Prostate cancer prevention by nutritional means to alleviate metabolic syndrome[1−4]

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ABSTRACT

In 1987 when Reaven introduced syndrome X (metabolic syndrome, or MS), we were studying skeletal muscle insulin resistance and found that when rodents were fed a high-fat, refined-sugar (HFS) diet, insulin resistance developed along with aspects of MS, including hyperinsulinemia, hypertension, hypertriglyceridemia, and obesity. MS was controlled in rodents by switching them to a low-fat, starch diet and was controlled in humans with a low-fat starch diet and daily exercise (Pritikin Program). Others reported inverse relations between serum insulin and sex hormone–binding globulin (SHBG). When subjects were placed on the Pritikin Program, insulin fell and SHBG rose and it was suggested that prostate cancer might also be an aspect of MS. A bioassay was developed with tumor cell lines grown in culture and stimulated with serum before and after a diet and exercise intervention. Diet and exercise altered serum factors that slowed the growth rate and induced apoptosis in androgen-dependent prostate cancer cells. Changes in serum with diet and exercise that might be important include reductions in insulin, estradiol, insulin-like growth factor-I (IGF-I), and free testosterone with increases in SHBG and IGF binding protein-1. Hyperinsulinemia stimulates liver production of IGF-I, plays a role in the promotion of prostate cancer, and thus is the cornerstone for both MS and prostate cancer. Adopting a low-fat starch diet with daily exercise controls MS and should reduce the risk of prostate cancer. *Am J Clin Nutr* 2007;86(suppl):889S–93S.

KEY WORDS Insulin, insulin-like growth factor-I, IGF-I, IGFBP-1, LNCaP, p53, exercise

INTRODUCTION

Even though insulin was discovered in the 1920s and was known to affect blood glucose, it was not until 1980 that insight was gained into its mode of action. In that year the Cushman and Kono labs independently reported the translocation hypothesis from studies done on fat cells (1, 2). They showed that insulin caused the movement of glucose transporters from a microsomal pool inside the cell out to the plasma membrane. Grimditch et al (3) postulated that skeletal muscle should be a more important target tissue for insulin action and developed a sarcolemmal membrane preparation to study muscle glucose transport. Sternlicht et al (4) confirmed the translocation hypothesis for insulin action in skeletal muscle, and the group started to investigate aging-induced insulin resistance, something common in humans. Much to their surprise, no aging-induced insulin resistance was found in their rodents (5). However, when the rodents were placed on a high-fat, refined-sugar (HFS) diet, insulin resistance and compensatory serum hyperinsulinemia were observed. Barnard et al (6) concluded that diet, not aging, causes insulin resistance. In 1987 Gerald Reaven gave his famous Banning Lecture and introduced the concept of what he called "syndrome X," an aggregation of atherosclerosis risk factors including insulin resistance and hyperinsulinemia, hypertension, hypertriglyceridemia, and depressed HDL cholesterol (7).

METABOLIC SYNDROME

At the time Reaven introduced syndrome X, it was felt that obesity was the underlying cause of the various components of the syndrome. However, Reaven suggested that the combination of insulin resistance and hyperinsulinemia was the underlying factor, which eventually resulted in the other aspects of the syndrome. In a prospective study, Haffner et al (8) found that elevated serum insulin, independent of body fat or fat distribution, preceded the other aspects of the syndrome and renamed it the "insulin-resistance syndrome." In rodents, not only did the HFS diet induce skeletal muscle insulin resistance, it also induced other aspects of the syndrome, including obesity, hypertension, hypertriglyceridemia, and enhanced clotting (9). In longitudinal studies in rodents, it was also found that insulin resistance preceded the other aspects of the syndrome (9). As the list of factors associated with the syndrome grew to include enhanced clotting and other lipid abnormalities such as small-dense LDL and VLDL, the name *metabolic syndrome* (MS) was adopted by most scientists.

Barnard et al (10) reported that after inducing insulin resistance with the HFS diet, the defect could be reversed by switching the rodents to a low-fat, complex carbohydrate (LFCC) diet before the animals normalized their body weight. In addition to controlling insulin resistance, switching to the LFCC diet also controlled other aspects of the syndrome, such as hypertension and hypertriglyceridemia (11). Studies in humans showed that

daily aerobic exercise combined with a low-fat, high-complex-carbohydrate diet could reduce serum insulin and control aspects of the metabolic syndrome including hypertension and hypertriglyceridemia in just 3 wk while the subjects remained overweight or obese (12). These results support the concept that lifestyle and not obesity per se causes the metabolic syndrome.

METABOLIC SYNDROME AND PROSTATE CANCER

While investigating the relation between lifestyle and the metabolic syndrome, Barnard et al (13) initiated studies on prostate cancer and suggested that it might also be an aspect of the metabolic syndrome. Several articles (13–17) had reported an inverse relation between insulin and sex hormone–binding globulin (SHBG). The hyperinsulinemia associated with the metabolic syndrome should reduce SHBG and increase the amount of free sex hormone (testosterone and estrogen) available to interact with tissue receptors and enhance the hormone-related cancers including prostate cancer. Tymchuk et al (18) reported that adopting a low-fat diet combined with daily exercise (Pritikin Program) for 3 wk resulted in a decrease in insulin and a rise in SHBG. The rise in SHBG was subsequently reported to reduce the serum concentration of free testosterone by 19% (19).

To investigate the relation between lifestyle and prostate cancer, Tymchuk et al (19) developed a bioassay to study the impact of serum stimulation on prostate cancer cell growth using prostate cancer cell lines in vitro. They found that just 11 d of following a low-fat diet and exercise program altered serum factors that reduced the growth of androgen-dependent LNCaP cells by 35%. Long-term compliance (14 y) with the low-fat diet and exercise lifestyle resulted in an additional 15% reduction in serum-stimulated LNCaP cell growth. Serum factors that had previously been shown to be reduced by the Pritikin diet and exercise program included insulin, estradiol, and free testosterone. Tymchuk et al (20) showed that each of these hormones could individually stimulate the growth of LNCaP cells. However, when they added all 3 back to the post-diet and exercise serum and studied LNCaP growth, they could account for a little less than one-half of the reduction in growth found with the diet and exercise program. Barnard et al (13) then turned to the insulin-like growth factor (IGF) axis and developed a model similar to **Figure 1**.

Ngo et al (21) measured serum concentrations of IGF-I and IGF binding protein-1 (IGFBP-1) in response to the low-fat diet and exercise intervention and found that IGF-I was reduced, whereas IGFBP-1 was increased with no change in IGFBP-3. They confirmed the reduction in LNCaP growth after the diet and exercise intervention and also found similar results with another androgen-dependent prostate cancer cell line, LAPC-4. When IGFBP-1 was added to the preintervention serum, LNCaP cell growth was reduced, and when IGF-I was added back to the postintervention serum, the reduction in growth was eliminated (21, 22). IGF-I is well known to stimulate cell growth and also to block apoptosis (23). When Ngo et al (21) studied apoptosis in the LNCaP cell cultures, they found almost no signs of apoptosis in the cultures stimulated with preintervention serum but a significant amount of apoptosis in the postintervention serum-stimulated cultures. This result is important because inducing apoptosis in tumor cells is considered to be more important than reducing growth (24).

WHAT IS MORE IMPORTANT: DIET OR EXERCISE?

In an attempt to study the independent effects of exercise versus diet and exercise, Barnard et al (25) compared results from long-term compliers with the Pritikin diet and exercise program with results for serum samples obtained from men who had participated in the University of Nevada, Las Vegas, Adult Fitness Program with no diet intervention. Serum insulin was lower in the diet and exercise group than in the exercise only group, but values in both groups were significantly lower than in the sedentary controls. Triacylglycerols, another aspect of MS, were also lower in both groups than in controls. Serum IGF-I was lower in both the diet and exercise and the exercise only group than in the sedentary controls. IGFBP-1 was higher in the exercise only group than in the controls but was not as high as in the diet and exercise group. When the serum was used to stimulate LNCaP cells, growth was lower in the exercise only group than for sedentary controls but was not as low as was observed in the diet and exercise group. Apoptosis in the serum-stimulated LNCaP cells was again very low in the sedentary controls, was significantly higher in the exercise only group, and was significantly higher in the diet and exercise group than in the exercise only group. These results suggest that daily exercise alone might control aspects of MS and reduce the risk of prostate cancer, but the combination of the low-fat diet and daily exercise should be more effective.

In the early rodent studies of diet and MS, it was reported that an HFS diet could induce MS, which could be reversed by switching the animals back to a low-fat, complex-carbohydrate diet (10, 11). To investigate the independent role of diet in the promotion of prostate cancer, Ngo et al (26) turned to studies in SCID mice with LAPC-4 tumor cells implanted subcutaneously. Earlier studies had reported that increasing fat in the diet resulted in an increase in prostate cancer development and promotion (27–29). Those results could have been due to the increased fat or to an increase in calories usually consumed with high-fat diets. Ngo et al (26) pair-fed their mice to control for calorie intake and thus focused specifically on the increased fat content of the diet. Fat in the diet was increased from 12% of calories to 42% of calories by adding corn oil, primarily an $n-6$ fatty acid. The LAPC-4 cells grew more rapidly in the high $n-6$ fatty acid group and serum prostate-specific antigen concentrations were higher. Serum insulin and tumor IGF-I mRNA were increased in the high $n-6$ fatty acid group.

High-Fat, Refined Sugar Diet Plus Physical Inactivity

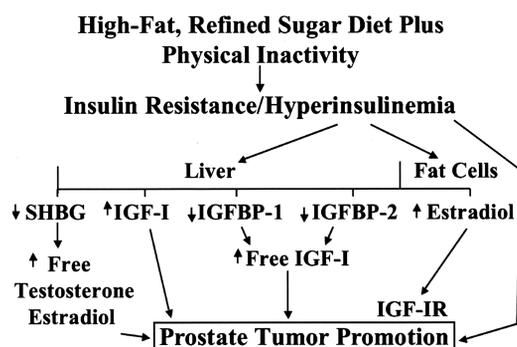**Insulin Resistance/Hyperinsulinemia**

FIGURE 1. A proposed scheme to explain the relations among lifestyle, insulin resistance and hyperinsulinemia, and prostate cancer promotion. IGF-I, insulin-like growth factor-I; IGF-BP, IGF binding protein; IGF-IR, IGF-I receptor; SHBG, sex hormone–binding globulin.

To further investigate in role of a high n−6 fatty acid diet on prostate cancer promotion, Kobayashi et al (30) conducted a study in SCID mice with LAPC-4 tumors by altering the ratio of dietary n−6 to n−3 fatty acids. Two groups of mice were fed isocaloric, 20%-fat calorie diets, one high in n−6 and one high in n−3 fatty acids. When the n−6 fatty acid content was balanced with n−3 fatty acid content at 1:1, the tumors were much smaller and the serum PSA concentration significantly lower. Because inflammation is thought to be important in the development of prostate cancer, and n−6 fatty acids are known to increase membrane arachidonic acid, which could increase prostaglandin E_2 (PGE_2) leading to inflammation, tumor concentrations of cyclooxygenase-2 (COX-2) and PGE_2 were measured. When the n−6 fatty acid content was balanced with n−3 fatty acids, the tumors showed decreased COX-2 mRNA and protein along with an 83% reduction in PGE_2. These results suggest that balancing the dietary intake of n−6 fatty acids with n−3 fatty acids should reduce inflammation and the risk of prostate cancer.

Epidemiologic studies support an inverse association between marine-derived n−3 fatty acids and prostate cancer risk as well as the risk of advanced prostate cancer (31–34). However, several studies do not support a protective role for n−3 fatty acids. In a recent literature review, MacLean et al (35) concluded that n−3 fatty acids do not protect against cancer. Although the conclusion may be correct on the basis of the epidemiologic studies reviewed, the science suggests that n−3 fatty acids should be protective. Dietary n−3 fatty acids replace the membrane arachidonic acid derived from n−6 fatty acids and reduce the production of proinflammatory eicosanoids implicated in promoting tumor growth and metastasis (36–40). The problem with the epidemiologic studies may be the fact that they were done, for the most part, on populations in industrialized countries where the diets are high in fat (30–40% of energy) and high in n−6 fatty acids, with minimal consumption of n−3 fatty acids. The dietary n−6 to n−3 fatty acid ratio in industrialized countries is on the order of 10–25:1 compared with the diet of Mesolithic man, which was 1–4:1 (37). The Pritikin diet has been reported to have an n−6 to n−3 fatty acid ratio of 2–4:1. Thus, it appears that the answer is to reduce the consumption of total dietary fat to <15% of energy to reduce the intake of n−6 fatty acids and to increase the intake of n−3 fatty acids by consuming coldwater fish; nuts high in n−3 fatty acids, such as walnuts; and dark-green leafy vegetables. An alternative would be to take fish oil capsules along with a low-fat diet.

On the basis of this scientific evidence, the following scheme (**Figure 2**) is proposed to explain how the typical lifestyle of industrialized countries, an HFS diet combined with a lack of exercise, leads to prostate cancer, and how adopting a low-fat diet (containing fruit, vegetables, and whole grains) with daily exercise might prevent prostate cancer.

THE LINK BETWEEN METABOLIC SYNDROME AND PROSTATE CANCER

Insulin resistance and hyperinsulinemia are the cornerstone of the metabolic syndrome and, as discussed earlier, can be induced by consuming an HFS diet. The HFS diet decreases insulin receptor autophosphorylation, which results in insulin resistance and compensatory hyperinsulinemia (41). The exact cause of the decrease in receptor autophosphorylation is not known but may be the result of nitration of the tyrosine components of the insulin
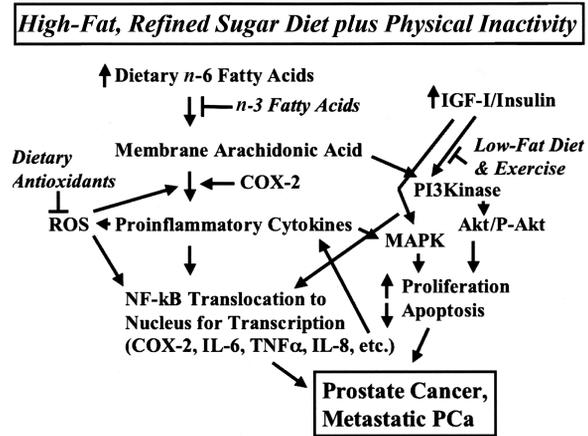

FIGURE 2. A proposed scheme to explain the relation of lifestyle to prostate cancer (PCa) promotion and metastasis and how they might be prevented by adopting a low-fat diet (containing fruit, vegetables, and whole grains) with a balanced ratio of n−6 to n−3 fatty acids along with daily exercise. COX-2, cyclooxygenase-2; IGF-I, insulin-like growth factor-I; IL-6 and −8, interleukin-6 and −8; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κ B; PI3Kinase; phosphatidylinositol 3 kinase; ROS, reactive oxygen species; TNFα, tumor necrosis factor-α.

receptor, because they are readily attacked by the nitrogen radicals that are increased with an HFS diet (42). The body compensates for the insulin resistance by increasing the output of insulin in an attempt to avoid type 2 diabetes.

The compensatory hyperinsulinemia of MS may be the cornerstone of prostate cancer promotion. As shown in Figure 1, insulin acts on the liver to reduce the production of SHBG and IGFBP-1 and −2 while stimulating the production of IGF-I. These circulating factors are involved in stimulating proliferation and blocking apoptosis in prostate cancer cell lines. The changes in the IGF axis seem to be the most important, because adding IGF-I back to the serum after diet or exercise or both prevents the decrease in cell growth and blocks the increase in apoptosis. Insulin also stimulates aromatase activity in fat tissue to increase estradiol production (43). In addition, n−6 fatty acids can increase aromotase when the cyclooxygenase pathway is activated (44). Estradiol can stimulate the growth of prostate cancer cells, an action that might be achieved by interaction with the IGF-I receptor (20, 45). Studies from the LeRoith laboratory (46–48) showed that in cells with damaged DNA, IGF-I could block the cells from going into apoptosis by stimulating the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, resulting in the degradation of p53, the guardian of the genome.

To see whether the decrease in serum IGF-I found after a diet or exercise intervention might be responsible for the increase in apoptosis seen in LNCaP cells, Leung et al (49, 50) measured p53 protein and one of its downstream factors, p21 (a cyclin kinase inhibitor), in exercise-serum-stimulated LNCaP cells. Compared with control-serum-stimulated LNCaP cells, the exercise samples had almost twice the amount of p53 and p21 protein after 2 d of cell growth. After 4 d of cell growth, the p53 protein content was still elevated in the exercise samples but the p21 protein had returned to basal levels. This was interpreted as a normal response of the cells converting from primarily growth arrest and repair to primarily apoptosis. In fact, apoptosis was significantly

increased in the exercise samples at 4 d compared with the increase observed at 2 d of growth. The increase in apoptosis in the exercise samples was associated with a reduction in Bcl-2, a factor known to block the mitochondrial, apoptotic pathway and inhibit caspase-induced apoptosis. Thus, the suggestion by Barnard et al (13) in 2002 that prostate cancer might be another aspect of MS appears to be true and has been confirmed in 2 recent epidemiologic studies (51, 52).

THE VALUE OF LIFESTYLE CHANGE IN THE TREATMENT OF PROSTATE CANCER

If the effect of serum changes resulting from diet or exercise observed in the cell culture studies in vitro can also occur in vivo, then a low-fat diet and daily exercise should be prescribed for men with diagnosed prostate cancer. To investigate this possibility, Ornish et al (53) designed a randomized clinical trial in men with diagnosed prostate cancer placed on "watchful waiting." The men were randomly assigned to control care (standard medical care) or the Ornish very-low-fat, vegetarian diet, daily exercise, and stress management program. In addition, the men were encouraged to increase their consumption of soy products and take a daily soy protein supplement (58 g). Serum samples from the subjects were used to study LNCaP growth and apoptosis. At the end of the first year, there was a small decrease (9%) in LNCaP growth in the control group but a major decrease (70%) in the experimental group. Apoptosis showed only a small increase in both groups, with no significant difference between the 2 groups (54). The fact that apoptosis was not increased significantly in the experimental group was unexpected in light of the significant increase in apoptosis previously observed with serum from participants in the Pritikin diet and exercise intervention. The unexpected results may have been because the men had prostate cancer or may have been due to the high intake of soy protein. The use of soy in Asian diets is theorized to be one of the reasons for the low incidence and mortality from prostate cancer in Asian men. Isoflavones, the phytoestrogens present in soy, have been reported to have antiproliferative and apoptotic effects on cancer cells (55–57). Other studies recently reported that high dietary soy protein may increase IGF-I and lower IGFBP-3 that would block apoptosis (58–62). Ironically, the amount of soy protein consumed by the experimental subjects in the Ornish study far exceeds the amount consumed by most Asian men.

Despite a lack of significant increase in apoptosis in the LNCaP cell culture studies, the experimental prostate cancer patients were doing much better clinically at the end of 1 y. PSA concentrations had gone up in the control group and had dropped in the experimental group. None of the 44 experimental patients were recommended for aggressive treatment of their prostate cancer, whereas 6 of 49 patients in the control group had aggressive treatment for raising PSA.

SUMMARY AND CONCLUSIONS

The information presented in this review indicates that prostate cancer is indeed another aspect of MS and is associated with consumption of a high-fat, refined-sugar diet combined with a lack of regular exercise. Insulin resistance and hyperinsulinemia are the cornerstone of MS and are also factors for prostate cancer. Insulin resistance and hyperinsulinemia precede other aspects of

MS and may, in part, be an underlying factor in their development. Insulin can directly stimulate prostate cancer cell growth, but probably is more important as the result of its effect on the liver to decrease SHBG and IGFBP-1 and −2 while increasing the production of IGF-I. The changes in the IGF axis stimulate prostate cancer cell growth and more importantly inhibit apoptosis. Adopting a low-fat (10–15% of energy, with a balanced ratio of n−6 to n−3 fatty acids), complex-carbohydrate diet along with daily (60 min) aerobic exercise will control MS in most cases and should reduce the risk of prostate cancer.

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