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SIMILARITIES OF PROSTATE AND BREAST CANCER: EVOLUTION, DIET, AND ESTROGENS

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ABSTRACT

Environment determines the risk of both prostate and breast cancer, and this risk can vary >10-fold. In contrast, no risk exists for human seminal vesicle cancer demonstrating tissue specificity. There is also species specificity, because there is no risk for prostate cancer in any other aging mammal except the dog. A study of evolution indicates that the prostate and breast appeared at the same time 65 million years ago with the development of mammals. All male mammals have a prostate; however, the seminal vesicles are variable and are determined by the diet so that species primarily eating meat do not have seminal vesicles. The exception is the human, who has seminal vesicles and consumes meat, although this is a recent dietary change. Human lineage departed from other higher primates 8 million years ago. The closest existing primate to humans is the bonobo (pigmy chimpanzee), which does not eat meat but exists primarily on a high fruit and fresh vegetable diet. *Homo sapiens* evolved only about 150,000 years ago, and only in the last 10% of that time (10 to 15 thousand years ago) did humans and dogs dramatically alter their diets. This is the time when humans domesticated the dog, bred animals, grew crops, and cooked, processed, and stored meats and vegetables. All current epidemiologic evidence and suggestions for preventing prostate and breast cancer in humans indicates that we should return to the original diets under which our ancestors evolved. The recent development of the Western-type diet is associated with breast and prostate cancer throughout the world. It is believed that the exposure to and metabolism of estrogens, and the dietary intake of phytoestrogens, combined with fat intake, obesity, and burned food processing may all be related to hormonal carcinogenesis and oxidative DNA damage. An explanatory model is proposed. UROLOGY **57** (Suppl 4A): 31–38, 2001. © 2001, Elsevier Science Inc.

There has not been sufficient time for biological selection to evolve a proper defense for human DNA against the insults perpetuated by the modern Western diet. This may result in nutritional diseases such as prostate and breast cancer. Both prostate cancer and breast cancer primarily occur later in life, often after the optimum age for reproduction, thus severely limiting the evolutionary selection process against cancer. This medical dilemma appears to be enhanced by the speed of technology that enhances the imbalance between the rapid rate of changes in our food processing and dietary patterns, which far exceeds the slower rate of evolution of adequate biological defenses. The interplay of many dietary components, such as phytoestrogens, can induce hormonal changes that may contribute to the carcinogenic insults of our lifestyle on prostate and breast tissue. Insights into the development of the concept presented here have been derived from attempts to formulate plausible biological explanations of the following features and enigmatic phenomena observed in prostate and breast oncology:

1. *Species specificity of prostate cancer:* A significant incidence of spontaneous prostate cancer is observed only in humans and the dog. Of the thousands of other species of mammals with prostates, none that age in zoos or captivity have a significant incidence of prostate cancer that results in clinical diagnosis, metastasis, and death. Except for the dog, prostate cancer is also absent or extremely rare in all aging pets such as cats, hamsters, guinea pigs, and horses.
2. *Tissue specificity of cancer:* Prostate cancer is most common in humans; however, there are other adjacent reproductive organs that never present with cancers such as the vas deferens,

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0090-4295/01/$20.00
PII S0090-4295(00)00938-9

epididymis, and bulbourethral gland, or even the seminal vesicles, where it is extremely rare. In a given individual, all of these glands share similar genetics, age, and environments but yet have vast differences in their cancer rates. Neither genetics nor environment is sufficient to cause bulbourethral, epididymal, or vas deferens cancer in a man. At present, no molecular explanation is proposed to explain this selectivity.

3. *Geographical variations:* Compared with the United States, the incidence and age-adjusted mortality rates of both breast and prostate cancer can be >10-fold lower in Asian countries. When Asians migrate to the United States, their prostate and breast cancer rates tend to increase, with time, toward levels seen in the native US population. Although this seems to strongly implicate environmental factors, a precise explanation for this phenomenon is not currently available.[1–8]
4. *Similarities in epidemiologic factors:* There appear to be very similar lifestyle risk factors accompanying both prostate and breast cancer, including a lower risk associated with high intake of fruits, vegetables, fiber, and soy products and, alternatively, a higher risk associated with increased intake of red meat, animal fats, dairy products, and steroid exposure, as well as body mass and birth weight.[1–9] This similarity does not exist with other cancers, such as stomach cancer.
5. *Early events are common:* In contrast to clinical cancers, small incidental foci of prostate cancer, as well as early pathologic changes and benign prostatic hyperplasia, appear to have relatively high incidences with aging in both the United States and Asia. This suggests that promotion and not initiation may be the critical difference between the clinical rates of prostate cancer in different geographical areas.[10,11]
6. *Similarities between prostate and breast:* Both glands have many similarities with regard to physiology, endocrinology, benign tumors, and the age-adjusted incidence and mortality rates of cancer that appear to be correlated in various countries.[4]

It is the purpose of this overview to suggest unifying concepts that might provide a common denominator between the mechanisms involved in the above 6 observations. This has been accomplished by involving the roles of evolution, diet, and estrogens as central and interactive factors in the above biological and pathological processes. If this proves to be true, then the acquisition of both prostate and breast cancer may be primarily an acquired nutritional disease and may be prevented by lifestyle modifications that return us to the type of diet to which humans had evolved during the time preceding the recent technological changes that have altered our diets in such a dramatic manner.

SIMILARITIES BETWEEN HUMAN PROSTATE AND BREAST CANCER

Previously, many investigators have reviewed the similarities between breast and prostate cancer.[4–6] When 21 countries with excellent cancer registries report their incidences and age-adjusted rates for prostate cancer, the correlation coefficient is highest between prostate and breast cancer at 0.81, endometrium at 0.78, and ovary at 0.72.[4,5] This may implicate the study of estrogenic factors, because the breast, endometrium, and ovary are estrogen-responsive tissues, and estrogen exposure has been shown to affect carcinogenesis. The correlation of prostate cancer incidence with many other types of solid tumors then trails off with very low and insignificant correlative values (Table I).[5a] In Asia, the age-adjusted incidence rates for both prostate and breast cancer are <10% of those observed in the United States. It is observed that as people migrate from Asia to the United States, the low rates observed in Asia begin to rise with time and subsequent generations toward those observed commonly in the general United States population.[1–8] Furthermore, as Asian countries adapt Western-style diets, the incidence of prostate and breast cancer has started to rise. In all of these situations there is a close correlation between responses in the prostate and breast cancer rates.

There are striking similarities between the features of both breast and prostate cancer within the United States (Table II). The annual age-adjusted death rates are almost identical at approximately 25 per 100,000, and both glands also have a high incidence of both benign disease and small incidental cancers as well as early preneoplastic lesions. Both cancers also metastasize to the bone and can cause osteoblastic lesions. Both tumors require gonads for development and can be treated by hormonal manipulation. Both glands contain estrogen, androgen, and progesterone receptors. Reviews have pointed out that many prostate tissue markers, such as prostate-specific antigens, are also present in the breast, where they are also under androgenic regulation.[4]

ANDROGENS AND ESTROGENS ON BREAST AND PROSTATE GROWTH

Androgens and estrogens play a critical role in both normal prostate and breast development and may also be involved in hormonal carcinogenesis. If a male, with X and Y chromosomes, does not have a functional androgen receptor, a condition

TABLE I. ***Correlation coefficient of age-adjusted prostate cancer incidence with other cancers in 21 countries***

Cancer	Coefficient
Breast	0.81
Endometrium	0.78
Ovary	0.71
Colon	0.64
Rectum	0.40

Data adapted from Endocrinol Rev[4] *and* Cancer Causes Control.[5]

TABLE II. ***Cancer comparison in the United States***

Feature	Breast	Prostate
Benign disease	High	High
Inflammation	Low?	High
Incidental cancer, microscopic (early onset)	High (yes)	High (yes)
Malignant cancer		
Incidence	184,200	180,400
Deaths	41,200	31,900
Deaths/incidence	0.22	0.18
Deaths/100,000 (age adjusted)	25.4	25.6
Lifetime risk	12.6%	19.8%
% Inherited	≈10%	≈10%
Gonads required	Yes	Yes
Metastasize to bone	High	High
Osteoblastic	Moderate	High
Hormonal therapy	Yes	Yes

Data adapted from Cancer Facts and Figures, 2000.[5a]

develops termed *androgen insensitivity syndrome*, wherein he will develop a phenotypic female body, with an absence of penis, scrotum, seminal vesicles, and prostate but with prominent breasts and female genitalia and form (Figure 1). Therefore, males who inherit such an androgen-insensitive syndrome appear at birth and early life to be female, and their gender is often confused until adulthood. They do not have ovaries but do have internal undescended and functional testes and normal serum androgen levels, yet they still present with a predominantly female phenotype because of the absence of the androgen receptor. In contrast, in a normal male, it is apparent that androgens, in the presence of a functional androgen receptor, almost completely suppress the development of breasts. Even normal males can experience a very low rate of breast cancer (400 deaths per year in United States) in their residual breasts, and if made hypogonadal, they have an increased rate of breast cancer, albeit much lower than that observed in females. In addition, suppressing androgens in the presence of estrogens in a normal male can induce breast enlargement and gynecomastia. In summary, androgens suppress and estrogens induce breast formation in both males and females.

It is well known that androgens are involved in the development and maintenance of the male sex accessory tissues, such as the prostate and seminal vesicles. In patients who inherit 5α-reductase deficiency and do not form dihydrotestosterone (DHT), it appears that testosterone alone develops the seminal vesicles that originate from the wolffian ducts. In contrast, the urogenital sinus requires the presence of DHT to develop the prostate gland, and it is missing in these patients. This difference in steroid specificity for development is of interest because only the prostate gland has a high susceptibility for cancer, whereas the seminal vesicle is almost inert.

In classic studies of the effects of steroid hormones on canine prostate growth by Walsh and Wilson,[12] and later expanded in larger studies by the Johns Hopkins group,[13,14] it was observed that estrogen markedly synergizes androgen effects, and this induces a >4-fold increase in total prostate weight and DNA content. This enhancement of prostate growth requires the specific combination of estrogens with a 5α-reduced steroid like DHT or one of its close metabolites.[12,13] In contrast, testosterone plus estrogen does not enhance canine prostate growth beyond that of the normal prostate (see Table III). Treating a castrated dog only with estrogen causes the basal cells to develop into squamous cell metaplasia; however, if androgens are added, it suppresses these estrogenic effects to produce either normal glandular growth with testosterone or glandular hyperplasia if DHT is used with the estrogen.[13] It is believed that the changing estrogen to androgen levels that occur with aging may promote abnormal growth of the prostate.[14]

STEROID IMPRINTING

Understanding the role of estrogens and androgens during periods of prostate gland development, such as the neonatal period, as well as during puberty and aging, is complex. Estrogens administered for very short times of only 48 hours within the neonatal period of a male rat can permanently reduce the size of the prostate gland throughout the remainder of life and markedly reduce the prostate's ability to respond to exogenous androgens later in life.[15–19] This dramatic effect of transient estrogens on the morphology and function of the prostate gland is a permanent marking or imprinting. However, if the estrogen is administered later in life, say at the weaning period or at adulthood, then the estrogens can have dramatically dif-

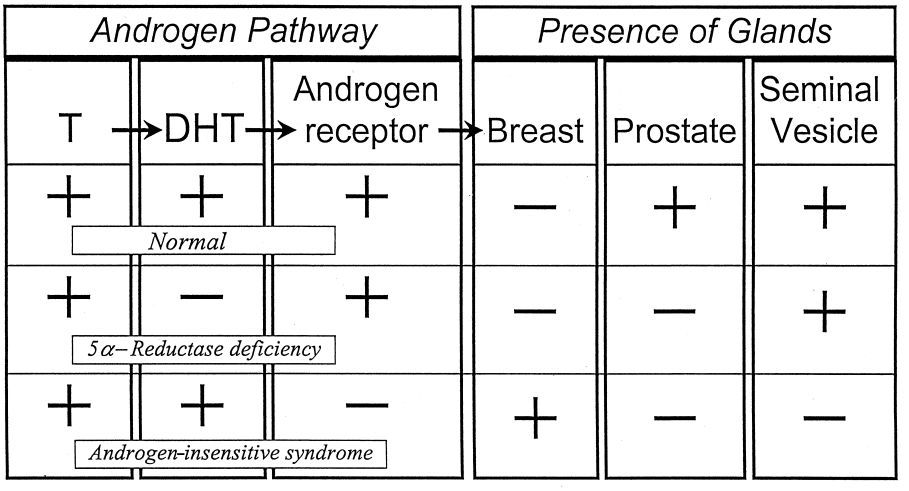

FIGURE 1. *Hormonal effects in males (X and Y chromosomes). Males who inherit certain genetic deficiencies show abnormalities in the development of the male secondary sex characteristics and the breast. In the absence of 5α-reductase, no dihydrotestosterone (DHT) is formed, there is no breast or prostate development, and only the seminal vesicle is stimulated. In the androgen-insensitive syndrome, the androgen receptor is absent and the phenotype is that of a female body with breast and vagina but with no penis, prostate, or seminal vesicle. These patients have undescended testes and normal androgen levels of the serum but the phenotype of a female.*

TABLE III. *Estrogens on dog prostate*

Hormonal Treatment	Prostate Growth
Testosterone	Normal (+)
Testosterone + estrogen	Normal (+)
Dihydrotestosterone	Normal (+)
Dihydrotestosterone + estrogen	Abnormal (++++) (hyperplasia)

ferent effects, ranging from inhibitory to stimulatory, on prostate growth.[16]

Estrogens not only imprint and affect the growth and development of the prostate but can also imprint a marked inflammation process within the prostate that is of unknown origin.[17] Likewise, there is a marked increase in spontaneous prostate inflammation that can occur in rodents on a long-term, soy-free diet, and raising the level of soy dramatically decreases the presence of prostatic inflammation.[20] With soy treatment, it was shown that genistein and isoflavonoids were dramatically increased in the serum and urine of rats receiving the soy diet.[20] It is unknown how soy in the diet acts as an anti-inflammatory agent. This could be related to the phytoestrogens in the soy that act as weak estrogens or antiestrogens as well as soy's ability to function as an antioxidant and inhibitor of tyrosine kinase. The dietary effects of soy have been reviewed elsewhere.[3,21,22]

Angelo M. De Marzo recently developed a new stem cell model that provides insight into the development of prostate cancer.[23] Together with William G. Nelson, he extended this concept to include a new model of the early, premalignant lesion preceding prostatic intraepithelial neoplasia. This new early lesion is termed "proliferative inflammatory atrophy."[18] De Marzo demonstrated 2 types of atrophy in the prostate. The first is a diffused variety with a low rate of cell replication, such as that caused by hormonal deprivation after androgen withdrawal. A second type of atrophy exists in the prostate and is more focal; it is associated with increased proliferation indicated by cell cycle markers. This focal atrophy with proliferation is often associated with marked inflammation; thus, this lesion is termed "prostatic inflammatory atrophy."[24] It appears that this prostate inflammation produces highly reactive oxygen species as well as nitric oxide, which are powerful oxidative agents that can damage the DNA and produce early changes in the genome associated with cancer. This is particularly the case if these cells are not protected by type 2 enzymes such as glutathione-S-transferase π or glutathione peroxidase.[25] Observing that estrogens in the neonatal period can produce marked inflammation of the prostate later in life, as well as the role of soy in the diet in reducing spontaneous inflammation, suggests both a causative and potentially protective agent in this DNA-damaging process. Oxidative damage to DNA has been reported to be asso-

TABLE IV. ***Diet associated with presence of sex accessory tissue: mammals***

Diet	Species	Prostate	Seminal Vesicles
Meat	Dog, cat, sea lion	Yes	No
Insect	Bat	Yes	Variable
Plants	Great apes, horse, bull	Yes	Yes

ciated with prostate cancer.[26,27] It is of great interest that prostatic inflammatory atrophy may be a very early precursor lesion of another early neoplastic lesion (prostatic intraepithelial neoplasia) in the prostate. Prostatic inflammatory atrophy has a close anatomical and proximal location to prostatic intraepithelial neoplasia (Putzi and De Marzo, unpublished observations, 2001).

ABSENCE OF A HIGH INCIDENCE OF CANCER IN THE SEMINAL VESICLE

Fewer than 40 cases of seminal vesicle cancer have ever been reported in the world literature. This is in contrast to the plethora of prostate cancers that can occur clinically in 1 of almost 10 American men and at a microscopic level at much higher rates of incidental prostate cancer that is diagnosed at autopsy in $>$ 50% of older men. It is a common observation that inflammation of the prostate is very prevalent in the human; this must be contrasted with prostatitis, which is a symptom. Prostate inflammation is a pathologic observation that is usually not associated with any defined pathogen. Why do the seminal vesicles not have cancer? Inflammation is not observed in human seminal vesicles that are essentially devoid of cancer.[25] The marked tissue specificity of cancer may involve more than just inflammation. Compared with the seminal vesicles, DNA is organized in the prostate in a different manner in relation to DNA loop organization and genes anchored to the nuclear matrix.[28] There may also be other differences between the prostate and seminal vesicle glands in the level of glutathione-S-transferase and protective enzymes.[24]

EVOLUTION

Can diet affect the development of prostate and seminal vesicle cancer in a different manner? Insight may be available from studies of evolution. In 1859, Charles Darwin, in *The Origin of Species*, stated, "Species of the same group differ from each other more widely in the secondary sex characteristics than in any other part of their organization."[29] It is recognized that all of the thousands of different species of male mammals have a prostate gland; thus, this is a common denominator. However, mammals that eat meat, such as dogs, cats, and sea lions, do not have a seminal vesicle whereas those that eat primarily plants, such as the great apes, horses, bulls, and rodents, do have a seminal vesicle (Table IV). It is apparent that during evolution, diet is associated in some way with the selection for the presence or absence of the seminal vesicle. Can diet also be involved in why humans do not get seminal vesicle cancer but do get prostate cancer? What is confusing about the above analogy is that the human appears to be an exception in that we eat large quantities of meat but we still have a seminal vesicle. This may be the problem. This apparent exception may be the result of a very recent change and diversion in our diet and food processing from the plant and fruit diet used over the main part of human evolution.

Approximately 7 million years ago humans evolved from a common ape ancestor, with our closest relative being the pigmy chimpanzee called the bonobo. Like the other great apes, the bonobo eats primarily fruits and vegetables and no meat. Other types of chimpanzees occasionally eat meat as opportunist scavengers, sometimes even with very limited hunting. Even in humans, highly effective hunting was not the major source of high meat caloric intake until later in human development. When early hominoids such as "Lucy" came down from the trees 4 million years ago and began to roam the savannas, they picked up the ability to become hunter-gatherers. This hunting was still at the most primitive level until approximately 12,000 years ago when the dog was brought into human hunting society, which tremendously increased the ability to catch animals, owing to the dog's speed and olfactory abilities. The dogs chased and corralled the game at bay for the human to subsequently kill, and the human then shared the kill with the dog. Thus, humans acted as the "alpha male" for the dog, which was easily controlled. This sharing of diet between human and dog allowed the dog to be domesticated and trained to herd animals. This major phase shift in food style occurred only about 10,000 years ago, when humans became farmers and domesticated both plants and animals. This technology quickly evolved into a tighter focusing of human diets from wild fresh vegetables and fruits to an eating pattern toward limited plants that could be domesticated and grown in great quantities and stored, like

wheat, rice, barley, corn, potatoes, and other tubers. This resulted in approximately 20 plant types rapidly replacing the high diversity of >3,000 plants and fruits that were earlier eaten fresh as they came into season and were gathered from the wild. With large-scale domestication and breeding of cattle came a high meat intake, and this was combined with storage, curing, drying, and cooking as well as a propensity to use milk and cheese from dairy processing. Cooking, burning, and smoking produce high levels of heterocyclic molecules, many of which make adducts to DNA, and are carcinogens.

Since separating from the great apes and chimpanzees approximately 8 million years ago, humans evolved into *Homo sapiens sapiens* that are very similar to our present form in little as 150,000 years. However, we dramatically changed to a Western-style diet only in the very recent past (ie, 15,000 years)—at a pace much faster than we could biologically evolve (Table V). This Western diet consists of high meat and fat; dairy products; stored, processed, and cooked meats; and low fruit and fiber intake, along with a more sedentary lifestyle. In summary, we were not biologically selected by the evolution process to eat the way we do today, and the damage is manifested in prostate and breast cancer. Indeed, all of the present suggestions of the National Cancer Institute and the American Cancer Society as to how Americans might reduce their chances of getting prostate and breast cancer revolve around adapting dietary changes in our lifestyle back toward the early human diet of more fruits; a variety of fresh vegetables and fiber; less burning, cooking, and processing; diminished intake of dairy products, red meat, and animal fats, as well as decreasing weight and increasing aerobic exercise. That is, we must return to a diet and lifestyle that more closely matches the first 135,000 years before technology modified our lifestyle and diet.

Why might the breast and prostate respond similarly? Both glands appeared at the same time during evolution, because when animals developed a breast, they became mammals and also developed a prostate. In contrast, there are very few mammals, other than the human and the dog, that get breast and prostate cancer, even though both cancers occur at a much lower rate in the dog. It is of interest that many other types of mammals made no significant changes in their diets. Thus, it might be expected that they would have far fewer incidents of prostate and breast cancers, which is indeed the case. Prostate cancer is almost absent in other aging animals in captivity that do not share the human diet. In contrast, the dog, which lives closely with humans, has a significant but reduced rate.

Diets vary between cultures. For example, cheese and milk are rarely used in any Asian diet. The use of soy, tea, and many other foods varies, as do methods of curing and processing. This might indicate not only why peoples' lifestyles and diets in different geographies are closely related to their incidence of prostate and breast cancer, but also why prostate cancer does not correlate with other cancers, such as those of the colon and stomach. There are other carcinogenic factors involved for other types of cancers. Indeed stomach cancer is very high in Japan, but when Japanese people move to the United States, it dramatically decreases, in contrast to cancer of the prostate and breast. How the flora of the intestines, inflammation, diet, processing, cooking, and environmental carcinogens have differential effects on different organs obviously requires clarification.

TABLE V. ***Human development and the change of diet***

Diet	Time During Human Development (150,000 years)	
	First 90% (135,000 years)	Last 10% (15,000 years)
Fruit	High	Low
Fiber	High	Low
Plant diversity	High (3000)	Low (20)
Red meat	Low	High
Animal fat	Low	High
Dairy products	Low	High
Food	Fresh/wild	Cooked/preserved
Movement	High	Sedentary

TABLE VI. ***Estrogen's effects on the prostate***

1. Increases prostate growth 4-fold when given with 5α-reduced androgens (dihydrotestosterone)
2. Decreases cell death
3. Directs stem cell development
4. Imprints growth of gland
5. Affects stromal elements, collagen
6. Blocks epithelial function
7. Oxidizes damage or adds adducts to DNA
8. Induces inflammation
9. Affects microtubules
10. Blocks androgen-induced glandular secretions

INTERACTIONS BETWEEN DIET, BODY MASS, AND HORMONE ACTION

The relation between fat intake and breast cancer at once seemed simple and compelling, but additional studies have proved that it is actually quite complex. This may be because all fats cannot be equated with each other, because some metabolic products of fat metabolism become ligands for steroid orphan receptors and may either enhance or

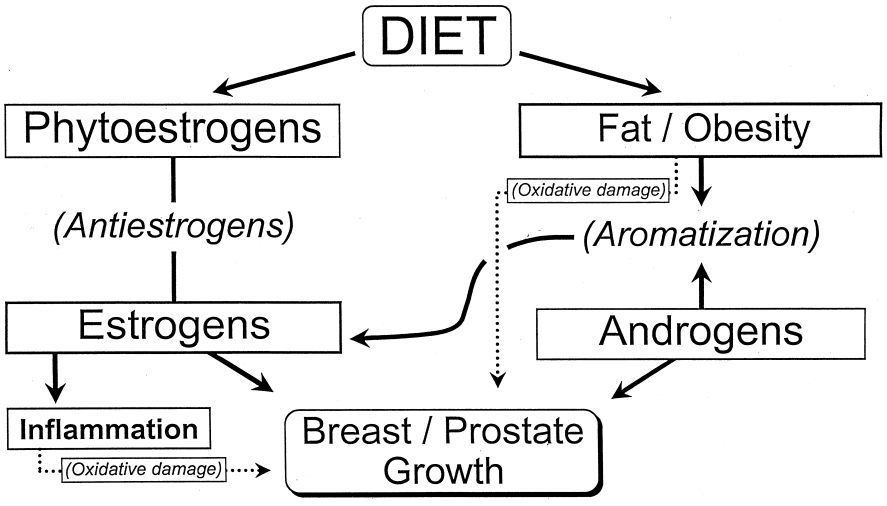

FIGURE 2. *Diet, fat, and hormones are combined in a unifying model indicating how they might affect the development of breast and prostate cancer. The diet, besides presenting carcinogens such as those formed in burned meat, also provides phytoestrogens, which can serve as weak antiestrogens affecting the hormonal status of the natural estrogens. Natural estrogens are made from aromatization of androgens that occur primarily in fat tissues. Fats also produce oxidative damage, as does inflammation, which is driven by estrogens. Phytoestrogens prevent the development of prostate inflammation.*

depress transcriptional functions. Thus, a "fat" used in a given diet study or experiment may not have the same effect as another fat based on its type, metabolism, and biologic properties. Therefore, the ratio of fat types and their metabolic patterns become very important in understanding the pathologic consequence of fat in the diet. In addition, the exact timing of fat types in the diet in relation to birth weight, neonate imprinting, puberty, and adult phases becomes a very complex matter. Fats also can alter hormonal status. Fat cells are a major source of the amortization of the A-steroid ring of testosterone to become a phenolic steroid that then can be metabolized into estrogens. Indeed estrogens are primarily made from testosterone, and the ratio of estrogens to androgens can be altered by the body mass and degree of fat within the body. Estrogen exposure has often been implicated as a high-risk factor in breast cancer, and we now know that estrogens with DHT likewise can induce abnormal prostate growth in dogs. Certainly the phytoestrogens that appear in our food sources have the ability to perturb hormone balance. Compounds such as genistein that have 2 hydroxyl groups separated by an angstrom's distance that is consistent with estrogenic function may function as weak estrogens or anti-estrogens.[25] Some phytoestrogens bind better to the β-estrogen receptor. Therefore, it might be possible to understand how a high-soy diet might perturb estrogenic function through its phytoestrogen components. Certainly estrogens induce a wide variety of biologic effects in the prostate, as summarized in Table VI. Estrogens can induce prostate growth when combined with a 5α-reduced metabolite such as DHT, but they also can produce reactive oxygen species and adducts that interact with DNA. The well-known effects of estrogens on microtubules and cytoskeleton components also raise the possibility of them perturbing mitotic events. There is little doubt that prostate cancer is associated with a tremendous amount of genetic instability that is seen in chromosomal rearrangements, changes in DNA methylation, and oxidative damage. Are estrogens carcinogens through initiation or promotion? This has long remained a subject of debate, but there is little doubt that they perturb the carcinogenic process.

The schematic model proposed in Figure 2 is a simplified overview of how soy (phytoestrogens), fat, and red meat might alter the androgen and estrogen milieu within the prostate and breast in a way that could either promote or induce cancer by genomic damage. Certainly, looking for simple relation will not be sufficient, but delineating the exact mechanisms of cell cycle control and stem cell development in prostate cancer should be helpful in understanding these early preneoplastic lesions and their relation to diet. In the end, we still must explain why approximately 90% of prostate and breast cancers are sporadic and acquired, and why only 10% are directly inherited in a Mendelian manner. The acquired cancers may indicate why this phenomenon is so geographically centered and may be capable of being altered. If these can-

cers are set in place within the neonatal or developmental periods, as has been proposed by many,[1] then this process will require far more research to unravel the timing of these critical events. The time is certainly ripe, with the new microarrays that allow high throughput analysis, to contribute to the patterns of gene expression that are turned on and off by these combinations of steroids and diet. It is hoped that the evolutionary and comparative analysis presented in this overview has provided further insight into the 6 questions posed at the beginning of this article.

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