0163-769X/98/$03.00/0
Endocrine Reviews 19(4): 365–396

Printed in U.S.A.

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

CARLOS LÓPEZ-OTÍN AND ELEFTHERIOS P. DIAMANDIS

Departamento de Bioquímica y Biología Molecular (C.L.-O.), Facultad de Medicina, Universidad de Oviedo 33006, Oviedo, Spain; and Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada, M5G 1X5 and Department of Laboratory Medicine and Pathobiology, University of Toronto (E.P.D.), Toronto, Ontario M5G 1L5, Canada

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

Address reprint requests to: E. P. Diamandis, M.D., Ph.D, FRCPC, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada. E-mail: ediamandis@mtsinai.on.ca

*The work done in the authors' laboratories was supported by grants from CICYT-Spain, Glaxo-Wellcome-Spain, EU-BIOMED-2, The Canadian Breast Cancer Foundation, The Canadian Breast Cancer Research Initiative, and Nordion International.

cancer in males. These include Klinefelter's syndrome, testicular atrophy, orchitis, undescended testes, testicular trauma, infertility, and defects in androgen receptor (AR) genes (6).

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 postmenopausally 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 reproductive 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-

TABLE 1. Correlation between breast and prostate cancer incidence rates and incidence rates of other cancers in 21 countries[a]

Cancer (x)	Cancer (y)	Pearson correlation coefficient
Breast	Prostate	0.81
	Endometrium	0.81
	Ovary	0.77
	Colon	0.74
	Rectum	0.65
Prostate	Endometrium	0.78
	Ovary	0.71
	Colon	0.64
	Rectum	0.40

[a] 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.

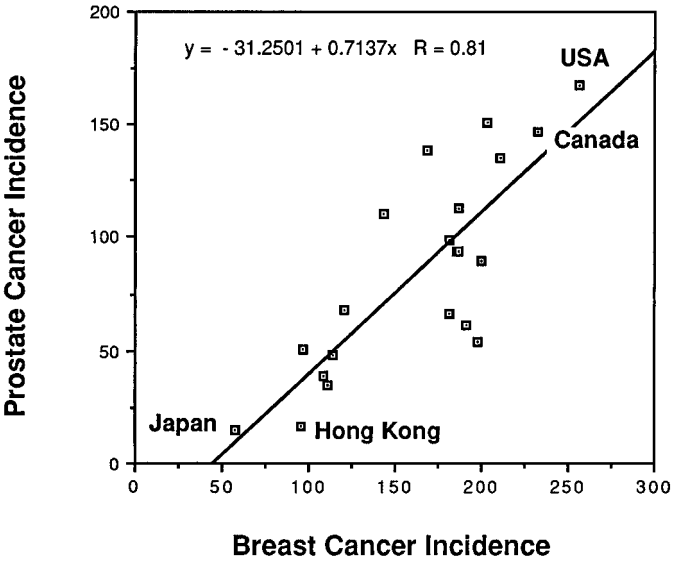

FIG. 1. Correlation between breast cancer and prostate cancer incidence rates in 21 countries listed in Table 1. Data are from Ref. 22. Lowest incidence rates for both breast and prostate cancer are found in Japan and Hong Kong and highest incidence rates are found in the United States and Canada.

cers (Fig. 1 and data not shown). The lowest incidence rates of both breast and prostate cancers were found in Japan and Hong Kong and the highest incidence rates were found in the USA and Canada. Similar data were obtained for endometrial cancer (not shown). These indirect findings, taken together with migrand studies, which suggest that cancer incidence rates change within two to three generations when low risk populations migrate to countries with high risk, suggest that common environmental factors may be responsible for these cancers.

Dietary factors are widely believed to play an important role in determining the risk of many cancers, including those of breast and prostate. Vitamin A and carotenoids are considered anticarcinogenic in experimental systems. Fruits and vegetables seem to confer protection (23). Heterocyclic amines, consumed with charbroiled food, have carcinogenic potential (24). Plant estrogens found in soy products such as tofu have been suggested to confer protection against breast cancer in Asian populations (25, 26). Vitamin D has been proposed as an anticarcinogenic compound for breast (27) and prostate cancer (28). High circulating levels of 1,25-dihydroxyvitamin D were associated with low incidence of prostate cancer. In the United States, it was found that prostate cancer mortality rates exhibit a marked North-South gradient with higher rates observed in the North (29, 30). This gradient correlates well with ambient levels of UV radiation, giving rise to the hypothesis that low UV exposure may be a risk factor for prostate cancer. Many reports suggest that vitamin D has potent antitumor properties, and its analogs may be modifiers of the growth of various cancers including those of breast and prostate (27, 28, 31-34). A recent report suggests that the higher levels of vitamin D in men at low risk of developing prostate cancer are associated with vitamin D receptor polymorphisms (35).

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.

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 immunoreactivity 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 (Val730 Met) 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

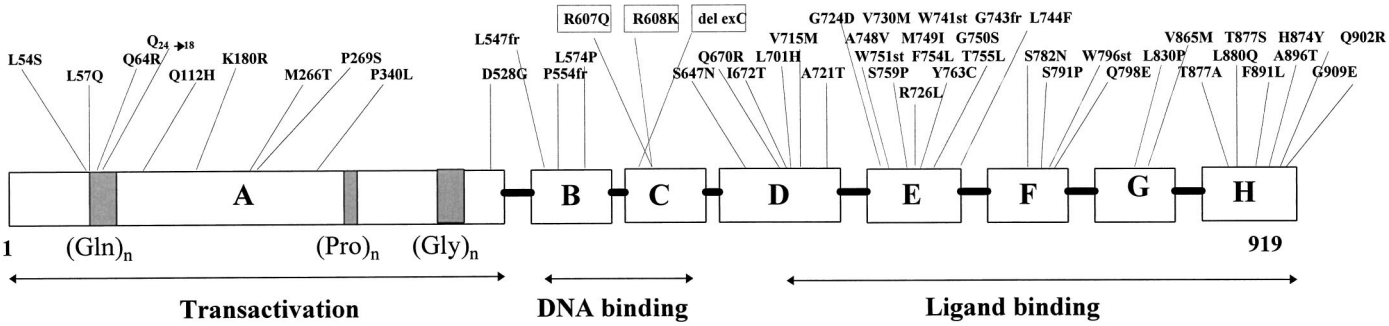

FIG. 2. AR abnormalities identified in prostate and breast carcinomas. The eight exons (A to H) of the AR gene and the three functional domains (transactivation, DNA binding, and ligand binding) identified in the AR protein are represented in the figure. Alterations described in breast carcinomas including 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 (W741st, W751st, W796st).

mutational analysis of AR have found a higher proportion of genetic abnormalities in either latent prostatic 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

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 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 descents 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 noncoding sequences. The fact that none of the sequence variants was identified in DNA from the control population suggests that they may represent alleles predisposing to disease. Finally, Struewing *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. Struewing *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), *PTI1* (179), *MXI1* (180), *PAC1* (181), *KAI1* (182), and thymosin β15 (183), whose relevance to the respective tumor processes has not as 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 (50-53). 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-α_2-glycoprotein (Zn-α_2-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 α_1-antichymotrypsin (PSA-ACT), α_2-macroglobulin (PSA-A2M), 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

TABLE 2. Biochemical markers common to breast and prostate cancer

Protein	Function	Hormonal regulation	
		Breast cancer	Prostate cancer
PSA	Proteinase	Up-regulated by androgens, progestins, and glucocorticoids in T-47D and BT-474 breast cancer cells. Produced by breast carcinomas, marker of favorable clinical prognosis.	Up-regulated by androgens in LNCaP prostate cancer cells. Highly sensitive marker for monitoring prostate cancer progression and response to therapy.
Apolipoprotein D	Lipocalin	Up-regulated by androgens and glucocorticoids in T-47D, MCF-7, and ZR-75-1 cells. Steroid-induced expression inversely correlated with cell proliferation. Produced by breast carcinomas, marker of favorable clinical prognosis.	Up-regulated by androgens in LNCaP cells. Expression inversely correlated with cell proliferation. Overexpression in prostate carcinomas.
Zn-α_2-glycoprotein	Soluble HLA?	Up-regulated by androgens and glucocorticoids in T-47D cells. Produced by breast carcinomas, marker of favorable clinical prognosis.	ND. It is a major glycoprotein in human prostatic fluid. Produced by benign and malignant prostatic tumors.
GCDFP-15	Immune response?	Up-regulated by androgens and glucocorticoids in T-47D and ZR-75-1 cells. Produced by breast carcinomas. Correlation with AR levels in breast carcinomas. Marker of favorable clinical prognosis. Increased levels in serum from androgen-treated breast cancer patients.	ND. Present in seminal fluid and normal prostate. Produced by prostatic carcinomas.
Pepsinogen C	Proteinase	Up-regulated by androgens and glucocorticoids in T-47D, MFM-223, SK-BR3, and ZR-75-1 cells. Correlation pg C expression with AR status of breast cancer cells. Produced by breast carcinomas, marker of good clinical prognosis.	ND. Present in seminal fluid and normal prostate. Produced by prostatic carcinomas. HRE in pgC gene very similar to those mediating androgen induction of PSA and glandular kallikrein in prostate cancer cells.
AIGF	Growth factor	Up-regulated by androgens in SC-3 mouse mammary cancer cells, and in MDA-MB-231 human breast cancer cells. Mitogenic for breast cancer cells.	Produced by LNCaP, and PC-3 prostate cancer cells. Strict androgen dependence not demonstrated. Overexpressed in high grade prostate carcinomas. Mitogenic for prostate cancer cells.
KGF	Growth factor	ND. Produced by breast carcinomas. Mitogenic for mammary epithelial cells. Induces mammary adenocarcinomas in transgenic mice.	Up-regulated by androgens in normal and tumor prostatic cells. Promoter activity induced by androgens in LNCaP cells. Overexpressed in hormone insensitive prostate carcinomas.

ND, Not done; HRE, hormone response element.

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 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 approximately 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 glucocorticoids (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-α_2-gp

Zn-α_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 α_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-α_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-α_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-α_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-α_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-α_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-α_2-gp (255, 256, 272-275). Interestingly, and also in agreement with data regarding apoD, higher levels of Zn-α_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-α_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-α_2-gp mRNA levels and protein secretion in breast cancer cells in culture.

The possibility that Zn-α_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-α_2-gp. Analysis of intraprostatic levels of Zn-α_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-α_2-gp expression in prostatic tissue after malignant transformation (280). In fact, Zn-α_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-α_2-gp and hormonal responsiveness of prostatic cancers is not known, and further studies are required to search for a correlation between Zn-α_2-gp, ARs, and tumor progression.

D. Gross cystic disease fluid protein-15

Gross cystic disease fluid protein-15 (GCDFP-15), together with the above mentioned apoD and Zn-α_2-gp, represents the major protein components found in cyst fluid from women with cystic disease of the breast (255) (Table 2). Similar to other cyst fluid proteins, GCDFP-15 is also produced and secreted by a subset of human breast carcinomas. The amino acid sequence of GCDFP-15, deduced from cDNA clones isolated from a human breast cancer cell cDNA library, is composed of 146 residues, with sequence similarity to a protein produced in the mouse submaxillary gland (281, 282). The biological function of GCDFP-15 remains unclear, although it has been suggested that it could modulate the immune response during tumor progression or viral infection by interfering with the functions mediated by CD4 in antigen presentation (283, 284). In addition, GCDFP-15 can exert mitogenic activity on breast cancer cell lines and on immortal mammary cells, but not on colon cancer, neuroblastoma, and small-cell lung carcinoma cell lines (285). Finally, the finding that extraparotid glycoprotein, a salivary protein identical in sequence to GCDFP-15, can bind to oral bacteria has suggested that this protein may be involved in modulating the colonization by bacteria in many biological fluids (286).

Studies on the distribution of GCDFP-15 in human tissues have shown that this protein is a normal constituent of all apocrine glands, being also present in cells of the mammary gland that have undergone apocrine metaplasia (287). This observation has suggested that GCDFP-15 could be a sensitive and specific marker for monitoring and defining apocrine differentiation in breast cancer. Studies directed to examine the presence of GCDGP-15 in breast carcinomas and its potential relationship to functional apocrine differentiation have shown that a significant percentage of breast carcinomas, likely showing apocrine differentiation, produce this protein (288). Interestingly, and also similarly to apoD and Zn-α_2-gp, tumors producing GCDFP-15 have a favorable clinical outcome, when compared with those lacking this protein (288, 289). Analysis of the mechanisms controlling GCDFP-15 expression has also revealed an interesting parallelism with those regulating the other major breast cyst fluid proteins (Table 2). Thus, androgens and glucocorticoids up-regulate GCDFP-15 mRNA levels and protein secretion in ZR-75-1 and T-47D breast cancer cells, whereas estrogens have a marked inhibitory effect on these parameters (290). Progestins also have a stimulatory effect on GCDFP-15 secretion by breast cancer cells, but their effects seem to be principally mediated by AR (276). These data, together with observations that fluoxymesterone, a synthetic androgen, increases the plasma concentration of GCDFP-15 in patients with metastatic breast cancer (291), and the finding of a correlation between GCDFP-15 production and AR levels within breast tumors (292), strongly suggest that synthesis and release of GCDFP-15 are mainly under androgenic control. Molecular cloning of the promoter region of the GCDFP-15 gene has revealed the presence in its 5′-flanking region of four half-TGTTCT sequences that could mediate this androgenic response, but no functional analysis of this sequence has as yet been reported (282).

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-α_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 progastricsin, 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-α_2-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 (AGAACTattTGTTCC) 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 (AGCACTtgcTGTTCT and AGCACTtggTGTTCC) 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 up-regulation 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, AIGF 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. Trichopoulos 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-

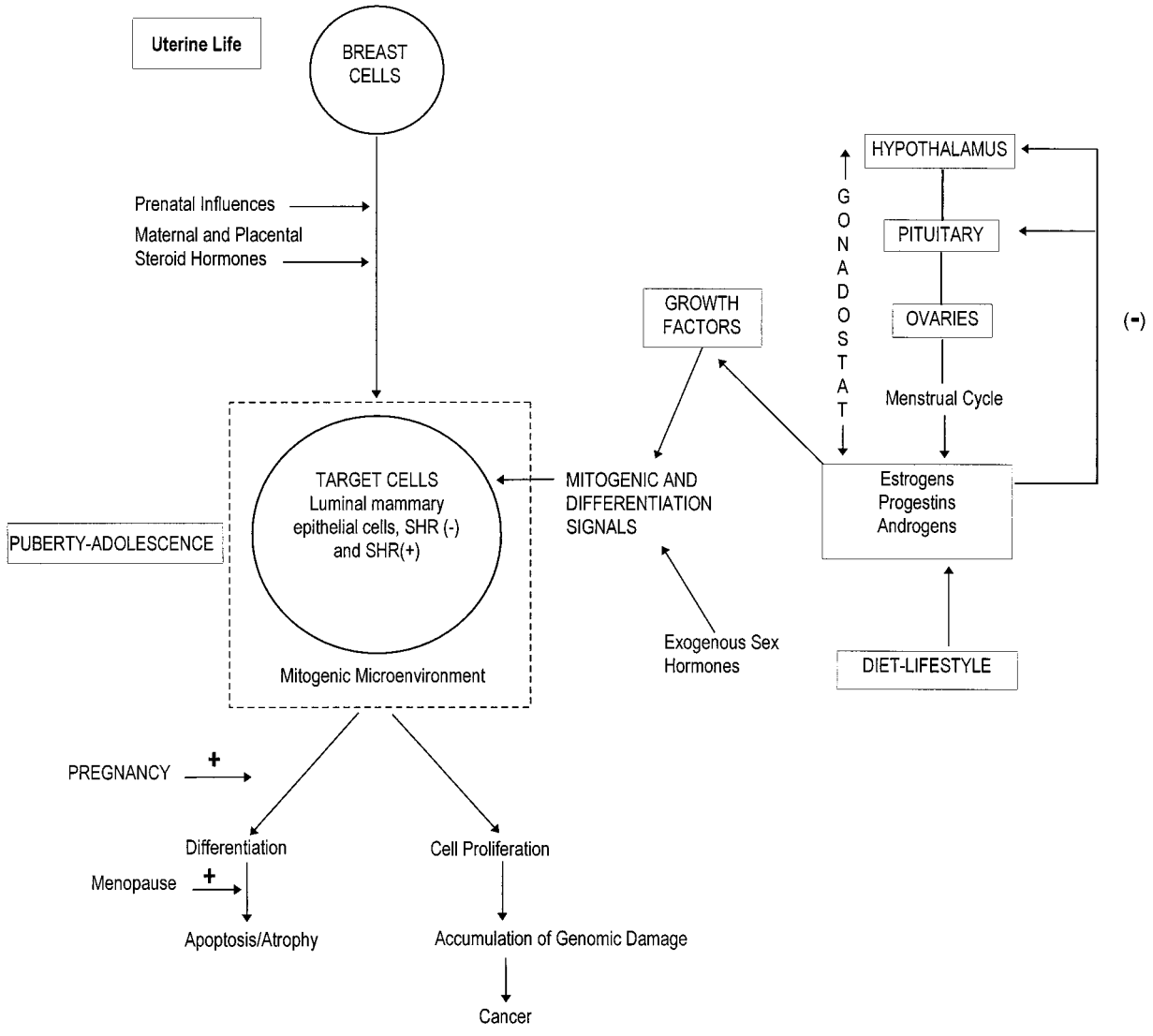

FIG. 3. Model explaining the pathogenesis of breast cancer. For discussion see text. SHR, Steroid hormone receptors.

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

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 dihydrostestosterone (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 reproductive system 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 α_1-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 5×10^9 tumor cells, we calculated how many

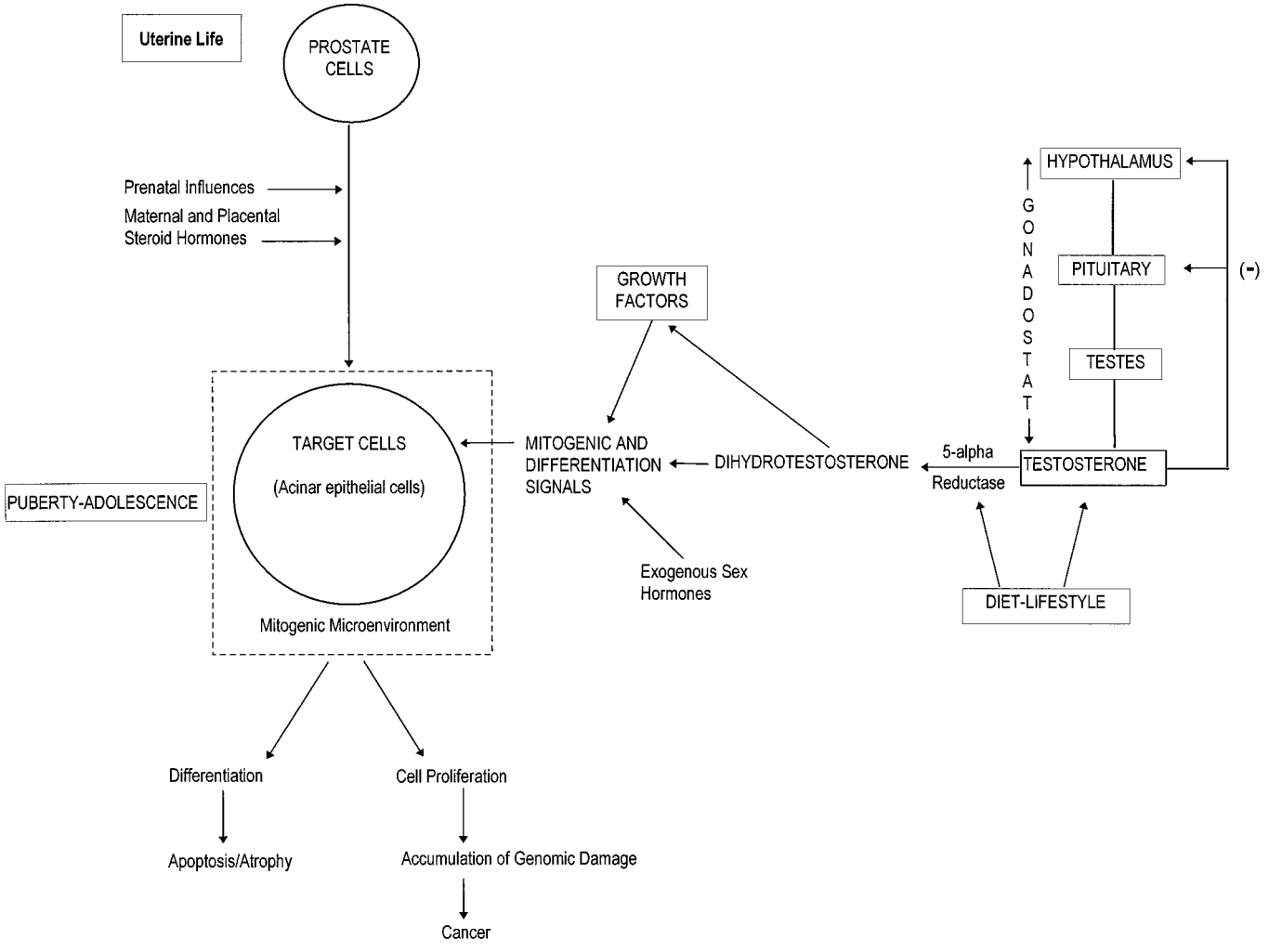

FIG. 4. Model explaining the pathogenesis of prostate cancer. For more discussion see text.

years are necessary for one tumor cell to progress with constant doubling to 5×10^9 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 5α-reductase enzyme in prostate cancer pathogenesis derives from its ability to regulate levels of DHT. Recently, a mutation in the 5α-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 5α- 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

TABLE 3. Similarities between breast and prostate cancer

Epidemiological	About the same incidence rates and lifetime risks. Coaggregation of the two cancers in some families.
Role of steroid hormones	Androgens, estrogens, progestins implicated in pathogenesis and progression.
Role of dietary factors	Fat, carotenoids, vitamins A, C, D, and E, minerals, fruits, vegetables implicated in pathogenesis and may have value for primary prevention.
Genetic alterations	Androgen receptor, BRCA1 and BRCA2. Other genes (oncogenes, tumor suppressors, cell cycle, cell adhesion, angiogenesis, DNA repair genes).
Biochemical markers [hormonally regulated by similar mechanisms]	Prostate specific antigen (hK3) Apolipoprotein D Zn-α_2-glycoprotein Gross cystic disease fluid protein-15 Pepsinogen C
Growth factors	Androgen-induced growth factor (AIGF) Keratinocyte growth factor (KGF)

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 *BRCA*1 and *BRCA*2 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 *BRCA*1 or *BRCA*2 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 Zumoff (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.

References

1. **Hulka BS, Stark AT** 1995 Breast cancer: cause and prevention. Lancet 346:883-887

2. **Bulbrook RD, Thomas BS** 1989 Hormones are ambiguous risk factors for breast cancer. Acta Oncol 28:841-847
3. **Dickson RB, Lippman ME** 1987 Estrogenic regulation of growth and polypeptide growth factor secretion in human breast carcinoma. Endocr Rev 8:29-43
4. **Labrie F, Simard J, de Launoit Y, Poulin R, Theriault C, Dumont M, Dauvois S, Martel C, Li SM** 1992 Androgen and breast cancer. Cancer Detect Prev 16:31-38
5. **Bezwoda WR, Mansoor N, Dansey R, Esser JD** 1987 Aromatisation of androstenedione by human breast cancer tissue: correlation with hormone receptor activity and possible biologic significance. Oncology 44:30-33
6. **Moore MP** 1996 Male breast cancer. In: Harris JR, Lippman ME, Morrow M, Hellman S (eds) Diseases of the Breast. Lippincott-Raven, Philadelphia, pp 859-863
7. **Adami HO, Baron JA, Rothman KJ** 1994 Ethics of a prostate cancer screening trial. Lancet 343:958-960
8. **Huggins C, Stevens AR** 1940 The effect of castration on benign hypertrophy of the prostate in man. J Urol 43:705
9. **Huggins C, Hodges CV** 1941 Studies on prostatic cancer: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1:293-297
10. **Osborne M, Boyle P, Lipkin M** 1997 Cancer prevention. Lancet 349:SII 27-32
11. **Macklin MT** 1954 The genetic basis of human mammary cancer. In Proceedings of Second National Cancer Conference. American Chemical Society, New York, pp 1074-1087
12. **Thiessen EU** 1974 Concerning a familial association between breast cancer and both prostatic and uterine malignancies. Cancer 34: 1102-1107
13. **Cannon L, Bishop DT, Skolnick M, Hunt S, Lyon JL, Smart CR** 1982 Genetic epidemiology of prostate cancer in the Utah Mormon genealogy. Cancer Surv 1:47-69
14. **Andrieu N, Clavel F, Auquier A, Gairard B, Brémond A, Lansac J, Piana L, Flamant R, Renaud R** 1991 Association between breast cancer and family malignancies. Eur J Cancer 27:244-248
15. **Rosenblatt KA, Thomas DB, McTiernan A, Austin M, Stalsberg H, Stemhagan A, Thompson WD, Curnen MGM, Satariano W, Austin DF, Isacson P, Greenberg RS, Key C, Kolonel L, West D** 1991 Breast cancer in men: aspects of familial aggregation. J Natl Cancer Inst 83:849-854
16. **Tulinius H, Egilsson V, Olafsdóttir GH, Sigvaldason H** 1992 Risk of prostate, ovarian, and endometrial cancer among relatives of women with breast cancer. Br Med J 305:855-857
17. **Anderson DE, Badzioch MD** 1992 Breast cancer risks in relatives of male breast cancer patients. J Natl Cancer Inst 84:1114-1117
18. **Isaacs SD, Kiemeney LALM, Baffoe-Bonnie A, Beaty TH, Walsh PC** 1995 Risk of cancer in relatives of prostate cancer probands. J Natl Cancer Inst 87:991-996
19. **Negri E, Braga C, La Vecchia C, Franceschi S, Parazzini F** 1997 Family history of cancer and risk of breast cancer. Int J Cancer 72:735-738
20. **Sellers TA, Potter JD, Rich SS, Drinkard CR, Bostick RM, Kushi LH, Zheng W, Folsom AR** 1994 Familial clustering of breast and prostate cancers and risk of postmenopausal breast cancer. J Natl Cancer Inst 86:1860-1865
21. **Anderson DE, Badzioch MD** 1993 Familial breast cancer risks: effects of prostate and other cancers. Cancer 72:114-119
22. **Prentice RL, Sheppard L** 1990 Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. Cancer Causes Control 1:81-97
23. **Trichopoulou A, Katsouyanni K, Stuver S, Tzala L, Gnardellis C, Rimm E, Trichopoulos D** 1995 Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. J Natl Cancer Inst 87:110-116
24. **Sugimura T, Nagao M, Wakabayashi K** 1994 Heterocyclic amines in cooked foods: candidates for causation of common cancers. J Natl Cancer Inst 86:2-3
25. **Adlercreutz H** 1995 Phytoestrogens: epidemiology and a possible role in cancer protection. Environ Health Perspect[Suppl 7]7:103-112
26. **Messina M, Barnes S** 1991 The role of soy products in reducing risk of cancer. J Natl Cancer Inst 83:541-546
27. **Colston KW, Berger U, Coombes RC** 1989 Possible role for vitamin D in controlling breast cancer cell proliferation. Lancet 1:188-191
28. **Corder EH, Guess HA, Hulka BS, Friedman GD, Sadler M, Vollmer RT, Lobaugh B, Drezner MK, Vogelman JH, Orentreich N** 1993 Vitamin D and prostate cancer: a prediagnostic study with stored sera. Cancer Epidemiol Biomarkers Prev 2:467-472
29. **Schwartz GG, Hulka BS** 1990 Is vitamin D deficiency a risk factor for prostate cancer? Anticancer Res 10:1307-1311
30. **Hanchette CL, Schwartz GG** 1992 Geographic patterns of prostate cancer mortality: evidence for a protective effect of ultraviolet radiation. Cancer 70:2861-2869
31. **Reichel H, Koeffler HP, Norman AW** 1989 The role of the vitamin D endocrine system in health and disease. N Engl J Med 320:980-991
32. **Skowronski RJ, Peehl DM, Feldman D** 1993 Vitamin D and prostate cancer: 1,25-dihydroxyvitamin D_3 receptors and actions in human prostate cancer cell lines. Endocrinology 132:1952-1960
33. **James SY, Mackay AG, Colston KW** 1995 Vitamin D derivatives in combination with 9-*cis* retinoic acid promote active cell death in breast cancer cells. J Mol Endocrinol:14 391-394
34. **Lucia MS, Anzano MA, Slayter MV, Anver MR, Green DM, Shrader MW, Logsdon DL, Driver CL, Brown CC, Peer CW, Roberts AB, Sporn MB** 1995 Chemopreventive activity of tamoxifen, *N*-(4-hydroxyphenyl)retinamide and the vitamin D analogue Ro24–5531 for androgen-promoted carcinomas of the rat seminal vesicle and prostate. Cancer Res 55:5621-5627
35. **Taylor JA, Hirvonen A, Watson M, Pittman G, Mohler JL, Bell DA** 1996 Association of prostate cancer with vitamin D receptor gene polymorphism. Cancer Res 56:4108-4110
36. **Boyd NF, Martin LJ, Noffel M, Lockwood GA, Trichler DL** 1993 A meta-analysis of studies of dietary fat and breast cancer risk. Br J Cancer 68:627-636
37. **Rose DP, Connolly JM, Rayburn J, Coleman M** 1995 Influence of diets containing eicosapentaenoic or docosahexaenoic acid on growth and metastasis of breast cancer cells in nude mice. J Natl Cancer Inst 87:587-592
38. **Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC** 1993 A prospective study of dietary fat and risk of prostate cancer. J Natl Cancer Inst 85:1571-1579
39. **Gann PH, Hennekens CH, Sacks FM, Grodstein F, Giovannucci L, Stampfer MJ** 1994 Prospective study of plasma fatty acids and risk of prostate cancer. J Natl Cancer Inst 86:281-286
40. **Brenner H, Savitz DA, Jockel KH, Greenland S** 1992 Effects of non-differential exposure misclassification in ecological studies. Am J Epidemiol 135:85-95
41. **Hunter DJ, Willett WC** 1996 Dietary factors. In: Harris JR, Lippman ME, Morrow M, Hellman S (eds) Diseases of the Breast. Lippincott-Raven, Philadelphia, pp 859-863
42. **Prentice RL, Thompson DJ, Clifford C, Gorbach S, Goldin B, Byar D** 1990 Dietary fat reduction and plasma estradiol concentration in healthy post-menopausal women. J Natl Cancer Inst 82:129-134
43. **Ross RK, Henderson BE** 1994 Do diet and androgens alter prostate cancer risk via a common etiologic pathway? J Natl Cancer Inst 86:252-254
44. **Wynder EL, Cohen LA, Muscat JE, Winters B, Dwyer JT, Blackhorn G** 1997 Breast cancer: weighing the evidence for a promoting role of dietary fat. J Natl Cancer Inst 89:766-775
45. **Tominaga S** 1985 Cancer incidence in Japanese in Japan, Hawaii and Western United States. Natl Cancer Inst Monogr 69:83-89
46. **Fay MP, Freedman LS, Clifford CK, Midthune DN** 1997 Effect of different types and amounts of fat on the development of mammary tumors in rodents: a review. Cancer Res 57:3979-3988
47. **Willett WC** 1997 Specific fatty acids and risks of breast and prostate cancer: dietary intake. Am J Clin Nutr 66[Suppl]:1557s–1563s
48. **Rose DP** 1996 The mechanistic rationale in support of dietary cancer prevention. Prev Med 25:34-37
49. **Rose DP** 1997 Dietary fatty acids and cancer. Am J Clin Nutr 66:998 s-1003 s
50. **Jones KA, Brown MA, Solomon E** 1995 Molecular genetics of sporadic and familial breast cancer. Cancer Surv 25:315-334
51. **Kallioniemi OP, Visakorpi T** 1996 Genetic basis and clonal evolution of human prostate cancer. Adv Cancer Res 68:225-254

52. **Walker RA, Jones JL, Chappell S, Walsh T, Shaw JA** 1997 Molecular pathology of breast cancer and its application to clinical management. Cancer Metastasis Rev 16:5-27
53. **Isaacs WB** 1995 Molecular genetics of prostate cancer. Cancer Surv 25:357-379
54. **Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, Puc J, Milaresis C, Rodgers L, McCombie R, Bigner SH, Giovanella BC, Ittmann Tycko B, Hibshoosh H, Wigler MH, Parsons R** 1997 PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 275:1943-1947
55. **Steck PA, Pershouse MA, Jasser SA, Yung A, Lin H, Ligon AH, Langford LA, Baumgard ML, Hattler T, Davies T, Frye C, Hu R, Svedlund B, Teng DHF, Tavtigian SV** 1997 Identification of a candidate tumour suppressor gene, *MMAC1*, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 15:356-362
56. **Liaw D, Marsh DJ, Li J, Dahia PLM, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacocke M, Eng C, Parsons R** 1997 Germline mutations of the *PTEN* gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 16:64-67
57. **Bentel JM, Tilley WD** 1996 Androgen receptors in prostate cancer. J Endocrinol 151:1-11
58. **Wooster R, Mangion J, Eeles R, Smith S, Dowsett M, Averill D, Barrett-Lee P, Easton DF, Ponder BAJ, Stratton MR** 1992 A germline mutation in the androgen receptor gene in two brothers with breast cancer and Reifenstein syndrome. Nat Genet 2:132-134
59. **Lobaccaro JM, Lumbroso S, Belon C, Galtier-Dereure F, Bringer J, Lesimple T, Namer M, Cutuli BF, Pujol H, Sultan C** 1993 Androgen receptor gene mutation in male breast cancer. Hum Mol Genet 2:1799-1802
60. **Lobaccaro JM, Lumbroso S, Belon C, Galtier-Dereure F, Bringer J, Lesimple T, Heron JF, Pujol H, Sultan C** 1993 Male breast cancer and the androgen receptor gene. Nat Genet 5:109-110
61. **Hall RE, Aspinall JO, Horsfall DJ, Birrell SN, Bentel JM, Sutherland RL, Tilley WD** 1996 Expression of the androgen receptor and an androgen-responsive protein, apolipoprotein D, in human breast cancer. Br J Cancer 74:1175-1180
62. **Zhu X, Daffada AA, Chan CMW, Dowsett M** 1997 Identification of an exon 3 deletion splice variant androgen receptor messenger RNA in human breast cancer. Int J Cancer 72:574-580
63. **Arason A, Barkardóttir RB, Egilsson V** 1993 Linkage analysis of chromosome 17q markers and breast-ovarian cancer in Icelandic families, and possible relationship to prostatic cancer. Am J Hum Genet 52:711-717
64. **Ford DF, Easton DF, Bishop DT, Narod SA, Goldgar DE** 1994 Risks of cancer in *BRCA1*-mutation carriers. Lancet 343:692-695
65. **Gao X, Zacharek A, Salkowski A, Grignon DJ, Sakr W, Porter AT, Honn KV** 1995 Loss of heterozygosity of the *BRCA1* and other loci on chromosome 17q in human prostate cancer. Cancer Res 55:1002-1005
66. **Langston AA, Stanford JL, Wicklund KG, Thompson JD, Blazej RG, Ostrander EA** 1996 Germ-line *BRCA1* mutations in selected men with prostate cancer. Am J Hum Genet 58:881-885
67. **Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA** 1997 The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. N Engl J Med 336:1401-1408
68. **Khan MA, McNeish TS, Struewing JP, Jones RT, Salabes A, Borkowski A, Vincent F, Bennett WP, Trump BF, Harris CC** 1997 Increased frequency of germline BRCA1 and BRCA2 mutations in prostate cancers from Jewish Ashkenazis. Proc Am Assoc Cancer Res 38:167 (Abstract 1118)
69. **Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Manglon J, Collins N, Gregory S, Gumbs C, Micklem G, Barfoot R, Hamoudi R, Patel S, Rice C, Biggs P, Hashim Y, Smith A, Connor F, Arason A, Gudmundsson J, Ficenec D, Kelsell D, Ford D, Tonin P, Bishop DT, Spurr NK, Ponder BAJ, Eeles R, Peto J, Devilee P, Cornelisse C, Lynch H, Narod S, Lenoir G, Egilsson V, Barkadottir RB, Easton DF, Bentley DR, Futreal PA, Ashworth A, Stratton MR** 1995 Identification of the breast cancer susceptibility gene *BRCA2*. Nature 378:789-792
70. **Tonin P, Ghadirian P, Phelan C, Lenoir GM, Lynch HT, Letendre F, Belanger D, Monté M, Narod SA** 1995 A large multisite cancer family is linked to BRCA2. J Med Genet 32:982-984
71. **Thorlacius S, Olafsdottir G, Tryggvadottir L, Neuhausen S, Jonasson JG, Tavtigian SV, Tulinius H, Ogmundsdottir HM, Eyfjord JE** 1996 A single *BRCA2* mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. Nat Genet 13:117-119
72. **Gudmundsson J, Johannesdottir G, Arason A, Bergthorsson JT, Ingvarsson S, Egilsson V, Barkardottir RB** 1996 Frequent occurrence of *BRCA2* linkage in Icelandic breast cancer families and segregation of a common *BRCA2* haplotype. Am J Hum Genet 58:749-756
73. **Sigurdsson S, Thorlacius S, Tomasson J, Tryggvadottir L, Benediktsdottir K, Eyfjord JE, Jonsson E** 1997 BRCA2: a possible marker in prostate cancer? Proc Am Assoc Cancer Res 38:427 (Abstract 2859)
74. **Easton DF, Steele L, Fields P, Ormiston W, Averill D, Daly PA, McManus R, Neuhausen SL, Ford D, Wooster R, Cannon-ALbright LA, Stratton MR, Goldgar DE** 1997 Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12–13. Am J Hum Genet 61:120-128
75. **Chang C, Saltzman A, Yeh S, Young W, Keller E, Lee HJ, Wang C, Mizokami A** 1995 Androgen receptor: an overview. Crit Rev Eukaryot Gene Expr 5:97-125
76. **Quigley CA, De Bellis A, Marschke KB, El-Awady MK, Wilson EM, French FS** 1995 Androgen receptor defects: historical, clinical, and molecular perspectives. Endocr Rev 16:271-321
77. **Deslypere JP, Young M, Wilson JD, McPhaul MJ** 1992 Testosterone and 5α-dihydrotestosterone interact differently with the androgen receptor to enhance transcription of the MMTV-CAT reporter gene. Mol Cell Endocrinol 88:15-22
78. **Chang C, Kokontis J, Liao S** 1988 Structural analysis of complementary DNA and amino acid sequences of human and rat androgen receptors. Proc Natl Acad Sci USA 85:7211-7215
79. **Barrack ER, Tindall DJ** 1987 A critical evaluation of the use of androgen receptor assays to predict the androgen responsiveness of prostatic cancer. Prog Clin Biol Res 239:155-187
80. **Sadi MV, Walsh PC, Barrack ER** 1991 Immunohistochemical study of androgen receptors in metastatic prostate cancer: comparison of receptor content and response to hormonal therapy. Cancer 67: 3057-3064
81. **Rundlett SE, Wu XP, Miesfeld RL** 1990 Functional characterization of the androgen receptor confirms that the molecular basis of androgen action is transcriptional regulation. Mol Endocrinol 4:708-714
82. **Jenster G, van der Korput HAGM, van Vroonhoven C, van der Kwast TH, Trapman J, Brinkmann AO** 1991 Domains of the human androgen receptor involved in steroid binding, transcriptional activation and subcellular localization. Mol Endocrinol 5:1396-1404
83. **Gottlieb B, Lehvaslaiho H, Beitel LK, Lumbroso R, Pinsky L, Trifiro M** 1998 The androgen receptor gene mutations database. Nucleic Acids Res 26:234-238
84. **Veldscholte J, Ris-Stalpers C, Kuiper GGJM, Jenster G, Berrevoets C, Claassen E, van Rooij HCJ, Trapman J, Brinkmann AO, Mulder E** 1990 A mutation in the ligand binding domain of the androgen receptor of human LNCaP cells affects steroid binding characteristics and response to anti-androgens. Biochem Biophys Res Commun 173:534-540
85. **Newmark JR, Hardy DO, Tonb DC, Carter BS, Epstein JI, Isaacs WB, Brown TR, Barrack ER** 1992 Androgen receptor gene mutations in human prostate cancer. Proc Natl Acad Sci USA 89:6319-6323
86. **Culig Z, Hobisch A, Cronauer MV, Cato ACB, Hittmair A, Radmayr C, Eberle J, Bartsch G, Klocker H** 1993 Mutant androgen receptor detected in an advanced-stage prostatic carcinoma is activated by adrenal androgens and progesterone. Mol Endocrinol 7:1541-1550
87. **Suzuki H, Sato N, Watabe Y, Masai M, Seino S, Shimazaki J** 1993 Androgen receptor gene mutations in human prostate cancer. J Steroid Biochem Mol Biol 46:759-765
88. **Castagnaro M, Yandell DW, Dockhorn-Dworhiczak B, Wolfe HJ, Pormeba C** 1993 Human androgen receptor gene mutations and

p53 analysis in advanced prostate cancer. Verh Dtsch Ges Pathol 77:119-123
89. **Evans BAJ, Harper ME, Daniells CE, Watts CE, Matenhelia S, Green J, Griffiths K** 1996 Low incidence of androgen receptor gene mutations in human prostatic tumors using single strand conformation polymorphism analysis. Prostate 28:162-171
90. **Elo JP, Kvist L, Leinonen K, Isomaa V, Hentu P, Lukkarinen O, Vihko P** 1995 Mutated human androgen receptor gene detected in a prostatic cancer patient is also activated by estradiol. J Clin Endocrinol Metab 80:3494-3500
91. **Peterziel H, Culig Z, Stober J, Hobisch A, Radmayr C, Bartsch G, Klocker H, Cato ACB** 1995 Mutant androgen receptors in prostatic tumors distinguish between amino-acid-sequence requirements for transactivation and ligand binding. Int J Cancer 63:544-550
92. **Suzuki H, Akakura K, Komiya A, Aida S, Akimoto S, Shimazaki J** 1996 Codon 877 mutation in the androgen receptor gene in advanced prostate cancer: relation to antiandrogen withdrawal syndrome. Prostate 29:153-158
93. **Ruizeveld de Winter JA, Janssen PJA, Sleddens HMEB, Verleun-Mooijman MCT, Trapman J, Brinkmann AO, Santerse AB, Schröder FH, van der Kwast TH** 1994 Androgen receptor status in localized and locally progressive hormone refractory human prostate cancer. Am J Pathol 144:735-746
94. **Takahashi H, Furusato M, Allsbrook Jr WC, Nishii H, Wakui S, Barrett JC, Boyd J** 1995 Prevalence of androgen receptor gene mutations in latent prostatic carcinomas from Japanese men. Cancer Res 55:1621-1624
95. **Gaddipati JP, McLeod DG, Heidenberg HB, Sesterhenn IA, Finger MJ, Moul JW, Srivastava S** 1994 Frequent detection of codon 877 mutation in the androgen receptor gene in advanced prostate cancers. Cancer Res 54:2861-2864
96. **Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, Keer HN, Balk SP** 1995 Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. N Engl J Med 332:1393-1398
97. **Tilley WD, Buchanan G, Hickey TE, Bentel JM** 1996 Mutations in the androgen receptor gene are associated with progression of human prostate cancer to androgen independence. Clin Cancer Res 2:277-285
98. **Crocitto LE, Henderson BE, Coetzee GA** 1997 Identification of two germline point mutations in the 5′UTR of the androgen receptor gene in men with prostate cancer. J Urol 158:1599-1601
99. **Schoenberg MP, Hakimi JM, Wang S, Bova GS, Epstein JI, Fischbeck KH, Isaacs WB, Walsh PC, Barrack ER** 1994 Microsatellite mutation (CAG_{24-18}) in the androgen receptor gene in human prostate cancer. Biochem Biophys Res Commun 198:74-80
100. **Koivisto P, Kononen J, Palmberg C, Tammela T, Hyytinen E, Isola J, Trapman J, Cleutjens K, Noordzij A, Visakorpi T, Kallioniemi OP** 1997 Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation therapy failure in prostate cancer. Cancer Res 57:314-319
101. **Koivisto P, Kolmer M, Visakorpi T, Kallioniemi OP** 1998 Androgen receptor gene and hormonal therapy failure of prostate cancer. Am J Pathol 152:1-9
102. **Chamberlain NC, Driver DE, Miesfeld RL** 1994 The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res 22:3181-3186
103. **Mhatre AN, Trifiro MA, Kaufman M, Kazemi-Esfarjani P, Figlewicz D, Rouleau G, Pinsky L** 1993 Reduced transcriptional regulatory competence of the androgen receptor in X-linked spinal and bulbar muscular atrophy. Nat Genet 5:184-187
104. **Coetzee GA, Ross RK** 1994 Prostate cancer and the androgen receptor. J Natl Cancer Inst 86:872-873
105. **Hardy DO, Scher HI, Bogenreider T, Sabbatini P, Zhang ZF, Nanus DM, Catterall JF** 1996 Androgen receptor CAG repeat lengths in prostate cancer: correlation with age of onset. J Clin Endocrinol Metab 81:4400-4405
106. **Stanford JL, Just JJ, Gibbs M, Wicklund KG, Neal CL, Blumenstein BA, Ostrander EA** 1997 Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk. Cancer Res 57:1194-1198
107. **Giovannucci E, Stamper MJ, Krithivas K, Brown M, Brufsky A, Talcott J, Hennekens CH, Kantoff PW** 1997 The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. Proc Natl Acad Sci USA 94:3320-3323
108. **Ingles SA, Ross RK, Yu MC, Irvine RA, La Pera G, Haile RW, Coetzee GA** 1997 Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. J Natl Cancer Inst 89:166-170
109. **Hakimi JM, Schoenberg MP, Rondinelli RH, Piantadosi S, Barrack ER** 1997 Androgen receptor variants with short glutamine or glycine repeats may identify unique subpopulations of men with prostate cancer. Clin Cancer Res 3:1599-1608
110. **Tan J, Sharief Y, Hamil KG, Gregory CW, Zang D-Y, Sar M, Gumerlock PH, deVere White RW, Pretlow TG, Harris SE, Wilson EM, Mohler JL, French FS** 1997 Dehydroepiandrosterone activates mutant androgen receptors expressed in the androgen receptors expressed in the androgen-dependent human prostate cancer xenograft CWR22 and LNCaP Cells. Mol Endocrinol 11: 450-459
111. **Saunders PTC, Padayachi T, Tincello DG, Shalet SM, Wu FCW** 1992 Point mutations detected in the androgen receptor gene of three men with partial androgen insensitivity syndrome. Clin Endocrinol (Oxf) 37:214-220
112. **Hiort O, Naber SP, Lehners A, Muletta-Feurer S, Sinnecker GHG, Zöllner A, Komminoth P** 1996 The role of androgen receptor gene mutations in male breast carcinoma. J Clin Endocrinol Metab 81: 3404-3407
113. **Secreto G, Zumoff B** 1994 Abnormal production of androgens in women with breast cancer. Anticancer Res 14:2113-2118
114. **Hill P, Garbaczewski L, Kasumi F** 1985 Plasma testosterone and breast cancer. Eur J Cancer 21:1265-1266
115. **Secreto G, Toniolo P, Pisani P, Recchione C, Cavalleri A, Fariselli G, Totis A, DiPietro S, Berrino F** 1989 Androgens and breast cancer in premenopausal women. Cancer Res 49:471-476
116. **Isola JJ** 1993 Immunohistochemical demonstration of androgen receptor in breast cancer and its relationship to other prognostic markers. J Pathol 170:31-35
117. **Kuenen-Boumeester V, Van der Kwast TH, Claassen CC, Look MP, Liem GS, Klijn JGM, Henzen-Logmans SC** 1996 The clinical significance of androgen receptors in breast cancer and their relation to histological and cell biological parameters. Eur J Cancer 32:1560-1565
118. **Broca PP 1866** Traité des Tumeurs. Asselin, Paris, vols 1 and 2
119. **Serova OM, Mazoyer S, Puget N, Dubois V, Tonin P, Shugart YY, Goldgar D, Narod SA, Lynch HT, Lenoir GM** 1997 Mutations in *BRCA1* and *BRCA2* in breast cancer families: are there more breast cancer-susceptibility genes? Am J Hum Genet 60:486-495
120. **Hall JM, Lee MK, Newman B, Morrow JA, Anderson LA, Huey B, King MC** 1990 Linkage of early-onset familial breast cancer to chromosome 17q21. Science 250:1684-1689
121. **Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholami Z, Shaffer D, Stone S, Bayer S, Wray C, Bodgen R, Dayananth P, Ward J, Tonin P, Narod S, Bristow PK, Norris FH, Helvering L, Morrison P, Rosteck P, Lai M, Barrett JC, Lewis C, Neuhausen S, Cannon-Albright L, Goldgar D, Wiseman R, Kamb A, Skolnick MH** 1994 A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. Science 250:1233-1238
122. **Koonin EV, Altschul SF, Bork P** 1996 Functional motifs and secreted tumour suppressors. Nat Genet 13:266-268
123. **Jensen RA, Thompson ME, Jetton TL, Szabo CI, van der Meer R, Helou B, Tronick SR, Page DL, King MC, Holt JT** 1996 BRCA1 is secreted and exhibits properties of a granin. Nat Genet 12:303-308
124. **Thompson ME, Jensen RA, Obermiller PS, Page DL, Holt JT** 1995 Decreased expression of *BRCA1* accelerates growth and is often present during sporadic breast cancer progression. Nat Genet 9:444-450
125. **Marquis ST, Rajan JV, Winshaw-Boris A, Xu J, Yin GY, Abel KJ, Weber BL, Chodosh LA** 1995 The developmental pattern of *BRCA1* expression implies a role in differentiation of the breast and other tissues. Nat Genet 11:17-26
126. **Hakem R, Pompa JL, Sirard C, Mo R, Woo M, Hakem A, Wake-**

man A, Potter J, Reitmair A, Billia F, Firpo E, Hui CC, Roberts J, Rossant J, Mak TW 1996 The tumor suppressor gene *BRCA1* is required for embryonic cellular proliferation in the mouse. Cell 85:1009-1023
127. **Chapman MS, Verma IM** 1996 Transcriptional activation by BRCA1. Nature 382:678-679
128. **Scully R, Chen J, Plug A, Xiao Y, Weaver D, Feunteun J, Ashley T, Livingston DM** 1997 Association of BRCA1 with Rad51 in mitotic and meiotic cells. Cell 88:265-275
129. **Marx J** 1997 Possible function found for breast cancer genes. Science 276:531-532
130. **Kinzler KW, Vogelstein B** 1997 Gatekeepers and caretakers. Nature 386:761-763
131. **Couch FJ, Weber BL, the Breast Cancer Information Core** 1996 Mutations and polymorphisms in the familial early-onset breast cancer (BRCA1) gene. Hum Mutat 8:8-18
132. **Szabo CI, King MC** 1997 Population genetics of BRCA1 and BRCA2. Am J Hum Genet 60:1013-1020
133. **Langston AA, Malone KE, Thompson JD, Daling JR, Ostrander EA** 1996 BRCA1 mutations in a population-based sample of young women with breast cancer. N Engl J Med 334:137-142
134. **Struewing JP, Abeliovich D, Peretz T, Avishai N, Kaback MM, Collins FS, Brody LC** 1995 The carrier frequency of the *BRCA1* 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nat Genet 11:198-200
135. **FitzGerald MG, MacDonald DJ, Krainer M, Hoover Y, O'Neil E, Unsal H, Silva-Arrieto S, Finkelstein DM, Beer-Romero P, Englert C, Sgrol DC, Smith BL, Younger JW, Garber JE, Duda RB, Mayzel KA, Isselbacher KJ, Friend SH, Haber DA** 1996 Germ-line *BRCA1* mutations in Jewish and non-Jewish women with early-onset breast cancer. N Engl J Med 334:143-149
136. **Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, Seal S, Tran T, Averill D, Fields P, Marshall G, Narod S, Lenoir GM, Lynch H, Feunteun J, Devilee P, Cornelisse CJ, Menko FH, Daly PA, Ormiston W, McManus R, Pye C, Lewis CM, Cannon-Albright L, Peto J, Ponder BAJ, Skolnick MH, Easton DF, Goldgar DE, Stratton MR** 1994 Localization of a breast cancer susceptibility gene, *BRCA2,* to chromosome 13q12–13. Science 265:2088-2090
137. **Tavtigian SV, Simard J, Rommens J, Couch F, Shattuck-Eidens D, Neuhausen S, Merajver S, Thorlacius S, Offit K, Stoppa-Lyonnet D, Belanger C, Bell R, Berry S, Bodgen R, Chen Q, Davis T, Dumont M, Frye C, Hattier T, Jammulapati S, Janecki T, Jiang P, Kehrer R, Leblanc JF, Mitchell JT, McArthur-Morrison J, Nguyen K, Peng Y, Samson C, Schroeder M, Snyder SC, Steele L, Stringfellow M, Stroup C, Swedlund B, Swensen J, Teng D, Thomas A, Tran T, Tranchant M, Weaver-Feldhaus J, Wong AKC, Shizuya H, Eyfjord JE, Cannon-Albrigth L, Labrie F, Skolnick MH, Weber B, Kamb A, Goldgar DE** 1996 The complete *BRCA2* gene and mutations in chromosome 13q-linked kindreds. Nat Genet 12:333-337
138. **Rajan JV, Wang M, Marquis ST, Chodosh LA** 1996 Brca2 is coordinately regulated with *Brca1* during proliferation and differentiation in mammary epithelial cells. Proc Natl Acad Sci USA 93: 13078-13083
139. **Sharan SK, Morimatsu M, Albrecht U, Lim D-S, Regel E, Dinh C, Sands A, Eichele G, Hasty P, Bradley A** 1997 Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking *Brca2.* Nature 386:804-810
140. **Connor F, Bertwistle D, Mee PJ, Ross GM, Swift S, Grigorieva E, Tybulewicz VLJ, Ashworth A** 1997 Tumorigenesis and a DNA repair defect in mice with a truncating *BRCA2* mutation. Nat Genet 17:423-430
141. **Phelan CM, Lancaster JM, Tonin P, Gumbs C, Cochran C, Carter R, Ghadirian P, Perret C, Moshlehi R, Dion F, Faucher MC, Dole K, Karimi S, Foulkes W, Lounis H, Warner E, Goss P, Anderson D, Larsson C, Narod SA, Futreal PA** 1996 Mutation analysis of the *BRCA2* gene in 49 site-specific breast cancer families. Nat Genet 13:120-122
142. **Couch FJ, Farid LM, DeShano ML, Tavtigian SV, Calzone K, Campeauo L, Peng Y, Bodgen B, Chen Q, Neuhausen S, Shattuck-Eidens D, Godwin AK, Daly M, Radford DM, Sedlacek S, Rommens J, Simard J, Garber J, Merajver S, Weber BL** 1996 BRCA2 germline mutations in male breast cancer cases and breast cancer families. Nat Genet 13:123-125
143. **Neuhausen S, Gilewski T, Norton L, Tran T, McGuire P, Swensen J, Hampel H, Borgen P, Brown K, Skolnick M, Shattuck-Eidens D, Jhanwar S, Goldgar D, Offit K** 1996 Recurrent *BRCA2* 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. Nat Genet 13:127-128
144. **Lancaster JM, Wooster R, Mangion J, Phelan CM, Cochran C, Gumbs C, Seal S, Barffot R, Collins N, Bignell G, Patel S, Hamoudi R, Larsson C, Wiseman RW, Berchuck A, Iglehart JD, Marks JR, Asworth A, Stratton MR, Futreal PA** 1996 BRCA2 mutations in primary breast and ovarian cancers. Nat Genet 13: 238-240
145. **Gayther SA, Mangion J, Russell P, Seal S, Barfoot R, Ponder BAJ, Stratton MR, Easton D** 1997 Variation of risks of breast and ovarian cancer associated with different germline mutations of the BRCA2 gene. Nat Genet 15:103-105
146. **Teng DHF, Bodgen R, Mitchell J, Baumgard M, Bell R, Berry S, Davis T, Ha PC, Kehrer R, Jammulapati S, Chen Q, Offit K, Skolnick MH, Tavtigian SV, Jhanwar S, Swedlund B, Wong AKC, Kamb A** 1996 Low incidence of *BRCA2* mutations in breast carcinoma and other cancers. Nat Genet 13:241-244
147. **Miki Y, Katagiri T, Kasumi F, Yoshimoto T, Nakamura Y** 1996 Mutation analysis in the *BRCA2* gene in primary breast cancers. Nat Genet 13:245-247
148. **Friedman LS, Gayther SA, Kurosaki T, Gordon D, Noble B, Casey G, Ponder BAJ, Anton-Culver H** 1997 Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. Am J Hum Genet 60:313-319
149. **Williams BJ, Jones E, Zhu XL, Steele MR, Stephenson RA, Rohr LR, Brothman AR** 1996 Evidence for a tumor suppressor gene distal to *BRCA1* in prostate cancer. J Urol 155:720-725
150. **Takahashi H, Behbakht K, McGovern PE, Chiu HC, Couch FJ, Weber BL, Friedman LS, King MC, Furusato M, Livolsi VA, Menzin AW, Liu PC, Benjamin Y, Morgan MA, King SA, Rebane BA, Cardonick A, Mikuta JJ, Rubin SC, Boyd J** 1995 Mutation analysis of the *BRCA1* gene in ovarian cancers. Cancer Res 55: 2998-3002
151. **Struewing JP, Brody LC, Erdos MR, Kase RG, Giambarresi TR, Smith SA, Collins FS, Tucker MA** 1995 Detection of eight *BRCA1* mutations in 10 breast/ovarian cancer families, including 1 family with male breast cancer. Am J Hum Genet 57:1-7
152. **Merajver SD, Pham TM, Caduff RF, Chen M, Poy EL, Cooney KA, Weber BL, Collins FS, Johnston C, Frank TS** 1995 Somatic mutations in the *BRCA1* gene in sporadic ovarian tumours. Nat Genet 9:439-443
153. **Foster KA, Harrington P, Kerr J, Russell P, DiCioccio RA, Scott IV, Jacobs Y, Chenevix-Trench G, Ponder BAJ, Gayther SA** 1996 Somatic and germline mutations of the *BRCA2* gene in sporadic ovarian cancer. Cancer Res 56:3622-3625
154. **Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, Yeo CJ, Jackson CE, Lynch HT, Hruban RH, Kern SE** 1996 Germline *BRCA2* gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res 56:5360-5364
155. **Tripathy D, Benz CC** 1993 Activated oncogenes and putative tumor suppressor genes involved in human breast cancers. In: Benz CC, Liu ET (eds) Oncogenes and Tumor Suppressor Genes in Human Malignancies. Kluwer Academic Publishers, Boston, pp 15-60
156. **Strohmeyer TG, Slamon DJ** 1994 Proto-oncogenes and tumor suppressor genes in human urological malignancies. J Urol 151:1479-1497
157. **Barbacid M** 1987 Ras genes. Annu Rev Biochem 56:779-827
158. **Hynes EN, Stern DF** 1994 The biology of erbB-2/neu/HER-2 and its role in cancer. Biochim Biophys Acta 1198:165-184
159. **Spencer CA, Groudine M** 1991 Control of c-myc regulation in normal and neoplastic cells. Adv Cancer Res 56:1-48
160. **Herman JG, Merlo A, Mao L, Lapidus RG, Issa JPJ, Davidson EN, Sidransky D, Baylin SB** 1995 Inactivation of the *CDKN2/p16/MTS1* gene is frequently associated with aberrant DNA methylation in all common human cancers. Cancer Res 55:4525-4530
161. **Oka H, Shiozaki H, Kobayashi K, Inoue M, Tahara H Kobayashi T, Takatskua Y, Matsuyoshi N, Hirono S, Takeichi M, Mori T** 1993

Expression of E-cadherin cell adhesion molecules in human breast cancer tissues and its relationship to metastasis. Cancer Res 53: 1696-1701
162. **Umbas R, Schalken JA, Aalders TW, Carter BS, Karthaus HFM, Schaafsma HE, Debruyne FMJ, Isaacs WB** 1992 Expression of the cellular adhesion molecule E-cadherin is reduced or absent in high-grade prostate cancer. Cancer Res 52:5104-5109
163. **Dickson RB, Lippman ME** 1992 Molecular determinants of growth, angiogenesis, and metastases in breast cancer. Semin Oncol 19:286-298
164. **Toyama T, Iwase H, Yamashita H, Iwata H, Yamashita T, Ito K, Hara Y, Suchi M, Kato T, Nakamura T, Kobayashi S** 1996 Microsatellite instability in sporadic human breast cancers. Int J Cancer 68:447-451
165. **Gao X, Wu N, Grignon D, Zacharek A, Liu H, Salkowski A, Li G, Sakr W, Sarkar F, Porter AT** 1994 High frequency of mutator phenotype in human prostatic adenocarcinoma. Oncogene 9:2999-3003
166. **Furuya Y, Krajewski S, Epstein JI, Reed JC, Isaacs JT** 1996 Expression of bcl-2 and the progression of human and rodent prostatic cancers. Clin Cancer Res 2:389-398
167. **Silvestrini R, Venerosi S, Daidone MG, Benini E, Borscchi P** 1994 The Bcl-2 protein: a prognostic indicator strongly related to p53 protein in lymph node-negative breast cancer patients. J Natl Cancer Inst 86:499-504
168. **Devilee P, Cornelisse CJ** 1994 Somatic genetic changes in human breast cancer. Biochim Biophys Acta 1198:113-130
169. **Ware JL** 1994 Prostate cancer progression. Am J Pathol 145:983-993
170. **Kallioniemi A, Kallioniemi OP, Piper J, Tanner M, Stokke T, Chen L, Smith H, Pinkel JW, Gray JW, Waldman FM** 1994 Detection and mapping of amplified DNA sequences in breast cancer by comparative genomic hybridization. Proc Natl Acad Sci USA 91:2156-2160
171. **Cher ML, Bova S, Moore DH, Small EJ, Caroll PR, Pin SS, Epstein JI, Isaacs WB, Jensen RH** 1996 Genetic alterations in untreated metastases and androgen-independent prostate cancer detected by comparative genomic hybridization allelotyping. Cancer Res 56: 3091-3102
172. **Graff JR, Herman JG, Lapidus RG, Chopra H, Xu R, Jarrard DF, Isaacs WB, Pitha PM, Davidson EN, Baylin SB** 1995 E-cadherin expression is silenced by DNA hypermethylation in human breast and prostate carcinomas. Cancer Res 55:5195-5199
173. **Jarrard DF, Bova GS, Isaacs WB** 1996 DNA methylation, molecular genetic, and linkage studies in prostate cancer. Prostate 6:36-44
174. **Fearon ER, Vogelstein B** 1990 A genetic model for colorectal tumorigenesis. Cell 61:759-767
175. **Lee SW** 1996 H-cadherin, a novel cadherin with growth inhibitory functions and diminished expression in human breast cancer. Nat Med 2:776-782
176. **Zou Z, Anisowicz A, Hendrix MJC, Thor A, Neveu M, Sheng S, Rafidi K, Seftor E, Sager R** 1994 Maspin, a serpin with tumor-suppressing activity in human mammary epithelial cells. Science 263:526-529
177. **Emi M, Katagiri T, Harada Y, Saito H, Inazawa J, Ito Y, Kasumi F, Nakamura Y** 1993 A novel metalloprotease/disintegrin-like gene at 17q21.3 is somatically rearranged in two primary breast cancers. Nat Genet 5:151-157
178. **Su Z, Lin J, Shen R, Fisher PE, Goldstein NI, Fisher PB** 1996 Surface-epitope masking and expression cloning identifies the human prostate carcinoma tumor antigen gene PCTA-1, a member of the galectin gene family. Proc Natl Acad Sci USA 93:7252-7257
179. **Shen R, Su Z, Olsson CA, Fisher PB** 1995 Identification of the human prostatic carcinoma oncogene PTI-1 by rapid expression cloning and differential RNA display. Proc Natl Acad Sci USA 92:6778-6782
180. **Eagle LR, Yin X, Brothman AR, Williams BJ, Atkin NB, Prochownik EV** 1995 Mutation of the MXI1 gene in prostate cancer. Nat Genet 9:249-255
181. **Sánchez Y, Lovell M, Marin MC, Wong PE, Wolf-Ledbetter ME, McDonnell TJ, Killary AM** 1996 Tumor suppression and apoptosis of human prostate carcinoma mediated by a genetic locus within human chromosome 10pter-q11. Proc Natl Acad Sci USA 93:2551-2556
182. **Dong JT, Lamb PW, Rinker-Schaeffer CW, Vukanovic J, Ichikawa T, Isaacs JT, Barrett JC** 1995 KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. Science 268:884-886
183. **Bao L, Loda M, Janmey PA, Stewart R, Anand-Apte B, Zetter BR** 1996 Thymosin β15: a novel regulator of tumor cell motility upregulated in metastatic prostate cancer. Nat Med 2:1322-1328
184. **Smith JR, Freije D, Carpten JD, Grönberg H, Xu J, Isaacs SD, Brownstein MJ, Bova GS, Guo H, Bujnovszky P, Nusskern DR, Damber JE, Bergh A, Emanuelsson M, Kallioniemi OP, Walker-Daniels J, Bailey-Wilson JE, Beaty TH, Meyers DA, Walsh PC, Collins FS, Trent JM, Isaacs WB** 1996 Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science 274:1371-1374
185. **Isaacs WB, Gronberg H, Isaacs SD, Bova GS, Freije D, Xu J, Meyers DA, Smith JR, Carpten JD, Collins FS, Trent JM, Walsh PC** 1997 Genetic predisposition to prostate cancer: implications for disease screening. Proc Am Assoc Cancer Res 38:651-652
186. **Ablin RJ, Bronson P, Soanes WA, Witebsky E** 1970 Tissue and species-specific antigens in normal human prostatic tissue. J Immunol 104:1329-1339
187. **Hara M, Koyanagi Y, Inoue T, Fukuyama T** 1971 Some physicochemical characteristics of gamma-seminoprotein; an antigenic component specific for human seminal plasma (Nippon Hoigaku Zasshi). Jpn J Legal Med 25:322-324
188. **Sensabaugh GF** 1978 Isolation and characterization of a semen-specific protein from human seminal plasma: a potential new marker for semen identification. J Forensic Sci 23:106-115
189. **Wang MC, Valenzuela LA, Murphy GP, Chu TM** 1977 Tissue specific and tumor specific antigens in human prostate. Fed Proc 36:1254
190. **Kuriyama M, Wang MC, Lee C, Papsidero LD, Killian CS, Inaji H, Slack NH, Nishiura T, Murphy GP, Chu TM** 1981 Use of human prostate-specific antigen in monitoring prostate cancer. Cancer Res 41:3874-3876
191. **Edson Pontes J, Chu TM, Slack N, Carr J, Murphy GP** 1982 Serum prostate antigen measurement in localized prostatic cancer: correlation with clinical course. J Urol 128:1216-1218
192. **Armbruster DA** 1993 Prostate-specific antigen: biochemistry, analytical methods, and clinical application. Clin Chem 39:181-195
193. **Malm J, Lilja H** 1995 Biochemistry of prostate specific antigen, PSA. Scand J Clin Lab Invest Suppl 55[Suppl 221]:15-22
194. **McCormack RT, Rittenhouse HG, Finlay JA, Sokoloff RL, Wang TJ, Wolfert RL, Lilja H, Oesterling J** 1995 Molecular forms of prostate-specific antigen and the human kallikrein gene family: a new era. Urology 45:729-744
195. **Partin AW, Oesterling JE** 1994 The clinical usefulness of prostate specific antigen: Update 1994. J Urol 152:1358-1368
196. **Peehl DM** 1995 Prostate specific antigen role and function. Cancer 75:2021-2026
197. **Riegman PH, Vlietstra RJ, van der Korput J, Brinkmann AO, Trapman J** 1991 The promotor of the prostate-specific antigen gene contains a functional androgen responsive element. Mol Endocrinol 5:1921-1930
198. **Schuur ER, Henderson GA, Kmetec LA, Miller JD, Lamparski HG, Henderson DR** 1996 Prostate specific antigen expression is regulated by an upstream enhancer. J Biol Chem 271:7043-7051
199. **Cleutjens KBJM, van der Korput HAGM, van Eekelen CEM, van Rooij HCJ, Faber PW, Trapman J** 1997 An androgen response element in a far upstream enhancer region is essential for high, androgen-regulated activity of the prostate specific antigen promotor. Mol Endocrinol 11:148-161
200. **Young CYF, Montgomery BT, Andrews PE, Qiu S, Bilhartz DL, Tindall DJ** 1991 Hormonal regulation of prostate-specific antigen messenger RNA in human prostatic adenocarcinoma cell line LNCaP. Cancer Res 51:3748-3752
201. **Robert M, Gibbs BF, Jacobson E, Gagnon C** 1997 Characterization of prostate-specific antigen proteolytic activity on its major physiological substrate, the sperm motility inhibitor precursor/semenogelin I. Biochemistry 36:3811-3819
202. **Cohen P, Peehl DM, Graves HCB, Rosenfeld RG** 1994 Biological effects of prostate specific antigen as an insulin-like growth factor-binding-3 protease. J Endocrinol 142:407-415

203. **Christensson A, Lilja H** 1990 Complex formation between protein C inhibitor and prostate-specific antigen *in vitro* and in human semen. Eur J Biochem 220:45-53
204. **Killian CS, Corral DA, Kawinski E, Constantine RI** 1993 Mitogenic response of osteoblast cells to prostate specific antigen suggests an activation of latent TGF-β and a proteolytic modulation of cell adhesion receptors. Biochem Biophys Res Commun 192:940-947
205. **Cramer SD, Chen Z, Peehl DM** 1996 Prostate specific antigen cleaves parathyroid hormone-related protein in the PTH-like domain: inactivation of PTHrP-stimulated cAMP accumulation in mouse osteoblasts. J Urol 156:526-531
206. **Fichtner J, Graves HCB, Thatcher K, Yemoto C, Shortliffe LMD** 1996 Prostate specific antigen releases a kinin-like substance on proteolysis of seminal vesicle fluid that stimulates smooth muscle contraction. J Urol 155:738-742
207. **Stenman UH, Leinonen J, Alfthan H, Rannikko S, Tuhkanen K, Alfthan O** 1991 A complex between prostate specific antigen and α_1-antichymotrypsin is the major form of prostate specific antigen in serum of patients with prostatic cancer: assay of the complex improves clinical sensitivity for cancer. Cancer Res 51:222-226
208. **Christensson A, Laurell CB, Lilja H** 1990 Enzymatic activity of the prostate-specific antigen and its reactions with extracellular serine proteinase inhibitors. Eur J Biochem 194:755-763
209. **Yu H, Diamandis EP, Sutherland DJA** 1994 Immunoreactive prostate specific antigen levels in female and male breast tumors and its association with steroid hormone receptors and patient age. Clin Biochem 27:75-79
210. **Van Krieken JH** 1993 Prostate marker immunoreactivity in salivary gland neoplasms. Am J Surg Pathol 17:410-414
211. **McLachlin CM, Srigley JR** 1992 Prostatic tissue in mature cystic teratomas of the ovary. Am J Surg Pathol 16:780-784
212. **Papotti M, Paties C, Peveri V, Moscuzza L, Bussolati G** 1989 Immunocytochemical detection of prostate specific antigen (PSA) in skin adnexal and breast tissues and tumors. Basic Appl Histochem 33:25-29
213. **Iwakiri J, Grandbois K, Wehner N, Graves HCB, Stamey T** 1993 An analysis of urinary prostate specific antigen before and after radical prostatectomy: evidence for secretion of prostate specific antigen by the periurethral glands. J Urol 149:783-786
214. **Nowels K, Kent E, Rinsho K, Oyasu R** 1988 Prostate specific antigen and acid phosphatase-reactive cells in cystitis cystica and glandularis. Arch Pathol Lab Med 112:734-737
215. **Pollen JJ, Dreilinger A** 1984 Immunohistochemical identification of prostatic acid phosphatase and prostate specific antigen in female periurethral glands. Urology 23:303-304
216. **Tepper SL, Jagirdar J, Heath D, Geller SA** 1984 Homology between the female paraurethral (Skene's) glands and the prostate. Arch Pathol Lab Med 108:423-425
217. **Wernert N, Albrech M, Sesterhenn I, Goebbels R, Bonkhoff H, Seitz G, Inniger R, Remberger K** 1992 The 'female prostate': location, morphology, immunohistochemical characteristics and significance. Eur Urol 22:64-69
218. **Yu H, Diamandis EP** 1993 Ultrasensitive time-resolved immunofluorometric assay of prostate specific antigen in serum and preliminary clinical studies. Clin Chem 39:2108-2114
219. **Ferguson RA, Yu H, Kalyvas M, Zammit S, Diamandis EP** 1996 Ultrasensitive detection of prostate specific antigen by time-resolved immunofluorometric assay and the Immulite® Immunochemiluminescent Third Generation Assay: potential applications in prostate and breast cancers. Clin Chem 42:675-684
220. **Zarghami N, Diamandis EP** 1996 Detection of prostate specific antigen mRNA and protein in breast tumors. Clin Chem 42:361-366
221. **Diamandis EP, Yu H, Sutherland DJA** 1994 Detection of prostate specific antigen immunoreactivity in breast tumors. Breast Cancer Res Treat 32:301-130
222. **Yu H, Giai M, Diamandis EP, Katsaros D, Sutherland DJA, Levesque MA, Roagna R, Ponsone R, Sismondi P** 1995 Prostate specific antigen is a new favorable prognostic indicator for women with breast cancer. Cancer Res 55:2104-2110
223. **Yu H, Diamandis EP, Monne M, Croce CM** 1995 Oral contraceptive-induced expression of prostate specific antigen in the female breast. J Biol Chem 270:6615-6618
224. **Yu H, Diamandis EP, Levesque M, Giai M, Roagna R, Ponzone R, Sismondi P, Monne M, Croce C** 1996 Prostate specific antigen in breast cancer, benign breast disease and normal breast tissue. Breast Cancer Res Treat 40:171-178
225. **Yu H, Diamandis EP, Zarghami N, Grass L** 1994 Induction of prostate specific antigen production by steroids and tamoxifen in breast cancer cell lines. Breast Cancer Res Treat 32:291-300
226. **Zarghami N, Grass L, Diamandis EP** 1997 Steroid hormone regulation of prostate specific antigen gene expression in breast cancer. Br J Cancer 75:579-588
227. **Sauter ER, Daly M, Lenahan K, Ehya H, Engstrom PF, Sorling A, Bonney G, Yu H, Diamandis EP** 1996 Prostate specific antigen in nipple aspirate fluid correlate with breast cancer risk. Cancer Epidemiol Biomarkers Prev 5:967-970
228. **Yu H, Diamandis EP** 1995 Prostate specific antigen in milk of lactating women. Clin Chem 41:54-58
229. **Diamandis EP, Yu H, López-Otín C** 1996 Prostate specific antigen - a new constituent of breast cyst fluid. Breast Cancer Res Treat 38:259-264
230. **Yu H, Diamandis EP** 1995 Prostate specific antigen immunoreactivity in amniotic fluid. Clin Chem 41:204-210
231. **Diamandis EP, Yu H, Melegos DN** 1996 Ultrasensitive prostate specific antigen assays and their clinical application. Clin Chem 42:853-857
232. **Giai M, Yu H, Roagna R, Ponzone R, Katsaros D, Levesque MA, Diamandis EP** 1995 Prostate specific antigen in serum of women with breast cancer. Br J Cancer 72:728-731
233. **Melegos DN, Yu H, Allen LC, Diamandis EP** 1996 Prostate specific antigen in amniotic fluid of normal and abnormal pregnancies. Clin Biochem 29:555-562
234. **Melegos D, Diamandis EP** 1996 Diagnostic value of molecular forms of prostate specific antigen for female breast cancer. Clin Biochem 29:193-200
235. **Diamandis EP** 1996 BRCA1 protein products: antibody specificity, functional motifs and secreted tumour suppressors. Nat Genet 13:268
236. **Lianidou ES, Melegos DN, Diamandis EP** 1997 The BRCA1 tumor suppressor gene product shares immunoreactive epitopes with a protein present in seminal plasma. Clin Biochem 30:425-532
237. **Yu H, Diamandis EP, Levesque M, Asa S, Monne M, Croce CM** 1995 Expression of the prostate-specific antigen gene by a primary ovarian carcinoma. Cancer Res 55:1603-1606
238. **Melegos D, Yu H, Ashok M, Wang C, Stanczyk F, Diamandis EP** 1997 Prostate specific antigen in female serum: a potential new marker of androgen excess. J Clin Endocrinol Metab 82:777-780
239. **Zarghami N, Grass L, Sauter ER, Diamandis EP** 1997 Prostate specific antigen levels in serum during the menstrual cycle. Clin Chem 43:1862-1867
240. **Tsuyuki D, Grass L, Diamandis EP** 1997 Frequent detection of mutations in the 5′ flanking region of the prostate specific antigen gene in female breast cancer. Eur J Cancer 33:1851-1853
241. **Salahifar H, Baxter RC, Martin JL** 1997 Insulin-like growth factor binding protein (IGFBP)-3 protease activity secreted by MCF-7 breast cancer cells: inhibition by IGFs does not require IGF-IGFBP interaction. Endocrinology 138:1683-1690
242. **Diamandis EP, Yu H** 1995 New biological functions of prostate specific antigen? J Clin Endocrinol Metab 80:1515-1517
243. **Diamandis EP, Yu H** 1997 Non-prostatic sources of prostate-specific antigen. In: Oesterling JE (ed) The Urologic Clinics of North America: Prostate-Specific Antigen: The Best Prostatic Tumor Marker. W.B. Saunders Co, Philadelphia, vol 24:275-282
244. **McConathy WJ, Alaupovic P** 1973 Isolation and partial characterization of apolipoprotein D: a new protein moiety of the human plasma lipoprotein system. FEBS Lett 37:178-182
245. **Drayna D, Fielding C, McLean J, Baer B, Castro G, Chen E, Comstock L, Henzel W, Korh W, Rhee L, Wion K, Lawn R** 1986 Cloning and expression of human apolipropotein D cDNA. J Biol Chem 261:16535-16539
246. **Francone OL, Gurakar A, Fielding C** 1989 Distribution and functions of lecithin:cholesterol acyltransferase and cholesteryl ester transfer protein in plasma lipoproteins. J Biol Chem 264:7066-7072
247. **Spreyer P, Schaal H, Kuhn G, Rothe T, Unterbeck A, Olek K, Muller HW** 1990 Regeneration-associated high levels expression of

apolipoprotein D mRNA in endoneural fibroblasts of peripheral nerve. EMBO J 9:2479-2484
248. **Milne RW, Rassart E, Marcel YL** 1993 Molecular biology of apolipoprotein D. Curr Opin Lipidol 4:100-106
249. **Peitsch MC, Boguski MS** 1990 Is apolipoprotein D a mammalian bilin-binding protein? New Biol 2:197-206
250. **Balbín M, Freije JMP, Fueyo A, Sánchez LM, López-Otín C** 1990 Apolipoprotein D is the major protein component in cyst fluid from women with human breast gross cystic disease. Biochem J 271: 803-807
251. **Morais Cabral JH, Atkins GL, Sánchez LM, López-Boado YS, López-Otín C, Sawyer L** 1996 Arachidonic acid binds to apolipoprotein D: implications for the protein's function. FEBS Lett 366:53-56
252. **Zeng C, Spielman AI, Vowels BR, Leyden JL, Bielmann K, Preti G** 1996 A human axillary odorant is carried by apolipoprotein D. Proc Natl Acad Sci USA 93:6626-6630
253. **Haagensen CD** 1971 The relationship of cystic disease to carcinoma of the breast. In: Haagensen CD (ed) Diseases of the Breast. W.B Saunders, Philadelphia, pp 168-172
254. **Bruzzi P, Dogliotti L, Naldoni C, Bucchi L, Costantini M, Cicognani A,, Torta M, Buzzi GF, Angeli A** 1997 Cohort study of association of risk of breast cancer with cyst type in women with gross cystic disease of the breast. Br Med J 314:925-928
255. **Mazoujian G, Haagensen DE** 1990 The immunopathology of gross cystic disease fluid proteins. Ann NY Acad Sci 586:188-197
256. **Sánchez LM, Vizoso F, Díez-Itza I, López-Otín C** 1992 Identification of the major protein components in breast secretions from women with benign and malignant breast diseases. Cancer Res 52:95-100
257. **Díez-Itza I, Vizoso F, Merino A, Sánchez LM, Tolivia J, Fernández J, Ruibal A, López-Otín C** 1994 Expression and prognostic significance of apolipoprotein D in breast cancer. Am J Pathol 144:310-320
258. **Simard J, Dauvois S, Haagensen DE, Lévesque C, Mérand Y, Labrie F** 1990 Regulation of progesterone-binding breast cyst protein GCDFP-24 secretion by estrogens and androgens in human breast cancer cells: a new marker of steroid action in breast cancer. Endocrinology 126:3223-3231
259. **Haagensen DE, Stewart P, Dilley WG, Wells SA** 1992 Secretion of breast gross cystic disease fluid proteins by T47D breast cancer cells in culture. Breast Cancer Res Treat 23:77-86
260. **Simard J, Veilleux R, de Launoit Y, Haagensen DE, Labrie F** 1991 Stimulation of apolipoprotein D secretion by steroids coincides with inhibition of cell proliferation in human LNCaP prostate cancer cells. Cancer Res 51:4336-4341
261. **Sugimoto K, Simard J, Haagensen DE, Labrie F** 1994 Inverse relationships between cell proliferation and basal or androgen-stimulated apolipoprotein D secretion in LNCaP human prostate cancer cells. J Steroid Biochem Mol Biol 51:167-174
262. **Aspinall JO, Bentel JM, Horsfall DJ, Haagensen DE, Marshall VR, Tilley WD** 1995 Differential expression of apolipoprotein D and prostate specific antigen in benign and malignant prostate tissues. J Urol 154:622-628
263. **López-Boado YS, Tolivia J, López-Otín C** 1994 Apolipoprotein D gene induction by retinoic acid is concomitant with growth arrest and cell differentiation in human breast cancer cells. J Biol Chem 269:26871-26878
264. **López-Boado YS, Puente XS, Alvarez S, Tolivia J, Binderup L, López-Otín C** 1997 Growth inhibition of human breast cancer cells by 1,25-dihydroxyvitamin D_3 is accompanied by induction of apolipoprotein D expression. Cancer Res 57:4091-4097
265. **Bürgi W, Schmid K** 1961 Preparation and properties of Zn-α_2-glycoprotein of normal human plasma. J Biol Chem 236:1066-1074
266. **Araki T, Gejyo F, Takagaki K, Haupt H, Schwick HG, Bürgi W, Marti T, Schaller J, Rickli E, Brossmer R, Atkinson PH, Putnam FW, Schmid K** 1988 Complete amino acid sequence of human plasma Zn-α_2-glycoprotein and its homology to histocompatibility antigens. Proc Natl Acad Sci USA 85:679-683
267. **Freije JP, Fueyo A, Uría J, López-Otín C** 1991 Human Zn-α_2-glycoprotein cDNA cloning and expression analysis in benign and malignant breast tissues. FEBS Lett 290:247-249
268. **Ueyama H, Niwa M, Tada T, Sasaki M, Ohkubo I** 1991 Cloning and nucleotide sequence of a human Zn-α_2-glycoprotein cDNA and chromosomal assignment of its gene. Biochem Biophys Res Commun 177:696-703
269. **Freije JP, Fueyo A, Uría JA, Velasco G, Sánchez LM, López-Boado YS, López-Otín C** 1993 Human Zn-α_2-glycoprotein: complete genomic structure, identification of a related pseudogene and relationship to class I major histocompatibility complex genes. Genomics 18:575-587
270. **Poortmans JR, Schmid K** 1968 The level of Zn-α_2-glycoprotein in normal body fluids and kidney extract. J Lab Clin Med 71:807-811
271. **Sánchez LM, López-Otín C, Bjorkman PJ** 1997 Biochemical characterization and crystalization of human Zn-α_2-glycoprotein, a soluble class I major histocompatibility complex homolog. Proc Natl Acad Sci USA 94:4626-4630
272. **Bundred NJ, Miller WR, Walker RA** 1987 An immunohistochemical study of the tissue distribution of the breast cyst fluid protein Zn-α_2-glycoprotein. Histopathology 11:603-610
273. **Díez-Itza I, Sánchez LM, Allende MT, Vizoso F, Ruibal A, López-Otín C** 1993 Zn-α_2-glycoprotein levels in breast cancer cytosols and correlation with clinical, histological and biochemical parameters. Eur J Cancer 29:1256-1260
274. **Hurlimann J, van Melle G** 1991 Prognostic value of serum proteins synthesized by breast carcinoma cells. Am J Clin Pathol 95:835-843
275. **Weber-Chappuis K, Bieri-Burger S, Hurlimann J** 1996 Comparison of prognostic markers detected by immunohistochemistry in male and female breast carcinomas. Eur J Cancer 32:1686-1692
276. **Chalbos D, Haagensen D, Parish T, Rochefort H** 1987 Identification and androgen regulation of two proteins released by T-47D breast cancer cells. Cancer Res 47:2787-2792
277. **López-Boado YS, Díez-Itza I, Tolivia J, López-Otín C** 1994 Glucocorticoids and androgens up-regulate the Zn-α_2-glycoprotein messenger RNA in human breast cancer cells. Breast Cancer Res Treat 29:247-258
278. **Frenette G, Dubé JY, Lazure C, Paradis G, Chrétien M, Tremblay RR** 1987 The major 40-kDa glycoprotein in human prostatic fluid is identical to Zn-α_2-glycoprotein. Prostate 11:257-270
279. **Foti AG, Herschman H, Cooper JF** 1977 Isoenzymes of acid phosphatase in normal and cancerous human prostatic tissue. Cancer Res 37:412-424
280. **Gagnon S, Têtu B, Dubé JY, Tremblay RR** 1990 Expression of Zn-α_2-glycoprotein and PSP-94 in prostatic adenocarcinoma. Am J Pathol 136:1147-1152
281. **Murphy LC, Tsuyuki D, Myal Y, Shiu RPC** 1987 Isolation and sequencing of a cDNA clone for a prolactin-inducible protein (PIP): regulation of PIP gene expression in the human breast cancer cell line T-47D. J Biol Chem 262:15236-15241
282. **Myal Y, Robinson DB, Iwasiow B, Tsuyuki D, Wong P, Shiu RPC** 1991 The prolactin-inducible protein (PIP/GCDFP-15) gene: cloning, structure and regulation. Mol Cell Endocrinol 80:165-175
283. **Autiero M, Cammarota G, Friedlein A, Zulauf M, Chiappetta G, Dragone V, Guardiola J** 1995 A 17-kDa CD4-binding glycoprotein present in human seminal plasma and in breast tumor cells. Eur J Immunol 25:1461-1464
284. **Autiero M, Gaubin M, Mani J-C, Castejon C, Martin M, El Marhomy S, Guardiola J, Platier-Tonneau D** 1997 Surface plasmon resonance analysis of gp17, a natural CD4 ligand from human seminal plasma inhibiting human immunodeficiency virus type-1 gp120-medited syncytium formation. Eur J Biochem 245:208-213
285. **Cassoni P, Sapino A, Haagensen DE, Naldoni C, Bussolati G** 1995 Mitogenic effect of the 15-kDa gross cystic disease fluid protein (GCDFP-15) on breast cancer cell lines and on immortal mammary cells. Int J Cancer 60:216-220
286. **Schenkels LCPM, Walgreen-Weterings E, Oomen LCJM, Bolscher JGM, Veerman ECI, Amerongen AVN** 1997 In vivo binding of the salivary glycoprotein EP-GP (identical to GCDFP-15) to oral and non-oral bacteria detection and identification of EP-GP binding species. Biol Chem Hoppe-Seyler 378:83-88
287. **Mazoujian G, Pinkus GS, Davis S, Haagensen DE** 1983 Immunohistochemistry of a gross cystic disease fluid protein (GCDFP-15) of the breast. Am J Pathol 110:105-112
288. **Pagani A, Sapino A, Eusebi V, Bergnolo P, Bussolati G** 1994 PIP/GCDFP-15 gene expression and apocrine differentiation in carcinomas of the breast. Virchows Arch 425:459-465

289. **Hähnel R, Hähnel E** 1996 Expression of the PIP/GCDFP-15 gene and survival in breast cancer. Virchows Arch 429:365-369
290. **Simard J, Hatton AC, Labrie C, Dauvois S, Zhao HF, Haagensen DE, Labrie F** 1989 Inhibitory effect of estrogens on GCDFP-15 mRNA levels and secretion in ZR-75-1 human breast cancer cells. Mol Endocrinol 3:694-702
291. **Dilley WG, Haagensen DE, Leight GS, Ammirata S, Davis SR, Silva JS, Zamcheck N, Lokich JL, Wells SA** 1986 Fluoxymesterone stimulation of tumor marker secretion in patients with breast carcinoma. Breast Cancer Res Treat 8:205-215
292. **Miller WR, Shivas AA, Franchimont P, Haagensen DE** 1988 Breast gross cystic disease protein 15 in human breast cancer in culture. Eur J Cancer Clin Oncol 24:223-228
293. **Schaller J, Akiyama K, Kimura H, Hess D, Affolter M, Rickli EE** 1991 Primary structure of a new actin-binding protein from human seminal plasma. Eur J Biochem 196:743-750
294. **Osawa M, Seto Y, Yukawa N, Saito T, Takeichi S** 1996 A 20-kDa protein in human seminal plasma that is identical to gross cystic disease fluid protein 15 and prolactin-inducible protein. Arch Androl 36:29-39
295. **Wick MR, Lillemoe TJ, Copland GT, Swanson PE, Manivel JC, Kiang DT** 1989 Gross cystic disease fluid protein-15 as a marker for breast cancer: immunohistochemical analysis of 690 human neoplasms and comparison with alpha-lactalbumin. Hum Pathol 20: 281-287
296. **Foltmann B** 1981 Gastric proteinases: structure, function, evolution and mechanism of action. Essays Biochem 17:52-84
297. **Moore SA, Sielecki AR, Chernaia MM, Tarasova NI, James MNG** 1995 Crystal and molecular structures of human progastricsin at 1.62 A resolution. J Mol Biol 247:466-485
298. **Samloff IM** 1989 Peptic ulcer: the many proteinases of aggression. Gastroenterology 96:586-595
299. **Hayano T, Sogawa K, Ichihara Y, Fujii-Kuriyama Y, Takahashi K** 1988 Primary structure of human pepsinogen C. J Biol Chem 263: 1382-1385
300. **Taggart RT, Cass LG, Mohandas TK, Derby P, Barr PJ, Pals G, Bell GI** 1989 Human pepsinogen C (progastricsin): isolation of cDNA clones, localization to chromosome 6, and sequence homology with pepsinogen A. J Biol Chem 264:375-379
301. **Sánchez LM, Freije JP, Merino AM, Vizoso F, Foltmann B, López-Otín C** 1992 Isolation and characterization of a pepsin C zymogen produced by human breast tissues. J Biol Chem 267:24725-24731
302. **Díez-Itza I, Merino AM, Tolivia J, Sánchez LM, López-Otín C** 1993 Expression of pepsinogen C in human breast tumours and correlation with clinicopathologic parameters. Br J Cancer 68:637-640
303. **Duffy MJ** 1996 Proteases as prognostic markers in cancer. Clin Cancer Res 2:613-618
304. **Vizoso F, Sánchez LM, Díez-Itza I, Merino AM, López-Otín C** 1995 Pepsinogen C is a new prognostic marker in primary breast cancer. J Clin Oncol 13:54-61
305. **Balbín M, López-Otín C** 1996 Hormonal regulation of the human pepsinogen C gene in breast cancer cells: identification of a *cis*-acting element mediating its induction by androgens, glucocorticoids and progesterone. J Biol Chem 271:15175-15181
306. **Beato M** 1989 Gene regulation by steroid hormones. Cell 56:335-344
307. **Tsai MJ, O'Malley BW** 1994 Molecular mechanisms of action of steroid/thyroid receptor superfamily members. Annu Rev Biochem 63:451-486
308. **Reid WA, Vongsorak L, Svasti J, Valler MJ, Kay J** 1984 Identification of the acid proteinase in human seminal fluid as a gastricsin originating in the prostate. Cell Tissue Res 236:597
309. **Reid WA, Liddle CN, Svasti J, Kay J** 1985 Gastricsin in the benign and malignant prostate. J Clin Pathol 38:639-643
310. **Szecsi PB, Halgreen H, Wong RNS, Kjaer T, Tang J** 1995 The cellular origin, cDNA and N-terminal sequences of human seminal progastricsin. Biol Reprod 53:227-233
311. **Young CYF, Andrews PE, Montgomery BT, Tindall DJ** 1992 Tissue-specific and hormonal regulation of human prostate-specific glandular kallikrein. Biochemistry 31:818-824
312. **Murtha P, Tindall DJ, Young CYF** 1993 Androgen induction of a human prostate-specific kallikrein, hKLK2: characterization of an androgen response element in the 5′ promoter region of the gene. Biochemistry 32:6459-6464
313. **Uria JA, Velasco G, Santamaria I, Ferrando A, Lopez-Otin C** 1997 Prostate-specific membrane antigen in breast carcinoma. Lancet 349:1601
314. **Kumar A, Mikolajczyk SD, Goel AS, Millar LS, Saedi MS** 1997 Expression of pro form of prostate-specific antigen by mammalian cells and its conversion to mature, active form by human kallikrein 2. Cancer Res 57:3111-3114
315. **Hsieh M-L, Charlesworth MC, Goodmanson M, Zhang S, Seah T, Klee GG, Tindall DJ, Young CFY** 1997 Expression of human prostate-specific glandular kallikrein protein (hK2) in the breast cancer cell line T47-D. Cancer Res 57:2651-2656
316. **Liu X-L, Waxer DE, Watanabe K, Band V** 1996 Identification of a novel serine protease-like gene, the expression of which is down-regulated during breast cancer progression. Cancer Res 56:3371-3379
317. **Anisowicz A, Sotiropoulou G, Stenman G, Mok SC, Sager R** 1996 A novel protease homolog differentially expressed in breast and ovarian cancer. Mol Med 2:624-636
318. **Dickson RB, Lippman ME** 1995 Growth factors in breast cancer. Endocr Rev 16:559-589
319. **Ware JL** 1993 Growth factors and their receptors as determinants in the proliferation and metastasis of human prostate cancer. Cancer Metastasis Rev 12:287-301
320. **Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M** 1998 Plasma insulin-like growth factor–I and prostate cancer risk: a prospective study. Science 279: 563-566
321. **Pollak M, Hankinson S, Deroo B, Michaud D, Willett W, Speizer F** 1997 Relationship of circulating insulin-like growth factor–I level to breast cancer risk. Proceedings of the Fourth International Symposium on Insulin-Like Growth Factors, Tokyo, Japan (Abstract C-29)
322. **Barinaga M** 1998 Study suggests new way to gauge prostate cancer risk. Science 279:475
323. **Tanaka A, Miyamoto K, Minamino N, Takeda M, Sato B, Matsuo H, Matsumoto K** 1992 Cloning and characterization of an androgen-induced growth factor essential for the androgen-dependent growth of mouse mammary carcinoma cells. Proc Natl Acad Sci USA 89:8928-8932
324. **Tanaka A, Miyamoto K, Matsuo H, Matsumoto K, Yoshida H** 1995 Human androgen-induced growth factor in prostate and breast cancer cells: its molecular cloning and growth properties. FEBS Lett 363:2276-230
325. **Ohuchi H, Yoshioka H, Tanaka A, Kawakami Y, Nohno T, Noji S** 1994 Involvement of androgen-induced growth factor (FGF-8) in mouse embryogenesis and morphogenesis. Biochem Biophys Res Commun 204:882-888
326. **Heikinheimo M, Lawshé A, Shackledford GM, Wilson DB, MacArthur CA** 1994 Fgf-8 expression in the post-gastrulation mouse suggests roles in the development of the face, limbs and central nervous system. Mech Dev 48:129-138
327. **Mahmood R, Bresnick J, Hornbruch A, Mahony C, Morton N, Colquhoun K, Martin P, Lumsden A, Dickson C, Mason Y** 1995 A role for FGF-8 in the initiation and maintenance of vertebrate limb bud outgrowth. Curr Biol 5:797-806
328. **Crossley PH, Minowada G, MacArthur CA, Martin GR** 1996 Roles for FGF8 in the induction, initiation, and maintenance of chick limb development. Cell 84:127-136
329. **Crossley PH, Martínez S, Martin GR** 1996 Midbrain development induced by FGF8 in the chick embryo. Nature 380:66-68
330. **Kouhara H, Koga M, Kasayama S, Tanaka A, Kishimoto T, Sato B** 1994 Transforming activity of a newly cloned androgen-induced growth factor. Oncogene 9:455-462
331. **Koga M, Kasayama S, Matsumoto K, Sato B** 1995 Molecular mechanism of androgen-dependent growth in transformed cells: pathway from basic science to clinical application. J Steroid Biochem Mol Biol 54:1-6
332. **Payson RA, Wu J, Liu Y, Chiu IM** 1996 The human FGF-8 gene localizes on chromosome 10q24 and is subjected to induction by androgen in breast cancer cells. Oncogene 13:47-53
333. **Schmitt JF, Hearn MTW, Risbridger GP** 1996 Expression of fi-

broblast growth factor-8 in adult rat tissues and human prostate carcinoma cells. J Steroid Biochem Mol Biol 57:173-178
334. **Leung HY, Dickson C, Robson CN, Neal DE** 1996 Over-expression of fibroblast growth factor-8 in human prostate cancer. Oncogene 12:1833-1835
335. **Finch PW, Rubin JS, Miki T, Ron D, Aaronson SA** 1989 Human KGF is FGF-related with properties of a paracrine effector of epithelial cell growth. Science 245:752-755
336. **Miki T, Bottaro DP, Fleming TP, Smith CL, Burgess WH, Chan AML, Aaronson SA** 1992 Determination of ligand-binding specificity by alternative splicing: two distinct growth factors receptors encoded by a single gene. Proc Natl Acad Sci USA 89:246-250
337. **Cunha GR** 1994 Role of mesenchymal-epithelial interactions in normal and abnormal development of the mammary gland and prostate. Cancer 74:1030-1044
338. **Yan G, Fukabori Y, Nikolaropoulos S, Wang F, Mckeehan WL** 1992 Heparin-binding keratinocyte growth factor is a candidate stromal to epithelial cell andromedin. Mol Endocrinol 6:2123-2128
339. **Alarid ET, Rubin JS, Young P, Chedid M, Ron D, Aaronson SA, Cunha GR** 1994 Keratinocyte growth factor functions in epithelial induction during seminal vesicle development. Proc Natl Acad Sci USA 91:1074-1078
340. **Sugimura Y, Cunha GR, Hayward S, Hayashi N, Arima K, Kawamura J, Rubin J, Aaronson S** 1993 Keratinocyte growth factor (KGF) is a mediator of testosterone-induced prostatic development. Mol Cell Diff 1:423-426
341. **Fasciana C, van der Made AC, Faber PW, Trapman J** 1996 Androgen regulation of the rat keratinocyte growth factor (KGF/FGF7) promoter. Biochem Biophys Res Commun 220:858-863
342. **Finch PW, Lengel C, Chedid M** 1995 Cloning and characterization of the promoter region of the human keratinocyte growth factor gene. J Biol Chem 270:11230-11237
343. **Thomson AA, Foster BA, Cunha GR** 1997 Analysis of growth factor and receptor mRNA levels during development of the rat seminal vesicle and prostate. Development 124:2431-2439
344. **Yan G, Fukabori Y, McBride G, Nikolaropolous S, McKeehan WL** 1993 Exon switching and activation of stromal and embryonic fibroblast growth factor (FGF)-FGF receptor genes in prostate epithelial cells accompany stromal independence and malignancy. Mol Cell Biol 13:4513-4522
345. **Miki T, Fleming TP, Bottaro DP, Rubin JS, Ron D, Aaronson SA** 1991 Expression cDNA cloning of the KGF receptor by creation of a transforming autocrine loop. Science 251:72-75
346. **Culig Z, Hobisch A, Cronauer MV, Radmayr C, Trapman J, Hittmair A, Bartsch G, Klocker H** 1994 Androgen receptor activation in prostatic tumor cell lines by insulin-like growth factor-I, keratinocyte growth factor, and epidermal growth factor. Cancer Res 54:5474-5478
347. **Leung HY, Mehta P, Gray LB, Collins AT, Robson CN, Neal DE** 1997 Keratinocyte growth factor expression in hormone insensitive prostate cancer. Oncogene 15:1115-1120
348. **Wilson SE, Weng J, Chwang EL, Gollhon L, Leitch AM, Shay JW** 1994 Hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), and their receptors in human breast cells and tissues: alternative receptors. Cell Mol Biol Res 40:337-350
349. **Coleman-Kmacik S, Rosen JM** 1994 Differential temporal and spatial gene expression of fibroblast growth factor family members during mouse mammary gland development. Mol Endocrinol 8:218-229
350. **Imagawa W, Cunha GR, Young P, Nandi S** 1994 Keratinocyte growth factor and acidic fibroblast growth factor are mitogens for primary cultures of mammary epithelium. Biochem Biophys Res Commun 204:1165-1169
351. **Ulich TR, Yi ES, Cardiff R, Yin S, Bikhazi N, Biltz R, Morris CF, Pierce GF** 1994 Keratinocyte growth factor is a growth factor for mammary epithelium *in vivo*. Am J Pathol 144:862-868
352. **Yi ES, Bedoya AA, Lee H, Kim S, Housley RM, Aukerman SL, Tarpley JE, Starnes C, Yin S, Pierce GF, Ulich TR** 1994 Keratinocyte growth factor causes cystic dilation of the mammary glands of mice. Am J Pathol 145:1015-1022
353. **Kitsberg DI, Leder P** 1996 Keratinocyte growth factor induces mammary and prostatic hyperplasia and mammary adenocarcinoma in transgenic mice. Oncogene 13:2507-2515
354. **Koos RD, Banks PK, Inkster SE, Yue W, Brodie AMH** 1993 Detection of aromatase and keratinocyte growth factor expression in breast tumors using reverse transcription-polymerase chain reaction. J Steroid Biochem Mol Biol 45:217-225
355. **Adnane J, Gaudray P, Dionne CA, Crumley G, Jaye M, Schlessinger J, Jeanteur P, Birnbaum D, Theillet G** 1991 Bek and Flg, two receptors to members of the FGF family are amplified in subsets of human breast cancers. Oncogene 6:659-663
356. **Bansal GS, Cox HC, Marsh S, Gomm JJ, Yiangou C, Luqmani Y, Coombes RC, Johnston CL** 1997 Expression of keratinocyte growth factor and its receptor in human breast cancer. Br J Cancer 75: 1567-1574
357. **Grönberg H, Xu J, Smith JR, Carpten JD, Isaacs SD, Freije D, Bova GS, Walsh PC, Collins FS, Trent JM, Meyers DA, Isaacs WB** 1997 Early age at diagnosis in families providing evidence of linkage to the hereditary prostate cancer locus (HPC1) on chromosome 1. Cancer Res 57:4707-4709
358. **McIndoe RA, Stanford JL, Gibbs M, Jarvik GP, Brandzel S, Neal CL, Li S, Gammack JT, Gay AA, Goode EL, Hood L, Ostrander EA** 1997 Linkage analysis of 49 high-risk families does not support a common familial prostate cancer-susceptibility gene at 1q24–25. Am J Hum Genet 61:347-353
359. **Horwitz KB, Tung L, Takimoto GS** 1996 Novel mechanisms of antiprogestin action. Acta Oncol 35:129-140
360. **Key TJA** 1995 Hormones and cancer in humans. Mutat Res 333: 59-67
361. **Collaborative Group on Hormonal Factors in Breast Cancer** 1996 Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 347:1713-1727
362. **Ewertz M** 1996 Hormone therapy in the menopause and breast cancer risk - a review. Maturitas 23:241-246
363. **Speroff L** 1996 Postmenopausal hormone therapy and breast cancer. Obstet Gynecol 87[Suppl]:44S–54S
364. **Prichard KI, Roy J-A, Sawka CA** 1996 Sex hormones and breast cancer: The issue of hormone replacement. Recent Results Cancer Res 140:285-293
365. **Weiss NS** 1996 Health consequences of short- and long-term postmenopausal hormone therapy. Clin Chem 42:1342-1344
366. **Adami H-O, Persson I, Ekbom A, Wolk A, Ponten J, Trichopoulos D** 1995 The aetiology and pathogenesis of human breast cancer. Mutat Res 333:29-35
367. **Haenszel W, Kurihara M** 1968 Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst 40:43-68
368. **Merzenich H, Boeing H, Wahrendorf J** 1993 Dietary fat and sports activity as determinants for age at menarche. Am J Epidemiol 138:217-224
369. **Tretli S** 1989 Height and weight in relation to breast cancer morbidity and mortality: a prospective study of 570,000 women in Norway. Int J Cancer 44:23-30
370. **MacMahon B** 1994 A biologic framework for the risk factors for breast cancer. Adv Oncol 10:3-9
371. **Nandi S, Guzman RC, Yang J** 1995 Hormones and mammary carcinogenesis in mice, rats and humans: A unifying hypothesis. Proc Natl Acad Sci USA 92:3650-3657
372. **Woods MN, Barnett JB, Spiegelman D, Trail N, Hertzmark E, Longcope C, Gorbach SL** 1996 Hormone levels during dietary changes in premenopausal African-American women. J Natl Cancer Inst 88:1369-1374
373. **Shimizu H, Ross RK, Bernstein L, Pike MC, Henderson BE** 1990 Serum oestrogen levels in postmenopausal women: comparison of American whites and Japanese in Japan. Br J Cancer 62:451-453
374. **Key TJA, Chen J, Wang DY, Pike MC, Boreham J** 1990 Sex hormones in women in rural China and in Britain. Br J Cancer 62: 631-636
375. **Wang DY, Key TJA, Pike MC, Boreham J, Chen J** 1991 Serum hormone levels in British and rural Chinese females. Breast Cancer Res Treat 18:s41–s50
376. **Fishman J, Osborne MP, Telang NT** 1995 The role of estrogen in mammary carcinogenesis. Ann NY Acad Sci 768:91-100
377. **Fishman J, Bradlow HL, Fukushima DK, O'Connor J, Rosenfeld**

RS, Graepel GJ, Elston R, Lynch H 1983 Abnormal estrogen conjugation in women at risk for familial breast cancer at the periovulatory stage of the menstrual cycle. Cancer Res 43:1884-1890
378. **Michnovicz JJ, Adlercreutz H, Bradlow HL** 1997 Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans. J Natl Cancer Inst 89:718-723
379. **Trichopoulos D** 1990 Hypothesis: does breast cancer originate *in utero*? Lancet 335:939-940
380. **Ekbom A, Trichopoulos D, Adami H-A, Hsieh C-C, Lan S-J** 1992 Evidence of prenatal influences on breast cancer risk. Lancet 340: 1015-1018
381. **Anbazhagan R, Gusterson BA** 1994 Prenatal factors may influence predisposition to breast cancer. Eur J Cancer 30A:1-3
382. **Colditz GA, Frazier AL** 1995 Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. Cancer Epidemiol Biomarkers Prev 4:567-571
383. **Hilakivi-Clarke L, Onojafe I, Raygada M, Cho E, Clarke R, Lippman ME** 1996 Breast cancer risk in rats fed a diet high in n-6 polyunsaturated fatty acids during pregnancy. J Natl Cancer Inst 88:1821-1827
384. **Hilakivi-Clarke L, Clarke R, Onojafe I, Raygada M, Cho E, Lippman ME** 1997 A maternal diet high in n-6 polyunsaturated fats alters mammary gland development, puberty onset and breast cancer risk among female rat offspring. Proc Natl Acad Sci USA 94:9372-9377
385. **vom Saal FS, Timms BG, Montano MM, Palanza P, Thayer KA, Nagel SC, Dhar MD, Ganjam VK, Parmigiani S, Welshons WV** 1997 Prostate enlargement in mice due to fetal exposure to low doses of estradiol or diethylstilbestrol and opposite effects at high doses. Proc Natl Acad Sci USA 94:2056-2061
386. **Ekbom A, Hsieh CC, Lipworth L, Wolk A, Ponten J, Adami HO, Trichopoulos D** 1996 Perinatal characteristics in relation to incidence of and mortality from prostate cancer. Br Med J 313:337-341
387. **Polednak AP** 1995 Pre-eclampsia, autoimmune diseases and breast cancer etiology. Med Hypotheses 44:414-418
388. **Tibblin G, Eriksson M, Cnattingius S, Ekbom A** 1995 High birthweight as a predictor of prostate cancer risk. Epidemiology 6:423-424
389. **Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, Colditz GA, Hankinson SE, Speizer FE, Willett WC** 1996 Birthweight as a risk factor for breast cancer. Lancet 348:1542-1546
390. **Anbazhagan R, Bartek J, Monaghan P, Gusterson BA** 1991 Growth and development of the human infant breast. Am J Anat 192:407-417
391. **Russo J, Tay LK, Russo IH** 1982 Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat 2:5-73
392. **Russo J, Romero AI, Russo IH** 1994 Architectural pattern of the normal and cancerous breast under the influence of parity. Cancer Epidemiol Biomarkers Prev 3:219-224
393. **Russo J, Russo IH** 1994 Toward a physiological approach to breast cancer prevention. Cancer Epidemiol Biomarkers Prev 3:353-364
394. **Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG** 1983 'Hormonal' risk factors, 'breast tissue age' and the age incidence of breast cancer. Nature 303:767-770
395. **Levine AC** 1995 Pathogenesis and medical management of benign prostatic hyperplasia. Trends Endocrinol Metab 6:128-132
396. **Swyer GIM** 1944 Postnatal growth changes in the human prostate. J Anat 78:130-145
397. **Berry SJ, Coffey DS, Walsh PC, Ewing LL** 1984 The development of benign prostatic hyperplasia with age. J Urol 132:474-479
398. **Zumoff B, Strain GW, Kream J, O'Connor J, Rosenfeld RS, Levin J, Fukushima DK** 1982 Age variation of the 24-hour mean plasma concentrations of androgens, estrogens, and gonadotropins in normal adult men. J Clin Endocrinol Metab 54:534-538
399. **Srinivasan G, Campbell E, Bashirelahi N** 1995 Androgen, estrogen, and progesterone receptors in normal and aging prostates. Microsc Res Tech 30:293-304
400. **Imperato-McGinley J, Gautier T, Zirinsky K, Hom T, Palomo O, Stein E, Vaughan DE, Markisz JA, Ramirez de Arellano E, Kazam E** 1992 Prostate visualization studies in males homozygous and heterozygous for 5α-reductase deficiency. N Engl J Med 327:1185-1191
401. **Wilding G** 1992 The importance of steroid hormones in prostate cancer. Cancer Surv 14:113-130
402. **Nakhla AM, Khan MS, Romas NP, Rosner W** 1994 Estradiol causes the rapid accumulation of cAMP in human prostate. Proc Natl Acad Sci USA 91:5402-5405
403. **Farnsworth WE** 1996 Roles of estrogen and SHBG in prostate physiology. Prostate 28:17-23
404. **Castagnetta LA, Miceli MD, Sorci CM, Pfeffer U, Farruggio R, Oliveri G, Calabro M, Carruba G** 1995 Growth of LNCaP human prostate cancer cells is stimulated by estradiol via its own receptor. Endocrinology 136:2309-2319
405. **Hess RA, Bunick D, Lee KH, Bahr J, Taylor JA, Korach KS, Lubahn DB** 1997 A role for oestrogens in the male reproductive system. Nature 390:509-512
406. **Diamandis EP, Yu H** 1996 Does prostate cancer start at puberty? J Clin Lab Anal 10:468-469
407. **Makridakis N, Ross RK, Pike MC, Chang L, Stanczyk FZ, Kolonl LN, Shi C-Y, Yu MC, Henderson BE, Reichardt JKV** 1997 A prevalent missense substitution that modulates activity of prostatic steroid 5α-reductase. Cancer Res 57:1020-1022
408. **Hakimi JM, Rondinelli RH, Schoenberg MP, Barrack ER** 1996 Androgen receptor gene structure and function in prostate cancer. World J Urol 14:329-337
409. **Yang NN, Venugopalan M, Hardikar S, Glasebrook A** 1996 Identification of an estrogen response element activated by metabolites of 17B-estradiol and raloxifen. Science 273:1222-1225
410. **An G, Christofferson S, Luo GZ, Hefty PS, Veltri RW** 1997 Preliminary characterization of a novel gene (UC28) overexpressed in prostate and breast cancer. Proc Am Assoc Cancer Res 38:420 (Abstract 2812)