Breast and Prostate Cancer: An Analysis of Common Epidemiological, Genetic, and Biochemical Features*

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I. Introduction

Breast cancer is the most common malignancy among females in North America. Statistics show that in the United States alone, about 200,000 new cases are diagnosed every year and about 50,000 women die annually from the disease. Worldwide, the approximate figures are about 10-fold higher (1). Overall, about 15% of all women will be diagnosed with breast cancer during their lifetime. Despite intense research efforts, which are increasing worldwide, the pathogenesis of the disease is still largely not well understood. Although diagnosis is now more effective through mammographic screening, mortality rates remain almost unchanged. Steroid hormones, including estrogens, androgens, and progestins, have long been implicated in the pathogenesis and progression of breast cancer. Early efforts to control breast cancer included either hypophysectomy or ovariectomy, which represent an attempt to remove the steroid hormones from the tumor environment. Such efforts, which are still used but with utilization of pharmacological agents instead of surgery, have clearly beneficial but mostly transient effects. A convincing finding that directly implicates steroid hormones in breast cancer development and progression is that women who have bilateral oophorectomy at an early age (<40 yr) are at markedly reduced risk of subsequently developing breast cancer; the earlier oophorectomy is done, the greater the risk reduction (1). Added to this finding are the well known modifying risks of breast cancer related to age at first full-term pregnancy, age of menarche and menopause, number of menstrual cycles in a lifetime, oral contraceptive use, number of pregnancies, etc. However, despite the wealth of literature on steroid hormone involvement in breast cancer, we do not as yet have definitive answers to even simple questions such as: Are steroid hormones carcinogens? Do steroid hormones control breast cancer cell proliferation and growth rates (2)? More recently, it has become evident that steroid hormones not only have direct actions on certain types of cells, but they can trigger additional effects through growth factors that are regulated by them; the latter act on neighboring cells in an autocrine/paracrine fashion (3). Lately, it has also been shown that steroid hormones are produced locally by cells that then use them intracellularly. Usually, the parent molecules are precursor steroids produced by the adrenals. This mode of hormone action is now referred to as 'intracrine' and further expands the possible implications of steroid hormones in breast cancer pathogenesis in humans (4, 5).

In males, the breasts are rarely affected by breast cancer. The androgenic dominance over estrogens in males keeps the breasts underdeveloped throughout life. However, even for male breast cancer, the major contributing role of steroid hormones is evident from clinical observations. For example, a number of conditions have been established, almost all related to hypoandrogenism, that increase the risk of breast cancer.

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Prostate cancer is the most common malignancy among males in North America. In the United States, about 200,000 new cases are diagnosed every year and about 45,000 men die annually from the disease. Overall, about one in every nine men will be diagnosed with prostate cancer during their lifetime. These numbers are strikingly similar to those already mentioned for breast cancer (7). Similarly to breast cancer, the pathogenesis of the disease is also obscure. Major risk factors include age, ethnicity, family history, and steroid hormones. While the rate of increase of breast cancer incidence declines postmenopauseally in women (1), the rate of increase of prostate cancer incidence increases continually with age. This phenomenon is likely linked to the continuation of testicular function in males throughout life and the cessation of ovarian function during the female menopause. The involvement of steroid hormones in the pathogenesis and progression of prostate cancer has been suggested for many years. Huggins, as early as 1940, was able to achieve transient remission of prostate cancer with orchiectomy and with administration of estrogens (8, 9). Currently, pharmacological androgen ablation therapy is achieved either by blocking androgen production or activity by administration of antiandrogens or other agents. Males who have diminished androgen production due to castration, hypogonadism, or enzyme defects of androgen metabolism (e.g., 5α-reductase) have minimal risk for prostate cancer.

We and others have hypothesized that breast and prostate cancer may represent, in some aspects, homologous cancers in females and males, respectively. Breast and prostate cancer are now the two most common cancers with a roughly equal lifetime risk. They are both influenced strongly by steroid hormones, gonadal removal reduces the risk dramatically in both sexes, and antiestrogens are beneficial and possibly preventive for breast cancer while antiandrogens are beneficial and possibly preventive for prostate cancer (10). Additionally, these two cancers have parallel incidence rates in various countries, and there is evidence suggesting that they are both influenced by the same dietary factors (e.g., fat consumption). Macklin, as early as 1954, provided evidence for a significantly higher frequency of prostate cancer among relatives of breast cancer patients and proposed for the first time that prostate cancer may be the male equivalent of some female breast cancers (11). In the last few years, additional epidemiological, genetic, and biochemical findings support the view that these two cancers have many similar features. Here, we review the current knowledge, focusing on common features, in an attempt to understand these malignancies better and possibly trigger some new thinking into their pathogenesis and progression. The reader, however, should be aware that there may be a bias in our presentation since we have selected literature that cites a connection between the two cancers. Other literature that either does not cite a connection or cites a connection of breast or prostate cancer with other cancers was not systematically reviewed since it falls outside the scope of our manuscript. This biased presentation may be specially relevant in the discussion of the putative genetic and biochemical abnormalities shared by breast and prostate cancer, since many of the associations described in the literature are not exclusive of these tumors and could merely reflect the general process of carcinogenesis. Thus, in the case of genetic abnormalities, it is well known that breast and prostate cancer, as well as other human carcinomas, result from the accumulation of genetic lesions in a variety of oncogenes and tumor suppressor genes. However, none of these genes is exclusively damaged in breast and/or prostate carcinomas, thus limiting their value in the context of this review. Consequently, we have focused the discussion on those few genes like AR or breast cancer susceptibility genes BRCA1 and BRCA2, which have a high degree of specificity for one of the two tumors (prostate or breast cancer, respectively), but whose involvement in the other tumor (breast or prostate cancer) has been suggested through epidemiological, biochemical, or mutational analysis. Nevertheless, it must be emphasized that the contribution of common genetic factors to the overall incidence of both tumor types may be low in quantitative terms and circumscribed to a specific subgroup of patients. A similar consideration must be done in the discussion of putative common biochemical features shared by breast and prostate carcinomas. In this case, the finding of commonalities in the expression pattern of diverse biomarkers associated with the development and progression of breast and prostate cancer may be only a consequence of general alterations of critical cell functions occurring during the malignant transformation of human cells, but not specifically of mammary or prostatic epithelial cells. Therefore, we have focused the discussion on those biochemical markers that may be of special interest for the biology of these two carcinomas because of their relative specificity of expression in breast or prostate carcinomas when compared with tumors from other sources, or by the occurrence of shared mechanisms of hormonal control mediating their up- or down-regulation in these two hormone-sensitive cancers. Likewise, the discussion of commonalities in the expression and regulation of growth factors associated with breast and prostate cancer may be of limited value because many growth factor pathways are universally altered in most human malignancies. Consequently, and as in the case of biochemical markers discussed above, we have focused our attention on those growth factors that may be of special relevance in the context of breast and prostate cancer by both the relative specificity of the alterations and the finding of common hormonal networks underlying their effects on these carcinomas. Taken together, we must conclude from these observations that, based on data of the few comparative analyses currently available, the existence of common factors in breast and prostate cancer is still speculative in many aspects. The next sections present a summary of available epidemiological, genetic, and biochemical data supporting associations between both tumors, with a special emphasis on describing the common hormonal aspects underlying the observed associations.
II. Epidemiological Evidence Associating Breast and Prostate Cancer

The first observations regarding a familial association between breast and prostate cancer were performed more than four decades ago by Macklin (11) who, in her pioneering work designed to look for the genetic basis of human breast cancer, found a significantly higher frequency of prostate cancer among relatives of women with breast cancer than among relatives of control groups. According to these results, she proposed that prostate cancer could be the male equivalent of at least some female mammary carcinomas. Since then, several genetic epidemiological studies performed by different groups in different populations have provided further support to this original proposal.

Thiessen (12), in 1974, after analysis of the familial incidence and distribution of all malignancies in a group of 145 breast cancer patients, compared with that of 139 randomized control patients, reported that significantly higher incidences of only uterine, prostatic, and breast cancer were found among both maternal and paternal relatives of the breast cancer patients. On this basis, he proposed that the mammary gland is part of an integrated genital organ system whose different parts share unique biological and pathological characteristics, including hormone responsiveness and cancer susceptibility. He also hypothesized the existence of some common etiological factor that could operate in the development of tumors in diverse reproductve organs, including breast and prostate. In 1982, Cannon et al. (13), in a study of genetic epidemiology of prostate cancer in a population from the Utah Mormon genealogy, showed a significant coaggregation of prostate cancer with breast cancer. More recently, in case-control studies based on anamnestic data, Andrieu et al. (14) and Rosenblatt et al. (15) did not find evidence of association between these two tumors. By contrast, Tulinius et al. (16) in a large cohort study including 1539 Icelandic women with breast cancer, reported that the risk of prostate cancer was significantly raised for all male relatives, as well as for first-degree relatives, and second-degree relatives of breast cancer patients. It is noteworthy that in this study the information concerning which family members had cancer was obtained from the Icelandic Cancer Registry, whereas genealogical trees were constructed by using information from records of the genetics committee of the University of Iceland, thus avoiding possible bias generated by directly asking the family members about the structure and cancer cases in their families. Similarly, Anderson and Badzioch (17) found that a family history of prostate cancer in male breast cancer patients resulted in a 4-fold increased breast cancer risk in first-degree female relatives compared with that in male breast cancer families with no history of prostate cancer. By contrast, a family history of lung cancer, colon cancer, or melanoma had no effect on increasing risk of breast cancer. Finally, a series of recent studies concerning the putative familial clustering of breast and prostate cancer have provided opposite results. Thus, Isaacs et al. (18) in a study of families selected because of the presence of prostate cancer did not find increased risks for cancer at other sites, such as breast, ovary, or endometrium. Similarly, Negri et al. (19) did not observe an elevated risk of prostate cancer in relatives of breast cancer patients. By contrast, Sellers et al. (20), in a large prospective cohort study of Iowa women, noted that a family history of breast and prostate cancers is a stronger risk factor for postmenopausal breast cancer than is a family history of breast cancer alone. The reasons for the discrepancies between the different epidemiological studies are unclear, although Anderson and Badzioch (21) have pointed out a number of potential explanations, including differences in the study populations, variability in the size of families, or some peculiarity of sampling. It is also possible that methodological aspects could influence the final results, since coaggregations between breast and prostate cancers were specially noted in those studies involving very large pedigrees in which only those relatives with medically documented tumors were considered eligible for the study.

Therefore, it seems clear that not all data on the potential association between breast cancer in females and prostate cancer in males are univocal. However, a number of studies performed by different groups in populations of different geographic origin appear to indicate that a family history of breast cancer may have a significant influence on prostate cancer risk and vice versa. This observed association between breast cancer and prostate cancer suggests that, at least in some cases, both tumors may share common factors, either genetic or epigenetic, that could finally lead to the development and progression of these malignancies. Among the different factors that can be shared by breast and prostate cancers, three of them deserve special attention. First, and considering that both carcinomas arise in hormonally regulated tissues, it is conceivable that common hormone alterations could play a role in the development or progression of both tumors. On the other hand, and since the above mentioned studies suggested a familial coaggregation of breast and prostate cancer in different populations from different origins, it seems clear that in addition to being hormonally related, these tumors may also share some genetic abnormalities that could contribute to the acquisition of the malignant phenotype by both mammary and prostatic epithelial cells. Finally, it is also possible that the coaggregation of these highly prevalent tumors may be also influenced by a number of lifestyle and environmental factors, including dietary factors, whose importance in the development of human cancer is becoming increasingly apparent.

III. Incidence of Breast and Prostate Cancer in Different Countries: Dietary Factors

Another epidemiological element linking breast and prostate cancer is the incidence rate of these two cancers among different countries. Prentice and Sheppard published age-adjusted cancer incidence rates of males and females of ages 55-69 during years 1978-1982, in 21 countries with reputations for accurate cancer registries (22). We have plotted these data in simple linear regression formats to examine whether there is any correlation of the incidences of various cancers with those of breast and prostate cancer. The observed correlation coefficients are summarized in Table 1. The highest correlation between cancer incidences was observed between breast and prostate and breast and endometrial can-
Among all dietary factors, fat consumption has received the greatest attention (36). The connection between high-fat diet and increased cancer risk is supported by animal studies (37). In humans, breast cancer risk (22, 36) and prostate cancer risk (22, 38, 39) were found to increase with increased fat consumption. Although such associations are consistent between many studies, others question the validity of the data because of the presence of many confounders and the poor accuracy of obtaining food intake data (40, 41). It is expected that the role of dietary fat in the development of breast cancer will be further elucidated when a primary prevention trial among women age 50-79 is complete (1, 10). The Women’s Health Initiative is a randomized, placebo-controlled trial with three different interventions, one of which is dietary, aiming to reduce fat intake to 20% of total calories (from about 40% currently) and to increase intake of fruits and vegetables. In the same trial, another intervention includes vitamin D and calcium supplements (1). Other chemoprevention trials are underway in many countries (10). Prentice and Sheppard calculated, based on fat disappearance data, that a 50% reduction in fat consumption may reduce the relative risk of women of age 55-69 yr for breast cancer from 1.00 to 0.39 and in men for prostate cancer from 1.00 to 0.17. Such benefits, they postulate, may also be seen for endometrial, colon, rectal, and ovarian cancer (22). The biological basis of fat consumption and risk for breast and prostate cancer is not known, but there is evidence that fat intake alters steroid hormone concentration in serum. For example, it has been reported that plasma estradiol levels are reduced in postmenopausal women on low-fat diets (42). Also, there is evidence that a low-fat diet may reduce testosterone levels in adulthood (43) or may modify 5α-reductase activity (39).

The association between breast cancer and fat consumption has recently been reviewed, and it was concluded that, in the absence of data from dietary intervention trials, the weight of available evidence suggests that the type and amount of fat in the diet is related to postmenopausal breast cancer (44). The associations between diet and breast and prostate cancer are also evident from migrant studies. Migrant groups usually adopt dietary patterns similar to those of their new country within a few years after migration.

### Table 1. Correlation between breast and prostate cancer incidence rates and incidence rates of other cancers in 21 countries

<table>
<thead>
<tr>
<th>Cancer (x)</th>
<th>Cancer (y)</th>
<th>Pearson correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Prostate</td>
<td>0.81</td>
</tr>
<tr>
<td>Breast</td>
<td>Endometrium</td>
<td>0.81</td>
</tr>
<tr>
<td>Breast</td>
<td>Ovary</td>
<td>0.77</td>
</tr>
<tr>
<td>Breast</td>
<td>Colon</td>
<td>0.74</td>
</tr>
<tr>
<td>Breast</td>
<td>Rectum</td>
<td>0.65</td>
</tr>
<tr>
<td>Prostate</td>
<td>Endometrium</td>
<td>0.78</td>
</tr>
<tr>
<td>Prostate</td>
<td>Ovary</td>
<td>0.71</td>
</tr>
<tr>
<td>Prostate</td>
<td>Colon</td>
<td>0.64</td>
</tr>
<tr>
<td>Prostate</td>
<td>Rectum</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Countries are Australia, Canada, Denmark, Germany, Finland, France, Hong Kong, Hungary, Israel, Italy, Japan, New Zealand, Norway, Poland, Romania, Spain, Sweden, Switzerland, United Kingdom, United States, and Yugoslavia. Detailed data are reported in Ref. 22.*
Statistical analysis has shown that dietary fat alone can provide an explanation for the major changes in cancer risk that followed Japanese migration to the United States. For example, Tominaga (45) reported relative risks (RR) of 3.5 and 5.7 for breast and prostate cancer, respectively, in Japanese migrants to the United States. The calculated higher risks, based on changes in fat consumption alone, are 2.9 and 7.2, respectively, in close agreement with the observed risks.

The current epidemiological data suggest that the epidemic of breast and prostate cancer may be partially attributable to increased fat consumption, increased caloric intake during growth, low fiber, vegetable, and fruit consumption, and other lifestyle factors including exercise, alcohol, and smoking (22, 41, 43). Refinements in our knowledge regarding fat consumption and its connection to cancer suggest that specific fatty acids (e.g., the n-6 polyunsaturated fatty acids) may be more potent tumor enhancers than other unsaturated or saturated fatty acids (46-49). Hopefully, the studies that are now underway will provide us with more insights that will be useful in designing successful prevention strategies.

### IV. Genetic Abnormalities Common to Breast and Prostate Cancer

The epidemiological findings showing a potential association between breast and prostate cancers have prompted studies directed to search the putative molecular factors common to these two highly prevalent tumors. Similar to other tumors, a large number of factors, including oncogenes, tumor suppressor genes, or hormonal receptors, may be altered in breast and prostate carcinomas. In fact, acquired or inherited abnormalities in a wide variety of genes have been implicated in the pathogenesis of these tumors (reviewed in Refs. 50-53). However, it should be emphasized that most of these genetic abnormalities, including those recently described in the *PTEN/MMAC1* gene (54-56), are not exclusive of breast and prostate carcinomas and represent alterations in oncogenes or tumor suppressor genes commonly mutated in human tumors from different origins. Thus, until more data become available, our presentation on this issue should be regarded at present as speculative. Nevertheless, mutational studies on some genes, including the AR gene and those involved in hereditary breast cancer (*BRCA1,BRCA2*), have provided some results that may be of relevance in the context of putative genetic abnormalities common to breast and prostate cancer. The interest in AR as a potential factor common to both tumors arises from recent observations indicating that genetic abnormalities in this hormonal receptor are shared by these two hormonally dependent tumors, but admittedly in only a small proportion of patients (53-62). Similarly, genetic epidemiological data have suggested that some cases of prostate cancer could be linked to the recently described breast cancer-associated genes *BRCA1* (63-68) and *BRCA2* (67-74). Finally, and since it seems clear that these genes are not the only molecular factors that may be common to breast and prostate cancers, in the last part of this section, we examine other candidate genes that could contribute to establish associations between these two highly prevalent malignancies.

#### A. AR alterations in prostate cancer

The AR is a transcription factor that plays an essential role in a wide number of biological functions, from development and maintenance of male reproductive functions to modulation of immune responses or development of neural tissues (75). Like other nuclear receptors, AR exerts its biological effects after binding of circulating androgens mainly transported to target tissues by carrier proteins (76). Androgen binding induces a conformational change in the AR that facilitates receptor homodimerization, nuclear transport, and interaction with DNA. The binding of the AR to the hormone response elements (HRE) present in target genes results in the regulation of their transcriptional activity (77). The structure of the AR is also similar to that of the other members of the steroid-receptor family of ligand-dependent transcription factors, with an N-terminal transactivating domain (exon A), a central DNA-binding domain (exons B and C), and a C-terminal hormone-binding domain (exons D through H) (78).

Because of the essential participation of AR in the regulation of prostate growth and in the maintenance of prostatic function, over the last years many groups have tried to define the potential role of this hormone receptor in the development and progression of prostate cancer. The first studies in this regard were based on analysis of the AR functionality in prostate carcinomas by using ligand-binding activity assays and immunohistochemical techniques (79, 80). However, results of a series of structure-function relationship studies of mutated ARs have revealed that ligand binding or immunoactivity are not the most appropriate indicators of AR functionality. Thus, investigators have described the occurrence of mutant ARs that do not bind androgens but are constitutively active, or receptors that bind steroids with high affinity but are nonfunctional as transcription factors (81, 82). As a consequence of these observations, more recent studies have examined the possibility that alterations in the integrity of the AR gene in prostate carcinomas could be a more accurate index of the AR functionality in these tumors (83) (Fig. 2). The first indication that structural changes in the AR could be important in the progression of prostate cancer was provided by the detection in LNCaP prostate cancer cells of a point mutation in the ligand-binding domain of this receptor (84). Interestingly, this mutation (Thr877Ala) leads to a decrease in steroid-binding specificity and completely reverses the effect of commonly used antiandrogens (84). After these findings in established cancer cell lines, several groups have attempted to demonstrate the putative occurrence of AR gene mutations also in tumor tissue specimens. The first description of an AR abnormality in human prostate cancer was done by Newmark et al. in 1992 (85). These authors found a point mutation (Val730Met) in 1 of 26 early-stage prostatic carcinomas. Thereafter, other groups have reported that AR mutations may also occur in a small percentage of advanced cancers (86-92). By contrast, Ruizeveld de Winter et al. (93) did not detect mutations in AR genes from 18 patients with hormone-resistant, locally progressive prostate cancer. Although these studies appear to indicate that the frequency of AR mutations is low, even in advanced prostate cancer, recent work using improved strategies for
mutational analysis of AR have found a higher proportion of genetic abnormalities in other latrogenic carcinomas or in metastatic disease. Thus, Takahashi et al. (94) have found that a significant proportion of latent prostate carcinomas from Japanese men contain genetic alterations in the AR gene (18 of 79), while no such mutations were found in 43 latent carcinomas from American men. On the other hand, Gaddipati et al. (95) have shown the presence of the above described mutant Thr877Ala, in 6 of 24 prostatic tissue specimens obtained from patients with metastatic prostate cancer, providing the first evidence that a mutational hotspot may occur in the AR gene in a subset of these tumors. More recently, Taplin et al. (96) have shown the presence of AR gene mutations in metastatic cells from 5 of 10 patients with androgen-independent prostate cancer, which has led them to conclude that mutations in this gene are not as rare as previously considered by other authors. Consistent with this, Tilley et al. (97) have found somatic mutations in 44% of primary prostate tumors taken before initiation of androgen ablation therapy. The presence of AR amino acid substitutions was found not only in the hormone-binding domain, which is the region examined in most studies mentioned above, but also in the remaining functional domains of this protein. In fact, about 50% of the mutations found by Tilley et al. in prostatic tumors were within exon A of the AR, which encompasses 58% of the coding region of the gene, but whose integrity has not been examined in virtually any mutational study of the AR gene. These results demonstrate the need to examine the complete AR-coding region before any conclusion on the structural integrity of the AR gene in prostate carcinomas can be reached. It is also remarkable that Tilley et al. (97) have provided evidence that mutations found in AR are not a consequence of the generalized genetic instability inherent to different malignant processes, suggesting that they have functional relevance and do not simply reflect the neoplastic state. In fact, these authors have observed that the occurrence of the AR mutations in the studied prostatic carcinomas was associated with a rapid failure of subsequent hormonal therapies. Therefore, it seems that AR gene mutations may occur commonly in advanced prostate cancers before endocrine treatment, thereby contributing to the observed altered androgen responsiveness of these tumors, and finally leading to their progression to androgen independence. Finally, two germline point mutations in the 5'-untranslated region of the AR gene have been recently described in men with prostate cancer. It has been proposed that these mutations may contribute to the disease by altering rates of transcription and/or translation of this gene (98).

In addition to all these point mutations detected in different prostatic carcinomas, other types of AR structural alterations have been found in specimens of these tumors. These genetic abnormalities include the somatic contraction of the polymorphic CAG microsatellite present in exon A of the AR gene (99) and the amplification of the AR gene in a series of hormone-refractory tumors (100, 101). The first of these alterations was described by Schoenberg et al. (99) after a study designed to evaluate whether the polymorphic CAG repeats that encode the polyglutamine region of the AR protein were altered in prostatic carcinomas. This study led to the identification of a patient with metastatic disease having 24 CAG repeats in this region of the AR gene from normal tissue but a mixture of 24 CAG and 18 CAG in the AR gene from tumor tissue. Interestingly, this patient manifested a paradoxical agonistic response to hormonal therapy with the antiandrogen flutamide. The possibility that a reduction of the number of CAG trinucleotide repeats in the AR gene could be of importance in prostate cancer is in good agreement with previous in vitro studies indicating that elimination of the CAG repeats results in increased transcriptional activity of the receptor (102). In contrast, expansion of the CAG tract, as observed in Kennedy’s disease, results in partial loss of AR function (103). Kennedy’s disease, also known as X-linked spinal bulbar muscular atrophy, is a form of adult-onset progressive motor neuron degenerative disease associated with male hypogonadism. Signs of androgen resistance, which generally appear after the third decade of life, include development of gynecomastia, azoospermia, impotence, and testicular atrophy (76). Also in relation with alterations in CAG repeats in the AR gene, a series of epidemiological studies have suggested that the increased risk of developing prostate cancer in Black Americans is related to a reduced frequency of CAG repeat numbers in this population (104). Similar findings associating shorter CAG repeat lengths with the development and progression of prostate cancer have been reported by different groups (105-108). Hakimi et al. (109) have recently studied both CAG and GGC

Fig. 2. AR abnormalities identified in prostate and breast carcinomas. The eight exons (A to H) of the AR gene and the three functional domains (transactivation, DNA binding, and ligand binding) identified in the AR protein are represented in the figure. Alterations described in breast carcinomas including point mutations at residues Arg 607 and Arg 608 and deletion of exon C (del exC) are boxed. AR gene abnormalities identified in prostate carcinomas include point mutations, contraction of CAG trinucleotide repeats in exon A (Q24Y18), frameshifts (L547fr, P554fr, G743fr), and generation of premature stop codons (W741fr, W751fr, W796fr).
repeats in patients with prostate cancer and found that AR alleles with shorter CAG repeats define a subpopulation of patients with aggressive cancer, and AR alleles with shorter GGC repeats define a subpopulation of men who are at higher risk of developing prostate cancer. Finally, Koivisto et al. (100) have shown that amplification of the AR gene plays a role in the progression of some recurrent, hormone-refractory tumors. These authors have also suggested that AR amplification emerges during androgen deprivation therapy and facilitates tumor cell growth in low androgen concentrations (100, 101).

In conclusion, it appears that AR gene alterations in prostate carcinomas and in metastatic tissue derived from these tumors are much more frequent than originally suggested. These genetic defects include point mutations, gene amplification, or variations in the length of trinucleotide repeats. At present, there is a lack of compelling evidence associating receptor variants with response to endocrine therapy, or clinical course of the disease. However, functional analysis of AR variants appear to indicate that they confer upon this receptor a broadening of ligand specificity, making it capable of activation by estrogens, progesterone, antiandrogens, and adrenal androgens in addition to testicular androgens (57, 84, 86, 90-92, 96, 97, 110). This is in marked contrast with the findings in other diseases involving abnormalities in the AR gene, such as androgen insensitivity syndromes or diseases generated by trinucleotide expansion in the CAG region of the AR, which are usually accompanied by loss of AR function (76). As a consequence of these gain-of-function mutations detected in prostatic carcinomas, tumor cells may proliferate in an androgen-deficient environment or during antiandrogen therapy. Therefore, these findings may explain why these carcinomas become refractory to endocrine therapy and could lead to the development of more effective hormonal therapeutic strategies as well as predictive tests for therapy failure.

B. AR alterations in breast cancer

Since, according to the above mentioned data, there was a significant body of epidemiological evidence suggesting an association between breast and prostatic cancer, it seemed likely that if AR gene alterations are important in the development of prostate cancer, similar abnormalities could also occur in some cases of breast cancer. The first indication that AR may also be altered in breast carcinomas was provided by Wooster et al. (58) who reported an AR germline mutation in two brothers with breast cancer and Reifenstein syndrome, a partial androgen insensitivity syndrome originally described as an X-linked familial syndrome of hypospadias, infertility, and gynecomastia in association with normal 17-ketosteroid excretion and high FSH levels (76). The mutation results in the substitution Arg607Gln, within the region encoding the DNA-binding domain of the receptor. More recently, Lobaccaro et al. (59, 60) identified another germline mutation in the AR gene, in a man with lobular carcinoma of the breast and partial androgen insensitivity syndrome. This mutation leads to an Arg608Lys substitution, also in the DNA-binding domain of the receptor and is identical to an alteration previously described in a patient with partial androgen insensitivity syndrome (111). Two main hypotheses have been proposed to explain breast cancer development linked to AR mutations (58-60). The first one involves the loss of a putative protective effect of androgens, which could explain the low incidence of breast carcinomas in males. However, in light of the above observations in prostate carcinomas, it is also possible that the development of breast carcinomas associated with AR mutations could be a consequence of the acquisition of additional properties by the mutated AR proteins. Thus, they could have an altered pattern of hormone responsiveness, including the acquisition of the ability to bind ligands other than testicular androgens, thereby extending their transactivating properties. In any case, elucidation of the potential role of AR in the development of some breast carcinomas will require the identification of additional cases and functional studies with the identified mutant receptors. Finally, it would also be of interest to look for the presence of somatic AR gene alterations in sporadic cases of breast carcinomas in both males and females. In this regard, Hiort et al. (112) have recently reported the absence of mutations in exons 2-8 of the AR gene in breast carcinomas from 11 males without clinical evidence of androgen insensitivity, suggesting that AR gene mutations do not play a major role in the development of sporadic male breast cancer. By contrast, one should note the recent identification of an exon 3-deleted splicing variant AR in breast cancer cell lines and tissues (62). This AR variant is expressed at high levels in some breast carcinomas (7 of 31), whereas in normal breast tissues its expression is undetectable. Also, recent immunohistochemical analysis in breast tumor specimens has suggested that structurally altered forms of the receptor, including amino-terminal truncated variants, may be present in a significant proportion of breast carcinomas (61).

In summary, a series of recent studies performed by different groups has revealed that inherited and acquired AR alterations may occur in breast carcinomas (58-62). The number of described AR abnormalities in breast cancer is low, suggesting that these would only affect a small subgroup of patients. However, it is also remarkable that this field has been largely unexplored and few studies have specifically addressed the role of AR mutations in breast cancer. Nevertheless, these preliminary mutational data, together with the finding of abnormalities in androgen levels in patients with breast cancer (113-115) and the widespread expression of AR in primary breast carcinomas (61, 116, 117), suggest that AR-mediated pathways may be of biological and clinical relevance in breast cancer. Further studies and functional characterization of AR variants in breast carcinomas, in a similar fashion to studies performed in prostatic carcinomas, will be required to clarify the putative contribution of AR to breast cancer cell growth and response or resistance to hormonal therapies.

C. BRCA1 and BRCA2 alterations in breast cancer

Evidence for a genetic component in breast cancer risk was first noted by Paul Broca more than one century ago, when he described four generations of breast cancer in his wife’s family (118). Since then, extensive epidemiological analyses
of breast cancer cases that appear to be clustered in families have been reported. The results of these analyses suggest that about 5% of breast carcinomas may be explained by inherited mutations in one or more genes. Despite the genetic heterogeneity of breast cancer and the high prevalence of sporadic disease, several breast cancer susceptibility loci have been identified (119). The first of these genes, named BRCA1, was mapped in 1990 to chromosome 17q21 by genetic linkage analysis of large families that included many cases of early-onset breast carcinomas (120) and has been recently identified by Miki et al. (121) using positional cloning methods. BRCA1 is composed of 22 coding exons distributed over more than 100 kb of genomic DNA and encodes a 1863-amino acid protein, with two RING finger domains at its N-terminal part, which are thought to be involved in DNA-binding or in protein-protein interactions. In addition, BRCA1 shares a conserved region with 53bp1 (a p53-binding protein) and rad9 (a yeast protein involved in the control of the DNA damage-induced cell cycle arrest), which has suggested that BRCA1 is likely to function in the cell nucleus and may be involved in one or more cell cycle checkpoints (122). In marked contrast with this proposal, it has also been suggested that BRCA1 may play a role as a secreted protein, exhibiting properties of a granin (123). To date, the function of BRCA1 remains unclear, although a recent study has shown that this protein inhibits the growth of breast epithelial cells (124). In addition, studies on the developmental pattern of BRCA1 expression in mice suggest that it is involved in the process of proliferation and differentiation in multiple tissues, notably in the mammary gland in response to ovarian hormones (125). Furthermore, analysis of BRCA1−/− mutant mice has suggested that this protein may be a positive regulator of the cellular proliferative processes that occur in early embryonic development (126). On the other hand, Chapman and Verma (127) have recently reported that the carboxy-terminal fragment of BRCA1 acts as a strong transcriptional activator when fused to the GAL4 DNA-binding domain. In addition, this activity is completely abolished in sequences corresponding to four different mutations found in BRCA1-linked families, thus providing direct evidence for the possible function of BRCA1 as a transcription factor. Finally, a new insight into BRCA1 function has been provided by the observation that it associates with the DNA-repair protein Rad51, suggesting that BRCA1 may be a component of the double-strand-break DNA repair pathway (128-130).

Mutations in the BRCA1 gene are thought to account for about half of the families susceptible to early-onset breast cancer and for at least 80% of families with clustered breast and ovarian cancers (131, 132). To date, germline BRCA1 mutations have been reported in more than 200 families from different geographic origins (131, 132). Germline BRCA1 mutations have also been found in young women with breast cancer who do not belong to families with multiple affected members (133). All classes of mutations are represented in these reported cases, including missense mutations, nonsense mutations, deletions, insertions, or intronic mutations, although the majority result in the production of a truncated protein. The finding of this large percentage of loss-of-function mutations is consistent with the hypothesis that BRCA1 acts as a tumor suppressor gene. It is also remarkable that most of the reported BRCA1 gene mutations have been identified in a single family, but a small number have been detected repeatedly. Of particular interest is a frameshift mutation caused by deletion of an AG dinucleotide (185delAG), which has been identified in more than 20 families of Ashkenazi Jewish descent and is estimated to occur at a frequency of about 1% in this population (134, 135).

The observation that less than half the families with multiple cases of breast cancer showed linkage to BRCA1 led to the proposal that there was at least an additional gene associated with breast cancer susceptibility. This result prompted another genomic linkage search and a second breast cancer susceptibility gene, named BRCA2, was located on chromosome 13q12 (136) and subsequently cloned (69, 137). BRCA2 is composed of 27 exons and encodes a protein of 3418-amino acid residues, which does not appear to be significantly similar to other proteins. Recent studies have shown that BRCA2 expression is coordinately regulated with BRCA1 expression during proliferation and differentiation in mammary epithelial cells, suggesting that both genes may act in the same pathway (138). Similarly to BRCA1, BRCA2 interacts with Rad51, providing additional support to the proposal that these proteins may be essential cofactors in the Rad51-mediated DNA repair of double-strand breaks (139). In fact, Connor et al. (140) have found evidence of a DNA repair defect in mice with a truncating BRCA2 mutation. Clinical studies have revealed that BRCA2 probably accounts for a proportion of early-onset breast cancer roughly equal to that resulting from BRCA1, and it may be of special importance in families with a high incidence of male breast cancer, but not in those with multiple cases of ovarian cancer. Mutational analysis of the BRCA2 gene in different populations has revealed that as in BRCA1, the identified mutations are widely distributed throughout the coding sequence of the gene, although evidence of some recurrent mutations has also been found (71, 141-144). Also of interest is the finding that BRCA2 mutations in families with the highest risk of ovarian cancer relative to breast cancer are clustered in a single exon of this gene (145). Finally, and also in common with BRCA1, diverse studies have shown that BRCA2 is a very infrequent target for somatic inactivation in breast and ovarian cancers (144-148).

D. BRCA1 and BRCA2 alterations in prostate cancer

As mentioned above, genetic epidemiological studies have provided evidence for clustering of prostate and breast cancer in some families. In addition, there is preliminary evidence that some plausible prostate cancer genes, like AR, may be altered in some breast tumors. Therefore, it seemed of interest to evaluate the possibility that genetic abnormalities in breast cancer susceptibility genes, such as BRCA1 and BRCA2, may also be associated with an increased risk of prostate cancer in men. The first of these studies was performed by Arason et al. (63) in seven large Icelandic breast cancer families, two of which showed evidence of linkage to BRCA1. These authors found that among presumed paternal carriers of mutant breast cancer gene alleles, 7 of 16 (44%) had developed prostate cancer, which led them to conclude that...
breast cancer genes may predispose to prostate cancer in male carriers (63). Additional evidence regarding the potential associations between BRCA1 and prostate cancer risk comes from an analysis of 33 BRCA1-linked families performed by Ford et al. (64). This analysis attempted to explore whether BRCA1 gene carriers are at increased risk of cancer at sites other than breast or ovary. According to the obtained results, there were statistically significant excesses of prostate cancer and colon cancer in BRCA1 carriers but not of cancer at any other sites. The maximum likelihood estimate of the relative risk of prostate cancer in BRCA1 carriers compared with the general population was 3.33. More recently, Gao et al. (65) in a study designed to establish the possible involvement in prostate cancer of BRCA1 and other potential tumor suppressor genes on chromosome 17q, have reported a high frequency of loss of heterozygosity at loci D17S856 and D17S855 (intragenic to BRCA1) in prostate cancer. These results suggest that BRCA1 and possibly other genes located within this region (149) may be important in this cancer.

Although these studies seemed to confirm the hypothesis that some connection could exist between breast cancer susceptibility genes and prostate cancer, very recent work performed by Langston et al. (66) has provided more definitive evidence. These authors, in a study aimed at directly examining the potential role of BRCA1 mutations in the etiology of prostate cancer, have screened for germ-line BRCA1 mutations in a subset of men with prostate cancer. The subgroup of cases selected included men in whom genetic factors were most likely to be relevant, including early-onset and family history of both breast cancer and prostate cancer. Interestingly, a total of seven germ-line alterations in a series of 49 cases were found. One of them corresponded to the above mentioned frameshift mutation (185delAG), which is the most common germ-line BRCA1 mutation reported to date (134, 135). In addition, five structural abnormalities were identified in six patients but not in the 145 population-based controls. One of them is a 12-bp insertion in intron 20, which was identified in two different cases, and which had previously been found in a woman diagnosed with cervical cancer and breast cancer (133) and also in a woman with a history of breast and ovarian cancer (150). Although the functional consequences of this genetic alteration are unknown, it seems likely that this 12-bp insertion may affect RNA processing. The remaining four sequence variants have not been reported previously and are located in both coding and non-coding sequences. The fact that none of the sequence variants identified in DNA from the control population suggests that they may represent alleles predisposing to disease. Finally, Struwing et al. (151) have also detected a BRCA1 frameshift mutant (5256delG) in a male patient affected with both breast and prostate cancer.

In addition to these genetic alterations in the first breast cancer susceptibility gene, studies of families linked to BRCA2 have revealed that prostate cancer risk is significantly increased in these families (67-74). Further analysis of some of these families has shown that in three of four BRCA2-linked Icelandic families, all prostate cancers tested are carriers of a 5-bp deletion in exon 9 (999del5), which is a recurrent mutation in Icelandic patients (71). Interestingly, prostate cancer patients carrying this mutation have significantly worse survival, which suggests that the BRCA2 mutation may be a possible marker for an aggressive disease in prostate cancer patients (73). Taken together, these data appear to indicate that mutations in the BRCA2 gene may also confer some risk of developing other malignancies, including prostate cancer, although detailed BRCA2 mutational studies in prostate carcinomas need to be done before more definitive conclusions can be reached.

Although it is clear that the basis for the hypothesis of common genetic features between some breast and prostate cancers is still speculative, two recently published studies have provided new and interesting insights. Struwing et al. (67), in an extensive study of the risk of cancer in a large group of Ashkenazi Jews, found a significantly elevated estimated risk of prostate cancer among carriers of BRCA1 or BRCA2 mutations. According to these data, the authors suggest that prostate cancer is part of the phenotype for these carriers. Similarly, Khan et al. (68), after analysis of germline BRCA1 and BRCA2 mutations in prostate carcinomas from a different population of Ashkenazi Jews, have concluded that mutations in these breast cancer susceptibility genes may increase the risk of prostate cancer.

In summary, there are some data indicating that alterations in the structural integrity of breast cancer susceptibility genes may indeed occur in prostate carcinomas. Nevertheless, according to available information, it appears that the contribution of germline BRCA1 or BRCA2 mutations to the overall incidence of prostate cancer is very small. In addition, the genetic association between breast and prostate cancer, due to BRCA1 and BRCA2, seems somewhat diluted by the fact that mutations in these genes also play a role in other tumors, including ovarian (150-153) and pancreatic carcinomas (154). Further studies and identification of additional prostate cancer patients with genetic alterations of BRCA1 and BRCA2 will be necessary to clarify the putative involvement of these genes in at least some cases of prostate cancer.

E. Other genes associated with breast or prostate cancer

In addition to the above described alterations in AR and BRCA genes, acquired or inherited abnormalities in other genes may occur in breast and prostate cancer. Analysis of reported alterations in oncogenes and tumor suppressor genes in both breast and prostate carcinomas reveals that somatic abnormalities are heterogeneous in terms of involved genes and mechanisms operating for their generation (reviewed in Ref. 50-53). The class of genes that is altered during the progression of normal mammary or prostatic cells to hormone-independent or to highly aggressive metastatic cancer cells includes classic tumor suppressor genes (p53, RB1) and oncogenes (ras, myc, neu) (50-53, 155-159), as well as genes involved in other processes such as cell-cycle inhibition, cell-cell adhesion, angiogenesis, DNA repair, and apoptosis (160-167). The mechanisms underlying these alterations are also diverse and include point mutations, allelic deletions, high-level amplifications, or de novo DNA methylation (50-53, 155-160, 168-173). This heterogeneity is consistent with the idea, as originally proposed for colorectal cancer (174), that breast and prostate carcinomas result from
the accumulation of genetic changes affecting a variety of genes associated with critical cell functions. However, it must be emphasized again that most of these genetic abnormalities are not exclusive to these tumors and have lesser value in the context of this review, which attempts to bring together factors common preferentially to breast and prostate cancer. Nevertheless, it is clear that new oncogenes and tumor suppressor genes important in the pathogenesis of these tumors are yet to be identified. In this regard, it is noteworthy that very recent studies from different groups have led to the identification in breast or prostate carcinomas of a series of candidate oncogenes, tumor suppressor, or metastasis suppressor genes, including H-cadherin (175), maspin (176), MDC (177), PCTA1 (178), PTII (179), MXII (180), PACI (181), KAI1 (182), and thymosin β15 (183), whose relevance to the respective tumor processes has not yet been definitively established. In this context, it will be interesting to explore the possibility that alterations in some of the new candidate genes associated with breast cancer may be also found to occur in prostate carcinomas and vice versa, thus helping to extend the genetic associations between these two hormone-sensitive tumors. It is also remarkable that the vast majority of genetic changes reported in both breast and prostate carcinomas arise in somatic cells but inherited defects may also predispose to both cancers. Interestingly, studies of familial aggregation in both diseases have revealed that the same percentage of breast or prostate cancers (~5%) may be directly attributable to inherited cancer susceptibility alleles (50-55). Familial breast and prostate cancer genes have now been mapped and, in the case of breast cancer-susceptibility genes, some associations with prostate cancer have been reported (63-74). Therefore, it will also be of future interest to evaluate the possibility that alterations in the familial prostate cancer gene (HPC1), recently mapped to the long arm of chromosome 1 (184), may also occur in a subset of breast carcinomas. Of interest is the preliminary report of a modest increase in the occurrence of breast cancer in HPC1 families (185). Further studies directed to examine the putative genetic commonalities between breast and prostate cancers could provide better insights into the mechanisms of progression of these hormonally dependent tumors and generate novel ideas to improve therapeutic strategies.

V. Common Biochemical Features of Breast and Prostate Cancer

The accumulation of the above mentioned genetic lesions in mammary or prostatic epithelial cells could lead to uncontrolled cell proliferation, disruption of normal pathways of cell differentiation, hormone responsiveness or programmed cell death, and, ultimately, promotion of mechanisms that facilitate tumor invasion and metastasis. These functional alterations may be connected to the biosynthesis of specific proteins that could be very useful as biochemical markers of the respective tumor processes. In recent years, molecular and biochemical analyses of breast or prostate carcinomas have led to the identification of a number of proteins that could be useful for predicting the clinical course of these diseases or monitoring their response to hormonal therapy. Among the growing list of tumor markers of potential interest in these malignancies, we have noticed that some of them, including prostate-specific antigen (PSA), pepsinogen C, apolipoprotein D, Zn-α2-glycoprotein (Zn-α2-gp), and GCDFP-15, show a striking parallel expression in both breast and prostate cancers. Importantly, such expression is either very low or absent in other tumors. Thus, all of them are up-regulated or down-regulated in a significant percentage of tumors of both sites and in most cases, their production appears to be dependent of common regulatory hormonal mechanisms. This section summarizes the current evidence in the literature supporting our proposal that these five proteins may represent examples of biochemical similarities between breast and prostate cancer.

A. PSA

PSA was initially discovered in seminal plasma in the 1970s (186, 187). Purification was first achieved by Sensabaugh (188). PSA was found to be a prostatic protein in 1977 (189) and was identified in serum shortly afterward. Of paramount clinical importance were the findings that serum PSA is increased in patients with prostate cancer in comparison to normals and that changes of serum PSA concentration are associated with cancer metastasis, recurrence, response to treatment, and survival (190, 191). Currently, PSA is considered to be the most valuable tumor marker due to its tissue specificity and it is used widely for prostate cancer screening, diagnosis, and management. Several reviews examine these issues in detail (192-196).

PSA is a 30-kDa serine protease that shares significant protein and gene sequence homology with pancreatic/renal kallikrein (hK1) and glandular kallikrein (hK2). PSA is also known as hK3. The PSA gene has been extensively characterized (197). The 5'-untranslated region contains regulatory elements, two of which are androgen response elements (ARE I and ARE II), and the other is a strong enhancer (198, 199). PSA gene transcription in the prostate is known to be regulated by androgens through the action of the AR (197-200) (Table 2). In seminal plasma, in which PSA is present at very high amounts (~1-2 g/liter), it appears that the role of PSA is proteolytic cleavage of the sperm motility inhibitor semenogelin, resulting in semen liquefaction post ejaculation (193, 194, 201). However, other substrates for PSA have been proposed including insulin-like growth factor binding protein-3 (IGFBP-3) (202), protein C inhibitor (203), transforming growth factor-β (TGF-β) (204), PTH-related peptide (205), and an unknown precursor protein that releases a putative vasoactive peptide (206). In male serum, PSA is present as a complex with α1-antichymotrypsin (PSA-Act), α1-macroglobulin (PSA-AM2), and as free PSA (207, 208).

The tissue specificity of PSA was not challenged until our first publication in 1994 (209). Earlier literature focused on single or a few case reports that were presented as exceptions to the rule that PSA is expressed only in the prostate. For example, PSA was reported in salivary gland neoplasms (210), ovarian teratomas (211), and in some apocrine breast carcinomas, but PSA was not found at that time in the most common form of breast cancer, the ductal carcinomas (212). Moreover, these findings were usually explained as artifacts.
of polyclonal antibodies since the results could not be confirmed by immunohistochemistry with PSA-specific monoclonal antibodies. Nonprostatic tissues that produce PSA include the periurethral glands (213-216). Female periurethral glands are positive for PSA, and their histological structure is similar to that of male prostate, but they remain underdeveloped due to lack of androgenic stimulation (217). The study of PSA expression in nonprostatic tissues has been greatly improved by the introduction of ultrasensitive PSA assays and PCR-based assays that facilitated measurement of PSA protein and mRNA levels with extreme sensitivity. Using such assays (218-220), we were able to produce substantial new information on PSA in breast tissue. We first demonstrated that PSA protein is present in at least 30% of breast carcinomas, marker of favorable clinical prognosis. Increased levels in serum from androgen-treated breast cancer patients. Produced by breast carcinomas. Marker of favorable prognosis.

**KGF**

Growth factor

- **Breast cancer**
  - Mitogenic for mammary epithelial cells.
- **Prostate cancer**
  - Mitogenic for prostate cancer cells.

**TABLE 2. Biochemical markers common to breast and prostate cancer**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
<th>Breast cancer</th>
<th>Hormonal regulation</th>
<th>Prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA</strong></td>
<td>Proteinase</td>
<td>Up-regulated by androgens, progesterins, and glucocorticoids in T-47D and BT-474 breast cancer cells.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Produced by breast carcinomas, marker of favorable clinical prognosis.</td>
<td></td>
<td>Up-regulated by androgens in LNCaP prostate cancer cells.</td>
</tr>
<tr>
<td><strong>Apolipoprotein D Lipocalin</strong></td>
<td>Up-regulated by androgens and glucocorticoids in T-47D, MCF-7, and ZR-75-1 cells. Steroid-induced expression inversely correlated with cell proliferation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Produced by breast carcinomas, marker of favorable clinical prognosis.</td>
<td></td>
<td>Up-regulated by androgens in LNCaP cells.</td>
</tr>
<tr>
<td><strong>Zn-α2-glycoprotein</strong></td>
<td>Soluble HLA?</td>
<td>Up-regulated by androgens and glucocorticoids in T-47D cells.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Produced by breast carcinomas, marker of favorable clinical prognosis.</td>
<td></td>
<td>Produced by benign and malignant prostatic tumors.</td>
</tr>
<tr>
<td><strong>Pepsinogen C</strong></td>
<td>Proteinase</td>
<td>Up-regulated by androgens and glucocorticoids in T-47D, MFM-223, SK-BR3, and ZR-75-1 cells.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Correlation with C expression with AR status of breast cancer cells.</td>
<td></td>
<td>Producing by clinical assessment of patients with low level prostate cancer cells.</td>
</tr>
<tr>
<td><strong>AIGF</strong></td>
<td>Growth factor</td>
<td>Up-regulated by androgens in SC-3 mouse mammary cancer cells, and MDA-MB-231 human breast cancer cells.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitogenic for breast cancer cells.</td>
<td></td>
<td>Overexpression in high grade prostate carcinomas.</td>
</tr>
<tr>
<td><strong>KGF</strong></td>
<td>Growth factor</td>
<td>ND. Produced by breast carcinomas.</td>
<td></td>
<td>Mitogenic for prostate cancer cells.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitogenic for mammary epithelial cells.</td>
<td></td>
<td>Up-regulated by androgens in normal and tumor prostatic cells.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induces mammary adenocarcinomas in transgenic mice.</td>
<td></td>
<td>Overexpression in hormone insensitive prostate carcinomas.</td>
</tr>
</tbody>
</table>

**ND**, Not done; HRE, hormone response element.

The study of PSA expression in nonprostatic tissues has been greatly improved by the introduction of ultrasensitive PSA assays and PCR-based assays that facilitated measurement of PSA protein and mRNA levels with extreme sensitivity. Using such assays (218-220), we were able to produce substantial new information on PSA in breast tissue. We first determined that PSA protein is present in at least 30% of breast tumors and that PSA presence is not a random event but is associated closely with the presence of steroid hormone receptors (209, 221). We now know that, with newer PSA assays exhibiting detection limits of approximately 1 ng/liter, about 70% of breast tumors contain measurable PSA protein (219). Breast tumors containing PSA are more frequently steroid hormone receptor positive, are smaller, have low S-phase fraction, and are diploid and patients have earlier stage disease. Moreover, such patients appear to live longer and relapse less frequently (222). There is little doubt that PSA is a favorable prognostic marker in breast cancer, and this parallels data available for other androgen-regulated genes (see further discussion later in this review). Importantly, PSA is also present in extracts from normal female breasts, and we provided evidence for overexpression induced by progestin-containing oral contraceptives (223). These and other data listed below suggest that in breast cancer, the regulation of PSA is disturbed and the expression may be reduced or lost as the cells lose differentiation. Highest expression of PSA was seen in tissue extracts from patients with benign breast diseases (224). PSA is also present in breast fluids. The breast epithelial cells produce and secrete PSA into the lumen, under the influence of steroid hormones. A tissue culture system has shown that, in some breast carcinoma cell lines, PSA expression is induced by androgens and progestins and to a lesser extent by glucocorticoids and mineralocorticoids.
Estrogens not only do not induce expression but block the action of androgens and progestins (225, 226). Breast discharge fluid obtained by nipple aspiration contains very high levels of PSA (up to ~5,000 μg/liter; about 1,000-fold higher than normal male serum). We found reduced levels of PSA in nipple aspirate fluid obtained from women who are either at high risk or have breast cancer (227). These data provide evidence that PSA may have some value in assessing breast cancer risk.

PSA has also been detected in the milk of lactating women (228) or women with prolactinoma (our unpublished data), in breast cyst fluid (229), and amniotic fluid (230). In female serum, PSA is present at levels of about 1,000-fold lower than male serum (231). We failed to find any association between total serum PSA and clinicopathological features of breast cancer (232). However, PSA in serum increases during pregnancy (233). More recently, we were able to determine the molecular forms of PSA in female serum and concluded that: 1) in serum of normal women or women without breast pathology (e.g., hirsute women), the predominant form is always PSA-bound to α1-antichymotrypsin (PSA-ACT); 2) in presurgical sera from breast cancer patients, about half of them have free PSA as the major molecular form. Similar data were found for women with benign breast diseases (Ref. 234 and unpublished results). These data suggest that serum-free PSA, which is an enzymatically inactive form of PSA, is overexpressed in patients with benign or malignant breast disease. The mechanism of such changes is unknown but the data are in contrast to changes in prostate cancer where serum PSA-ACT increases and free PSA decreases in cancer patients in comparison to patients with benign prostatic hyperplasia (207). Finally, we identified some similarities between PSA expression in the breast and expression of the BRCA1 protein, which is believed by some to be a granin (123). Thus, we speculated that BRCA1 may be a substrate for PSA but as yet there is no experimental evidence for this proposal (235). Furthermore, a protein that appears to be immunologically identical to BRCA1 has been found in seminal plasma (236).

How is PSA regulated in the breast and in breast tumors? We have evidence that PSA is up-regulated by progestins in vivo (223) and in vitro (225, 226). Similar data exist for glucoorticoids (225, 237). In vitro, androgens up-regulate PSA at levels as low as 10−11 M, similarly to progestins (226). We have also generated evidence that PSA up-regulation by androgens occurs in vivo because women with hyperandrogenic states have higher PSA than normal controls (238). Other evidence suggests that serum PSA changes during the menstrual cycle (239). The observation that some breast tumors bearing steroid hormone receptors do not produce PSA, while others that are receptor negative may produce high levels of PSA, led us to examine the sequence of all PSA exons and the 5′-regulatory region of the PSA gene in such tumors. No mutations were identified in any of the PSA exons, but we found deletions and point mutations in the 5′-flanking region in all of these tumors (240). This finding suggests that PSA expression is aberrant in at least some breast tumors.

What is the physiological role of PSA in the breast? This is currently not known but based on the proteolytic activity of PSA, we speculate that this enzyme, regulated by steroid hormones in the female breast, must act upon a substrate to release other biologically active molecules. Others have already proposed that PSA may be a regulator of growth factors, cytokines, or PTH-related peptide, but the levels of PSA tested are much higher than those found in the breast (202, 204-206). In this regard, it is of interest that breast cancer cells secrete an IGFBP-3 protease with ability to release bound insulin-like growth factor-I (IGF-I), which can then act as a mitogen to stimulate breast cancer cell proliferation (241). Since IGFBP-3 is a substrate for PSA in seminal plasma (202), a similar role for PSA in breast carcinomas could be envisaged, although no data are available to support this hypothesis. On the other hand, the sequence homology of PSA to growth factors and growth factor-binding proteins suggests that this molecule may well be a growth factor in its own right (242). Also interesting is the proposal that PSA may act upon substrates to release vasoactive peptides, which could help in the expulsion of breast secretions, such as nipple aspirate fluid and milk, paralleling the semen liquefaction function of PSA in the prostate (206). Whatever the function of PSA is, the current evidence suggests that this molecule is a marker of differentiation and good prognosis in breast diseases, especially breast cancer. It is now very clear that this molecule, which wrongfully bears the name of a prostate-specific protein, is elegantly regulated by steroid hormones and is secreted at relatively high concentrations by breast epithelial cells. Notably, only prostate cells in males and breast cells in females produce appreciable amounts of PSA, the levels in other tumors being much lower (243).

B. Apolipoprotein D (apoD)

apoD is a protein component of the human plasma lipid transport system that was first identified and characterized by McConathy and Alaupovic (244). This glycoprotein is mainly associated with high-density lipoprotein particles and consists of a single polypeptide chain of about 30 kDa that exhibits sequence similarity to members of the lipocalin family of proteins, whose common function is to bind and transport small hydrophobic ligands in the plasma (245) (Table 2). The functional role of apoD in the metabolism of plasma lipoproteins remains elusive, but it has been proposed that it may be involved in transport of cholesterol or cholesteryl esters (246-248). In addition, recent studies from different groups indicate that apoD is able to bind and transport a wide variety of ligands other than cholesterol, including heme-related compounds (249), progesterone (250), arachidonic acid (251), or odorant substances (252), thus extending its potential functional significance to a number of different biological processes.

The unexpected connection between apoD and breast diseases arose after the observation that apoD accumulates to extremely high concentrations (~1000-fold higher than in plasma) in cyst fluid from women with gross cystic disease of the breast (250), a benign condition associated with an increased risk of subsequent breast cancer (253, 254). The relationship of apoD to breast pathology was further supported by the finding of a certain type of breast carcinoma that is able to produce and secrete this glycoprotein (255-257).
Analysis of putative correlations between apoD levels in breast carcinomas and clinical outcome of the disease has revealed that low apoD values are significantly associated with a shorter relapse-free and overall survival (257). A possible explanation as to why apoD confers a prognostic advantage to women with breast cancer is that its presence may reflect the existence of a complete hormone receptor pathway. To date, the hormonal stimuli potentially responsible for the expression of apoD by breast carcinomas are unclear, but several data suggest that androgens could play a major role in apoD overproduction. Thus, apoD is one of the few proteins that are up-regulated by androgens in human breast cancer cells (257-259). This stimulatory effect is blocked by the antiandrogen flutamide, indicating that the action of androgen is presumably mediated via an AR mechanism. Finally, apoD has been found to be produced by either normal or tumor prostatic cells, under androgen stimulation (260-262).

The first indication that apoD could also be a marker of steroid action in prostate cancer cells was provided by Simard et al. (260), who examined the regulation of apoD secretion by sex steroids in LNCaP cells, the most widely used in vitro model of human prostate cancer. According to their data, physiological concentrations of androgens exert a biphasic pattern of action on both apoD secretion and cell proliferation in LNCaP cells. Thus, low concentration of androgens stimulates proliferation of prostate cancer cells and inhibits apoD secretion, whereas higher concentrations of androgens increase the expression of apoD and inhibit cell proliferation. Interestingly, such an opposite action of sex steroids on apoD secretion and cell proliferation is in complete agreement with similar studies in breast cancer cells demonstrating that the action of androgens and estrogens on apoD secretion is inversely related to cell proliferation in breast cancer cells (258, 263). On the basis of these results, apoD has been proposed as a marker of hormone action in both breast and prostate cancer cells, which could be associated with inhibition of cell growth and tumor regression (262-264). This potential value of apoD as a marker of growth arrest, together with its specific pattern of hormone responsiveness in both breast and prostate cancer cells, may be of interest from the clinical point of view. Thus, quantitation of intratumor apoD values could help to identify subgroups of breast or prostate cancer patients with low or high risk for recurrence or death, and who could benefit from specific hormone therapies.

C. Zn-\(\alpha_2\)-gp

Zn-\(\alpha_2\)-gp was originally isolated from human plasma, and its name was derived from its ability to be precipitated by zinc acetate, its electrophoretic mobility in the \(\alpha_2\)-region of the plasma globulins, and its high carbohydrate content (265). Amino acid sequence analysis of the protein purified from plasma has revealed that it consists of a single polypeptide chain of 276 amino acids with a high degree of similarity to class I antigens of the major histocompatibility complex (MHC) (266) (Table 2). The isolation and characterization of cDNA and genomic clones for human Zn-\(\alpha_2\)-gp have provided additional information on the relationship between this protein and transplantation antigens (267-269). Thus, the exon-intron organization and nucleotide sequence of the Zn-\(\alpha_2\)-gp gene are very similar to those of the first four exons encoding the signal peptide and the three extracellular domains characteristic of all class I MHC molecules. However, the Zn-\(\alpha_2\)-gp gene lacks the coding information for the transmembrane and cytoplasmic domains present in class I MHC genes, which explains its presence as a soluble protein in several human body fluids (270). The biological function of Zn-\(\alpha_2\)-gp is unknown but, according to its structural properties, this glycoprotein may play a role in the immune response as a soluble HLA adapted to bind and transport some nonpolymorphic substance in the plasma (271).

The potential interest of Zn-\(\alpha_2\)-gp in relation to breast cancer has arisen after the observation that, similar to apoD, this soluble HLA-like protein is accumulated at high concentrations in breast cyst fluid from women with gross cystic disease of the breast (255, 256). Furthermore, analysis of breast cancer tissues and secretions has revealed the existence of a significant percentage of mammary tumors (~40%) that produce and secrete appreciable amounts of Zn-\(\alpha_2\)-gp (255, 256, 272-275). Interestingly, and also in agreement with data regarding apoD, higher levels of Zn-\(\alpha_2\)-gp were detected in histopathologically well differentiated tumors than in moderately or poorly differentiated tumors (273, 275), suggesting that this protein may be a marker of tumors with high degree of differentiation, low metastatic potential, and therefore with favorable clinical outcome. Analysis of the molecular mechanisms controlling Zn-\(\alpha_2\)-gp expression in breast cancer cells has also provided interesting parallelisms between this protein and apoD (259, 276, 277). Chalbos et al. (276) were the first to observe that this protein can be induced by androgens in T-47D breast cancer cells. These results were subsequently confirmed and extended by Haagensen et al. (259) and López-Boado et al. (277), who demonstrated that androgens and also glucocorticoids up-regulate Zn-\(\alpha_2\)-gp mRNA levels and protein secretion in breast cancer cells in culture.

The possibility that Zn-\(\alpha_2\)-gp could also be relevant to prostate cancer was first suggested by Frenette et al. (278), after their finding that the major 40-kDa glycoprotein from human prostatic fluid is identical to Zn-\(\alpha_2\)-gp. Analysis of intraprostatic levels of Zn-\(\alpha_2\)-gp in prostatic diseases including prostate cancer revealed that these values are strikingly higher in benign prostatic hyperplasia than in adenocarcinomatous prostates, probably reflecting the dedifferentiation of cancerous prostates with the loss of secretory activity. These results agree with other studies showing that levels of other relevant prostatic proteins such as PSA and prostatic acid phosphatase are significantly decreased in prostatic tumors (262, 279). Further immunohistochemical studies have confirmed the partial loss of Zn-\(\alpha_2\)-gp expression in prostatic tissue after malignant transformation (280). In fact, Zn-\(\alpha_2\)-gp was present in benign hyperplastic glands in 91% of cases, but in only 41% of poorly differentiated prostatic adenocarcinomas, 48% of well differentiated adenocarcinomas, and 8% of metastases. The relationship between Zn-\(\alpha_2\)-gp and hormonal responsiveness of prostatic cancers is not known, and further studies are required to search for a correlation between Zn-\(\alpha_2\)-gp, ARs, and tumor progression.
The first indication that GCDFP-15 could also be relevant to prostate function resulted from the finding that the amino acid sequence of an actin-binding protein present in human seminal plasma was identical to that of GCDFP-15 (293, 294).

In addition, an analysis of the expression of GCDFP-15 in tumors from different origins revealed that in addition to mammary carcinomas, the major tumor types that expressed GCDFP-15 were carcinomas of prostate, salivary glands, and sweat glands, all of them being androgen dependent (295).

Therefore, and although further studies will be required to evaluate its clinical significance in prostate cancer, GCDFP-15 may be added to the list of proteins produced by both breast and prostate cancers, under similar hormone control. On this basis, GCDFP-15, together with apoD, Zn-2-gp, and PSA, may have potential usefulness as a biochemical marker of a specific subset of hormone-responsive tumors essentially driven by androgens and clinically characterized by a favorable outcome.

E. Pepsinogen C

Pepsinogen C is the precursor of pepsin C, an aspartyl proteinase that is mainly synthesized in the gastric mucosa and secreted into the gastric lumen where it is converted to the corresponding active enzyme under acidic conditions (296, 297). Pepsinogen C, also known as progastricisin, is widely distributed in the gastrointestinal tract and in some species, such as rodents, constitutes the major proteolytic enzyme present in gastric fluid (298). Isolation and characterization of cDNA and genomic clones for human pepsinogen C have shown that this protein is composed of a single polypeptide chain of 488 residues, with significant sequence similarity to other aspartyl proteinases, such as pepsinogen A, procathepsin D, procathepsin E, and prorenin (299, 300).

The relationship of pepsinogen C to human breast pathology, including breast cancer, was suggested after the finding that pepsinogen C is a major proteolytic enzyme in the cyst fluid from women with gross cystic disease of the breast (301). Further studies indicated that a significant percentage of breast carcinomas (~30%) have the ability to synthesize and secrete this proteolytic enzyme (302). These observations, together with the absence of pepsinogen C in normal resting mammary gland, raised the possibility that this proteinase might be involved in the lytic processes associated with invasive breast cancer lesions, as described for other enzymes such as matrix metalloproteinases, plasminogen activators, or secreted lysosomal enzymes (303). However, clinical studies demonstrated that this preliminary hypothesis was wrong. In fact, analysis of the putative relationship between intratumor pepsinogen C levels and clinical outcome of the corresponding patients have shown that pepsinogen C production by breast cancer cells is associated with lesions of favorable evolution (304). A possible explanation for this unexpected finding is that extragastric expression of pepsinogen C may only be a consequence of the hormonal alterations presumably involved in the development of breast tumors, without having any direct effect on the spread of cancer. In fact, recent studies on the hormonal regulation of pepsinogen C in breast cancer cells have revealed that androgens, glucocorticoids, and, to a lesser extent, proges-
terone, are able to induce the expression of this gene in different breast cancer cell lines, including T-47D, MFM-223, SK-BR3, and ZR75-1 (305). The pepsinogen C pattern of hormone responsiveness is similar to that of genes encoding PSA, apoD, Zn-α2-gp, and GCDFP-15, suggesting that all of them share common regulatory mechanisms that could be responsible for their expression in some breast carcinomas, as well as for the accumulation of their encoded proteins in pathological breast fluids (Table 2).

In relation to the molecular mechanisms mediating the expression of these genes associated with breast cancer, it is of interest that recent functional analysis of the promoter region of the human pepsinogen C gene has led to the identification of a 15-bp cis-acting element that plays a major role in the observed pepsinogen C induction by steroid hormones in breast cancer cells (305). The nucleotide sequence of the identified hormone-responsive element (AGAATCTTGT-TCC) closely resembles the consensus sequence for DNA binding of androgen, glucocorticoid, and progesterone receptors (G/A)GAACAxxxTGTTCT), including the four major guanine/cytosine contact points for receptor binding (306, 307). Despite the similarity in their response elements, it is clear that androgens, glucocorticoids, and progesterone display distinct physiological activities. To date, the relative importance of the in vivo hormonal factors controlling pepsinogen C production in breast cancer is unclear. Nevertheless, and although the possibility that pepsinogen C expression may be under multihormonal control cannot be ruled out, several data indicate that androgens could be the most relevant steroid hormones involved in its expression by breast carcinomas. Thus, there is a close correlation between androgen inducibility of pepsinogen C expression and AR status of breast cancer cells (305). In addition, pepsinogen C is accumulated in cyst fluid from women with gross cystic disease of the breast, a pathological entity proposed to be linked to androgen dysfunction (253, 255). Finally, several groups have demonstrated that normal prostate and prostatic carcinomas are able to produce pepsinogen C (308-310). In this regard, it is noteworthy that the nucleotide sequence of the hormone-responsive element identified in the promoter of the pepsinogen C gene is strikingly similar to two elements (AGACATgctGTTCG and AGACATggGTTCG) that confer androgen responsiveness to the genes coding for PSA and glandular kallikrein, two serine proteinases expressed at high levels in human prostate (197, 198, 311, 312). Taken together, these results indicate that pepsinogen C, by virtue of its overproduction in breast and prostate tumors, and its specific pattern of hormone responsiveness in cultured cells, could be added to the list of biochemical markers common to both carcinomas.

F. Other proteins

The list of biomarkers that are expressed in prostate and breast tissues is increasing. Prostate-specific membrane antigen was widely considered to be a specific marker of prostate carcinomas until we demonstrated its expression in breast tumors (313). The supposedly prostate-specific glandular kallikrein (hK2), which activates PSA by proteolytic digestion (314), has been found in the breast carcinoma cell line T-47D, and its expression is regulated by steroid hormones in a fashion similar to PSA (315). Liu et al. (316) have identified a novel serine protease-like gene, the expression of which is down-regulated during breast cancer progression, a situation similar to all other proteins mentioned above. This gene, NES-1 (normal epithelial cell-specific), is also expressed in the prostate and some other tissues. Its hormonal regulation is still unknown. Another serine protease of the kallikrein gene family has been cloned recently by Anisowicz et al. (317). This protein (protease M) is expressed in mammary and ovarian cancer cells as well as in prostate. Strikingly, protease M is down-regulated in metastatic breast cancer, in comparison to primary tumors, and may be a marker of aggressiveness. The hormonal regulation of protease M is unknown. This recent literature indicates that the number of biomarkers that are expressed in breast and prostate cancer will likely increase in the near future. Studies on hormonal regulation of these genes will be required before they can be included among the biochemical features that can help to establish connections between both carcinomas.

VI. Growth Factors in Breast and Prostate Cancer

Over the last few years, it became evident that growth factors play a determinant role in the control of proliferation of breast and prostate cancer. Several proteins with cell growth-stimulatory activities have been identified in the mammary gland and in the prostate and implicated in the normal and abnormal mammary and prostatic cell growth. Recent reviews have described growth factor families including different members of the fibroblast growth factor (FGF) family, EGF, TGFα, or IGF (3, 318, 319). Therefore, in this review we focus on androgen-induced growth factor (AIGF) and keratinocyte growth factor (KGF), which may be especially relevant in the context of potential associations between breast and prostate cancer (Table 2). However, it is tempting to mention a provocative new study that has shown that elevated serum levels of IGF-I are associated with increased risk of developing prostate cancer (320). Similar studies are now underway to determine whether a higher risk exists for breast cancer in women whose serum IGF-I levels are elevated. Interestingly, preliminary observations suggest an increased risk in premenopausal women (321, 322).

A. AIGF

AIGF was originally isolated by Tanaka et al. (323) from the conditioned medium of androgen-stimulated mouse mammary carcinoma cells SC-3. Isolation and characterization of cDNAs encoding this protein have revealed that it is composed of 215 amino acids, which share significant sequence similarity with members of the FGF family, AIGF being the eighth identified member of this family (FGF-8). More recently, the gene encoding the human homolog of AIGF has been cloned and characterized (324). The amino acid sequence derived from these genomic clones has revealed that human AIGF is completely identical in sequence to its murine counterpart. This extreme conservation in the amino acid sequence of AIGF in different species suggests a highly
conserved and important function. In fact, recent studies performed by different groups have shown that AIGF plays an important role in embryonic development, especially in gastrulation, limb, and facial morphogenesis and brain development (325-329). In addition to this proposed in vivo function of AIGF as a signaling molecule involved in developmental processes, in vitro studies have shown that this growth factor also exhibits oncogenic properties (330). Thus, NIH3T3 cells stably transfected with an AIGF expression vector have the abilities of tumor formation in nude mice, focus formation in monolayer culture, and colony formation in soft agar. It has also been demonstrated that AIGF exerts its transforming activity through an interaction with FGF receptor-1 (330).

Analysis of the mechanisms controlling the expression of the AIGF gene in SC-3 mammary cancer cells has shown that the level of AIGF mRNA is undetectable in androgen-unstimulated cells but it is markedly up-regulated in response to physiological concentrations of testosterone. Glucocorticoids also induce AIGF expression but at much lower levels than androgens, whereas estrogens do not show any significant effect on AIGF expression (331). These results are in parallel to those on steroid hormone-induced growth of SC-3 cells. Very recent studies have also provided evidence that AIGF is induced by androgens in human breast cancer cells (332). In addition, experiments designed to directly evaluate the role of AIGF in mediating androgen-induced growth have shown that this growth factor has indeed a remarkable stimulatory effect on proliferation of SC-3 cells in the absence of androgen (331). Finally, inhibition of the translation of AIGF mRNA by specific antisense oligonucleotides is accompanied by a complete block of androgen-induced DNA synthesis (330). These observations have led to the conclusion that the androgen-dependent growth of SC-3 mammary carcinoma cells is mediated by AIGF through an autocrine mechanism. In fact, AIGF was the first sex hormone autocrine-induced growth factor structurally characterized, thereby providing definitive support to the proposals that growth factors mediate hormonal action on the proliferation of hormone-responsive cancers.

Since AIGF has oncogenic and androgen-inducible properties in mammary carcinoma cells, it was likely that this mitogen could also play a local role on the growth of the androgen-responsive prostate cancer. Several studies have shown that AIGF is expressed in the prostate cancer cell lines LNCaP and PC-3, under both testosterone-stimulated and nonstimulated conditions, suggesting that its dependence on androgens is not as strict as in mammary cancer cells (324, 333). In addition, recombinant AIGF markedly stimulated the growth of LNCaP cells, which suggests that AIGF could be part of an autocrine loop in prostate cancers, in a similar way to that proposed in mammary cancer cells (324). Consistent with this hypothesis, analysis of AIGF expression in human prostatic carcinomas has revealed a significant upregulation of its mRNA levels in these tumors, and particularly in those corresponding to the high-grade subgroup (334). By contrast, none of the examined cases of benign prostatic hyperplasia expressed significant levels of AIGF. In summary, and although further analysis of the clinical and biological relevance of AIGF expression in breast and prostate carcinomas will be required, the present data suggest that this growth factor may play important roles in the progression of these two hormone-sensitive cancers. It will also be of interest to examine whether abnormal expression of AIGF or utilization of the different isoforms reported for AIGF may contribute to progression to hormone insensitivity in both breast and prostate cancer.

B. KGF

KGF, also known as FGF-7, is a member of the fibroblast growth factor family consisting of 194 amino acids with a calculated molecular mass of 24 kDa (335). KGF is exclusively produced by mesenchymal and stromal cells of different organs and has a potent mitogenic activity on epithelial cells that express the KGF receptor, a splice variant of FGF receptor-2 (336). Because of this distinctive pattern of fibroblast production and epithelial response, KGF has attracted much interest as a paracrine mediator of stromal-epithelial interactions, which are considered critical in many processes occurring during normal development and malignant transformation in both prostate and mammary gland (337).

The putative relevance of KGF in relation to prostatic function was first described by Yan et al. (338). These authors found that expression of KGF mRNA in stromal cells from normal rat prostate and rat prostate tumors is androgen-responsive, suggesting that KGF mediates the indirect control of epithelial cell proliferation by steroid hormones in this organ. The possible role of KGF in androgen-driven development has been further examined by in vitro organ culture experiments. Administration of a KGF-neutralizing antibody to the culture medium of in vitro grown newborn mouse seminal vesicles and rat ventral prostates caused a striking inhibition of both organ growth and epithelial branching morphogenesis (339, 340), supporting the idea that KGF has a major role during development of androgen-dependent organs. Recent functional studies involving the promoter region of the rat KGF gene have provided additional support to the concept that KGF acts as an andromedin in the development of male accessory sex glands. Thus, it has been described that the rat KGF promoter activity is regulated by androgens in prostate cancer cells (341). A search for the nucleotide sequence corresponding to this promoter segment has revealed the presence of several half-sites of the consensus HRE, but not a complete HRE that could mediate the observed KGF induction by androgens. Similar findings have been reported in the sequence of the human KGF promoter, suggesting that AR contributes to the control of KGF expression through these half-sites by cooperation with other transcription factors binding adjacent promoter elements (342). Finally, Thomson et al. (343) have demonstrated that antiandrogens are able to block KGF-stimulated development of the rat seminal vesicle and prostate. These results, together with the finding that KGF regulates androgen target genes in the prostate, suggest that KGF and AR signaling may interact, although in vivo evidence has not been found supporting the possibility that this growth factor is a direct mediator of androgen action (343).

KGF has not as yet been definitively associated with tumor processes, but a series of reports have suggested that aberrant
expression of KGF or its receptor may be important in the development and progression of human malignancies, including prostate cancer (344-346). Thus, it has been proposed that exon switching and activation of stromal and embryonic FGF receptor genes, including KGF receptor, in prostate epithelial cells may be an event involved in progression toward malignancy (344). On the other hand, abnormal expression of KGF receptor in mesenchymal cells results in the creation of a transforming autocrine loop, which leads to the appearance of transformed foci formed by the cells expressing both KGF and its receptor (345). Also of interest is the observation that KGF can directly activate AR in the absence of androgens in prostatic cancer cells, which means that the androgen signaling chain may be activated by this mitogen in an androgen-depleted environment. This aberrant activation of the AR by KGF may therefore be one mechanism contributing to progression of prostatic cancer to an androgen-independent stage (346). Furthermore, recent studies have demonstrated significant up-regulation of KGF expression in hormone-resistant prostate cancer, while KGF expression was not detected in benign prostatic hyperplasia (347). Finally, functional assessment of human recombinant KGF in a proliferation assay demonstrated a mitogenic effect of up to 100% on cultured prostatic epithelial cells, while other growth factors such as FGF-2 did not have any effect (347).

The finding that KGF expression by stromal cells is hormonally regulated in normal and tumor prostatic cells has prompted studies directed to delineate its possible role in other hormone-dependent organs such as the human breast in both normal and pathological conditions. Consistent with this idea, it has been reported that, similar to observations in other tissues, KGF is expressed in human mammary stromal cells but not in epithelial cells (348). Also similar to other tissues, KGF receptor mRNA was present in all analyzed human mammary epithelial cell strains, but in none of the mammary stromal cells. Subsequent analysis of temporal and spatial expression of KGF during mouse mammary gland development has revealed that KGF is expressed in stroma during the ductal phase of mammary development as well as in mammary preneoplastic cells, tumor cells, and immortalized cell lines, although at lower levels than those seen during normal mammary growth (349). On this basis, it has been suggested that KGF could also be an important paracrine growth factor in the mammary gland. In fact, addition of exogenous KGF to mammary epithelial cells strongly stimulates their proliferation (350). In addition to these in vitro experiments, KGF has also been shown to be a potent growth factor for mammary epithelium in vivo. Thus, intravenous injection of KGF in rats was found to cause a dramatic proliferation of mammary epithelium in their mammary glands that was rapidly reversible after cessation of KGF treatment (351). Similar studies performed in mice have revealed that the proliferative effects of KGF are even more prominent than in rats, causing a striking cystic dilation in the mammary glands, which is histologically similar to that of fibrocystic disease in the human female breast (352). This observation raises the interesting possibility that KGF could also play a role in the development of human gross cystic disease of the breast. It is also remarkable that the mammary epithelium of lactating rats is resistant to the proliferative action of KGF, which may be of importance in relation to epidemiological observations showing that pregnancy in women decreases susceptibility to breast cancer. Finally, Kitsberg and Leder (353) have recently reported that transgenic mice carrying the KGF gene under the control of the mouse mammary tumor virus promoter develop a severe mammary and prostatic hyperplasia and mammary adenocarcinomas.

Based on these effects of KGF in rodents, it seemed likely that KGF could also play a role in the aberrant proliferation of mammary epithelial cells occurring during breast cancer progression. Consistent with this idea, Koos et al. (354) reported the presence of KGF in 12 of 15 breast carcinomas. An additional study has detected amplification of the KGF receptor gene (also called bek gene) in breast carcinomas (355) although no data are available on the possibility that amplification of this receptor is a prognostic indicator as shown for other receptors amplified in breast cancer such as HER-2/neu (50, 52). Bansal et al. (356) have confirmed and extended these studies concerning expression of KGF and KGF receptor in human breast cancer. They have observed that the expression of this androgen-induced growth factor and its high affinity receptor FGF receptor-2-IIIb is usually retained in breast carcinomas. This observation is in marked contrast to the case of other growth factors such as FGF-1, -2, -3, and -4, which are not expressed or are produced at very low levels in these tumors, and suggests that KGF may influence the progression of breast cancer through stimulation of cell division. Therefore, and although much more information is required at both basic and clinical levels, the presence of KGF mRNA in normal mammary gland and in breast tumors, together with its potent proliferative effect, suggests that KGF may be a paracrine growth factor important in the control of proliferation of normal and neoplastic mammary epithelium. In summary and on the basis of cellular localization, hormonal regulation, and biological activities, KGF may be added to the increasing list of growth factors with potential roles in the progression of prostate and breast carcinomas.

VII. Theories of Breast and Prostate Cancer Development: Role of Steroid Hormones

The development of the female breast and the male prostate is highly dependent on the availability and action of steroid hormones released by the gonads. Steroid hormones regulate the expression of numerous growth factors that act locally, mediating growth and differentiation signals. Two growth factors, AIFG and KGF, have been described earlier in some detail. It is not within the scope of this article to review the growth factor literature as it relates to breast and prostate development. Recent reviews describe growth factor families such as FGF, EGF, TGF, and IGF in breast and prostate cancer (3, 318, 319).

Despite the extraordinary wealth of literature on breast and prostate cancer, their pathogenesis is still not well understood. Familial breast cancer, which accounts for about 5% of all breast carcinomas, is due to mutations of a few genes, two of which have already been cloned (69, 121).
Similarly, a familial prostate cancer gene, responsible for about 5% of all prostate cancers, has been mapped to chromosome 1 but not as yet cloned (184, 357). In addition, the existence of other prostate cancer-susceptibility loci has been recently proposed (358). Nevertheless, the familial breast and prostate cancer genes do not appear to play a major role in the sporadic forms of these diseases. In the absence of any other direct genetic leads, alternative models for breast and prostate cancer pathogenesis have been developed.

Epidemiological studies conducted by many different groups over the last 40 yr provided strong evidence that the pathogenesis of breast and prostate cancer is linked to the endogenous sex steroid hormones. Any model that describes breast or prostate cancer pathogenesis must be able to accommodate the unequivocal epidemiological knowledge that has been accumulated. In the following paragraphs, we will attempt to briefly review the epidemiological evidence and then describe models for breast and prostate cancer pathogenesis. Many authors have already proposed such models, and the features described previously will be synthesized in an attempt to present a more or less integrated model for both cancers.

Breast cancer. If hormones are so intimately linked to breast cancer pathogenesis, then groups of patients who receive exogenous sex hormones for many years should provide important information. Unfortunately, the impact of oral contraceptives and hormone replacement therapy on breast cancer remains controversial. This is in sharp contrast to the endometrial cancer situation in which estrogens are clearly inducing and progestins are clearly protecting against endometrial cancer (359, 360). The last review of the vast literature on oral contraceptives has concluded that there is a slightly increased risk of breast cancer in current users, but this risk disappears after 10 yr from cessation (361). Interestingly, women using oral contraceptive pills, when diagnosed, have less advanced cancer. The issue of postmenopausal hormone therapy and breast cancer remains controversial, but the consensus is that any impact is unlikely to be great (362-365). Since these exogenously administered hormones are given after the age of 18 yr, well after puberty, it is reasonable to assume that the major changes in the breast that predispose to breast cancer may have originated earlier in life (see also below).

A few other pieces of epidemiological data are also important. Women are at a 100-fold higher risk for developing breast cancer than men. This may underline, among other possibilities, the importance of either the cycling changes of steroid hormones during the menstrual cycle, the estrogen/progestin dominance over androgen, or the protective effect of androgen. Also, it is clear that the rate of increase of breast cancer incidence slows down significantly after menopause (366). This finding is one of the most compelling in implicating ovarian steroids in the pathogenesis of breast cancer. Other important findings implicating sex steroids include the increase in breast cancer incidence associated with early age of menarche and late age of menopause (1). An even more direct effect is seen with bilateral oophorectomy, which reduces the risk of breast cancer, and the protection is greater the earlier the ovaries are removed before menopause (1, 366).

Studies of migrants have clearly demonstrated that breast cancer is not exclusively due to genetic factors. Women who live in low-risk areas (e.g., Japan) do not increase their risk after moving to high risk areas (e.g., United States). The risk increases to that of the native population by the third generation (367). The environmental factor most intensely studied is diet. Although the issue is controversial, many believe that high-fat, low-fiber, high-energy food, especially if consumed early in life, may increase the risk (22, 41, 368, 369).

The link between diet and breast cancer may be the serum sex hormone levels. Although the comparison of various serum and urinary hormone levels between patients and controls provided equivocal results (48, 370), other studies have demonstrated reductions in estrogen levels after dietary modifications (371, 372). Most studies favor the view that serum estrogen levels are lower in the low-risk groups (e.g., Japanese or Chinese women) in comparison to high-risk groups (e.g., American or British women) (373-375). Recently, increased emphasis was given not only to the steroid hormones themselves but also to their metabolism. Fishman et al. (376, 377) reviewed the evidence linking increased C16 α-hydroxylation of estradiol and the abnormal estrogen conjugation and increased cancer risk. On the other hand, Michnovicz et al. (378) showed that oral indole-3-carbinol treatment in humans induces estrogen 2-hydroxylation which, in turn, results in decreased concentrations of several metabolites known to activate the estrogen receptor.

Among the newer observations and proposals regarding breast cancer pathogenesis, the issue of prenatal-perinatal exposures appears to be important. Trichopoulous and coworkers (379, 380) hypothesized that exposure of the fetus to high levels of estrogen during pregnancy may affect future breast cancer risk; the higher the exposure, the higher the risk. This proposal has not as yet been tested epidemiologically since it will require many decades of investigation, but there is some indirect support from studies of cerebral asymmetry and breast cancer risk (381). The importance of early events in life and their connection to future breast cancer risk have been reviewed recently (382). It appears that breast cancer prevention programs should shift the focus to adolescent years. Rat models of breast cancer indicate that exposure to high fat (primarily in the form of n-6 polyunsaturated fatty acids) and/or estrogens during pregnancy increases the risk of developing breast cancer in the offspring (383, 384). Similarly, prostate cancer risk in rodents is increased upon exposure of the fetus to small doses of estrogens, but the risk is decreased if higher doses are used (385).

Human studies have indicated that both preeclampsia and prematurity significantly decrease prostate cancer risk, and a suggestion has been made that these effects are likely related to the correlation of these conditions with levels of steroid hormones and growth factors (386). Preeclampsia is also negatively associated with breast cancer risk (387), while high birth weight is a predictor of higher prostate cancer risk (388) and breast cancer risk (389). Later in this review we will borrow a concept proposed by Ross and Henderson (43) for prostate cancer to incorporate prenatal exposures in our model for breast cancer development. The last phenomeno-
logical clue regarding breast cancer risk comes from studies of breast structure in infants and adults. There are striking differences between breast structures in infants (390). Russo and colleagues (391, 392) reported dramatic changes in the mammary gland during puberty and adolescence. During pregnancy, complete differentiation of the glandular epithelium takes place. The changes induced by pregnancy more characteristic of differentiation than cell proliferation may confer protection against breast cancer (392, 393).

The epidemiological clues summarized above draw our attention to the following points: 1) Breast cancer is not a purely genetic disease with the exception of a small proportion of familial breast cancer; 2) Environmental factors either acting alone or in association with genetic factors are likely very important; 3) Endogenous and exogenous sex hormones appear to be linked to the pathogenesis. The fact that exogenous hormones have no dramatic effects suggests that the endogenous hormonal milieu is very important especially early in life; 4) It appears that the risk is established at a very early stage, e.g., during prenatal, neonatal, and pubertal life and is continuously modified during the entire lifespan by pregnancy, exogenous hormones, and lifestyle. All these considerations have been included in the schematic diagram of Fig. 3, which was developed based on models proposed by Adami et al. (366), Nandi et al. (371), and Pike et al. (394), and by Ross and Henderson (43) for prostate cancer.

Central to the model is the presence in breast tissue of a population of target cells that are either susceptible or are already transformed during puberty but remain dormant. The population of target cells can increase by proliferation or decrease by differentiation. Proliferation signals may be generated by steroid hormones released from the ovaries or by exogenously administered hormones. Such signals may be direct, affecting steroid hormone receptor-positive cells. Alternatively, steroid hormone receptor-positive cells may release growth factors that act upon target cells that are steroid hormone receptor-negative. Such a model accommodates the clinical observation of occurrence of steroid hormone receptor-positive and -negative breast tumors (371). The sex hormone-proliferating pressure on target cells may be variable.

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**Fig. 3.** Model explaining the pathogenesis of breast cancer. For discussion see text. SHR, Steroid hormone receptors.
between individuals (genetic component) and may be modified by diet and lifestyle. The differences in sex hormone levels in serum between patients and controls may reflect this proliferative pressure which, if persistent for many years, may increase the chances of cancer development. Differences in serum sex steroid levels may also reflect a situation of low set point of the ‘gonadostat’. The gonadostat is a feedback loop mechanism that regulates the sex hormone concentration in blood through a complicated circuit involving the hypothalamus, pituitary, and ovaries. The gonadostat set point of the fetus may be influenced by the levels of sex hormones in the maternal circulation during pregnancy (43). Target cells may undergo terminal differentiation, a process that is enhanced during pregnancy. Postmenopausally, the risk decreases due to either induced cell apoptosis and/or atrophy. The target cells of breast tissue are the luminal epithelial cells from which more than 85% of the spontaneous breast cancers originate. Although the precise changes and mechanisms involved regarding breast cancer development are not known, it is clear that the proliferative pressure intensifies dramatically during puberty and continues throughout life.

Prostate cancer. Similar to the situation in breast cancer, prostate cancer is not purely a genetic disease with the exception of about 5% of the familial prostate cancer cases. Work is in progress to clone the familial prostate cancer susceptibility genes (184, 357, 358). Most of the clues regarding prostate cancer pathogenesis have also come from epidemiological studies. There are only three well established risk factors for prostate cancer: age, family history, and ethnic group/country of residence. Highest incidence is seen in African-Americans followed by white Americans. The lowest rates are seen among Chinese and Japanese. The differences among white and black Americans underline the genetic component of the disease. Migrant studies have shown that there is no dramatic shift in prostate cancer incidence after migration from a low risk (e.g., Japan) to a high risk (e.g., United States) area. However, the risk increases to that of the native men within a few generations. Similar to the situation with breast cancer, it can be speculated that environmental factors play a crucial role. Recent studies have focused on diet where a consistent association, especially with fat, red meat, low fiber, and levels of α-linolenic acid were seen (38, 39, 43, 48).

The role of hormones and especially androgens in the pathogenesis of prostate cancer is not disputed. The most convincing demonstration of androgen involvement is the dramatic reduction of prostate cancer risk in prepubertal castrates. Other studies have shown that African-Americans have at least 10% higher circulating testosterone levels than whites. The active metabolite of testosterone, dihydrotestosterone, is generated by the action of the enzyme 5α-reductase. Studies have shown that Japanese and Chinese men have substantially lower 5α-reductase activity than American men, and this may account for the differences in prostate cancer incidence. Additional risk factors for prostate cancer include vasectomy, early first intercourse, large number of sexual partners, and history of sexually transmitted disease (43).

It is well known that cell proliferation in the prostate is controlled by testosterone after intracellular conversion to dihydrotestosterone (43). There are two major peaks in prostate growth in humans. At puberty, prostatic growth accelerates with appearance of PSA in serum when androgen levels rise (395-397). At about the age of 50, a second increase in prostatic growth occurs simultaneously with an increase in the ratio of estrogens to androgens (398). Since receptors for androgen, estrogen, and progesterone are present in the prostate (395, 399), it can be assumed that all these hormones affect prostate growth. Among the androgenic hormones, dihydrotestosterone (DHT) is much more potent than testosterone in mediating prostate growth since patients with deficiency in 5α-reductase enzyme possess very small prostates that never develop prostate cancer (400). This finding suggests that DHT but not testosterone is a major player in prostate cancer pathogenesis and that the 5α-reductase enzyme is crucial in mediating DHT production. In addition to this widely recognized role of androgens in prostate cancer, several studies have indicated that estrogens, alone or synergizing with androgens, may be relevant to the etiology of both benign prostatic hyperplasia and prostatic carcinoma (401-404). Furthermore, recent studies have shown that functions in the male reproductivesystem that were previously ascribed to androgens are now known to be the result of estrogen action (405). These data, together with the presence of estrogen receptors in prostate, suggest that changes in the hormonal milieu not specifically circumscribed to androgens and concomitant changes in the steroid receptor profile in normal prostate with aging should be taken in consideration in the genesis of prostate cancer.

There are four major cell types in the prostate. The acinar epithelial cells possess AR and keratinocyte growth factor receptor and produce PSA. These cells are the origin of the vast majority of prostate cancers. The basal epithelial cells contain insulin-like growth factor receptors (IGF-R), epidermal growth factor receptors, and estrogen receptors. The smooth muscle cells express α1-adrenergic receptors (α1-R) and estrogen receptor. The prostatic fibroblasts express AR and a variety of growth factors including insulin-like growth factor II (IGF-II) and KGF. The 5α-reductase enzyme is localized in the fibroblasts (stroma) (395). Clearly, the prostatic cells and the secreted growth factors create the mitogenic microenvironment depicted in Fig. 4.

Our model for prostate cancer development is similar in many respects to the one proposed for breast cancer. Important aspects of the model include the existence of target cells that are under proliferative pressure by DHT, either directly or indirectly through growth factors. Higher DHT levels can occur either through excess supply of testosterone [low gonadostat set point determined during uterine life as proposed by Ross and Henderson (43)] or higher activity of 5α-reductase determined by genetic and/or dietary life-style factors (39).

Different lines of evidence suggest that the initiating events in prostate cancer appear very early during life. We have calculated the tumor-doubling time of prostatic carcinoma cells in vivo, shortly after radical prostatectomy and subsequent follow-up of patients. Tumor-doubling times vary between 67 and 600 days. Assuming a mean volume at diagnosis of 5 × 10^6 tumor cells, we calculated how many
years are necessary for one tumor cell to progress with constant doubling to $5 \times 10^9$ cells, provided that the tumor-doubling time is about 600 days. The time calculated is about 50 yr, suggesting that the tumor probably initiated around the time of puberty. We speculated that the initiating event in prostate cancer, and possibly in breast cancer, occurs during the abrupt and massive increase of steroid hormone production during puberty (406).

The central role of $5\alpha$-reductase enzyme in prostate cancer pathogenesis derives from its ability to regulate levels of DHT. Recently, a mutation in the $5\alpha$-reductase gene has been reported that decreases the ability of the enzyme to convert testosterone to DHT (407). Since this mutation is prevalent among Asians, it has been postulated that it may be responsible for the low risk of prostate cancer in this population. More recently, other mechanisms of ‘functional hyperandrogenism’ have been investigated, targeting the AR as the important mediating molecule. The current status indicates that the role of androgen in prostate cancer carcinogenesis is usually mediated by normal, wild-type AR rather than by mutated forms (408). However, an increasing number of AR genetic defects conferring a gain of function upon the receptor have been described (85, 97, 101). In addition, variant AR alleles containing variable CAG or GGC repeats have different abilities to mediate the effects of androgens. The hyperandrogenism and higher prostate cancer risk in blacks (Africans and African-Americans) may be due to higher testosterone levels, higher $5\alpha$-reductase activity, and AR alleles with higher activity due to a smaller number of CAG repeats than whites (109). AR alleles with shorter GGC repeats appear to be associated with higher risk for prostate cancer, presumably due to higher transactivation potential in mediating the effects of androgens. Unfortunately, it is still not understood how the proliferating signals generated by steroid hormones mediate genomic damage and in which genes and at which time during a lifetime.

VIII. Conclusions

Although this is the first time that putative common features of breast and prostate cancer are reviewed, there is already a substantial body of recent literature dealing with common epidemiological, genetic, biochemical, and mechanistic aspects of these two cancers. Incidence rates, lifetime risks, death rates, ethnic trends, and country of residence are

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FIG. 4. Model explaining the pathogenesis of prostate cancer. For more discussion see text.
among the common epidemiological features. Similarly, dietary factors, especially high-fat and low-fiber nutrients, appear to play a major role in the pathogenesis of both cancers. The central role of steroid hormones in the pathogenesis of both cancers is not disputed. Once the gonads are removed at an early age, the risk of both cancers decreases dramatically. Blockade of hormone action later in life by pharmacological agents may confer primary prevention. Dietary factors appear to influence risk through alteration of steroid hormone homeostasis. Once the role of dietary compounds is more clearly defined, it may be possible to reduce risk by modified diets and adoption of healthier life-styles (e.g., weight reduction and exercise) (10). Unfortunately, we do not as yet have a clear understanding of how steroid hormones induce breast or prostate cancer. In the last few years, it has become apparent that steroid hormones exert their actions by binding and activating transcription factors (the steroid hormone receptor family) which, in turn, regulate a large number of other genes. These other gene products mediate additional events by acting as growth factors in an autocrine/paracrine fashion. Steroid hormones with very different biological activities (e.g., estrogens, progestins, androgens) can be interconverted by action of enzymes. Tissues that are traditionally thought to be responsive to one class of such steroids are now known to contain receptors for other classes (e.g., the breast has ARs in addition to estrogen and progesterone receptors, and the prostate has estrogen and progesterone receptors in addition to ARs). Recently, new mechanisms of steroid hormone receptor action were proposed and may revise the way we believe steroid hormones work (409).

In this review, we have given examples of genes that are altered in both breast and prostate cancer. These include the AR gene as well as BRCA1 and BRCA2 genes. Since the frequency of common genetic abnormalities is very low, the basis for the hypothesis of common genetic features in both cancers must be considered speculative and of a narrow scope. Nevertheless, recent findings demonstrating a significantly elevated risk of prostate cancer among carriers of BRCA1 or BRCA2 mutations (67, 68, 73, 74) have provided additional support to previous epidemiological observations describing associations between breast and prostate cancer (11-13, 16, 17, 20, 21). Among the other features that we have presented, the common biochemical alterations are of special interest. The finding of proteins overproduced or underproduced by tumors from both sources suggests that they might be regulated by similar mechanisms, although other possibilities cannot be ruled out. Thus, the dedifferentiation of steroid-responsive breast or prostate cells may uncover common developmental processes (337) and shared expression of proteins. Further studies directed to identify putative common regulatory pathways shared by the two tumors are necessary to clarify whether the finding of biochemical similarities may be relevant to the biology of these carcinomas. Notably, all five proteins identified as being commonly expressed between the two cancers are androgen regulated and appear to be good prognostic markers for breast cancer. This may imply that either androgens have some protective effect against breast cancer or that there is a subset of breast cancers that is androgen dependent and has a better prognosis than estrogen-dependent tumors. In this regard, Secreto and Zummoff (113) have suggested that hypertestosteronism is a consistent feature of breast cancer patients. We anticipate that the list of genes that are coexpressed in the breast and prostate will grow further in the future. In fact, An et al. (410) have reported the preliminary characterization of a novel gene (UC28) overexpressed in prostate and breast cancers but not in other tumors. Similarly, recent studies have shown that prostate-specific membrane antigen and prostate-specific glandular kallikrein, widely assumed to be specific prostatic markers, are also produced by breast carcinomas (313, 315), thus increasing the list of potential biochemical similarities between both tumors.

The current theories for breast and prostate cancer development attempt to incorporate hormonal, dietary, and other factors into a common pathogenetic framework. One emerging common idea is that hormones appear to influence risk during the prenatal life, and they continue to do so throughout life but especially during puberty. Clearly, we will need more detailed descriptions on how hormones influence risk, which are the genes involved, and whether these genes are structurally altered or their expression is modified by environmental factors. We hope that the common features of breast and prostate cancer that we have highlighted (Table 3) will trigger interest in finding more connections between these two cancers and ultimately lead to strategies for common diagnostic procedures, prevention, monitoring, and cures.

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