Borrower: WSM

Lending String: *ME6,CHS,MXC,MCL,ONE
Patron: Glaser, Rebecca-122042
Journal Title: Cancer epidemiology, biomarkers & prevention ; a publication of the American Association for Cancer Research /
ISSN: 1055-9965
System: OCLC
PMID: 23441645

Volume: 16 **Issue:** 9
Month/Year: sept 2007 **Pages:** 1775-83

Article Author:

Article Title: Wedren; Associations between androgen and vitamin D receptor Microsatellites and postmenopausal breast cancer

Imprint: Philadelphia, PA ; American Association

ILL Number: 33819357

Location:
Odyssey: 206.107.42.197
ARIEL No
Ariel:
Regular
Charge
Maxcost: 15.00IFM

Shipping Address:
Fordham Health Sciences Library
Wright State University- ILL
3640 Colonel Glenn Highway
Dayton, OH 45435-0001
Billing Address:
Fordham Health Sciences Library
Fax:
Email:
Phone:
Notes:

Associations between Androgen and Vitamin D Receptor Microsatellites and Postmenopausal Breast Cancer

Sara Wedrén,[1] Cecilia Magnusson,[1] Keith Humphreys,[1] Håkan Melhus,[2] Andreas Kindmark,[2] Fredrik Stiger,[2] Maria Branting,[2] Ingemar Persson,[1,3] John Baron,[4] and Elisabete Weiderpass[1,5,6]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [2]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [3]Swedish Medical Products Agency, Uppsala, Sweden; [4]Department of Medicine, Dartmouth Medical School, Hanover, New Hampshire; [5]Department of Etiological Research, The Cancer Registry of Norway, Oslo, Norway; and [6]Samfundet Folkhalsan, Helsinki, Finland

Abstract

We investigated the association between polymorphism in the androgen receptor (*AR*) and vitamin D receptor (*VDR*) genes and breast cancer risk in a large population-based case-control study of genetically homogenous Swedish women. We successfully determined both *AR* CAG_n and *VDR* A_n genotype in 1,502 women with invasive breast cancer and in 1,510 control women. We did not find any associations between *AR* or *VDR* microsatellite lengths and breast cancer when we used a priori determined cutoffs (≤21 or ≥22 repeats for *AR* and ≤18 or ≥19 for *VDR*) to define long and short alleles. There was statistically significant interaction between *VDR* genotype and parity, such that women with two short alleles had a halved risk for breast cancer, irrespective of parity, compared with nulliparous women with two long alleles. Homozygosity for the long *VDR* allele was associated with a more advanced clinical stage at diagnosis. In exploratory analyses, we determined cutoffs based on visual inspection of distributions of allele lengths among cases and controls and found that women carrying two alleles with <20 *AR* CAG_n repeats had an increased risk for breast cancer, odds ratio of 1.67 (95% confidence interval, 1.17-2.38), compared with those with two alleles with ≥20 repeats. Women carrying two *VDR* alleles with <21 A_n were also at an increased risk, odds ratio of 1.26 (95% confidence interval, 1.04-1.51). Our data do not support major roles for *AR* or *VDR* polymorphism as breast cancer risk factors. However, we did find an interaction between *VDR* genotype and parity that remains to be corroborated. (Cancer Epidemiol Biomarkers Prev 2007;16(9):1775–83)

Introduction

The role of androgen stimulation in breast carcinogenesis has been disputed. Although *in vitro* experiments indicate that androgens inhibit breast cell growth (1, 2), higher circulating androgen levels in breast cancer cases compared with controls (3) point to a possible adverse influence of androgenic stimulation in breast cancer tissue. Androgens act through the androgen receptor (*AR*), which is genetically polymorphic. There is a (microsatellite) trinucleotide repeat polymorphism (CAG_n) in exon 1 of the gene. This polymorphism affects the transactivation capacity of the receptor; the longer the repeat the less efficient the transactivation (4-6). In line with this, the short CAG_n has been associated with an increased risk of prostate cancer (7-10), and the long CAG_n with male infertility (11-13). Investigations of the relation between the *AR* polymorphism and breast cancer (Table 1) have been conflicting, variably reporting that short repeats are associated with a decreased risk (14-18) or are not associated with risk (19-21) or are associated with decreased breast cancer survival (16, 22, 23).

1α,25-Dihydroxyvitamin D3 (vitamin D) is another steroid hormone involved in cell growth and differentiation (24, 25). Vitamin D acts via a specific nuclear receptor, the vitamin D receptor (*VDR*). There are several strongly linked polymorphisms in the 3′ untranslated region of *VDR* that are of unclear functional significance (26-28) but that nevertheless have been associated with risk of prostate cancer (29-31) and osteoporosis (28, 32–34). Some investigators have also shown associations between variants in this region of the gene and breast cancer risk (35–40), whereas others (20, 41–44) have shown no association (Table 2).

We have chosen to study the *AR* CAG microsatellite and a polyadenylic acid [poly(A)] microsatellite in the 3′ untranslated region of *VDR* in relation to breast cancer in a large case-control study in a genetically homogenous population.

Materials and Methods

Parent Study. As described previously in detail (45), this nationwide population-based case-control study encompassed all incident cases of primary invasive

Received 1/11/07; revised 6/1/07; accepted 6/15/07.

Grant support: U.S. Army, Department of Defense award no. DAMD17-98-1-8301 and Swedish Cancer Society grant 3915.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Elisabete Weiderpass, Department of Etiological Research, The Cancer Registry of Norway, 0310 Oslo, Norway. Phone: 35-840-845-3406; Fax: 47-22-45-13-70. E-mail: elisabete.weiderpass@kreftregisteret.no

doi:10.1158/1055-9965.EPI-06-1096

Table 1. Summary of the literature about *AR* CAG microsatellite and breast cancer

Author, year	Type of study	Main outcome	Study size	Population	Result
Cox, 2006 (19)	Case-control (nested)	Breast cancer	5,603/7,480	From five cohorts in United States and Europe	No association between 1CAG in the *AR* gene and risk of breast cancer
Iobagiu, 2006 (23)	Case-control	Breast cancer	139/145	French	Genotypes comprising one or two short CAG_n sequences had higher risk of breast cancer compared with genotypes with two long alleles
Suter, 2003 (18)	Case-control	Breast cancer before age 45 y	524/461	United States (mostly Caucasian)	Increased risk with long repeats
Liede, 2003 (15)	Case-control	Breast cancer	299/229	Philippines	≤25 repeats had halved risk
Dagan, 2002 (58)	Case-control	Breast cancer in BRCA1/2 carriers (penetrance)	227 (149 with cancer, 78 without)	Israeli Jewish	Short allele-early onset
Haiman, 2002 (17)	Case-control	Breast cancer, plasma hormone levels	727/969	United States (nurses)	Increased risk with long alleles among those with family history
Kadouri, 2001 (60)	Case-control	Penetrance of breast cancer among BRCA1/2 mutation carriers.	122/66, 166/156	Israeli, mostly Ashkenazi	No influence on penetrance
Elhaji, 2001 (16)	Case-control	Breast cancer in women over 40 y	111/36 +212	White Caucasian	Alleles with ≥26 repeats were 2.4 times more common in breast cancer samples than in tissue from controls
Giguère, 2001 (14)	Case-control	Breast cancer	255/461	French Canadian	Those with low repeat sum had half the risk, homozygous for ≤20 repeats had half the risk
Menin, 2001 (62)	Cross sectional	Age at breast cancer diagnosis in high-risk families	101	Italian	No association with age at diagnosis
Yu, 2000 (22)	Cross sectional, cohort	Breast cancer characteristics	133	Chinese	Higher total number of repeats was associated with less aggressive breast cancer, fewer lymph node metastases, and longer survival
Given, 2000 (61)	Cross sectional	Age at breast cancer diagnosis among <65 y	178	Irish	No association with age at diagnosis
Dunning, 1999 (20)	Case-control	Breast cancer	508/426	United Kingdom Caucasian	No association
Rebbeck, 1999 (57)	Case-control	Breast cancer risk among BRCA1 mutation carriers	165/139	Unites States	Increased risk and earlier diagnosis with at least one long allele ≥28
Spurdle, 1999 (21)	Case-control (family)	Breast cancer in women below age 40 y	368/284	Australian	No association

breast cancer among women 50 to 74 years of age resident in Sweden between October 1993 and March 1995. Cases of breast cancer *in situ* were not included. Breast cancer patients were identified at diagnosis through the six Swedish regional cancer registries, to which reporting of all malignant tumors is mandatory. All Swedish residents are assigned a unique national registration number. This number is recorded in all registries, including the Total Population Register. It is possible for researchers, provided that the appropriate permissions are granted, to approach the authority in charge of the Total Population Register (currently the Tax Authority) and ask for national registration number and addresses of people that fulfill certain criteria specified by the researcher. Control women were randomly selected from the general population according to the expected age frequency distribution (in 5-year age groups) of cases.

Cases were asked to participate in the study by their respective physicians. When patients consented, they received a mailed questionnaire asking for detailed information about intake of menopausal hormones and oral contraceptives, weight, height, reproductive history, medical history, and other lifestyle factors. Controls were contacted directly with the questionnaire. Eighty-four percent (n = 3,345) of eligible cases and 82% (n = 3,454) of the controls ultimately participated in the parent study. Among the participating controls, 455 who failed to return the mailed questionnaire were interviewed by phone. Results from the parent study are available in previous publications (45-48).

Selection of Present Study Population. We randomly selected 1,500 women with invasive breast cancer and 1,500 controls (frequency matched by age) among postmenopausal participants without any previous malignancy (except *in situ* cervix carcinoma or non-melanoma skin cancer) in the parent study. To increase statistical power in subgroup analyses, we additionally selected all remaining eligible cases and controls

who had taken menopausal hormone treatment (either preparations with medium potency estrogen only, mainly estradiol and conjugated estrogens, or medium potency estrogen in combination with progestin) for at least 4 years (191 cases and 108 controls) and all women with self-reported diabetes mellitus (110 cases and 104 controls). In total, 1,801 cases and 1,712 controls were selected. In addition, 345 controls from the parent study selected for a parallel endometrial cancer study (49) who fulfilled the inclusion criteria could be added to our sample of breast cancer–free controls. The present study was approved by the Institutional Review Boards at Karolinska Institutet and in the six other Swedish regions and was done in compliance with the Helsinki Declaration.

Collection of Biological Samples. We contacted all selected living women by mail and those who gave informed consent received a blood sampling kit by mail. Whole blood samples were drawn at a primary health care facility close to the woman's home. Breast cancer cases who declined to donate a blood sample were asked to authorize our use of archived paraffin-embedded tissue taken at breast cancer surgery. We also attempted to retrieve archived tissue samples from all deceased breast cancer cases. We obtained blood samples from 1,322 (73% of selected cases) and archived tissue samples for 247 (14% of selected cases; total participation rate among gases is 87% of all selected) breast cancer patients. Among the chosen control women, 1,524 (74%) contributed blood samples. Reasons for nonparticipation included lack of interest in or skepticism about genetic research and, in some instances, advanced disease or death. We thus obtained final population-based participation rates of 73% and 61% in cases and controls, respectively.

DNA Extraction. We isolated DNA from 3 mL whole blood using Wizard Genomic DNA Purification kit (Promega) according to the manufacturer's instructions. From nonmalignant cells in paraffin-embedded tissue, we extracted DNA using a standard phenol/chloroform/isoamylalcohol protocol (50). Slides from each block were scrutinized by a pathologist. Areas found to contain malignant cells were marked on the slides and removed from the 50-μm cuts used for DNA extraction.

Genetic Analyses. We amplified fragments corresponding to the CAG_n in the *AR* gene and the A_n in the *VDR* gene by PCR using the following primers: 5′-AGAGGCCGCGAGCGCAGCACCTC-3′ (AR, forward), 5′-GCTGTGAAGGTTGCTGTTCCTCAT-3′ (AR, reverse), 5′-GTGTAGTGAAAAGGACACCGGA-3′ (VDR, forward), and 5′-GACAGAGGAGGGCGTGACTC-3′ (VDR, reverse). A "touch-down" PCR was used, in which both

Table 2. Summary of the literature about *VDR* polymorphism and breast cancer

Author	Polymorphism	Type of study	Main outcome	Study size	Population	Main results
Guy, 2004 (40)	Bsm1, Fok1, poly(A)	Case-control	Breast Cancer	398/427	United Kingdom Caucasian	Bsm1 and poly(A) associated with breast cancer risk, Fok1 no association when analyzed in isolation, but increased risk associated with the bb/LL genotype
Sillanpää, 2004 (39)	Apa1, Taq1	Case-control	Breast cancer	483/482	Finnish	Presence of Apa1 decreased risk
Guy, 2003 (65)	Bsm1, Fok1	Case-control	Breast cancer	313/410	United Kingdom Caucasian	Presence of Bsm1 increased risk
Buyru, 2003 (44)	Taq1, Bsm1	Case-control	Breast cancer	78/27	Turkish	No association
Newcomb, 2002 (41)	Taq1	Case-control	Breast cancer	403/383	United States	No association. Suggestion that menopausal hormone users with tt had lower risk
Hou, 2002 (35)	Apa1, Taq1, Bsm1	Case-control	Breast cancer	34/169	Chinese (Taiwan)	AA had higher risk
Bretherton-Watt D, 2001 (36)	Bsm1, poly(A)	Case-control	Breast cancer	181/241	United Kingdom Caucasian	OR bb vs. BB genotype = 2.32 (95% CI, 1.23-4.39). Similar association with long poly(A). LD between Bsm1 and poly(A)
Ingles, 2000 (37)	Poly(A)	Case-control	Breast cancer	143/300	U.S. Latina	Trend for increasing risk with short poly(A) alleles
Dunning, 1999 (20)	Taq1	Case-control	Breast cancer	951/627	United Kingdom Caucasian	No association
Curran, 1999 (38)	Apa1, Taq1, Fok1	Case-control	Breast cancer	135/110	Australian	Increased risk with Apa1 or Taq1 but no association with Fok1
Lundin, 1999 (42)	Taq1	Case-control	Breast cancer	111/130, cases <37 y	Swedish	No overall association. TT increased risk for lymph node metastasis. Increased survival among those with tt who were ER^+ and tamoxifen treated.
Ruggiero, 1998 (43)	Bsm1	Case-control, cross sectional	Breast cancer prognosis	88/167 (50 incident, 38 relapsed)	Italian	No association with risk overall. Those with bb had increased risk of metastatic breast cancer

Table 3. Selected characteristics for breast cancer cases and controls successfully genotyped for *AR* and *VDR* microsatellites

	Cases/controls*	Cases, mean (SD)	Controls, mean (SD)
Age (y)	1,502/1,510	63.3 (6.5)	63.2 (6.4)
Age at menarche (y)	1,364/1,382	13.5 (1.4)	13.5 (1.4)
Age at menopause (y)	1,492/1,497	50.4 (3.5)	50.1 (4.0)
Parity	1,502/1,510	1.8 (1.2)	2.2 (1.3)
Age at first birth (y)	1,278/1,364	25.4 (4.9)	24.8 (4.7)
Body mass index (kg/m^2)	1,493/1,489	25.8 (4.1)	25.5 (4.2)
	Cases/controls	Cases, %	Controls, %
Duration of menopausal hormone use (y)†	1,491/1,485		
0		67	73
<4		13	13
>4		20	15
Oral contraceptive use	1,444/1,447	32	35
History of breast cancer in mother or sister	1,466/1,374	16	9
Previous benign breast disease	1,502/1,510	14	10
Smoking‡	1,502/1,510	43	43
Self-reported diabetes mellitus	1,500/1,396	9	8
AR genotype§	1,502/1,510		
Homozygous ≥22 repeats		28	28
Heterozygous		47	48
Homozygous <22 repeats		25	23
VDR genotype‖	1,502/1,510		
Homozygous ≥19 repeats		38	37
Heterozygous		45	46
Homozygous <19 repeats		17	18

*Number of cases and controls for whom information was available.
† Note that long-term users (≥4 y) are oversampled both among cases and among controls (i.e., the proportion of users in our sample is not representative of the Swedish population).
‡ Ever smoking is defined as having smoked a total at least 100 cigarettes or having smoked regularly for at least 1 y.
§ $P = 0.44$, χ^2, comparing genotype distribution between cases and controls.
‖ $P = 0.87$, χ^2, comparing genotype distribution between cases and controls.

reactions were simultaneously run in an ABI Prism 877 Integrated Thermal Cycler robot (PE Applied Biosystems). We used AmpliTaq Gold kits and standard reagents (Applied Biosystems). The amplification profile consisted of denaturation at 95° for 10 min followed by 36 cycles of denaturation at 96° for 30 s, annealing at 59° to 57° for 40 s, elongation at 72° for 60 s, and final extension at 72°. The annealing temperature was 59° in the first 3 cycles, 58° in the following 12 cycles, and 57° in the last 21 cycles. We set up separate PCRs for samples that could not be amplified in the touch-down reaction. These reactions were done on a GeneAmp PCR System 9700 (Perkin-Elmer Co.) programmed for denaturation at 96° for 10 min followed by 36 cycles of denaturation at 96° for 30 s, annealing at 55° or 56° for 40 s, elongation at 72° for 60 s, and final extension at 72° for 7 min. The amplification products were read on a Genescan run ABI 377 DNA gel-slab electrophoresis sequencer (Perkin-Elmer) with a TAMRA-labeled internal length standard (Genescan-500 TAMRA, Applied Biosystems). We used Genotyper software to determine the genotypes (Genotyper version 2.0, Perkin-Elmer).

Genotyping Results. We were able to successfully genotype 1,542 breast cancer cases for the AR microsatellite and 1,511 cases for the VDR microsatellite and 1,260 controls for both polymorphisms. For both the AR CAG_n and VDR A_n, the exact number of repeats for a range of fragment lengths was determined by direct DNA sequencing of the fragments (data not shown). In the following statistical analysis, we included 251 additional genotyped controls from the same source population that were genotyped for the parallel endometrial cancer study (see above). Thus, the total number of controls included was 1,511.

Statistical Analyses. We determined whether AR and VDR genotype frequencies were in Hardy-Weinberg equilibrium using the web version of the Genepop software (51). Based on a priori decisions, we dichotomized the AR CAG_n at the median repeat length among controls (22 repeats) and VDR A_n between the two peaks in the bimodal distribution of repeat lengths among controls (18 repeats). In secondary analyses, we also used cutoffs determined after visually examining the distributions of allele lengths among cases and controls.

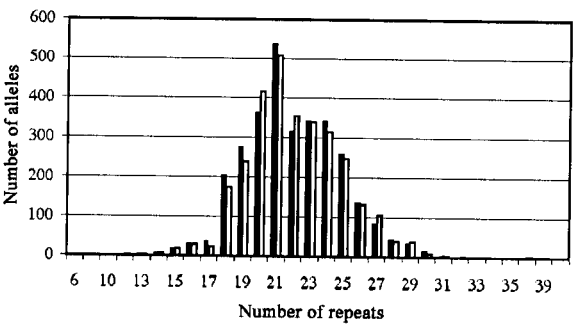

Figure 1. Distribution of *AR* CAG_n alleles by case-control status.

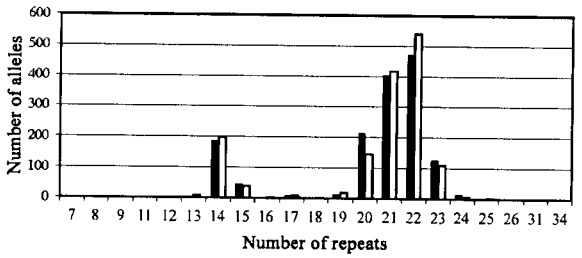

Figure 2. Distribution of *VDR* poly(A) repeat alleles by case-control status.

We calculated odds ratios (OR) and 95% confidence intervals (95% CI) from conditional logistic regression models using maximum likelihood methods. We conditioned on the variables used for selection (i.e., age in 5-year categories, use of menopausal hormones for 4 years or more, and self-reported diabetes mellitus). For detailed descriptions of how the above variables were defined, please see ref. 47. All covariates were introduced into the logistic regression model to detect confounding, indicated by changes in risk estimates, or other associations potentially affecting the primary association between genotypes and breast cancer. We investigated interactions between *AR* or *VDR* genotype and duration of menopausal hormone use, body mass index, parity, diabetes mellitus, and family history of breast cancer by doing separate analyses over strata of these exposures. Formal tests for interaction were done by comparing models containing interaction terms with models containing only main effects using likelihood ratio tests.

We did all analyses using SAS system PHREG procedure (release 8.02, SAS Institute, Inc.).

Results

Selected characteristics of the breast cancer cases and controls (Table 3) largely conformed to known epidemiologic breast cancer case-control differences. On average, cases had fewer children, were older at first birth, heavier, and more often had a family history of breast cancer. We found 30 alleles of the *AR* microsatellite (range, 6-43 CAG_n) that were approximately normally distributed (Fig. 1). In the *VDR* microsatellite locus, we found 21 alleles that were bimodally distributed (range, 7-34; Fig. 2). The genotype frequencies at the two loci were not in Hardy-Weinberg equilibrium, neither when dichotomized nor when all alleles were considered ($P < 0.001$ for both *AR* and *VDR* microsatellites). When we considered the alleles as long or short among controls, there were no associations between *AR* genotype and other known or suspected breast cancer risk factors (data not shown). However, the *VDR* SS genotype was more common among women who had their first child above the age of 30 years ($P = 0.02$) and the *VDR* LL genotype was more common among women who had a lean body build at ages 7 and 18 years ($P = 0.07$ and 0.05, respectively; data not shown).

There was no difference in the mean repeat length between cases and controls for the *AR* ($P = 0.22$) or the *VDR* microsatellite ($P = 0.96$) and no association between mean repeat length and age at breast cancer diagnosis (data not shown). When modeled by logistic regression, neither *AR* nor *VDR* genotypes (with alleles divided into long or short) were significantly associated with breast cancer risk overall (Table 4). Similarly, there was no association when breast cancers were subclassified into ductal and lobular types (Table 4). When we considered only short alleles, only long alleles, or the sum of alleles as continuous variables, we also found no significant association. The ORs for each unit increase in length for short, long, and sum of alleles for *AR* were 0.99 (95% CI, 0.96-1.03), 0.98 (95% CI, 0.96-1.01), and 0.99 (95% CI, 0.98-1.01), respectively. For the *VDR*, these estimates were 1.00 (95% CI, 0.98-1.02), 1.00 (95% CI, 0.97-1.02), and 1.00 (95% CI, 0.99-1.01), respectively. There was no indication of interaction between *AR* and *VDR* genotypes in effects on breast cancer risk ($P_{interaction} = 0.50$). In subgroup analyses (Tables 5 and 6), we found only one statistically significant interaction, namely one between *VDR* genotype and parity. Women with two short alleles had a reduced risk for breast cancer, irrespective of parity, compared with nulliparous women with two long alleles.

In exploratory analyses, we defined new cutoffs that were intended to maximize the contrasts between cases and controls. With these cutoffs, carrying two short (<20) *AR* CAG repeats or two short (<21) *VDR* poly(A) was associated with increased breast cancer risks overall, ORs of 1.63 (95% CI, 1.13-2.35) and 1.25 (95% CI, 1.03-1.51), respectively. These overall associations were also present in subgroup analyses; no indications of interaction

Table 4. *AR* or *VDR* genotype in relation to breast cancer risk with ORs and 95% CIs using *a priori* cutoffs

Genotype*	LL		LS		SS	
	Cases/controls	OR† (95% CI)	Cases/controls	OR† (95% CI)	Cases/controls	OR† (95% CI)
AR						
All cancers	422/388	1 (Ref)	698/651	0.98 (0.82-1.17)	376/301	1.11 (0.90-1.37)
Ductal (n = 1,138)	315/388	1 (Ref)	519/651	0.98 (0.81-1.19)	273/301	1.10 (0.88-1.37)
Lobular (n = 182)	56/388	1 (Ref)	80/651	0.90 (0.61-1.31)	36/301	0.81 (0.51-1.28)
VDR						
All cancers	547/499	1 (Ref)	656/614	0.98 (0.83-1.15)	256/234	0.98 (0.79-1.22)
Ductal (n = 1,115)	408/499	1 (Ref)	486/614	0.99 (0.82-1.18)	187/234	0.98 (0.77-1.24)
Lobular (n = 180)	58/499	1 (Ref)	81/614	1.15 (0.8-1.66)	30/234	1.11 (0.68-1.80)

*The *AR* alleles are as follows: L, ≥22 repeats; S, <22 repeats. The *VDR* alleles are as follows: L, ≥19 repeats; S, <19 repeats.
† The logistic regression model contained only genotype. Women who had used of menopausal hormones for at least 4 y and women with diabetes mellitus were oversampled; thus, the logistic regression models were conditional on age group and sampling scheme.

Table 5. *AR* genotype in relation to breast cancer risk in subgroups according to breast cancer risk factors with ORs and 95% CIs

	Genotype*	LL		LS		SS		$P_{interaction}$
		Case/controls	OR (95% CI)	Case/controls	OR† (95% CI)	Case/controls	OR† (95% CI)	
Menopausal hormone treatment	Never any kind	285/312	1 (Ref)	478/527	1.0 (0.8-1.2)	258/243	1.1 (0.9-1.5)	
	<4 y any kind	61/55	1 (Ref)	91/81	1.0 (0.6-1.6)	51/45	1.1 (0.6-1.8)	0.34‡
	≥4 y any kind	86/61	1 (Ref)	144/104	1.0 (0.6-1.5)	74/51	1.0 (0.6-1.6)	
	<years E+P	45/41	1 (Ref)	69/64	1.0 (0.6-1.7)	27/37	0.7 (0.4-1.3)	0.36‡
	≥4 y E+P	51/33	1 (Ref)	102/69	1.0 (0.6-1.7)	58/34	1.1 (0.6-2.0)	
	<years E only	21/21	1 (Ref)	27/37	0.8 (0.4-1.7)	29/14	2.0 (0.8-4.9)	0.30‡
	≥4 y E only	36/23	1 (Ref)	40/32	0.8 (0.4-1.7)	19/17	0.8 (0.3-1.8)	
Parity	Nulliparous	72/44	1 (Ref)	100/56	1.1 (0.7-1.8)	54/46	0.7 (0.4-1.2)	0.26
	1 childbirth	92/75	0.7 (0.5-1.2)	156/130	0.7 (0.5-1.1)	88/65	0.8 (0.5-1.3)	
	2 childbirths	158/165	0.6 (0.4-0.9)	294/289	0.6 (0.4-0.9)	133/120	0.6 (0.4-1.0)	
	>2 childbirths	116/151	0.5 (0.3-0.6)	168/254	0.4 (0.3-0.6)	111/116	0.6 (0.4-0.9)	
Body mass index (kg/m^2)	<25	205/209	1 (Ref)	349/358	1.0 (0.8-1.3)	186/174	1.1 (0.8-1.4)	0.66
	25 to <28	109/132	0.9 (0.6-1.2)	176/205	0.9 (0.7-1.2)	100/91	1.1 (0.8-1.6)	
	>28	124/87	1.5 (1.0-2.0)	186/159	1.2 (0.9-1.6)	98/75	1.3 (0.9-1.9)	
Diabetes mellitus	No	411/378	1 (Ref)	645/621	1.0 (0.8-1.1)	345/291	1.1 (0.9-1.3)	0.65‡
	Yes	27/26	1 (Ref)	73/52	1.3 (0.7-2.5)	39/29	1.3 (0.6-2.6)	
First-degree family history	No	362/359	1 (Ref)	578/597	1.0 (0.8-1.2)	319/291	1.1 (0.9-1.3)	0.73
	Yes	67/41	1.6 (1.1-2.5)	119/61	1.9 (1.4-2.7)	60/26	2.2 (1.3-3.5)	

*The *AR* alleles are as follows: L, ≥22 repeats; S, <22 repeats.
† The logistic regression model contained only genotype. Long-term users of menopausal hormone users and women with diabetes mellitus were oversampled; thus, the logistic regression models were conditional on age group and sampling scheme.
‡ $P_{interaction}$, for menopausal hormone use and diabetes mellitus, was calculated on 4 or 2 degrees of freedom, respectively, because the main effect of the covariate cannot be estimated due to oversampling.

emerged using these cutoffs and the *VDR*-parity interaction was weakened (data not shown).

There was no association between *AR* genotype and histologic type, tumor size, or clinical stage at diagnosis (data not shown). *AR* genotype and estrogen receptor status in the tumor were not associated among the 65% cases for whom receptor information was available. *VDR* genotype was associated with stage at diagnosis

Table 6. VDR genotype in relation to breast cancer risk in subgroups according to breast cancer risk factors with ORs and 95% CIs

	Genotype*	LL		LS		SS		$P_{interaction}$
		Case/controls	OR (95% CI)	Case/controls	OR† (95% CI)	Case/controls	OR† (95% CI)	
Menopausal hormone treatment	Never any kind	390/401	1 (Ref)	447/487	0.9 (0.8-1.1)	164/193	0.9 (0.7-1.1)	
	<4 y any kind	70/73	1 (Ref)	91/87	1.1 (0.7-1.7)	40/28	1.6 (0.9-2.9)	0.19‡
	≥4 y any kind	107/79	1 (Ref)	134/103	1.0 (0.6-1.4)	57/35	1.1 (0.7-1.9)	
	<4 y E+P	43/55	1 (Ref)	67/66	1.3 (0.8-2.2)	30/21	1.9 (0.9-3.8)	0.26‡
	≥4 y E+P	80/53	1 (Ref)	88/61	0.9 (0.6-1.5)	40/23	1.1 (0.6-2.0)	
	<4 y E only	26/29	1 (Ref)	35/31	1.3 (0.6-2.8)	15/13	1.6 (0.6-4.1)	0.72‡
	≥4 y E only	27/24	1 (Ref)	48/39	1.2 (0.6-2.3)	17/9	1.6 (0.6-4.3)	
Parity	Nulliparous	75/46	1 (Ref)	118/67	1.1 (0.7-1.7)	30/34	0.5 (0.3-0.9)	0.006
	1 childbirth	147/100	0.9 (0.6-1.4)	134/117	0.7 (0.4-1.1)	47/53	0.5 (0.3-0.9)	
	2 childbirths	198/222	0.5 (0.3-0.8)	267/257	0.6 (0.4-0.9)	112/95	0.7 (0.4-1.1)	
	>2 childbirths	153/190	0.5 (0.3-0.7)	158/246	0.4 (0.2-0.6)	72/84	0.5 (0.3-0.8)	
Body mass index (kg/m^2)	<25	287/272	1 (Ref)	321/334	0.9 (0.7-1.1)	121/135	0.8 (0.6-1.1)	0.07
	25 to <28	138/167	0.8 (0.6-1.1)	159/195	0.8 (0.6-1.0)	79/66	1.2 (0.8-1.7)	
	>28	147/111	1.3 (0.9-1.7)	190/146	1.2 (0.9-1.6)	60/64	0.9 (0.6-1.3)	
Diabetes mellitus	No	525/468	1 (Ref)	610/587	0.9 (0.8-1.1)	237/234	0.9 (0.7-1.1)	0.72‡
	Yes	48/43	1 (Ref)	65/50	1.1 (0.6-2.0)	24/14	1.5 (0.7-3.1)	
First-degree family history	No	471/451	1 (Ref)	552/572	0.9 (0.7-1.1)	210/223	0.9 (0.7-1.1)	0.54
	Yes	90/52	1.6 (1.1-2.4)	106/55	1.8 (1.3-2.6)	46/21	2.1 (1.2-3.6)	

*The *VDR* alleles are as follows: L, ≥19 repeats; S, <19 repeats.
† The logistic regression model contained only genotype. Long-term users of menopausal hormone users and women with diabetes mellitus were oversampled; thus, the logistic regression models were conditional on age group and sampling scheme.
‡ *P* for interaction, for menopausal hormone use and diabetes mellitus, was calculated on 4 or 2 degrees of freedom, respectively, because the main effect of the covariate cannot be estimated due to oversampling.

(P = 0.05). Homozygosity for the short allele was overrepresented among stage I tumors and homozygosity for the long allele overrepresented in stage IV. *VDR* genotype was not associated with any other clinical characteristic (data not shown).

Discussion

We show that *AR* and *VDR* microsatellites do not have any substantial influence on the risk of postmenopausal breast cancer among Swedish women. Shorter alleles at one or the other locus might entail a slightly increased risk, but these findings were data driven and should be interpreted with considerable caution.

Our study was population based and large and it was done in a genetically homogenous population. The latter limits the potential for confounding by population stratification. There are no convincing reasons to believe that differential participation associated to genotype would operate to cause selection bias. We had extensive information about other breast cancer risk factors, which enabled us to evaluate effect modification or confounding. The genotyping methods that we used are well established. The laboratory personnel were blinded to case-control status and could thus not have scored genotypes systematically with regard to case-control status.

The genotype frequencies of the *AR* and *VDR* microsatellites, although similar to previously published reports, were not in Hardy-Weinberg equilibrium. The reason for this deviation is unclear. The Swedish population is not particularly inbred, and there is no reason to believe that there has been recent mutations at the *AR* and *VDR* microsatellite loci nor significant genetic admixture. It is very unlikely that our study participation was dependent on genotype. For quality control reasons, we repeated the genotyping analyses of ~1% of our samples with identical results, which indicates that our allele calling procedure was reproducible. It is possible, however, that preferential amplification of the shorter of two alleles occasionally occurred in heterozygotes. In samples of very low DNA yield, one of the peaks of a heterozygote may have been below the detection limit of our assays. Factors such as these would have caused misclassification of some heterozygotes as homozygotes and could explain the deviation from Hardy-Weinberg equilibrium. Such misclassification would weaken observed associations, especially for recessive or codominant penetrance. This scenario has to be mentioned as a possible reason for our finding of nonassociation despite previous reports (14-16, 35-40) of significant associations.

The role of androgens in the development of breast cancer is complex. Whereas *in vitro* experiments show that androgen stimulation inhibits the stimulatory effect of estrogens in breast epithelium (52), epidemiologic studies indicate that high circulating levels of androgens confer an increased breast cancer risk (3), possibly because androgens are precursors for estrogens. Recently, there has been an increased interest in the feasibility of administering androgens to women with menopausal symptoms, the underlying idea being that the side effect profile, including cancer risks, of androgen therapy may be more beneficial than that of estrogen or estrogen-progestin therapy (53). Because we do not see an effect of androgen signaling, our results suggest that the androgen strategy might indeed be safer, at least in relation to breast cancer risk.

Several studies have established that long CAG_n causes reduced AR transactivation (4, 6). In line with this, there is also fairly consistent evidence for an increased risk of prostate cancer with short CAG_n, (consistent with enhanced androgen signaling) and an increased risk for male infertility with long repeats (consistent with attenuated androgen signaling). Because *AR* is located on the X chromosome, men only have one copy of the *AR* gene. Women, on the other hand, have two copies of the gene and one of them is inactivated, most likely in a random fashion, at least with regard to CAG length. Unmeasured X inactivation status may be one explanation for the divergent results about the influence of *AR* CAG_n on diseases and conditions in women. In a recent investigation, short CAG_n was associated with an earlier age at menarche (54), whereas Westberg et al. (55) found that short repeats were associated with higher androgen levels in women.

Several previous studies (Table 1) have shown long CAG_n to be associated with increased sporadic breast cancer risk among women (14-18), with breast cancer risk among men (56) and increased risk among BRCA1 (57) or BRCA1/2 (58) mutation carriers. Other studies, now supported by us, have reported no association (20, 21, 59), no modifying effect on BRCA1/2 mutation penetrance (60), and no association with age at breast cancer presentation (61, 62). However, there is one report that breast cancers in women with shorter CAG are of higher grade and confer a shorter survival (22).

Vitamin D is involved in cell growth and differentiation (24, 25) and seems to have antiproliferative effects (63). Although *VDR* is expressed in normal as well as malignant breast tissue (64), the functional significance of genetic variants of the receptor is unresolved (26, 27). Previous studies of the receptor gene variants and breast cancer risk have been conflicting (Table 2), some showing association (35-40, 65) and others showing no association (20, 41-44). The ambiguous state of knowledge in conjunction with our present results point that *VDR* polymorphism has no major overall influence on the risk for breast cancer. The interaction between *VDR* genotype and parity present in our data has not been described previously. Bearing in mind the number of comparisons in this study, it probably represents a chance finding. On the other hand, both parity and vitamin D are assumed to influence the breast in a prodifferentiating manner and thus there is a basis for further hypotheses about their interaction.

Our data do not support major roles for *AR* or *VDR* polymorphism as breast cancer risk factors.

Acknowledgments

We thank all women who participated in this study; Anna Christensson, Boel Bissmarck, and Anders Holmberg for providing invaluable people skills and logistic expertise to the project; Hans-Olov Adami for contributing scientific input during all stages of the study; and primary health care centers and pathology departments all over Sweden for cooperating unselfishly in the collection of biological samples.

References

1. Ferro P, Catalano M, Dell'Eva R, Fortunati N, Pfeffer U. The androgen receptor CAG repeat: a modifier of carcinogenesis? Mol Cell Endocrinol 2002;193:109.
2. Ortmann J, Prifti S, Bohlmann MK, Rehberger-Schneider S, Strowitzki T, Rabe T. Testosterone and 5α-dihydrotestosterone inhibit *in vitro* growth of human breast cancer cell lines. Gynecol Endocrinol 2002;16:113–20.
3. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
4. Knoke I, Allera A, Wieacker P. Significance of the CAG repeat length in the androgen receptor gene (AR) for the transactivation function of an M780I mutant AR. Hum Genet 1999;104:257–61.
5. Beilin J, Ball EM, Favaloro JM, Zajac JD. Effect of the androgen receptor CAG repeat polymorphism on transcriptional activity: specificity in prostate and non-prostate cell lines. J Mol Endocrinol 2000;25:85–96.
6. Irvine RA, Ma H, Yu MC, Ross RK, Stallcup MR, Coetzee GA. Inhibition of p160-mediated coactivation with increasing androgen receptor polyglutamine length. Hum Mol Genet 2000;9:267–74.
7. Mononen N, Ikonen T, Autio V, et al. Androgen receptor CAG polymorphism and prostate cancer risk. Hum Genet 2002;111: 166–71.
8. Hsing AW, Chokkalingam AP, Gao YT, et al. Polymorphic CAG/CAA repeat length in the AIB1/SRC-3 gene and prostate cancer risk: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2002;11:337–41.
9. Ekman P, Gronberg H, Matsuyama H, Kivineva M, Bergerheim US, Li C. Links between genetic and environmental factors and prostate cancer risk. Prostate 1999;39:262–8.
10. Andersson P, Varenhorst E, Soderkvist P. Androgen receptor and vitamin D receptor gene polymorphisms and prostate cancer risk. Eur J Cancer 2006;42:2833–7.
11. Eckardstein SV, Schmidt A, Kamischke A, Simoni M, Gromoll J, Nieschlag E. CAG repeat length in the androgen receptor gene and gonadotrophin suppression influence the effectiveness of hormonal male contraception. Clin Endocrinol (Oxf) 2002;57:647–55.
12. Kukuvitis A, Georgiou I, Bouba I. Association of oestrogen receptor α polymorphisms and androgen receptor CAG trinucleotide repeats with male infertility: a study in 109 Greek infertile men. Int J Androl 2002;25:149–52.
13. Dowsing AT, Yong EL, Clark M, McLachlan RI, de Kretser DM, Trounson AO. Linkage between male infertility and trinucleotide repeat expansion in the androgen-receptor gene. Lancet 1999;354: 640–3.
14. Giguère Y, Dewailly E, Brisson J, et al. Short polyglutamine tracts in the androgen receptor are protective against breast cancer in the general population. Cancer Res 2001;61:5869–74.
15. Liede A, Zhang W, De Leon Matsuda ML, Tan A, Narod SA. Androgen receptor gene polymorphism and breast cancer susceptibility in the Philippines. Cancer Epidemiol Biomarkers Prev 2003;12:848–52.
16. Elhaji YA, Gottlieb B, Lumbroso R, et al. The polymorphic CAG repeat of the androgen receptor gene: a potential role in breast cancer in women over 40. Breast Cancer Res Treat 2001;70:109–16.
17. Haiman CA, Brown M, Hankinson SE, et al. The androgen receptor CAG repeat polymorphism and risk of breast cancer in the Nurses' Health Study. Cancer Res 2002;62:1045–9.
18. Suter NM, Malone KE, Daling JR, Doody DR, Ostrander EA. Androgen receptor (CAG)n and (GGC)n polymorphisms and breast cancer risk in a population-based case-control study of young women. Cancer Epidemiol Biomarkers Prev 2003;12:127–35.
19. Cox DG, Blanche H, Pearce CL, et al. A comprehensive analysis of the androgen receptor gene and risk of breast cancer: results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3). Breast Cancer Res 2006;8:R54.
20. Dunning AM, McBride S, Gregory J, et al. No association between androgen or vitamin D receptor gene polymorphisms and risk of breast cancer. Carcinogenesis 1999;20:2131–5.
21. Spurdle AB, Dite GS, Chen X, et al. Androgen receptor exon 1 CAG repeat length and breast cancer in women before age forty years. J Natl Cancer Inst 1999;91:961–6.
22. Yu H, Bharaj B, Vassilikos EJ, Giai M, Diamandis EP. Shorter CAG repeat length in the androgen receptor gene is associated with more aggressive forms of breast cancer. Breast Cancer Res Treat 2000;59: 153–61.
23. Iobagiu C, Lambert C, Normand M, Genin C. Microsatellite profile in hormonal receptor genes associated with breast cancer. Breast Cancer Res Treat 2006;95:153–9.
24. Escaleira MT, Sonohara S, Brentani MM. Sex steroids induced up-regulation of 1,25-(OH)2 vitamin D3 receptors in T 47D breast cancer cells. J Steroid Biochem Mol Biol 1993;45:257–63.
25. Zhao XY, Peehl DM, Navone NM, Feldman D. 1α,25-Dihydroxyvitamin D3 inhibits prostate cancer cell growth by androgen-dependent and androgen-independent mechanisms. Endocrinology 2000;141:2548–56.
26. Yamagata M, Nakajima S, Tokita A, et al. Analysis of the stable levels of messenger RNA derived from different polymorphic alleles in the vitamin D receptor gene. J Bone Miner Metab 1999;17:164–70.
27. Durrin LK, Haile RW, Ingles SA, Coetzee GA. Vitamin D receptor 3'-untranslated region polymorphisms: lack of effect on mRNA stability. Biochim Biophys Acta 1999;1453:311–20.
28. Morrison NA, Qi JC, Tokita A, et al. Prediction of bone density from vitamin D receptor alleles. Nature 1994;367:284–7.
29. Ingles SA, Ross RK, Yu MC, et al. Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. J Natl Cancer Inst 1997;89:166–70.
30. Correa-Cerro L, Berthon P, Haussler J, et al. Vitamin D receptor polymorphisms as markers in prostate cancer. Hum Genet 1999;105: 281–7.
31. Veronique-Baudin J, Dieye M, Kouyoumdjian JC, Vacheron F, Draganescu C, Azaloux H. [Case-control study of the genes of receptors of the androgens of vitamin-D and of 5-αreductase in a population of Afro-Caribbean population with prostate cancer]. Prog Urol 2006;16:303–10.
32. Giguère Y, Dodin S, Blanche C, Morgan K, Rousseau F. The association between heel ultrasound and hormone replacement therapy is modulated by a two-locus vitamin D and estrogen receptor genotype. J Bone Miner Res 2000;15:1076–84.
33. Feskanich D, Hunter DJ, Willett WC, et al. Vitamin D receptor genotype and the risk of bone fractures in women. Epidemiology 1998;9:535–9.
34. Sainz J, Van Tornout JM, Loro ML, Sayre J, Roe TF, Gilsanz V. Vitamin D-receptor gene polymorphisms and bone density in prepubertal American girls of Mexican descent. N Engl J Med 1997;337:77–82.
35. Hou MF, Tien YC, Lin GT, et al. Association of vitamin D receptor gene polymorphism with sporadic breast cancer in Taiwanese patients. Breast Cancer Res Treat 2002;74:1–7.
36. Bretherton-Watt D, Given-Wilson R, Mansi JL, Thomas V, Carter N, Colston KW. Vitamin D receptor gene polymorphisms are associated with breast cancer risk in a UK Caucasian population. Br J Cancer 2001;85:171–5.
37. Ingles SA, Garcia DG, Wang W, et al. Vitamin D receptor genotype and breast cancer in Latinas (United States). Cancer Causes Control 2000;11:25–30.
38. Curran JE, Vaughan T, Lea RA. Association of A vitamin D receptor polymorphism with sporadic breast cancer development. Int J Cancer 1999;83:723–6.
39. Sillanpää P, Hirvonen A, Kataja V, et al. Vitamin D receptor gene polymorphism as an important modifier of positive family history related breast cancer risk. Pharmacogenetics 2004;14:239–45.
40. Guy M, Lowe LC, Bretherton-Watt D, et al. Vitamin D receptor gene polymorphisms and breast cancer risk. Clin Cancer Res 2004;10: 5472–81.
41. Newcomb PA, Kim H, Trentham-Dietz A, Farin F, Hunter D, Egan KM. Vitamin D receptor polymorphism and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:1503–4.
42. Lundin AC, Soderkvist P, Eriksson B, Bergman-Jungestrom M, Wingren S; South-East Sweden Breast Cancer Group. Association of breast cancer progression with a vitamin D receptor gene polymorphism. Cancer Res 1999;59:2332–4.
43. Ruggiero M, Pacini S, Aterini S, Fallai C, Ruggiero C, Pacini P. Vitamin D receptor gene polymorphism is associated with metastatic breast cancer. Oncol Res 1998;10:43–6.
44. Buyru N, Tezol A, Yosunkaya-Fenerci E, Dalay N. Vitamin D receptor gene polymorphisms in breast cancer. Exp Mol Med 2003; 35:550–5.
45. Magnusson C, Baron J, Persson I, et al. Body size in different periods of life and breast cancer risk in post-menopausal women. Int J Cancer 1998;76:29–34.
46. Magnusson C, Colditz G, Rosner B, Bergstrom R, Persson I. Association of family history and other risk factors with breast cancer risk (Sweden). Cancer Causes Control 1998;9:259–67.
47. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. Int J Cancer 1999;81:339–44.
48. Magnusson CM, Persson IR, Baron JA, Ekbom A, Bergstrom R, Adami HO. The role of reproductive factors and use of oral contraceptives in the aetiology of breast cancer in women aged 50 to 74 years. Int J Cancer 1999;80:231–6.

49. Rylander-Rudqvist T, Wedren S, Jonasdóttir G, et al. Cytochrome *P*450 1B1 gene polymorphisms and postmenopausal endometrial cancer risk. Cancer Epidemiol Biomarkers Prev 2004;13:1515–20.
50. Isola J, DeVries S, Chu L, Ghazvini S, Waldman F. Analysis of changes in DNA sequence copy number by comparative genomic hybridization in archival paraffin-embedded tumor samples. Am J Pathol 1994;145:1301–8.
51. Raymond M, Rousset F. Genepop (version 1.2): population genetics software for exact tests and ecumenicism. J Hered 1995;86:248–9. Available from: http://genepop.curtin.edu.au/.
52. Aspinall SR, Stamp S, Davison A, Shenton BK, Lennard TW. The proliferative effects of 5-androstene-3β, 17β-diol, and 5α-dihydrotestosterone on cell cycle analysis and cell proliferation in MCF7, T47D, and MDAMB231 breast cancer cell lines. J Steroid Biochem Mol Biol 2004;88:37–51.
53. Somboonporn W, Davis SR. Testosterone effects on the breast: implications for testosterone therapy for women. Endocr Rev 2004; 25:374–88.
54. Comings DE, Muhleman D, Johnson JP, MacMurray JP. Parent-daughter transmission of the androgen receptor gene as an explanation of the effect of father absence on age of menarche. Child Dev 2002;73:1046–51.
55. Westberg L, Baghaei F, Rosmond R, et al. Polymorphisms of the androgen receptor gene and the estrogen receptor β gene are associated with androgen levels in women. J Clin Endocrinol Metab 2001;86:2562–8.
56. MacLean HE, Brown RW, Beilin J, Warne GL, Zajac JD. Increased frequency of long androgen receptor CAG repeats in male breast cancers. Breast Cancer Res Treat 2004;88:239–46.
57. Rebbeck TR, Kantoff PW, Krithivas K, et al. Modification of BRCA1-associated breast cancer risk by the polymorphic androgen-receptor CAG repeat. Am J Hum Genet 1999;64:1371–7.
58. Dagan E, Friedman E, Paperna T, Carmi N, Gershoni-Baruch R. Androgen receptor CAG repeat length in Jewish Israeli women who are BRCA1/2 mutation carriers: association with breast/ovarian cancer phenotype. Eur J Hum Genet 2002;10:724–8.
59. Spurdle AB, Antoniou AC, Duffy DL, et al. The androgen receptor CAG repeat polymorphism and modification of breast cancer risk in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res 2005;7: R176–83.
60. Kadouri L, Easton DF, Edwards S, et al. CAG and GGC repeat polymorphisms in the androgen receptor gene and breast cancer susceptibility in BRCA1/2 carriers and non-carriers. Br J Cancer 2001;85:36–40.
61. Given HF, Radbourne R, Oag H, et al. The androgen receptor exon 1 trinucleotide repeat does not act as a modifier of the age of presentation in breast cancer. Eur J Cancer 2000;36:533–4.
62. Menin C, Banna GL, De Salvo G, et al. Lack of association between androgen receptor CAG polymorphism and familial breast/ovarian cancer. Cancer Lett 2001;168:31–6.
63. Colston KW, Hansen CM. Mechanisms implicated in the growth regulatory effects of vitamin D in breast cancer. Endocr Relat Cancer 2002;9:45–59.
64. Friedrich M, Axt-Fliedner R, Villena-Heinsen C, Tilgen W, Schmidt W, Reichrath J. Analysis of vitamin D-receptor (VDR) and retinoid X-receptor α in breast cancer. Histochem J 2002;34:35–40.
65. Guy M, Lowe LC, Bretherton-Watt D, Mansi JL, Colston KW. Approaches to evaluating the association of vitamin D receptor gene polymorphisms with breast cancer risk. Recent Results Cancer Res 2003;164:43–54.