SOY AND PANCREATIC CANCER:
A Brief Review of the Literature

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The impact of diet on pancreatic cancer — a leading cause of cancer mortality among Americans — risk has yet to be established. This fact sheet will explore the interplay between soy and pancreatic cancer.

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PREVALENCE OF PANCREATIC CANCER

Estimates are that in 2020, nearly 58,000 Americans will be diagnosed with pancreatic cancer and about 47,000 will die of this disease.[1] In terms of U.S. cancer mortality, pancreatic cancer ranks behind only lung and colon cancer. Once diagnosed, the 5-year survival rate is only about 10%, in part because symptoms of pancreatic cancer usually do not appear until the disease is at an advanced stage.[1] Such sobering statistics emphasize the need to identify lifestyle factors that can reduce risk of developing pancreatic cancer. Does diet play a role? Do soyfoods affect the chances of having pancreatic cancer? Let us look at the evidence.

PANCREATIC CANCER: RISK FACTORS

According to the American Cancer Society, cigarette smokers have about twice the risk of pancreatic cancer as those who have never smoked; type 2 diabetes and excess body weight also increase risk.[1] That diabetes[2] and obesity[3] are associated with pancreatic cancer suggests that, at least indirectly, diet may play a role in the etiology of this disease. This is because red and processed meat intake is associated with an increased risk of diabetes whereas whole grain and cereal fiber consumption is associated with a decreased risk.[4] Regarding obesity, plant-based consumers have a lower body mass index (BMI) than nonvegetarians,[5] although identifying specific dietary patterns that promote weight loss or prevent weight gain has proven difficult.[6]

SOY AND PANCREATIC CANCER: OBSERVATIONAL STUDIES

Comparisons among pancreatic cancer rates in different countries can be used as a first step in identifying differences among countries that possibly play a role in the etiology of this disease. Parenthetically, initial enthusiasm about the role soy might play in preventing breast cancer was partially based on the historically low rates of breast cancer in soyfood-consuming countries, especially Japan.[7] However, although recent data show that China has a pancreatic prevalence rate about 50% lower than the U.S., the Japanese rate is slightly higher than the U.S. rate.[8] Since both China and Japan consume soyfoods, these ecological comparisons don't provide much insight into a possible role for soy.

Having said that, it has only been within the past several decades that Japanese rates have risen to the level of the United States.[9-11] In fact, in Japan, the overall age-adjusted mortality rates for pancreatic cancer between 1968–1972 and 1998–2002 increased by 70.3% among males and by 68.3% among females.[12] During this period soyfood intake has remained relatively stable.[13] In contrast, with Westernization there have been marked increases in the consumption of alcohol, animal protein, eggs, and milk/milk products.[14]

More informative than differences among countries or trends within a country, are cohort studies that directly assessed the relationship between soy intake and pancreatic cancer risk. One such example is recent research by Yamagiwa et al.,[15] which involved 90,185 participants of the Japan Public Health Center-based Prospective Study. During a median follow-up of 16.9 years, 577 cases of pancreatic cancer were identified. Total soyfood intake was associated with an approximate 50% increased risk of pancreatic cancer. However, sub-analysis revealed the association was only with unfermented soyfoods, and only among women when participants of all body weights were considered in the analysis. Unfermented soy intake included tofu consumed in various forms and soymilk, but the former represented the bulk of the intake. When sub-analyzing the data according to participant BMI, unfermented soyfood intake was associated with an increased

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risk only among those with a BMI ≥25 kg/m2. In Japan, a BMI of ≥25 kg/m2 is classified as obese (in much of the rest of the world the cutoff is 30).[16]

Yamagiwa et al.[15] acknowledged the limitations of their study and called for further research to determine whether their findings could be replicated. For example, they pointed out that dietary intake was assessed only at a single timepoint using a 5-year follow-up survey. Dietary intake may have changed over the follow up period. Also, the number of incident cases may not have been sufficient for analyses stratified by exposure subgroup and risk factor, and the stratified analysis findings may in part be due to chance. And finally, the findings may have been affected by residual confounding effects and unmeasured confounding variables. While true, this limitation applies to all observational studies. One more finding from this study warrants highlighting. Among women in the second and third unfermented soy intake quartiles, risk was increased by 30 and 35%, respectively. The mean of the second and third unfermented soyfood intake quartiles were 22 and 37 g/d, respectively. In the U.S., 3-4 ounces, or about 85 g, is considered one serving of tofu, and provides about 8 g of protein. Thus, Yamagiwa et al.[15] observed associations between pancreatic cancer and as little as ¼ serving of tofu. From a biological perspective, such a strong association with such low exposure seems unlikely, although not impossible. Since observational studies are not designed to establish cause and effect, it is necessary to consider other types of evidence to make meaningful conclusions.



HAWAII–LOS ANGELES MULTIETHNIC COHORT STUDY

The intake of legumes, which included soy products, was inversely related to pancreatic cancer risk, although the finding did not quite reach statistical significance (p for trend, 0.099).[17] Among the 183,522 participants, 529 pancreatic cancer cases were identified during the 8.3 year follow up period.

ADVENTIST HEALTH STUDY

When comparing high versus low intake of vegetarian protein products, risk of fatal pancreatic cancer was reduced by 85% (relative risk, 0.15; 95% confidence interval: 0.03, 0.89).[18] The intake of beans/lentils/peas was also inversely related to risk. Among the 34,000 Seventh-day Adventists who participated in this study, 40 deaths due to pancreatic cancer were reported. Although most of the vegetarian protein products consumed by the participants were likely derived from soy, these products were described as vegetarian protein products such as gluten, soy, or nuts.

JAPAN COLLABORATIVE COHORT STUDY OR EVALUATION OF CANCER RISK

When comparing almost daily tofu intake with infrequent intake (0-2 times/month), no relationship was found with pancreatic cancer risk regardless of gender and smoking status.[19] Among the 46,465 men and 64,327 women aged 40–79 years who participated in this study, 300 deaths due to pancreatic cancer were identified over the approximate 10 year follow up period. Census Based Large Scale Cohort Study in Japan The sex and age adjusted relative risks for non-, rare, occasional and daily soybean paste soup (miso) were 1.00, 1.21, 1.52, and 1.77, respectively (p for trend, 0.055).[9] Not clear is the extent to which other potential confounding factors were controlled for besides sex and age. Among the 122,261 men and 142,857 women at least 40 years of age included in this cohort, 679 men and women died from pancreatic cancer during the 17 year follow up period.

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Before examining that evidence, several other relevant observational studies warrant mention.

In summary, of the five cohort studies thatexamined the relationship between soy intake and pancreatic cancer, one found miso intake was unrelated to risk[15] whereas another found it was positively related.[9] One found tofu (unfermented soy) intake was associated with an increased risk[15] whereas one found no association.[19] In one study, vegetarian protein products were markedly inversely related to risk[18] whereas in another study, legume intake, which included soy, tended to be protective, but the finding did not reach statistical significance.[17] Overall, no clear pattern emerges between the intake of various soy products and pancreatic cancer incidence or mortality.

POSSIBLE MECHANISMS ISOFLAVONES | PROTEASE INHIBITORS

Isoflavones

There are ways in which soy intake could theoretically affect the development of pancreatic cancer. For example, the soybean isoflavone genistein significantly improved survival, almost completely inhibited metastasis, and increased apoptosis in an orthotopic model of pancreatic cancer.[20] The authors of this study also found that in vitro genistein treatment resulted in apoptosis in all pancreatic cancer cell lines tested. In another study, it was found that pretreatment of pancreatic carcinoma cells with genistein down-regulated NF-kappaB (nuclear factor kappa-light-chain-enhancer of activated B cells, a protein complex that controls transcription of DNA, cytokine production and cell survival) activity and enhanced the apoptosis-inducing effect of the chemotherapeutic cisplatin, leading to greater antitumor activity in vivo.[21] Despite these studies and others which focused on isoflavones,[22-24] early interest in the relationship between soy and pancreatic cancer stemmed from the presence of protease inhibitors in soybeans.

Protease Inhibitors

Protease inhibitors (PI) have been identified in a large range of foods,[25] but are most often identified with cereals and legumes.[26,27] PI, which interfere with protein digestion, are a type of antinutritional factor that plants have developed as part of their defense mechanisms in response to biotic stressors.[28] However, the effect of PI content on protein digestibility is not straightforward.[29] The extent to which PI activity is inactivated by heat is a function of temperature, duration of heating, particle size, and moisture conditions. Since heat also denatures protein and thus lowers quality, there is a compromise between the amount used to inactivate TI and that which does not significantly destroy protein quality.[30,31] The two main protease inhibitors in soybeans are the Kunitz inhibitor (KI, trypsin inhibitor), which was first isolated by Kunitz in 1945[32] and the Bowman Birk chymotrypsin and trypsin inhibitor (BBI), which was isolated for the first time in soybeans by Bowman in 1946[33] and later characterized by Birk et al.[34] Soybeans tend to be higher in PI content than other legumes.[29,35] Early concerns that PI were connected to pancreatic cancer were based on the observation that raw soybeans caused pancreatic hypertrophy (an increase in the size of the acinar cells) in rodents as a result of an increased secretion of digestive enzymes, including trypsin, chymotrypsin and elastase.[36,37]

Protease Inhibitors and the Pancreas

To clarify the relationship between trypsin inhibitors (TI) and pancreatic function, the United States Department of Agriculture conducted an 18-month rat study in which the relative proportion of toasted and raw soy flour was altered to produce diets with 5 different levels of TI content.[38,39] The results showed there was a direct relationship between dietary TI content and pancreatic nodules [38,39] However, pancreatic



hypertrophy was not observed in rats fed soy flour even when about half of the TI activity remained. Furthermore, although hamsters and mice also displayed pancreatic hypertrophy in short-term feeding experiments fed raw soy flour, there was no evidence of pancreatic lesions after long term feedings.[40,41] This difference among animal species in response to the carcinogenic effect of the long-term feeding of TI indicates that caution must be exercised in extrapolating the results obtained with one animal species to another.[42] Much research aimed at understanding the connection between PI and pancreatic hypertrophy has been conducted. Evidence indicates there is a negative feedback control mechanism whereby the secretory activity of the pancreas is subject to control by the level of trypsin in the intestinal tract.[43] Intraluminal trypsin inhibits pancreatic secretion by inhibiting the release of the hormone cholecystokinin (CCK) from the intestinal mucosa, such that the binding of trypsin by a TI results in the unfettered release of CCK. In the rat, a peptide consisting of 61 amino acids is the agent responsible for signaling the release of CCK from the intestine. This peptide is trypsin sensitive; when intestinal levels of trypsin are high, it loses its ability to trigger the release of CCK. When levels are low, as is the case when it is bound by a TI, the peptide is active. The feeding of raw soy flour or TI to rats does in fact produce a marked rise in the concentration of circulating CCK,[44] and it is this continuous release of excessive levels of CCK that is responsible for the hypertrophy and hyperplasia of the pancreas of rats fed raw soy flour. As already noted, pancreatic hypertrophy in response to PI appears to be species specific. Rats, chickens, young but not adult guinea pigs, quails, mice, and hamster experience an enlargement, whereas the adult guinea pig, dog, pig and calf do not. On the basis of this variation, it was proposed that animals who have a pancreas less than 0.3% of body weight do not exhibit pancreatic enlargement.[45-47] In theory therefore, the human pancreas would not be expected to exhibit enlargement as it weighs no more than 0.12% of body weight.[45] A specific example of species variation in response to TI comes from work by Struthers et al.[48] They found that neither raw soy flour nor any other soy product produced pancreatic enlargement in pigs or monkeys, whereas in rats, pancreatic size increased. Also, growth was depressed by 60% in rats and 84% in pigs, but not at all in monkeys. Interestingly, the lack of increase in pancreatic weight in pigs occurred despite the digestibility of raw soy protein being only 45%. Although based on research animals, expectations are that the pancreatic hypertrophy would not develop in humans. Nevertheless, Calam et al.[49] found that feeding of a meal containing raw soy flour to human subjects led to a greater peak plasma CCK response in 11 study participants in comparison to the feeding of heat-treated soy flour (16.8 ± 8.1 vs. 4.9 ± 2.8 pmol/l). However, humans do not consume raw soy. More relevant therefore is the extent to which residual PI content remains in soy products after processing and whether this activity affects protein digestion. Research shows that soy protein isolate (SPI by definition is ≥90% protein), which is used in soy infant formula (SIF) is nearly completely devoid of PI content.[50,51] This finding is notable because infants have been identified as a group potentially vulnerable to any adverse effect of PIs since SIF can be the sole source of nutrition for infants.[52] The PI content of tofu [53,54] is very low as is the PI content of soymilk in Japan[54] and sterilized soymilk.[53] However, Canadian researchers recently found that of the eight commercially available soymilks tested, three had nearly 50% of the TI content remaining, whereas only three had 20% or less.[51] Chymotrypsin inhibitor content was lower than TI content, but three milks still had at least 30% of the original activity remaining. In this analysis, the PI content of the raw soybean to which the milks were compared was not the actual bean from which the different milks were made, but it was considered by the investigators to be representative of soybeans overall. An earlier paper from Hong Kong also suggested that pasteurized and UHT (ultra-high-temperature) soymilk retained substantial amounts of PI activity.[53] Since boiling soymilk for just 10 minutes eliminates approximately 90% of the



TI content, the Canadian[51] and Chinese[53] results suggest that some of the processes used in the making of modern soymilks involve less heat and/or heat applied for shorter time periods than is needed for extensive inactivation of PI content.[54] However, based on their research, Rackis et al.[55] concluded that "reduction in trypsin inhibitor content of 40 to 50% is required to obtain a relatively large increase in rat growth and PER [protein efficiency ratio] values of diets containing soy flour." Thus, even if some soy products contain substantial amounts of PI content, protein digestion is unlikely to be affected. And as a result, CCK is unlikely to be excessively secreted. In fact, Lu et al.[56] found that the consumption of 36 oz of soymilk daily for 1 month led to a slight decrease in meal-induced CCK secretion.

SUMMARY AND CONCLUSION

Pancreatic cancer is a leading cause of cancer mortality among Americans. The impact of diet on pancreatic cancer risk has yet to be established. Observational studies that have examined the relationship between soy intake and risk of this disease have produced mixed results. Rodent studies indicate the consumption of raw soy, because it contains active PI content, increases pancreatichypertrophy. However, experimental evidence suggests the human pancreas does not respond to the presence of PI in the same way as do rodents. Heat denatures PI activity, although some residual activity remains in commercially available soyfoods. The amount remaining is not expected to increase levels of CCK or to affect digestion and therefore, is unlikely to affect pancreatic cancer risk.



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