when we come to consider potential discrepancies in the evidence base for soy, particularly in terms of strength of evidence as between cohorts in East Asia, where soy is a part of the traditional diet and has been for quite some time, and Western populations, where soy is more of a recent introduction. And indeed the bulk of the soy in a given Western diet may not necessarily be in the form of some of these more traditional foods. It may not be necessarily in the form of tofu or tempeh or natto, but it could largely be based on, for example, commercially produced soy milk.

Alan Flanagan:

And this concept is that of an equol producer. So there's varying estimates as to the percentage of individuals in a given population that are equol producers. So I think first is what is an equol producer? Well, it's a name given to people who appear to have specific gut bacteria that are specialized in the metabolism of daidzein, of the soy isoflavone into S-equol Now there isn't really any hard and fast definition of what an producer is beyond that, and there are various theories still as to whether is it just genetics, is it just background diet? Could I become an equol producer if at the age of, say, 30, I decided to focus my diet specifically on soy? There is a case for both in a sense. So with the genetic example, there was an interesting study of Chinese immigrants living in France, first generation if I remember

correctly, who were consuming more of what we might say a Western diet, or certainly a French diet, but still retaining aspects of soy consumption and still appeared to show this capacity for equol production.

Alan Flanagan:

So there may be a genetic component, and then there may be a role for habitual background diet as well, and it's not really sure necessarily where the distinction between equol and non-equol producers may lie. And that's an area of ongoing interest. Estimates vary as far as, say, in a Western population that maybe between 17 and 30% may show some equol producing capacity, whereas in East Asian population that can really extend up to 50 to 75% of the population. But again, there's a lot of future work and certainly better research. A lot of the research supporting equol producing capacity is based on cross-section or case control studies. So to round this all out, although soy overall contains an interesting and generally what we would consider health promoting macronutrient and micronutrient profile, it contains soy fibers, it's got the protein composition, as you outlined. It's got an interesting fat to carbohydrate ratio relative to its protein content as well.

Alan Flanagan:

So all of these things would make it a food that we could look at maybe objectively on its nutrient composition and say this is a healthy food. But really like a lot of these flavanoid rich foods, it's the flavanoid content that appears to be of most interest for impacts on health and disease processes. So these isoflavones are within the class of flavanoids. They are subclass of flavanoids. The two that we're primarily interested in are genistein and daidzein, and in particular, the production by gut bacteria of equol from daidzein, and the generation of that equol metabolite that is then absorbed and appears to show significant affinity for estrogen receptor binding, for example, which may be particularly relevant for breast cancer. These are all aspects of the metabolism and mechanism of action of soy isoflavones that make them particularly interesting to study from a health perspective.

Danny Lennon:

Again, as a brief recap on that, we're going to focus particularly on the polyphenols that are within this food, and within polyphenols, we have this group of flavanoids. Within that we have a subtype of flavanoids called isoflavones, which are what we're really going to focus on here. And then within that, you said, there's these three subclass of isoflavone, in particular daidzein, genistein, and glycitein, and then particularly focused in on daidzein of having this ability to produce equol. And we're going to circle back to all of that. But one of the important things that I think it's worth lingering on a bit for a moment is when we're considering this phytoestrogenic, or them as phytoestrogens and therefore having a potentially estrogen mimicking effect is where a lot of the claim that we're going to discuss today comes in.

Danny Lennon:

And one of the aspects on that is their affinity to bind to those estrogen receptors. So we have these two receptors, alpha and beta estrogen receptors, and there seems to be this affinity to bind to them. Now one of the important things that you outlined is that while it's known that the binding of isoflavones to those receptors is actually distinct from how estrogen binds them, in that it's not as strong an affinity, there may some difference in which receptors it more preferentially will bind to, but there's this other component that we now have to consider of not just how these isoflavones may interact with it, but as you noted more specifically, we're looking at the metabolites and the ability for,

say, equol to be able to bind to these receptors. And then therefore, does it have a similar effect as if estrogen was binding to that receptor? And if so, how does that compare to that estrogen effect? is there anything that we need to outline in relation to any of that before we start diving in?

Alan Flanagan:

No, I think when we discuss breast cancer specifically, and the evidence around that, we'll go into a little more detail on the difference between estrogen receptor alpha and beta, and then the division of breast cancer according to whether there's tumors expressed estrogen receptor alpha or don't. So either ER-positive or ER-negative. But what we'll go into that in a little bit more detail when we discuss BC specifically.

Danny Lennon:

Perfect. So maybe as a place to start, there's different hypotheses that get put forth based on the phytoestrogens that are within soy. Some being potentially positive for health, and then some being hypothesized to be bad for health. If we start on the negative side, probably one of the most common that people have likely heard of is given that there is this potential for it to have an estrogen mimicking effect or to have effects that are similar to elevated levels of estrogen in the body, could that be problematic, particularly for men in that it has some degree of feminizing effect, quote unquote. And this manifests in several ways.

Danny Lennon:

There is one on the more ridiculous end that consuming soy foods is in some way making men less of a man or whatever that even means, and then there's more serious hypotheses that people would put forth in relation to things like loss of libido or erectile dysfunction or gynecomastia, where we have this growth or swelling of breast tissue in men, based on the idea of we know these things can happen if there is a strong elevation in estrogen, or if someone sees a massive decline in testosterone, let's say, and that shifts that estrogen to testosterone ratio, as can happen if someone goes on a certain medication, then we can get cases of gynecomastia and this swelling, or even growth of breast tissue in men, and then we can even look at cases of transgender patients and going through that process of the provision of estrogen to try and have this effect of growth of breast tissue.

Danny Lennon:

So that then creates this hypothesis of if these phytoestrogens in soy can have a similar effect to estrogen, then is consuming soy regularly or in high amounts going to cause some of these effects, whether that's related to gynecomastia, loss of libido, erectile dysfunction, et cetera. I think this was actually something that you and I had mentioned on the Food Medic podcast at some stage last year on this particular topic. And I think at that time, in relation to the gynecomastia claims, there is indeed one case study that you can find, and I'm not aware of any others, but there's one particular case of a 60 year old patient that presented with this growth of breast tissue over a six month period, had loss of libido, and erectile dysfunction. On examination there was no physical trauma that would explain these symptoms. Most of the other tests seemed normal apart from a elevation in a couple of estrogen hormones.

Danny Lennon:

So then on re-interviewing the patient they found out he was drinking, I think, upwards of three liters of soy milk every day, and on cessation of you get a reduction of those symptoms. But that seems to be the

only published case that I was able to come across where you see that soy intake directly is causing gynecomastia. So in relation to that, or any of the impacts on, say, other male related issues like erectile dysfunction, libido, lowering of testosterone, is there any evidence that you are aware of that would give you a cause for concern in relation to soy consumption related to men? What is your sense of the evidence we have on any of these claims?

Alan Flanagan:

It just doesn't seem to be a cause for concern. Case are, are obviously an interesting part of the evidence base, but when there's only case study, and particularly when there's only isolated case studies, it basically means nothing if we're really stacking up evidence, when there are potential other avenues to look at. A lot of this was generated, in terms of the controversy or the dialogue from the 2007 intervention, which was looking at soy protein isolate, if I remember correctly, supplementation, I think they were consuming about 60 grams a day and it suggested a 19% decrease in circulating testosterone levels. Small intervention in 12 men, and it was over a four week period. But if you actually looked at the data and there were published rebuttals bringing this to light, the actual magnitude of this change appeared to be driven entirely by a single outlier whose baseline testosterone levels was double that of all of the other subjects, and 50% higher than the actual reference range.

Alan Flanagan:

So did that mean that they were using some sort of testosterone enhancement prior to the study? It's possible. But ultimately they were the individual that experienced a 40% decrease within just the four week intervention period, and it reduced again by 30% in the two week followup period post interventions. So factoring out an outlier, there's no effect, then, in that study specifically. And indeed, if we then parse the wider literature specific to testosterone levels in men, and especially as this kind of pushback largely comes from people either in some way shape or form strength and conditioning or in resistance training approach to physical training, then there's really a dearth of evidence at that point. There's research that compares soy to whey protein on testosterone levels and overall, although you can find an isolated study, there was another one in 2013 that suggested a small reduction from soy protein consumption that wasn't observed with whey, but there's a couple of meta analyses overall that don't show that soy protein alters testosterone levels, or that compared to whey it comparatively lowers testosterone levels.

Alan Flanagan:

And there's been more up to date research in interventions specifically in resistance trained young adults that compares soy to whey protein and looking at hormonal responses to resistance training and not finding, in a randomized clinical trial, that there was any alteration in testosterone. So I think overall, if we're talking about adult men and the consumption of soy, just because you can find an isolated study that says one thing doesn't mean that's actually what we're showing an effect of. You can find probably two studies, and the one that I just mentioned was driven almost exclusively by an individual outlier, that really, if you removed that you wouldn't see an effect. And then the other was a comparative, very small trial in 10 men. So when you bring the total body of evidence together, there's no real suggestion of altered circulating testosterone levels from soy consumption, soy protein isolate consumption, or certainly comparatively against, for example, whey, and certainly no suggestion that in resistance training individuals, there would be an adverse impact on the hormonal responses to training consuming soy protein consumption.

Alan Flanagan:

Now at the other end of the life... At the start of the life cycle, that's where some more of the vigorous debate has lied, because if we're just talking about circulating levels, there is evidence that would suggest that infants that are fed with soy formula would have a significantly higher level of circulating phytoestrogens than you would expect otherwise in that life stage. And in fact, the circulating level of phytoestrogens is higher than actual endogenous estrogen levels. And there's also research that has suggested that the levels of circulating phytoestrogens from soy formula consumption in infants, exclusively on soy formula consumption, would lead to higher estradiol levels, 50 times higher estradiol levels than would be present in a adult pregnant female. Now that leads to all sorts of jumps to conclusions that if this is this high, this must be having adverse effect.

Alan Flanagan:

Unfortunately there's a real lack of prospective evidence looking at the effect of this kind of exclusive exposure for soy based formula over time in terms of reproduction health or fertility, and what studies do exist are often cross sectional. And again, this is something then when we have to try and step back and parse multiple lines of evidence to try and come to a conclusion, there are not really any good published evidence, quality published evidence in humans, again, of this kind of long term outcomes. There are lines of evidence from animal models, particularly monkeys. They suggested perhaps a short term effect on circulating testosterone levels, and an earlier onset of puberty, but no adverse reproductive effects in the adulthood for the monkeys and that included overall fertility rates. So there are generally suggestions that this is otherwise fine in terms of as a substitute for cow's milk formula or exclusive breastfeeding. And those recommendations are generally made in the context of the, I guess, rather absence of evidence overall.

Alan Flanagan:

Now, in terms of what human evidence exists... We have these suggestions of this potential adverse effect, or a certainly short term effect on reproductive hormones in an early life stage that does not necessarily translate to adverse effects on reproductive function and fertility in adulthood in monkeys. But the overall evidence that we do have doesn't really suggest that there is any adverse long term effect in humans. So it's a difficult one. It's hard on a question like this, because on the one hand you do have this movement within the plant-based community to like hand wave off any gaps in the literature. And we see this with a number of exposures. On the other hand, you don't want to fill in absence of evidence is not evidence of absence with gaps. He the reality is evidence in this area is really poor.

Alan Flanagan:

There was a cross-sectional study in female infants that were exclusively soy based formula that reported a higher prevalence of breast buds during the second year of life. There was another study that suggested, again, this is human infants now, that they looked at an outcome where they said that there was a more estrogenized vaginal epithelium when you compared soy based formula to exclusively cow based or breast milk formula. So the suggestion here is that there might be some physiological estrogenization in a newborn, but there is really a dearth of evidence that suggests that would add up to any sort of adverse reproductive health or fertility health outcomes in adulthood.

Danny Lennon:

So in relation to this soy infant formula or in that infant life stage, as far as I'm aware, most dietetic organizations, and those who are registered nutritionists, that I'm aware of, tend to say that soy milk

wouldn't be recommended within the first six months of life. Some even say twelve months. And then from a year a on, it seems to be that there's less risk there given that there's this absence of evidence. So yeah, we don't have good human evidence it's going to necessarily do anything that is harmful in a long term, but given that uncertainty, it seems prudent, at least that first six, twelve months of life tends to be recommended against using it in place of something else, I think, for those reasons.

Alan Flanagan:

I think that's a prudent way of filling in the gaps in the research. And certainly that does seem to be potentially then getting into a stage of infancy where any sort of knock on effect might be less likely.

Danny Lennon:

So then just as a recap for any of those aspects related to, I suppose, men's health generally, but these feminizing effects of soy, based on that current evidence we're not really seeing a impact on testosterone levels to any clinically meaningful degree. We're not seeing that impact actual ability to build muscles, when you look at interventions where soy isolate, let's say, is used as the main supplementary protein. Doesn't seem to impact any ability to build muscle once you have an adequate overall protein intake. You can see that for plant-based dietary patterns that have a lot of soy, et cetera. And we don't have any cases of things like gynecomastia, erectile dysfunction, et cetera, being traced back to soy consumption or high levels of soy consumption in humans.

Danny Lennon:

And I think, I suppose, this is again something we'll probably come back to as a meta level idea that we've discussed before about research appraisal is that when you see most of the evidence that people point to for such claims and other ones that we're going to discuss later on, it comes back down to either laboratory or animal studies in combination with them using either an isolated isoflavone or an extremely high dose that isn't necessarily plausible or possible from a normal intake. And the combination of those two things can lead to distinctly different outcomes than you might see in human intervention data. And obviously animal studies can be really important where there's areas where we don't have good yet, or to maybe investigate a hypothesis initially. We don't have human intervention trials, but in this case where we've talked about some of these particular claims where we do have human intervention trials and we have epidemiology, it would seem strange to preferentially look to that animal data that the showed these negative outcomes in testosterone, et cetera.

Alan Flanagan:

And that's absolutely correct because if you do see some of the strong arguments put forward for no, it does have these effects, it's largely data on monkeys for the most part. Even though it's not necessarily always shown. Like I said, one of the monkey studies did show a lower testosterone level in the developmental phase, but the monkeys did not have any adverse reproductive or fertility issues in adulthood. Although you can find these effects in monkey studies and some other animal models, they're not what we see in humans, so it's really important to... And particularly if we're talking about the adverse effect that was potentially observed in that case report. And of course we don't really know whether the soy was necessarily exclusively the driver of that particular incident in the case report. But you don't see those adverse effects in any of the human interventions, in the intervention groups.

Alan Flanagan:

And there's studies that have looked at pretty high doses of isoflavones from foods using tofu, a 70 milligram a day dose from isoflavones, soy milk, providing 48 milligrams a day of isoflavones, or even just 22 milligrams a day showing no adverse effect on hormonal levels in adult men, and there's really little evidence... Independent of just the effect on testosterone levels, there's no evidence in adult men that there's any detrimental effect of these high levels of soy consumption on reproduction or fertility. So the gap that exists is longitudinal data in infant birth cohorts, but as you say, in the absence and gaps that exist in this literature, most advice is to not use an exclusive soy formula within the first year of infancy.

Danny Lennon:

One of the papers that attempted to look at this endocrine disruption hypothesis was a 2021 review paper by Messina and colleagues. This included a bunch of different trials, I think there's 417 trials included. That included 229 observational studies, 157 clinical trials, and 32 systematic reviews and meta analyses. And in this review, again, finding similar to what we just said of no negative impacts on testosterone or other parameters in men, such as sperm or semen parameters. One of the other things that was looked at there, because it comes up sometimes, is the impact on thyroid function. It seems that in that particular review, that isoflavone intake doesn't adversely affect thyroid function. But I think why hypothyroidism is sometimes discussed in relation to soy seems more to be in relation to how it may impact medication. In those with thyroid issues, they are often on...

Alan Flanagan:

Levothyroxin.

Danny Lennon:

Correct. So there is a potential for it to interfere with absorption, as far as I'm aware. So that it just recommended, take it in a window outside of the hour that you're taking that medication.

Alan Flanagan:

Exactly. There is some evidence that it can lower the absorption Levothyroxin, which is a synthetic thyroid hormone. Because the dose that any given individual with hypothyroid is on is titrated to their particular need in terms of restoring new thyroid function, it means you're basically tinkering with your dose. So yes, the potential for that is offset by simply consuming your Levothyroxin away from when one might eat soy.

Danny Lennon:

So with that, that brings us then to maybe issue specific to women. And probably the biggest topic in this area is perhaps a breast cancer. And again, a lot of hypotheses put forth as to the potential of soy foods and high intakes of phytoestrogens to impact either those with breast cancer or to increase risk of breast cancer or increased risk of a recurrence of breast cancer. And again, this seems to be something that's based on that mechanistic reasoning that we've outlined in relation to estrogen's effect. And then maybe extrapolating that across the phytoestrogens, again, in combination with some data in animal models from the 90s, I believe, that indicated this potential for increased risk.

Danny Lennon:

Again, this is an area where we do have human data that we can look to try and uncover if that animal data or that mechanistic reasoning does indeed play out. And I know there's been a couple of studies that you've covered in quite some detail particularly relating to this topic. So in relation to looking at the human data on breast cancer risk, breast cancer recurrence, et cetera, with soy/isoflavones, where is the best place to start weaving through this evidence?

Alan Flanagan:

So I think first it helps to set out some of factors related to breast cancer itself as a condition, because they're really relevant, indeed, almost sometimes the crux of resolving the evidence for certainly dietary exposures and breast cancer, because breast cancer can differ in terms of the diagnosis based on estrogen receptor type and also based on menopausal status. So those two factors can be particularly important and it can appear that there are then inconsistencies because some studies, for example, could show an effect in people who are estrogen receptor positive of, and then some other studies might show an effect in people who are estrogen receptor negative, and then people go, "Wow, this is confusing." Or you see and effect in postmenopausal women, not premenopausal, and another study finds in effect in premenopausal women and not postmenopausal women. So we'll set out these things first.

Alan Flanagan:

So there's two main types of estrogen receptors. So there's estrogen receptor alpha and estrogen receptor beta. So ER alpha and ER beta. ER alpha are expressed more in mammary tissue and the uterus, and ER beta's expressed more in the central nervous system and the immune system, and they have antagonistic effects to a degree. So estrogen ER beta counteracts the effects of cell proliferation, so the growth rate of cells, which is really relevant for cancer generally, but particularly for hormone dependent cancers. So it counteracts that effect of cell proliferation that can be induced by estrogen receptor alpha. So this is at one entry level where soy starts to come into play because soy isoflavones and particularly equol have a greater affinity for binding with ER beta receptors. So this is one proposed mechanism by which if you get a greater level of increased ER beta binding, that it acts as an antagonist to cell growth mediated by ER alpha.

Alan Flanagan:

So we have those two and then breast cancer then can be subdivided based on whether a tumor expresses cells positive for the estrogen receptor alpha or negative. So if cell do express estrogen receptor alpha, that's known as ER-positive, estrogen receptor positive breast cancer. If they don't express ER alpha, that's known as estrogen receptor negative breast cancer. And this is important because again, when estrogen receptor positive cells bind to circulating estrogens, it can stimulate tumor growth mechanistically. So this again is where the potential mild estrogenic effects of soy isoflavones comes into play, because they're structurally similar to 17-beta estradiol, we said at the outset. But in fact, they exert a much milder estrogenic effect. So they may have an antiestrogen effect, so to speak, but most importantly, the greater affinity for estrogen receptor beta receptors may be something that counteracts cell growth induced by estrogen receptor alpha. So that's the top line distinction of breast cancer types, and then also the link between why soy could mechanistically overall provide a benefit.

Alan Flanagan:

And there is a lot of actually, like you've said, human outcome evidence in relation to soy isoflavone intake in particular, and you can see differences relative to menopausal status, and you can see differences in relation to estrogen receptor status as well. So there's been... Meta analysis of observational research has suggested soy isoflavone research has a stronger risk reduction in women who are estrogen receptor positive. Remember, so that means they're expressing ER alpha, compared to estrogen receptor negative women. And again, the proposed mechanism there potentially could be that if they're estrogen receptor positive, they're prone to a very pro-estrogen effect of circulating estrogens binding to that estrogen receptor and stimulating and inducing cell proliferation. So our soy isoflavones, through their affinity to bind to the estrogen receptor, with their stronger affinity to estrogen receptor beta binding, act as an antagonist to that process occurring. So that's one potential mechanism.

Alan Flanagan:

And the overall evidence is not entirely always clear cut on that question either though. Other findings, there was another recent meta analysis Navchzech and colleagues 2019 paper. So that found a significant lower risk of breast cancer mortality in estrogen receptor negative breast cancer, but no effect in estrogen receptor positive. So there's another difference there in terms of, is it impacting mortality or is it impacting recurrence? So there are other aspects to outcomes that are important to parse with the literature. So ultimately you can find evidence of a reduction in breast cancer incidents from soy isoflavone consumption in both, in women that are both estrogen receptor positive and also estrogen receptor negative. So that just means that the exact underlying mechanisms relates to be fully teased out. The evidence does show both reductions in mortality, specifically as an outcome, and the evidence also does show a reduction in risk for cancer recurrence.

Alan Flanagan:

The strength of that evidence is actually stronger for reducing risk of breast cancer recurrence. So for example, some of the meta analysis of observational studies have shown relative risk reductions in mortality of between 9 to 16%, while some of the studies looking at recurrence of breast cancer have shown reductions of up to 27% lower risk of recurrence. And then there's also then the potential for differences in menopausal status. So they have also been shown, and there appears to be quite a strong risk reduction in postmenopausal women with breast cancer recurrence as an outcome as well. So yes, there are some interesting potential mechanisms that would explain why there are perhaps differences observed in any given cohort between estrogen receptor status. You can find evidence of a risk reduction in both. There's certainly a plausibility as to why there may be a stronger or more consistent signal in the noise in relation to estrogen receptor positive women, because of this potential antagonistic effect of the affinity of soy isoflavone metabolites to bind to estrogen receptor beta and have an antagonistic effect on cell proliferation induced by estrogen receptor alpha.

Alan Flanagan:

And then there are differences in relation to menopausal status. So you can, and you do in the research, see a risk reduction in premenopausal women, but you can often see a stronger magnitude of that effect in postmenopausal women, where breast cancer recurrence is the outcome. And then overall you do see significant reductions in mortality, the strength of which is not always consistently as high as the reduction in risk of recurrence. And I think as an important final aspect to the overall weight of evidence in this area, although we described at the start this potential difference between equol producers and non equol producers and how that might relate to genetic impact on diet and why it might be more prevalent in Asian cohorts, we don't see a regional or ethnic difference in these outcomes in the breast

cancer epidemiology related to soy isoflavones, and we see risk reduction relatively equally between Asian cohorts and cohorts in non-Asian women.

Danny Lennon:

I want to recap over a couple of important points that you just brought up there, and it circles back to something you had outlined earlier in the discussion as well, in relation to how these isoflavones are acting differently to estrogen, and in some slight but important ways. And then also the affinity for them for these different receptors. So as a recap for people, you'd stated that there are these two estrogen receptors that we're talking about in the human body, alpha and beta receptors. The hormone estrogen binds seemingly with relatively equal affinity to both of these receptors. And by affinity here, we just mean how strongly the hormone is binding to the receptor or how well it fits essentially with the receptor and how likely it is to bind to some degree.

Danny Lennon:

The isoflavones, though, while they do have estrogen mimicking actions, they don't act in the exact same way as if a certain amount of estrogen was around, and this may be explained by the fact that these isoflavones preferentially seem to bind to beta receptors as opposed to alpha receptors, so there's a difference there compared to estrogen. The reason why this might be important is because those alpha and beta receptors, as you noted, are present in differing amounts, in different tissues around the body. So because of this, the binding or the presence of isoflavones is slightly different to thinking about the presence of estrogen per se.

Danny Lennon:

So then that leads us to the idea that because these isoflavones are having potential actions that are similar to estrogen, they're not something that is necessarily stimulating more estrogen around the body or dramatically increasing estrogen concentrations. They're just having similar types of effects. So because of that, this may explain why we're seeing some of these difference in relation to the risk that would be predicted by the mechanisms or hypotheses put forward based on the action of estrogen versus what we actually see when we look at phytoestrogen intake and the potential outcomes in that area. Is that a decent recap of that? Is there anything you would add to that to fill in any gaps?

Alan Flanagan:

No, there's nothing else I can think of. The menopausal status, but overall that's pretty representative of the soy breast cancer literature.

Danny Lennon:

And so with that, one of the things that I looked at was the World Cancer Research Fund and their report that... The most recent one I could find was I think a 2017 one, updated in 2018, and their classification for soy and soy products is still set as limited/no conclusion in relation to breast cancer risk, which again, I think goes to highlight that we do have this emerging data, but it's certainly not a... Soy is something that we still don't have like conclusively, "Oh, there's no need to ever worry about this." It just seems that there's a lack of evidence for certain claims of harm, but there's still more to be done, and probably in relation to breast cancer still some more open questions.

Alan Flanagan:

I think the complication with any of this related to breast cancer is the complexity of breast cancer. If we consider breast cancer as part of the exposure, these differences in estrogen receptor expression, estrogen receptor status, and menopausal status I think will make it very difficult for a body to try and make a.... You can parse the evidence to see a more consistent pattern, but that type of parsing of evidence is not really what these big bodies want to do to make recommendations. They want a more homogenous evidence base. And you're never going to have a homogenous evidence base because breast cancer is such a complicated exposure itself with so many moving parts in relation to the actual diagnoses, that I don't think you'll ever... Even if the evidence is really strong, I don't think you'll ever get to that point of being able to say, yeah...

Danny Lennon:

And I think that's perfectly highlighted if you look at that report and they have these summary tables of all these factors, a whole bunch of factors that are investigated, and ones which we have strong evidence for or against, and then a classification of strong evidence or limited, unconclusive. And you have maybe two or three factors, which we can have strong evidence for or against either way, and then virtually everything else is in one of these intermediately limited evidence categories, which serves exactly to that point. It's not that we don't know anything about them, it's just the threshold for what would be comfortable to say, we are almost certain on a certain topic, is probably very difficult to meet, particularly with something like a phytonutrient.

Danny Lennon:

So with that, one of the other big areas that is important and has considerations on both sides, but I think fits in with the picture around women's health and particularly in relation to menopause, relates to cardiovascular disease for a couple of reasons. One is the change in estrogen levels that are seen during menopause, and then the potential proposed mechanisms on the back of that as to why that could impact cardiovascular disease. And then there's also, with menopause we tend to see changes in LDL cholesterol as well, which have this direct impact on cardiovascular disease. Again, there's a few different angles to look at this from. How would you set the stage for how we should think about the impact here of cardiovascular disease risk?

Alan Flanagan:

You know, it's got some similar themes in terms of some of the previous discussions we've had about flavanoids as a family and their potential cardiovascular benefits, and then it's got the added uniqueness of soy isoflavones having some potentially unique mechanisms, as each flavanoid subclass does itself. When it comes to the cardiovascular health benefits of flavanoids, typically overall, the considerations are impacts on, like you said, LDL levels. Although for flavanoids, they're pretty modest overall, and that includes for the effects of soy isoflavones and soy protein, which is also a generated interest for a potential lipid lowering effect. And then there's effects on blood pressure, and then there's effects on other processes involved in atherogenesis such as the protection against oxidative of stress or oxidation of LDL, and benefits to vascular endothelial function. So these are all the big picture of why flavanoids attract interest from a cardiovascular health perspective.

Alan Flanagan:

And then of course, there's the specific potential mechanisms associated with soy isoflavones and soy protein in particular. The soy protein one is quite interesting because it started with, in the 90s, an FDA, the US Food and Drug Administration approval of a health claim, which was based on a meta analysis of

give or take around 30 to 40 studies at that seemed to suggest that 25 grams of soy protein a day could reduce risk of heart disease via the effect that it had on LDL. Now, this claim then was then proposed to be revoked recently in 2018 or 19, and there's two ways to think about this. There's the overall evidence base, and then there's also the uniqueness of David Jenkins' portfolio diet that was developed at the university of Toronto.

Alan Flanagan:

And the portfolio diet is a total dietary pattern that was aimed at specifically targeting reductions in blood lipids with specific amounts of foods that are known to have a lipid lowering effect. So it involved 30 to 60 grams of almonds a day, there was specific... Two to three grams of like plant sterols. 20 grams of soluble fiber focusing on oats and cilium husks. And then 20 to 25 grams of soy protein. So that composite diet has a lot of interventions supporting its efficacy in lowering LDL cholesterol and total cholesterol levels, but that's separating a total dietary pattern intervention, like the portfolio diet, from the overall body of evidence, which doesn't necessarily always use that intervention.

Alan Flanagan:

The updated meta analysis that was after the FDA proposed to revoke the health claim associated with soy protein still suggested... And it included more studies. It included up to, I think, 46 trials total. And you see modest reductions in LDL cholesterol levels and in total cholesterol levels from soy protein specifically. And another caveat is that these interventions are often again using things like soy protein isolate. So if you look at the results, you might see things like a range of, say, three to six milligram per deciliter, 0.12 to 0.16 millimole per liter reductions in LDL cholesterol. And you might think, "Okay, that's fairly modest." But what's interesting is if you parse apart food based interventions from interventions using soy protein isolate, then there's actually a suggestion that food-based exposures might result in a greater magnitude of effect. And there was a meta analysis specifically that looked at this question of what's the effect of whole food exposures from soybeans or tofu or soy milk?

Alan Flanagan:

And actually the magnitude of active reduction in LDL cholesterol was higher, and the minimum benefit observed in that analysis was the average benefit observed in the meta analysis of all these studies that used soy protein isolate majority wise as an intervention. So there's the potential for the whole food matrix, similar to conversations we've had a lot about dairy, similar to the whole food matrix for soy also being an important determinant. And it may not be necessarily only because of the protein content or the isoflavone content, because at the start you outlined how soy actually has quite an interesting overall macro and micronutrient profile, including being predominantly unsaturated fat in terms of its fat composition, having an element of fiber, and also having then, of course, these additional benefits of the soy protein itself, and of course the isoflavones. So there is the potential for the soy whole foods to have a greater impact on blood lipids than an isolate version of soy protein.

Alan Flanagan:

In terms of the available evidence, then as far as actual outcomes, we've discussed, certainly like blood lipids, there is also evidence, I guess we should say, about the relationship with blood pressure. So there is evidence that, again, soy isoflavones can have a benefit on reducing blood pressure. That is potentially through the activation of endothelial nitric oxide synthase, or ENOS< which enhances the relaxation of blood vessels, so vasodilation, lowering blood pressure in the process. And there's also other benefits to vascular function, such as protection against monocyte adhesion to the vascular epithelium. And these

are mechanisms that would be consistent with the evidence that we have for other flavanoid subclasses. So they do seem to have this, particularly as it relates to blood pressure, activation of the ENOS pathway, which has a benefit on inducing vasorelaxation. So you've got these potential mechanisms underlying it.

Alan Flanagan:

The human outcome data, as far as cardiovascular disease goes overall, does suggest reductions from the consumption of soy foods. There is a suggestion that the magnitude of that effect is higher in some of the east Asian cohorts, but there is also still evidence from, for example, North American cohorts, like the Nurses' Health Study of a cardiovascular benefit to consumption of soy foods. We have human intervention studies that have looked specifically at some of the intermediate risk factors that may relate to the underlying mechanisms that we've discussed. So in general, like I said, there was a blood pressure lowering effect of soy. There was a meta analysis of RCTs looking up blood pressure specifically, and isoflavones associated with, again, modest reductions of blood pressure in normotensive individuals and a much higher reduction in hypertensive individuals.

Alan Flanagan:

And that difference was a lot. In the normotensive individuals, you're looking at nearly at two mercury minimal reduction in systolic blood pressure, which was five in the hypertensive individuals. So again, suggesting that people with hypertension would benefit more from soy isoflavone intake. And then, like I discussed before, that the actual magnitude of effect in relation to LDL is also there. It's also modest, but the magnitude of that effect may be better for soy. So I think on an overall examination of both the potential mechanisms of the action that we know that flavanoids have on vascular function in particular, and then potentially on LDL levels as the causal risk factor, and blood pressure also being a causal risk factor, human interventions that show these intermediate risk factor reductions, and observational evidence overall suggesting a reduction in incidents and mortality, again, that the strength of that association may be slightly stronger in east Asian cohorts, but again, a synthesis of the evidence suggests that soy is a beneficial food for the reduction of cardiovascular risk.

Danny Lennon:

So there's a number of those mechanisms you just outlined with this direct potential for the effect. I suppose then pragmatically, there's also the issue of if we're thinking about people who are going to start increasing the amount of soy based foods in their diet, typically, at least in Western populations at the moment, that's coming in replace of dairy and meat products. So given that soy products are low in saturated fat, and you're making a substitution of those, you're by nature, getting this reduction in saturated fat intake, which over a long period of time may be an important consideration for some people if that is moving them from a high intake now to a much lower one, base. If that's enough of a drop in their saturated fat intake, then it's having this indirect effect then on cardiovascular disease in the long run.

Danny Lennon:

One of the other areas, the last thing for us to get into here relates to menopause. And there's two areas on this. One actually does relate to cardiovascular disease. As people may have heard in an episode of a podcast with Avrum Bluming and Carol Tavris, in that we talked about in menopause at a time where you see distinct changes in estrogen levels, that can then cause a number of different

symptoms from that. One of the things that tends to happen is this discussion around changing cardiovascular disease risk from that, which I definitely want to ask about.

Danny Lennon:

And then there's also these other symptoms that, again, that there's still some open questions about, but something like hot flushes that occur with menopause seem to be related to that change in estrogen levels, which then again puts forth the hypothesis as well, if we can use something that has phytoestrogens, either supplementally or in these foods, could that offset some of those negative symptoms that can occur in menopause, whether that's something acute, like these hot flushes or something like cardiovascular disease risk more broadly. This, again, can be quite a complex area to work through. So on either of those, we can take them in whatever order you wish, what is your sense of evidence or lack of evidence we have in each of these areas?

Alan Flanagan:

This seems to be, certainly with the hot flashes, seems to be one of these areas where there appears to be, again, a divergence in prevalence between east Asian cohorts and other cohorts. As far as the actual intervention evidence goes, from what I can see, a complete inconsistency, but there seems to be a suggestion... There was a meta analysis in 2012 that showed reductions in frequency and severity of hot flashes, and that was from soy isoflavones as an addition, and then there seems to be a dose response potentially in terms of parsing why there could be some inconsistencies. So a minimum of nearly basically 19 milligrams of genistein. So that might be something that... As a dose threshold for effect, than trials that are using lower doses or 40 milligrams of total isoflavones.

Alan Flanagan:

And this is a really common theme as, as far as issues we've talked about with like parsing supposed inconsistencies in a nutrition evidence, it's just bases. Are there differences between observational and intervention research? If yes, what might it relate to and could there be an effective dose? So, yeah, it does strike me as an inconsistent evidence base overall, but it does appear that in synthesizing that evidence, there is a signal in the noise in terms of both outcomes and then in terms potentially of the dose required to actually achieve those outcomes.

Danny Lennon:

And in trying to look at this question the same, because I'd seen some places and dietetic associations and otherwise mention some of those interventions that you highlighted where you see something along like the equivalent of a couple of servings of soy foods per day. But a lot of them just use isoflavones as the intervention, but that amount seems to reduce the frequency or severity of these hot flushes. But when you try and look at why might be this the case or what explains this? No one really knows. What is the mechanism by which it's having in effect? Or at least I couldn't find like a good mechanistic reason for why this is happening or is it re repeatable or reliable in any way? But there is at least some inkling that there could be some benefit.

Alan Flanagan:

Right, and the proposal that it might also relate to isoflavone interaction with estrogen receptors. Now why that would suddenly become relevant for menopausal symptoms? I mean, we mentioned briefly that menopause is defined obviously by a shift away from ovarian estrogen production as the primary site of certainly 17-beta estradiol production, and you see a shift to the adrenals and to adipose tissue,

and is there something then that relates to receptor expression and estrogen metabolism that, again, the high affinity of soy isoflavone metabolites for binding. And again, does it suggest a role for ER beta as opposed to alpha? They're all open questions necessarily, but we still don't know how anesthetic work and I think everyone would be happy getting them if they were going under the knife.

Alan Flanagan:

So the outcome data does suggest a benefit, but it is suggestive of higher doses either of genistein in isolation or total isoflavones. So it is worth bearing that in mind, that a lot of... And again, it's an inconsistency... It's a theme of inconsistency in nutrition interventions that comes up a lot in relation to a number of nutrient exposures, is you have an apparent inconsistency in trials, but then you look at them and you can see that some trials just were likely really underdosed and these other factors that can influence the outcome. So there does appear to be some efficacy.

Danny Lennon:

But then again, I guess with... And this is probably more discussion for someone with their doctor, but given the availability of hormone replacement therapy that would obviously have a much more direct and meaningful benefit on some of these things than maybe trying to change your soy intake. With that, maybe as a way to round this out, I did want to leave people with some pragmatic recommendations as to any of the stuff we discussed, what that actually means for food choices, either for them or people maybe they're advising. So we know that the intake of soy foods is now accounted for in various dietary guidelines, whether that's in the UK, you can go to Eatwell Guide and see that. Various soy foods or soy based products in sections for dairy and dairy alternatives, as well as under beans and pulses, and then in the US dietary guidelines, the most recent version, you also see same thing, various soy foods and soy products represented across a number of different food groups from dairy to the protein group, to the vegetable group.,And then of course in oils, your favorite, soybean oil.

Alan Flanagan:

That's it

Danny Lennon:

The classic vegetable oil.

Alan Flanagan:

Yeah, soy boil.

Danny Lennon:

And it seems that most of those dietary guidelines are suggesting that one to two servings of soy foods per day seems to be relatively healthy or at least neutral once it's within a part of a overall healthful diet, and there's no reason to have any concern around that. In relation to what they mean by serving, just an example that might be useful for people, this would be something like 50 grams of soy mince, 90 grams of tofu, a quarter block of tempeh, 50 grams of edamame, a large glass of soy milks, so about 250 mills, or 200 grams of a plain soy yogurt. Those are examples of servings that would be one serving of these. And then you can work out isoflavone content if you were so inclined. I think it's typically between three and four or milligrams of isoflavones per gram of protein.

Danny Lennon:

One of the important things, I guess, that also comes up pragmatically is the fortification of these various soy products, given that most of the alternatives for dairy tend to be fortified with some degree of calcium so it's basically matching dairy foods. So with the idea that someone's probably going to be removing dairy from their diet and replacing it with this. You also get fortification of vitamin D, which can help with that calcium resorption. Iodine is another interesting one, given that whilst seafood and seaweeds and things like that are super rich in it, most people in Western populations get their iodine from dairy foods, given the ubiquity of that in their diet typically. Hence why iodine fortification of these products tends to be more common now, and that's something that people might be looking out for if they are indeed completely eliminating dairy from the diet.

Danny Lennon:

I suppose the final point, and this would be a separate conversation, is for those interested in the environmental sustainability part, the evidence seems to be relatively consistent, at least to me, and again, that's not my area, but compared to some of the products that these might be replacing, they have a lower carbon footprint, require or less water, less land, et cetera, in relation to production of dairy and/or meat products. So for those who are concerned. So there are just some pragmatic things for making dietary decisions. I don't know if there's a few others that you might add to that or emphasize?

Alan Flanagan:

No, I think just to plant the seed in people's mind, because we mentioned it beforehand, that there's always a conversation that rises in relation to genetic modification and genetically modified soy, but we feel that that's a conversation for another day that will require a more specific elucidation of that topic itself before consideration of GM soy, for example. So just to park that in your head that we are thinking of that. We'll get to it at some point.

Danny Lennon:

Yes, we will get to genetically modified foods for sure. The only other thing that I can think of that people might bring up is in relation to soy allergy, given it's one of the classic foods that people may have an allergy to, although its prevalence seems to be quite a bit lower than some of the other classic allergic foods that people have. Much lower than things like milk or wheat and so on. But it's something like between one in 200 to one in 1,000 people, something of that magnitude that do have an allergy. So of course in those cases intake of soy foods is contraindicated, but that would go without saying, I think, for our audience. So I think that is everything that we had planned to discuss.