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Short Communication

In 1950, Age-Adjusted Prostate Cancer Mortality was Forty-Fold Higher in the U.S. than in Japan: Could Moderate Protein Restriction and Ample Green Tea and Soy Isoflavone Intakes Explain This?

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ABOUT THE STUDY

Prostate cancer is currently the number 2 cause of cancer mortality in American men, second only to (highly preventable) lung cancer. It is therefore of considerable interest to recognize that, in 1950 post-war Japan, the age-standardized mortality from prostate cancer was only one-fortieth as high as in the United States (0.3 vs. 13.1 per 100,000) [1]. Since that time, this differential has closed gradually but inexorably, such that American men are now only twice as likely to die from this cancer; while American mortality has declined moderately, presumably owing to better early diagnosis and treatment, risk in Japan has increased markedly. These considerations suggest that genetic factors played at most a small role in the remarkable freedom of Japanese men from prostate cancer mortality in the mid-twentieth century.

In seeking to explain this disparity, suspicion falls upon the characteristic diet of poverty-stricken post-war Japan. While we currently think of the Japanese as heavy fish consumers, data published by Ernst Wynder indicate that, in the early 1950s, the average Japanese diet provided only 61 g of protein daily, only 16 g of which was from animal sources (primarily fish) [2]. A survey of Okinawa at about the same time found that protein provided only 9% of total calories, and only 4% of calories were from animal sources (again, mostly fish) [3]. Since plant protein tends to be relatively low in certain essential amino acids, the Japanese diet at the time was relatively restricted in this regard.

Could moderate restriction of essential amino acids have a protective effect with respect to risk for aggressive prostate cancer? This was interrogated by correlating World Health Organization data for daily food intakes in 59 countries (circa 1979-1981) with age-adjusted deaths rates from prostate cancer in those countries (circa 1985-1989), as reported by Dr. James Hebert and colleagues [4]. Six countries on the list (Egypt, Guatemala, Honduras, South Korea, Sri Lanka, and Thailand) were receiving less than 10% of their daily calories from animal products. In 20 of the listed countries, animal product consumption was over 1000 kcal daily. If one calculates the average prostate cancer death rates from the low-animal product and high-animal-product countries, these death rates were 15-fold higher in the countries that were heavy consumers of animal products [5].

How could essential amino acid restriction reduce risk for aggressive prostate cancer? Such restriction can activate the kinase GCN2, while reducing the activity of mTORC1 [6]. GCN2 functions as a detector of essential amino acid paucity; when one or more essential amino acids is in short supply within a cell, the kinase activity of GCN2 is activated. GCN2, in turn, is a driver of the "integrated stress response" that boosts synthesis of the ATF4 transcription factor [7]. ATF4, among other things, promotes the transcription of fibroblast growth factor 21 (FGF21) the so-called "longevity hormone" that markedly boosts average and maximal lifespan when genetically overexpressed in mice [8,9]. FGF21 of hepatic origin acts in an autocrine fashion to suppress the liver's responsiveness to growth hormone, consequently down-regulating the liver's secretion of insulin-like growth factor-I (IGF-I) [10].

Moreover, FGF21 acts on adipocytes to enhance their secretion of adiponectin [11]. Hence, vegan diets tend to up-regulate systemic levels of FGF21 and adiponectin, while down-regulating IGF-I activity [12,13]. Meta-analysis of pertinent epidemiology links increased IGF1 levels and decreased adiponectin levels with greater risk for prostate cancer or prostate cancer mortality [14,15]. These effects could be expected to decrease mTORC1 activity in prostate epithelium [16-19] an effect that would be amplified by diminished essential amino acid availability in the prostate. Conceivably, these effects could interact in an additive or synergistic way to suppress the evolution of aggressive prostate cancer. Examination of the impact of moderate essential amino acid restriction in rodent models of "spontaneous" prostate cancer–such as the TRAMP model would be an appropriate way to test these speculations. Also of likely pertinence is a study demonstrating that a 7%protein diet reduces the growth of a castrate-resistant prostate cancer in mice by 70%; replacing animal protein with plant protein also retarded tumor growth in this model [17].

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Nonetheless, risk of fatal prostate cancer was so low in post-war Japan that it seems likely that additional protective factors were involved. There is reason to suspect that these might include an ample intake of green tea and of soy isoflavones-key features of the traditional Japanese diet, each of which have been linked to reduced prostate cancer risk in epidemiological studies [20-23]. The chief catechin in green tea, epigallocatechin gallate (EGCG), has been shown to down-regulate the activity of certain tyrosine kinase growth factor receptors, including that of IGF-I-in low micromolar concentrations that may be physiologically relevant [24,25].

There is reason to suspect that this reflects the ability of EGCG to promote endosomal uptake of these receptors, an effect which requires ECGC's high affinity interaction with the 67 kDA laminin receptor [5]. With respect to soy isoflavones, when these are consumed in dietarily relevant amounts, genistein and equol (a absorbable bacterial metabolite of daidzein) achieve plasma concentrations sufficient to activate the beta-isoform of the estrogen receptor, while having minimal impact on the feminizing ER-alpha receptor [26,27]. ER-beta is expressed by prostate epithelium, and in its activated form suppresses expression of the androgen receptor and of genes which the androgen receptor targets [28]. Hence, there are reasonable mechanisms that might account for the protective impact of regular green tea and soy isoflavone consumption observed epidemiologically. A more expansive discussion of these speculations can be found here [29].

CONCLUSION

Further attempts to explain the remarkably low prostate cancer mortality rate that prevailed in post-war Japan may provide important insights into practical strategies for prostate cancer prevention. An analogous analysis has proposed that abandonment of a low-protein quasi-vegan diet, in conjunction with surging tobacco addiction, may largely account for the 9-fold increase in age-adjusted pancreatic cancer mortality which Japan experienced between 1950 and 1995. And such a diet may also afford protection from several other types of cancer, obesity, diabetes, atherosclerosis, and various autoimmune disorders [12].

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