Carcinogenesis vol.21 no.3 pp.427–433, 2000

Hormonal carcinogenesis

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Hormone-related cancers, namely breast, endometrium, ovary, prostate, testis, thyroid and osteosarcoma, share a unique mechanism of carcinogenesis. Endogenous and exogenous hormones drive cell proliferation, and thus the opportunity for the accumulation of random genetic errors. The emergence of a malignant phenotype depends on a series of somatic mutations that occur during cell division, but the specific genes involved in progression of hormone-related cancers are currently unknown. In this review, the epidemiology of endometrial cancer and breast cancer are used to illustrate the paradigms of hormonal carcinogenesis. Then, new strategies for early detection and prevention of hormonal carcinogenesis are discussed. This includes developing polygenic models of cancer predisposition and the further development of safe and effective chemopreventives that block target sequence activity. We developed polygenic models for breast and prostate cancer after hypothesizing that functionally relevant sequence variants in genes involved in steroid hormone metabolism and transport would act together, and also interact with well-known hormonally related risk factors, to define a high-risk profile for cancer. A combination of genes each with minor variation in expressed activity could provide a degree of separation of risk that would be clinically useful as they could yield a large cumulative difference after several decades. The genes included in the breast cancer model are the 17β-hydroxysteroid dehydrogenase 1 (*HSD17B1*) gene, the cytochrome P459c17α (*CYP17*) gene, the aromatase (*CYP19*) gene, and the estrogen receptor alpha (*ER*) gene. The prostate cancer model includes the androgen receptor gene (*AR*), steroid 5α-reductase type II (*SRD5A2*), *CYP17* and the 3β hydroxysteroid dehydrogenase (*HSD3B2*) gene. We present data from our multi-ethnic cohort to support these models.

In 1982, we summarized the available epidemiological and laboratory data that warranted the grouping of several cancers, namely breast, prostate, endometrium, testis, ovary, thyroid and osteosarcoma, under the general rubric of the hormone-related cancers (1). In contrast to the widely acknowledged paradigms involving chemicals and viruses as tumor initiators and promotors, the hormone-related cancers shared a quite different mechanism of carcinogenesis: hormones, both endogenous and exogenous, by driving cell proliferation, increased the number of cell divisions and the opportunity for random genetic errors.

The key distinction between this 'cell proliferation' model (Figure 1) compared with the chemical carcinogenesis model was that no specific initiator is required. Instead, DNA replication errors during cell division create random mutations. In the correct temporal or spatial cluster, these mutations give rise to a malignant phenotype. Equally important, the hormonal stimulus to cell division continues all along the progression pathway. Thus, interruption of this hormonal stimulus through anti-hormone therapy, such as tamoxifen, could be expected to slow the process of progression until actual hormone independence occurs late in the pathway. In more recent years, evidence in support of this cell proliferation model of hormone-related cancer etiology and progression has continued to accumulate (2). Anti-hormone therapies have been effective in stopping progression and thereby increasing the time to recurrence or death.

The emergence of a malignant phenotype depends on a series of somatic mutations that occur during cell division, but the specific genes involved in progression of hormone-related cancers are unknown at this time. Candidate genes include those in the endocrine pathway (3,4), as well as DNA repair genes, tumor suppressor genes and oncogenes (5–7). *BRCA1* and *BRCA2* are two such tumor suppressor genes that have been associated with susceptibility to breast, ovarian and possibly other cancers in certain kindreds (8,9). Germline mutations in *TP53* are also associated with an increased risk of breast cancer in certain families (10). However, mutations in these genes do not appear to be involved in the majority of sporadic breast cancer. The *HER2/neu* oncogene is overexpressed in advanced breast cancer and probably represents one critical event in the latter part of breast cancer progression (11).

In the following sections, the epidemiology of endometrial cancer and breast cancer is used to illustrate the accumulated data to support the paradigms of hormonal carcinogenesis. The remaining sections are devoted to important new directions for understanding, and ultimately preventing, this important group of cancers.

Role of hormones in endometrial cancer

The established risk factors for endometrial cancer (Table I) show that exposure to estrogens unopposed to progestins can predict risk of endometrial cancer (1,12). During the pre-menopausal period, risk of endometrial cancer can be attributed to mitotic activity during the first half of the menstrual cycle when estrogen is unopposed by progesterone (13). Use of sequential oral contraceptives (OCs) doubled the risk of endometrial cancer among women who used them prior to their removal from the market in 1976 (14). In contrast, combination oral contraceptives (COCs), which deliver

Abbreviations: AR, androgen receptor gene; COCs, combined oral contraceptives; *CYP17*, cytochrome P459c17a gene; E2, estradiol; *ER*, estrogen receptor alpha gene; HRT, hormone replacement therapy; *HSD17B1*, 17β-hydroxysteroid dehydrogenase 1 gene; *HSD3B2*, 3β-hydroxysteroid dehydrogenase gene; OCs, oral contraceptives; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin; *SRD5A2*, steroid 5α-reductase type II gene.

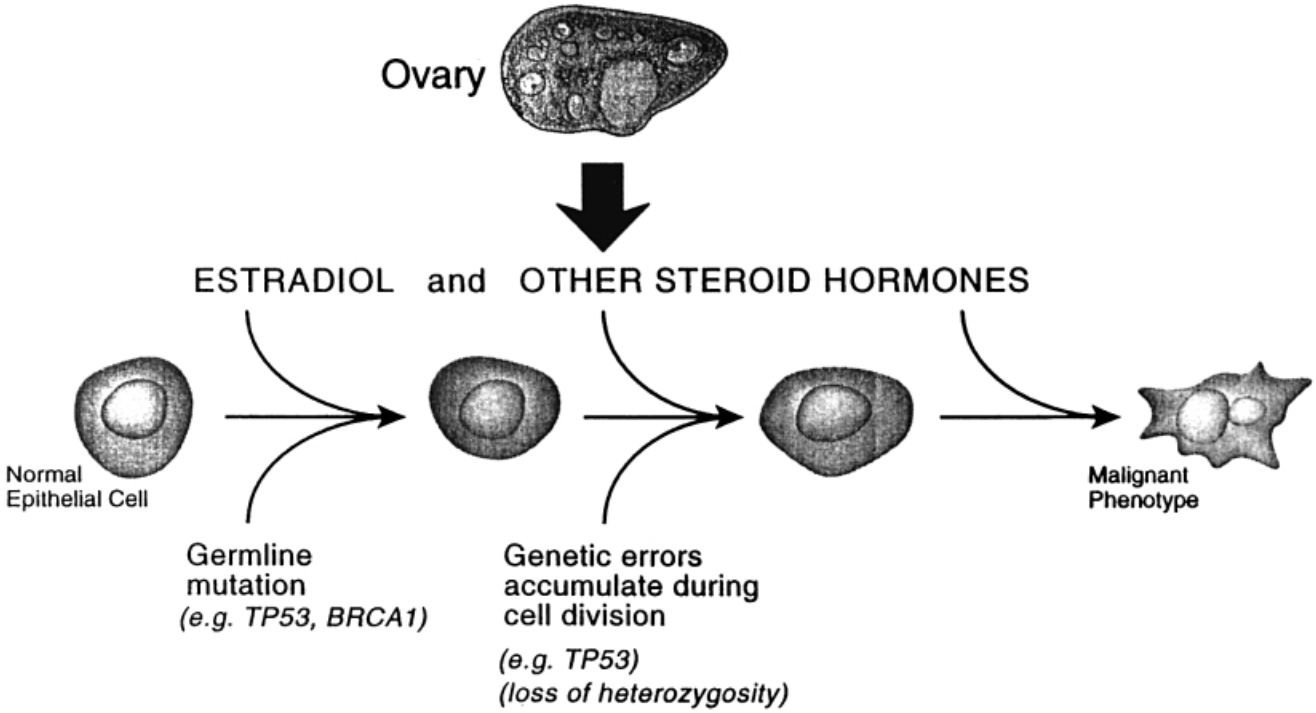

Fig. 1. Estradiol and, to a lesser degree, other steroid hormones, drive cell proliferation which facilitates fixation of genetic errors. Germline mutations in relevant tumor suppressor genes accelerate the transformation into the malignant phenotype.

Table I. Summary of established risk and protective factors for endometrial cancer

Risk factors (increased 'unopposed' estrogen exposure)
Late menopause
Sequential oral contraceptives
Obesity
Estrogen replacement therapy
Protective factors (decreased unopposed estrogen exposure)
Pregnancy
Combined oral contraceptives

Table II. Summary of established risk and protective factors for breast cancer

Risk factors (increased hormone exposure)
Early menarche
Late menopause
Alcohol consumption
Post-menopausal obesity
Hormone replacement therapy
Protective factors (decreased hormone exposure)
Young age at first full term pregnancy
Prolonged lactation
Exercise

estrogen and a high dose progesterone for 21 days of a 28 day cycle, decrease the risk of endometrial cancer (15–18).

Obesity is also an important risk factor for endometrial cancer. In post-menopausal women, it is postulated that the conversion of androstenedione to estrone in adipose tissue results in the increased risk. In premenopausal women, obesity is thought to operate through increased anovulatory cycles and associated progesterone insufficiency (19).

The protective effect of parity can also be explained by the unopposed estrogen hypothesis (13). The highest risk of endometrial cancer occurs in nulliparous women and risk decreases with each pregnancy. This is explained by the fact that no mitotic activity occurs during pregnancy due to the persistently high progesterone levels.

Role of hormones in breast cancer

A large and compelling body of epidemiological and experimental data implicates estrogens in the etiology of human breast cancer (2). Animal studies repeatedly demonstrated that estrogens can induce and promote mammary tumors in rodents and that removing the animals' ovaries or administering an anti-estrogenic drug had the opposite effect (20).

The most widely accepted risk factors for breast cancer, shown in Table II, can be thought of as measures of the cumulative 'dose' of estrogen that breast epithelium is exposed to over time. Early menarche and late menopause maximize the number of ovulatory cycles experienced over time. Prolonged lactation, and more importantly, physical activity can reduce the number of ovulatory cycles. Physical activity may delay the age of onset of regular ovulatory cycles, reduce the frequency of ovulatory cycles, and reduce circulating ovarian hormones levels (21–24). Physical activity has been shown to have a protective effect for breast cancer in some studies of lifetime activity (25,26), while other studies of specific periods of time reported no protective effect (27). Alcohol consumption has been associated with a linear increase in breast cancer incidence in women who drink up to 60 g of alcohol per day (2–5 drinks) (28). It is hypothesized that alcohol may increase breast cancer risk by increasing plasma estrogen as well as insulin-like growth factor levels (29). The primary source of estrogen in post-menopausal women is from the conversion of androstenedione to estrone in adipose tissue; thus, post-menopausal obesity increases the risk of breast cancer through increased production of estrogen. Obesity is also associated

with decreased SHBG production and increased proportions of free and albumin-bound estrogens. The protective effect of early age at first birth is complex. During the first trimester of pregnancy, the level of free estradiol rises rapidly. However, as the pregnancy continues, prolactin and free estradiol levels lower and SHBG levels rise, yielding a net overall benefit with respect to the endogenous estrogen profile. Perhaps more importantly, the effect of a first pregnancy may be to cause some pre-malignant cells to terminally differentiate, thereby losing their malignant potential.

The most carefully done international studies comparing estrogen levels in populations at differing risk of breast cancer support the role of estrogens, especially estradiol, in the pathogenesis of breast cancer. In the early 1970s, MacMahon *et al.* (30) conducted a series of studies on teenagers and young women in Asia and North America. They found that in overnight urine samples collected on the morning of day 21 of the menstrual cycle, total urinary estrogen was 36% higher in the North American teenagers. Similar differences were found among women aged 20–39 years. In two more recent studies, the relationship between serum estradiol and breast cancer risk have been characterized in Asian and North American populations (31,32). In one study, estradiol (E2) levels were 20% higher in Los Angeles compared with Shanghai pre-menopausal controls (31). In a comparison of post-menopausal women, E2 was 36% higher in Los Angeles than in age-matched Japanese women (32). Reasons for these differences remain poorly defined, but part of the explanation may be that there are genetic differences that affect steroid hormone biosynthesis.

The findings of 29 epidemiological studies of endogenous hormones and post-menopausal breast cancer have recently been summarized in a meta-analytic review (33). Taken together, the six prospective studies published to date show that post-menopausal women who subsequently develop breast cancer have a 15% higher mean serum estradiol concentration than unaffected women ($P = 0.0003$).

The role of hormones other than estrogens is less clear (34–39). The role of elevated progesterone levels in breast cancer etiology is controversial (40), but recent experimental data suggest that progestins are breast mitogens and, as such, are likely to increase breast cancer risk (41). One would hypothesize that lower SHBG would result in increased risk of breast cancer, because it would imply higher estrogen bioavailability. However, some studies have reported a positive association between SHBG and risk of breast cancer (37,39), while others have shown an inverse association (34,36,38). Similarly, testosterone has been shown to increase risk in some (36–39) but not all (34) studies, and only limited data on androstenedione exists (34). Further work is necessary to resolve the conflicting findings of the role of SHBG and breast cancer, and to confirm the association with testosterone and other androgens reported in some studies. There is a scientific basis for the association between risk of breast cancer and serum androgens, as androgens could provide a large pool of substrate for conversion to estrogen via the action of aromatase in breast tissue.

Exogenous hormones

In the past two to three decades, external sources of steroid hormones, which also influence cell proliferation and therefore risk of hormone-dependent cancers, have become widely used. Hormone replacement therapy and oral contraceptives are two forms of exogenous hormones that have been studied extensively. One or both of these agents play a role in the risk of breast, ovary, cervical, endometrial and colorectal cancers.

Oral contraceptives

COCs, which include an estrogen and high-dose progesterone, reduce the risk of ovarian and endometrial cancers. The relationship of OC use with breast cancer has been the topic of many review articles (42). A recent meta-analysis of 54 studies, that included over 150 000 women, provided important information about the risk of breast cancer among COC users (43). Results from the meta-analysis indicate that a modest increase in risk of breast cancer was associated with current (RR = 1.24; $P < 0.00001$) and recent (RR = 1.16; $P < 0.00001$) COC use. There is no evidence that this excess in risk continued to persist $\geqslant$10 years after cessation of COC use. However, the degree of the association was modified by age at first use of COCs. For recent users, risk was greatest for those who began to use COCs before the age of 20 years, and tended to decline with increasing age at diagnosis. However, total duration of COC use was not associated with increased risk of breast cancer once time of last use was taken into account. Although the scope of this meta-analysis was broad, there is still little information beyond 10 years after cessation of COC use. Moreover, most women who stopped use $\geqslant$10 years ago had used COCs for only short periods of time. In the next decade, women who began use as teenagers will reach their late 40s and early 50s. At that time, it will be important to re-examine the effects of long-term and early use of COCs.

Hormone replacement therapy (HRT)

Hormone replacement therapy increases the risk of breast cancer. A recent meta-analysis that included over 160 000 women showed that for current or recent use of HRT, the risk of breast cancer increases in relation to increasing duration of use (44). For women whose last use of HRT was $<$5 years before diagnosis, risk increased by 2.3% ($P = 0.0002$) for each year of use. However, women who stopped HRT use $\geqslant$5 years before diagnosis had no increased risk, regardless of duration of use.

Although this study was large and comprehensive, it may still fail to determine the true risk of breast cancer that can be attributed to HRT since many differences between HRT users and non-users exist. Users of HRT may have different opportunities for breast cancer diagnosis. For example, they may have more frequent mammographic and physician examinations. Women with a family history of breast cancer are more likely to be non-users, and HRT users are likely to be of higher social class and education. Laya *et al.* (45) have provided direct evidence that current HRT use reduces the sensitivity and specificity of mammographic screening, most likely by increasing radiographic density of the breast. Finally, genetic determinants, like those that determine endogenous hormone levels, may also play a role in determining HRT use.

New directions in hormonal carcinogenesis

The idea that endogenous levels of circulating hormones are the primary determinants of cancer risk is troubling, since endogenous hormones are not an easily modifiable risk factor, like diet or smoking. We simply cannot remove or lower endogenous hormones to reduce cancer risk. Thus, we are

forced to develop new strategies for early detection and prevention. These new strategies are just beginning to be explored. In the area of early detection, we must identify biomarkers of high risk, such as specific genotypes. In the area of prevention, new chemopreventives, such as tamoxifen, offer hope to high-risk individuals that cancer can be prevented.

Polygenic models and biomarkers

Although there is evidence that hormonal secretion and metabolism can be environmentally influenced, for example through diet and physical activity, the control of hormonal patterns is largely genetically regulated. Thus, we must begin to characterize the complex genetic arrays that contribute to carcinogenesis in hormone-responsive tissue and identify candidate loci in genes responsible for inter-individual differences in steroid hormone levels. These loci are likely to be relevant sequence variants involved in steroid hormone metabolism and transport. The term 'relevant sequence variants' refers to those mutations or polymorphisms that can be shown through laboratory experiments to alter the encoded protein structure, function, interaction with other proteins, or half-life and stability within the cell.

Breast cancer model

We have proposed a multigenic model of breast cancer predisposition that includes several genes involved in estrogen biosynthesis and intracellular binding and transport of E2 based on the assumption that individual variation in the levels of endogenous steroid hormones will result in differences in breast cancer risk (3). We have hypothesized that this individual variation results from polymorphisms in crucial genes which control hormone biosynthesis and transport. We are actively investigating four such genes: the 17β-hydroxysteroid dehydrogenase 1 (*HSD17B1*) gene, the cytochrome P459c17α (*CYP17*) gene, the aromatase (*CYP19*) gene and the estrogen receptor alpha (*ER*) gene. Recent findings suggesting a role of *CYP17* in the etiology of breast cancer are presented below.

The *CYP17* gene codes for the cytochrome p450c17α enzyme, which mediates both steroid 17α-hydroxylase and 17,20-lyase activities, and functions at key branch points in human steroidogenesis (46). The 5′-untranslated region (5′-UTR) of *CYP17* contains a single base pair polymorphism 34 bp upstream from the initiation of translation, and 27 bp downstream from the transcription start site (47). This base pair change creates a recognition site for the *Msp*AI restriction enzyme and has been used to designate two alleles, *A1* (the published sequence) and *A2*.

Carey *et al.* (47) used this polymorphism to analyze the segregation of *CYP17* in pedigrees with polycystic ovary disease and male pattern baldness (believed to be caused by a common underlying disorder of androgen biosynthesis or metabolism). They found an association (but not linkage) between the affected state and the A2 allele.

We were the first to show an association between risk of breast cancer and this *CYP17* polymorphism (48). In a case-control study of incident breast cancer among Asian, African-American and Latina women, we found a 2.5-fold increased risk of advanced breast cancer associated with the *CYP17 A2* allele. This suggested that serum hormone levels may differ by *CYP17* genotype. We pursued this finding in a separate study and found that *CYP17* genotype was associated with serum estradiol and progesterone levels among young nulliparous women (49). As shown in Figures 2 and 3, serum E2 measured around day 11 of the menstrual cycle was 11 and 57% higher ($P = 0.04$), respectively, among women hetero- and homozygous for the

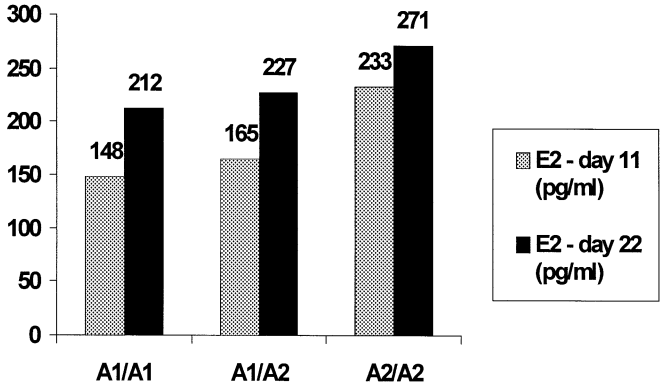

Fig. 2. Geometric mean serum E2 concentrations among young nulliparous women on days 11 and 22 of the menstrual cycle by *CYP17* genotype.

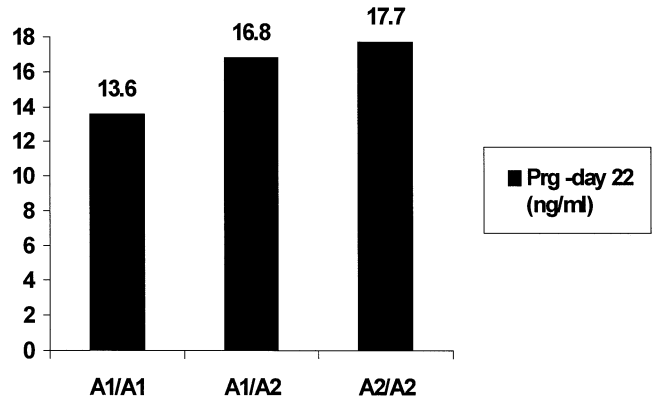

Fig. 3. Geometric mean serum progesterone (Prg) concentrations among young nulliparous women on day 22 of the menstrual cycle by *CYP17* genotype.

CYP17 A2 allele compared with *A1/A1* women. Similarly, around cycle day 22, E2 was 7 and 28% higher ($P = 0.06$) and progesterone was 24 and 30% higher ($P = 0.04$). These data provide direct evidence of genetic control of serum hormone levels; however, the sample size was small and the results needed confirmation and further exploration. A recent study conducted among a group of 297 post-menopausal women supports our findings. Haiman *et al.* (50) found that women with the *A2/A2* genotype had statistically significantly elevated levels of estrone (+14.2%; $P = 0.01$) and dehydroepiandrosterone (+14.4%; $P = 0.02$), and modest, non-significant elevations in estradiol (+18.8%; $P = 0.08$), testosterone (+8.6%; $P = 0.34$), androstenedione (+17.1%; $P = 0.06$) and dehydroepiandrosterone sulfate (+7.2%; $P = 0.26$) compared with women with the *A1/A1* genotype.

Since our original study of *CYP17* was published, five other studies have reported on *CYP17* and breast cancer (50–54). As shown in Table III, the results are inconsistent and show evidence of heterogeneity across ethnicity. Clearly, further work is necessary to resolve theses apparent inconsistencies. However, these data show how a multi-gene model of susceptibility based on a hormone biosynthesis can help us understand the underlying etiology of hormone-dependent tumors. We have applied a similar model to the study of prostate cancer.

Prostate cancer model

The two most important risk factors for prostate cancer are age and ethnicity. Prostate cancer is rare before 40 years of age, but the rate of increase with aging is greater than for any other cancer. African-American men have the highest incidence

Table III. Summary of all published studies of CYP17 and breast cancer

Study design	Ethnicity	No. of cases[a]	OR for breast cancer and CYP17[b]		Reference
			All cases	Advanced cases	
nested case-control	Asian African-American Latino	174	1.32 ($P = 0.19$)	2.52 ($P = 0.03$)	48
case-control	Caucasian	835	1.10 (ns)	0.88 (ns)	51
nested case-control	Caucasian	115	0.89 (ns)	1.39 (ns)	54
case-control	Caucasian	76	0.80 ($P = 0.45$)	1.7 (ns)	53
	African-American	20	1.40 ($P = 0.57$)	0.6 (ns)	
	Latina	27	1.93 ($P = 0.17$)	0.2 (ns)	
case-control	Asian (Taiwanese)	150	1.54 ($P = 0.15$)	–	52
nested	Caucasian case-control	464	0.97 (ns)	0.90 (ns)	50

ns, not statistically significant.
[a]Total cases, not specified by ethnicity.
[b]*P*-values shown where provided.

of prostate cancer in the world. In the USA, prostate cancer rates among African-Americans are ~50–70% higher compared with Caucasians (55). Unfortunately, adequate data do not exist on prostate cancer rates among Blacks in Africa. Lowest rates of prostate cancer are seen among Asian populations (Native Japanese and Chinese men). Japanese- and Chinese-American men have rates higher than men in their respective homelands; however, their rates still remain much lower than US Caucasians (4). Years of epidemiologic research has failed to uncover any environmental agents or lifestyle risk factors that can explain these pronounced differences found across different ethnic groups. Like breast cancer, risk of prostate cancer appears to be explained by endogenous hormone levels (4,56,57).

In developing a model of prostate carcinogenesis, genes involved in androgen biosynthesis, activation, inactivation and transport are all of interest. We have initially targeted four genes: the androgen receptor (*AR*), steroid 5α-reductase type II (*SRD5A2*), *CYP17* and 3β-hydroxysteroid dehydrogenase (*HSD3B2*) genes (4). *AR* is responsible for androgen transport, *SRD5A2* encodes the enzyme responsible for converting testosterone to the metabolically more active dihydrotestosterone, and *CYP17* (as described above) encodes an enzyme that functions at key branch points in human steroidogenesis. *HSD3B2* has a dual role: it encodes an enzyme that catalyzes a critical reaction in testosterone biosynthesis, and it is involved in the metabolism of dihydrotestosterone in the prostate (possibly different isozymes). Because of this dual role of *HSD3B2*, it is difficult to predict how functional variants of this gene might relate to prostate cancer risk. Although exploration has begun for all four genes, the focus initially has been on *AR* and *SRD5A2*.

Investigation of the *SRD5A2* gene began with a polymorphic dinucleotide repeat $(TA)_n$ in the 3′-UTR of the gene. Analysis of this marker suggested that a series of alleles with a relatively high number of repeats (17 or greater) was unique to African-Americans and somewhat more common in African-American men with prostate cancer compared with healthy African-American men (58). Subsequent sequencing of *SRD5A2* in a sample of men with either high or low levels of circulating androstanediol glucoronide (AAG; the biochemical serological correlate of prostatic 5α-reductase activity *in vivo*) identified numerous sequence variants. Two of these variants, V89L (valine→leucine at codon 89) and A49T (alanine→threonine at codon 49), have been proven to be strong candidates for conferring risk of prostate cancer (59,60). The V89L substitution showed marked differences among ethnic groups. The VV genotype is most common in African-Americans, Latinos and Caucasians, but is relatively rare among Chinese and Japanese. Among Asian men, V89L shows a strong correlation with AAG levels. Although the A49T mutation is uncommon in healthy men, it confers very high risk, especially for advanced prostate cancer. In African-American men, the OR = 7.22 ($P = 0.001$) for advanced disease and in Latino men the OR = 3.60 ($P = 0.04$). These epidemiologic findings are supported by *in vitro* data that showed that the A49T mutation has a 5-fold higher V_{max} for testosterone conversion than the normal enzyme, and the V89L has ~33% reduced activity compared with the wild-type.

Table IV. Selected candidate genes in hormone related cancers

Cancer site	Hormones	Potentially important genes
Breast	Estrogen, progesterone	*CYP17*, *CYP19*, *HSD17B1*, *ER*, *PR*
Prostate	Dihydrotestosterone	*CYP17*, *HSD17B3*, *SRD5A2*, *AR*
Ovary	FSH, progesterone	*FSH*, *FSHR*, *PR*
Endometrium	Estrogen	*CYP17*, *HSD17B1*, *HSD17B2*, estrogen receptor genes
Testis	*In utero* estrogen	*CYP17*, *HSD17B1*
Thyroid	TSH, estrogen	*TSH*, *CYP17*, *HSD17B1*

Within exon 1 of *AR*, two polymorphic polyamino acid tracts (trinucleotide repeats) have been studied: a polyglutamine $(CAG)_n$ and a polyglycine $(GGC)_n$. Androgen receptor activity has been shown to be negatively correlated with the number of CAG repeats, and several groups (61–65) have reported an association with the polyglutamine AR and risk of prostate cancer.

A third polymorphic marker at the AR locus has also been evaluated (4). A *Stu*I single-nucleotide polymorphism at codon 211, which designates two alleles, *S1* and *S2*, is located roughly halfway between the two trinucleotide repeats. Among African-American men the *S1* allele was associated with a statistically significant 3-fold increased risk of prostate cancer among men under the age of 65 years. An excess proportion of this allele was also found among prostate cancer cases with an affected

brother. The *Stu*I polymorphism did not seem to simply reflect short CAG repeats as a function of linkage disequilibrium. These preliminary data suggest that among African-American men, non-CAG repeat variation at the *AR* locus might contribute to hereditary prostate cancer.

This molecular model that is being developed for prostate cancer, and the similar model for breast cancer, illustrate the importance of molecular biology studies and epidemiologic studies working collaboratively to understand the disease process. We must begin thinking of these hormonally based cancers as being complex genetic traits and begin to both expand these models and develop similar multigenic models for the other hormone-related cancers. In Table IV, we provide a summary of likely candidate genes for such models.

Chemopreventives

Findings from last year's highly publicized tamoxifen trial provide the first information from a randomized clinical trial to support the hypothesis that breast cancer can be prevented among high risk women (66). Tamoxifen reduced the risk of invasive breast cancer by 49% ($P < 0.00001$) and non-invasive breast cancer by 50% ($P < 0.002$). These findings have to be tempered by variables that remain unknown. It is not known whether tamoxifen benefits women with BRCA mutations, nor whether the results of this trial apply to women of ethnic minorities. It is still to be determined whether this reduction in incidence is just a delay in the onset of tumor development and, if so, how long tamoxifen can be safely administered.

The risks and benefits of tamoxifen chemoprevention, and other cancer chemopreventives that are on the horizon, must be weighed carefully. While tamoxifen reduces the risk of certain breast cancers and bone fractures, it increases the risk of endometrial cancer. Whether tamoxifen can reduce the incidence of heart disease is unknown, and data from the trial suggests the drug may increase the risk of stroke and cataracts.

Similarly, chemopreventive treatments may decrease prostate cancer incidence and mortality, while avoiding surgery related morbidity. To determine the benefit of finasteride, an inhibitor of 5α-reductase activity (an enzyme in the androgen metabolism pathway), on prostate cancer risk the National Cancer Institute began a nationwide trial investigating long-term (7 year) finasteride treatments as a potential prostate cancer chemopreventive agent in 18 000 healthy adult men. Although the nationwide trial is just beginning, the chemopreventive potential of finasteride was investigated in a small group of men with elevated serum PSA. Although the drug effectively lowered serum PSA, more men using finasteride progressed to prostate cancer than men who did not take the inhibitor (67). The reasons for this unexpected finding may include that finasteride alters prostate size and therefore prostate tumor detection rate, or that finasteride alters the balance of DHT and testosterone levels in such a way that increases prostate cancer risk.

Concluding remarks

Neoplasia of hormone-responsive tissues currently account for >35% of all newly diagnosed cancers in men and >40% of all newly diagnosed cancers in women in the USA (68). The genetic basis of endogenous hormone levels as an important risk factor for hormone-dependent tumors has only recently been recognized. Long thought to be largely environmentally caused cancers, it is now increasingly obvious that genetic susceptibility, through germline polymorphisms in metabolic genes, plays a critical role. Some of the hormone-related cancers, e.g. prostate cancer, appear to be largely defined by this underlying genetic susceptibility, while others, like breast and ovary cancers, have environmental influences that can influence the lifetime hormone burden of an individual.

The control of these cancers rests first on the recognition of the genetic basis of each cancer, and secondly on developing suitable interventions that block target sequence activity. Tamoxifen and finesteride are early candidate therapies in breast and prostate cancer, respectively, and their activity is still under active investigation.

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Received July 7, 1999; accepted August 3, 1999