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HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEW

Ovarian Cancer and Polymorphisms in the Androgen and Progesterone Receptor Genes: A HuGE Review

Francesmary Modugno

From the Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.

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Ovarian cancer is the second most common gynecologic cancer among women and the second leading cause of death from gynecologic malignancy worldwide. Androgens, acting through androgen receptors (ARs), have been implicated in the disease, while progestins, acting through progesterone receptors (PGRs), may provide protection against the disease. The *PGR* gene contains several polymorphisms in the hormone-binding domain, three of which are in linkage disequilibrium (a complex referred to as *PROGINS*). *PROGINS* has been associated with increased risk of ovarian cancer. This association has not been found consistently, and it may be limited to women who do not use oral contraceptives. The *AR* gene contains a trinucleotide CAG repeat, the length of which has been inversely associated with the ability of the AR-ligand complex to transactivate androgen-responsive genes. Data on the association between the *AR* repeat length and ovarian cancer, both in general and among carriers of mutations in the breast cancer 1 and 2 (*BRCA1/2*) genes, are inconclusive. There is insufficient evidence that polymorphisms in either the *PGR* gene or the *AR* gene may be a risk factor for ovarian cancer, alone or in combination with other factors. The sensitivity, specificity, positive and negative predictive values, and clinical validity of the *PROGINS* and *AR* CAG repeat assays are unknown. No recommendations for population-based screening can be made.

epidemiology; genetics; ovarian neoplasms; polymorphism (genetics); receptors, androgen; receptors, progesterone; trinucleotide repeats

Abbreviations: AR, androgen receptor; BRCA, breast cancer; CI, confidence interval; OR, odds ratio; PCR, polymerase chain reaction; PGR, progesterone receptor.

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GENES

It has recently been hypothesized that androgens and progestins may play a role in ovarian cancer etiology (1). In particular, there is emerging evidence for a protective role of progestins in ovarian cancer. The presence of progesterone receptors (PGRs) in normal ovarian epithelial cells (2) supports the premise of an activity of progesterone and its synthetic variants in the epithelial tissue of the organ. Progestins induce apoptosis in the ovarian surface epithelium of female cynomolgus macaques (*Macaca fascicularis*) (3), constituting an animal model for human ovarian cancer. In humans, persons with tumors that express PGR may have

Correspondence to Dr. Francesmary Modugno, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, 516A Parran Hall, Pittsburgh, PA 15261 (e-mail: fm@cs.cmu.edu).

a better prognosis (4). Epidemiologic data support the possibility of an inverse association of progestin levels with ovarian cancer. Oral contraceptives, which are associated with reduced risk of ovarian cancer, increase progesterone levels in vivo (5). Progestin-only oral contraceptives are as protective against ovarian cancer as estrogen-progestin formulations (6), and high-dose progestin oral contraceptive formulations may be more protective against the disease than low-dose formulations (7). Together, these data suggest that it is the progestin component of oral contraceptives that provides, at least in part, the protective effect. Finally, progestin-containing hormone replacement formulations *used in a continuous regimen* have recently been shown not to be associated with increased ovarian cancer risk, whereas estrogen-only formulations and formulations in which the progestin component was used sequentially were both associated with increased risk (8).

There is also emerging evidence that androgens may be associated with ovarian cancer risk (see review by Risch (1)). Androgens are produced by ovarian theca lutein cells, are present in ovarian follicular fluid, and are the principal sex steroid of growing follicles (9). Androgen receptors (ARs) are found in the normal surface epithelium of the ovaries (10), suggesting that androgens are active in the organ. Interestingly, the postmenopausal ovary is androgenic (11), as evidenced by 15-fold higher testosterone concentrations in the ovarian vein in comparison with serum from peripheral veins (11). Most ovarian cancers express AR, and antiandrogens inhibit ovarian cancer growth (12, 13). Epidemiologic evidence supports the possibility of an androgen-ovarian cancer link. Oral contraceptives, the most effective chemopreventive agent against the disease, suppress ovarian testosterone production by 35–70 percent (14–18). A prospective study (19) found significantly higher levels of androstenedione in the serum of case women than in control women. In the Cancer and Steroid Hormone Study, case women were more likely to have a history of polycystic ovary syndrome (odds ratio (OR) = 2.4, 95 percent confidence interval (CI): 1.0, 5.9) (20), a condition that causes elevated androgen levels (21–23). Finally, in a cohort study of 31,000 healthy women followed for more than 7 years, the risk of ovarian cancer increased with increasing waist-to-hip ratio (24), a marker of central obesity. Central obesity correlates with androgen levels in women (25–33).

In contrast, there is evidence that the *AR* gene may have an ovarian tumor suppressor function. AR mRNA and protein are down-regulated in ovarian cancer (10, 34). Moreover, loss of heterozygosity in the region containing the gene has been reported in approximately 40 percent of ovarian cancers (35–37). Finally, nonrandom X-inactivation (38) has been reported in invasive ovarian cancer (39), with expression potentially favoring the allele producing the less active receptor protein (40).

Progesterone receptor

The physiologic effects of progestins depend on the presence of human PGR, a member of the steroid-receptor superfamily of nuclear receptors (41). The *PGR* gene is located at 11q22-q23 (42–45). PGR exists in two isoforms produced by the single gene with two different promoter and translational start sites. PGR-B is the full-length receptor, while PGR-A is missing the first 165 amino acids (46, 47). The PGR protein consists of an amino-terminal domain containing a ligand-independent activation function; a DNA-binding domain and hinge region in the central part of the protein; and a carboxy-terminal, ligand-binding domain containing a second activation function that is ligand-dependent (48). Although PGR-A and -B share these structural domains, they function as two distinct transcription factors (49) with distinct physiologic effects (50, 51). PGR-A has been shown to repress estrogen receptor and *PGR*-B gene activation, whereas PGR-B is a stronger activator of progesterone target genes (52).

Androgen receptor

Androgens exert their effects by first binding to ARs, members of the steroid hormone-thyroid hormone-retinoic acid family of nuclear receptors (48, 53). The resulting hormone-receptor complex then binds directly to DNA, thereby transactivating androgen-responsive genes. The *AR* gene, also known as dihydrotestosterone receptor, is located at Xq11.2-q12. It spans more than 90 kilobases and contains eight exons (54, 55). The AR protein consists of a highly acidic amino-terminal domain, which functions in transactivation and is located entirely in exon 1 (1,586 base pairs) (56); a highly conserved, cysteine-rich DNA-binding domain containing two DNA-binding fingers located in exons 2 (152 base pairs) and 3 (117 base pairs), respectively; and a mostly hydrophobic carboxy-terminal ligand-binding domain located in exons 4–8, which vary in size from 131 base pairs to 288 base pairs (57–60). The *AR* gene shares significant homology with both the estrogen receptor and *PGR* genes (54, 55, 61).

Two isoforms of AR have been identified in a variety of human tissues (62, 63). The two isoforms of AR are remarkably similar in structure to the A and B isoforms of PGR (62). AR-B is the full-length receptor, while AR-A lacks the normal N-terminus (62, 63). AR-A is derived from internal translation initiation at methionine-188 in the AR open-reading frame and usually constitutes 20 percent or less of the immunoreactive AR present in any tissue (64). Despite the differences in structure and abundance, the two isoforms do not appear to differ in their regulation or in their ability to bind with ligands and activate target genes (64).

GENE VARIANTS

PGR gene

Several polymorphisms in the *PGR* gene have been identified (65). A *Taq*I restriction fragment length polymorphism in the hormone-binding domain was the first one reported (66). The polymorphism is the result of a small 309-base-pair *Alu* direct repeat insertion inherited in a Mendelian fashion (67). Although the functional significance of this insertion remains unknown, it may have consequences for the integrity of the regulatory functions of the gene. Hormone binding and subsequent transcriptional activation by PGR depend on the presence of a complete and intact hormone-binding domain.

Alteration of part of this region induces a loss of hormone binding and transcriptional activity in vitro (68), as does the alternative splicing that may result from the *Alu* insertion (69). The *Alu* insertion has been associated with endometriosis (70) and breast cancer (71), both of which may be risk factors for ovarian cancer (72–81).

Two other polymorphisms, the Val660Leu polymorphism in exon 4 and the C→T Hist770Hist polymorphism in exon 5, are in complete linkage disequilibrium with the *Alu* insertion (65). Together, these three polymorphisms form a complex referred to as *PROGINS* (82). Recently, a fourth polymorphism, S344T, was reported (65), which was shown to have a standardized pairwise linkage disequilibrium ($D' = 0.99$) with the *PROGINS* polymorphisms. This new single-nucleotide polymorphism in conjunction with the other three polymorphisms creates a linkage disequilibrium region of approximately 75 kilobases (65), which is consistent with the observed average length of linkage disequilibrium in US populations of Northern European descent (83).

Other single-nucleotide polymorphisms in the *PGR* gene have been identified, including two variants in the coding region (S344T and G393G) and two in the promoter region (+44C/T and +331G/A) between the *PGR*-B and *PGR*-A transcriptional start sites (65). Interestingly, the +331G/A polymorphism creates a unique transcription start site and increases transcription of *PGR*, favoring the B isoform. Recently, the +331G/A polymorphism was found to be associated with endometrial cancer (65). No associations between the S344T, G393G, and +44C/T variants and endometrial cancer were found (65). To our knowledge, no studies have investigated these four *PGR* polymorphisms within the context of ovarian cancer.

Table 1 presents frequencies of the *PROGINS* alleles by ethnicity among relevant studies detected in a Medline (US National Library of Medicine) search of articles published between January 1, 1990, and March 30, 2003. We combined searches for the keywords "progesterone receptor," "polymorphisms," and "ovarian neoplasms" to identify relevant studies. We further searched the references of any identified paper to locate additional studies. Of the seven studies identified, three were conducted in North American (US) populations, three in European populations, and one in an Australian population. As table 1 shows, the frequency of the more common allele ranged from 0.82 to 0.93 among healthy women and from 0.79 to 0.86 among women with ovarian cancer. Two studies were conducted in the US state of North Carolina: one population-based study (84) and one hospital-based study utilizing noncancer controls enrolled through hospital outpatient clinics (85). Allele distributions between the two case groups and the two control groups were similar, suggesting that the distributions within the cases and controls are representative of women with ovarian cancer in the region.

AR gene

The most widely studied variant in the *AR* gene is the highly polymorphic CAG trinucleotide repeat, located within a polyglutamine tract in exon 1. The length of the repeat is inversely associated with the ability of AR to transactivate genes (86, 87). Alleles with fewer CAG repeats appear to be more active, even when within the normal polymorphic range (11–38 repeats). Persons with X-linked spinal and bulbar muscular atrophy (Kennedy disease) have 40 or more *AR* CAG repeats and manifest clinical androgen insensitivity (88). In men, shorter *AR* CAG repeat tracts have been associated with prostate cancer, a disease linked to androgens (see review by Nelson and Witte (89)). In women, shorter repeat lengths have been associated with hirsutism (90), alopecia (91), and acne (91), as well as with lower serum testosterone levels and anovulation among women with polycystic ovary disease (92). Conversely, longer repeat lengths have been associated with earlier age at onset of breast cancer among carriers of the breast cancer 1 (*BRCA1*) gene mutation (93).

The *AR*-CAG repeat may be in linkage disequilibrium with other polymorphisms, including the *Stu*I mutation (94) and the GGC repeat in exon 1 (95), although these associations have not been confirmed.

There are well-established population differences in the length of the *AR*-CAG allele. Among African Americans, the most common allele length is 18, as compared with 21 for Caucasians (96). Among Asian women, the most common allele length is 22 (92, 96).

Table 2 presents frequencies of *AR* CAG repeat lengths by ethnicity among relevant studies detected in a Medline search of articles published between January 1, 1990, and March 30, 2003. We combined searches for the keywords "androgen receptor," "trinucleotide repeats," and "ovarian neoplasms" to identify relevant studies. We further searched the references of any identified paper to locate additional studies. Only four studies identified (40, 97–99) have examined AR frequency: two Italian studies, one US study of Ashkenazi Jewish women, and one Australian study. Among the four studies, only two were case-control in design (40, 97). The remaining two studies (98, 99) were of case series. The mean length of the short *AR* repeat ranged from 17.0 to 20.5 repeats among women with ovarian cancer, and was 20.3 repeats among healthy control women from both case-control studies. The long *AR* repeat length ranged from 20.7 to 23.4 repeats among cases and from 22.8 to 23.6 repeats among controls. In the two studies conducted in Italy (40, 99), the mean number of long *AR* repeat lengths among cases was almost identical (23 vs. 23.4), while the mean number of short repeats was similar (19 vs. 20.3). The concordance of the findings of these studies, conducted by different investigators in different geographic locations in Italy, suggests that the findings are representative of Italian women with ovarian cancer.

DISEASE

Ovarian cancer incidence and mortality

In 2000, the worldwide incidence of ovarian cancer was 192.4 per 100,000 women, making the disease the sixth most common cancer among women (100). Worldwide, the highest incidence rates are found among White women in Europe and North America, and the lowest incidence rates are found in Asia. Rates in Central and South America lie

TABLE 1. Results of studies of progesterone receptor gene *PROGINS* polymorphisms and epithelial ovarian cancer, 1995–2003

Polymorphism and study	Location/ethnic group	Controls		Cases		Frequency of polymorphism			
		Description	No.	Description	No.	Controls	Cases	Controls	Cases
Alu repeat insertion in intron G						T1		T2	
McKenna et al., 1995 (66)	Pooled data	None provided	184	None provided	67	0.88	0.81	0.12	0.19
	Irish women		83		41	0.83	0.82	0.17	0.18
	German women		101		26	0.93	0.81	0.07	0.19
Manolitsas et al., 1997 (192)	United Kingdom—Southern England	Healthy volunteers; age unreported	220	Sporadic ovarian cancer cases; age unreported	231	0.86	0.86	0.14	0.14
Lancaster et al., 1998 (85)	United States—North Carolina	Cancer-free women recruited from outpatient clinics at Duke University Medical Center; age unreported	101	Patients with ovarian cancer treated at Duke University Medical Center; age unreported	96	0.87	0.86	0.13	0.14
Runnebaum et al., 2001 (186)	North America	*BRCA1/2**-positive women with no reported history of ovarian cancer from studies of familial breast-ovarian cancer; mean age, 42.5 years		Women with a self-reported history of ovarian cancer from studies of familial breast-ovarian cancer in North America; mean age, 41.6 years					
	All *BRCA1/2*-positive women		496		167	0.82	0.79	0.18	0.21
	BRCA1/2-positive/OC*-positive		370		78	0.80	0.84	0.20	0.16
	BRCA1/2-positive/OC-negative		126		89	0.85	0.74	0.15	0.26
*PGR** exon 5 C→T Hist770Hist						A1		A2	
Lancaster et al., 2003 (84)	United States—North Carolina	Population-based sample of women with no history of ovarian cancer identified through random digit dialing and HCFA* telephone lists, frequency-matched to cases by age and race; age range, 20–74 years; mean age, 52.1 years		Incident cases of primary epithelial ovarian cancer in a population-based study within 48 counties from 1999–2002; age range, 20–74 years; mean age, 51.1 years					
	All women		397		309	0.84	0.84	0.16	0.16
	OC users		264		202	0.81	0.85	0.19	0.15
	OC nonusers		133		107	0.88	0.82	0.12	0.18
Tong et al., 2001 (187)	Austria	Healthy volunteers from the Department of Obstetrics and Gynecology at the University of Vienna, matched to cases by age and ethnic background; age data not reported	194	Sporadic ovarian cancer patients from the Department of Obstetrics and Gynecology at the University of Vienna; age range, 71 cases aged <50 years; 152 cases aged ≥50 years; three cases with age unknown	226	0.86	0.85	0.14	0.15
PGR exon 4 G→T Val660Leu						Valine		Leucine	
Spurdle et al., 2001 (185)	Australia	Unrelated adult female monozyotic twin (one twin per pair) volunteers participating in a study of twins and alcohol drinking and selected to match the birth distribution of the cases; age range, 30–90 years; mean age, 50.9 years	298	Incident cases with primary epithelial ovarian carcinoma from 1985–1996; age range, 19–95 years; mean age, 57.4 years	551	0.83	0.85	0.17	0.15

* *BRCA1/2*, breast cancer gene 1 or 2; OC, oral contraceptive; PGR, progesterone receptor; HCFA, Health Care Financing Administration.

between the two (101). In 2003, approximately 25,400 women in the United States will be diagnosed with ovarian cancer, accounting for almost 4 percent of all cancers in US women (102). From 1992 to 1999, the age-adjusted incidence rate among US women was 17.1 per 100,000 (103). The age-adjusted incidence rates for Caucasians, Hispanics,

TABLE 2. Results of studies of androgen receptor gene polymorphisms and epithelial ovarian cancer, 1995–2003

Study	Location/ethnic group	Controls		Cases		Mean no. of CAG repeats (and SD* or 95% CI*)					
		Description	No.	Description	No.	Short allele		Long allele		Average of alleles	
						Cases	Controls	Cases	Controls	Cases	Controls
				Case series							
Levine et al., 2001 (98)	United States—New York City Ashkenazi Jewish women	N/A*		Consecutive Ashkenazi Jewish patients with pathologically confirmed invasive epithelial ovarian cancer from a single hospital diagnosed over a 12-year period that was genotyped for the 185delAG and 5382insC mutations in the *BRCA1** gene	179 total	17.2 (3.3)	N/A	21.0 (3.3)	N/A	19.1 (2.8)	N/A
				Age range, 30–79 years; mean age, 55 years for *BRCA1* carriers	85 *BRCA1*-positive	17.0 (3.4)	N/A	20.7 (3.0)	N/A	18.9 (2.7)	N/A
				Age range, 25–87 years; mean age, 64 years for sporadic cases	94 *BRCA*-negative	17.5 (3.2)	N/A	21.2 (3.5)	N/A	19.3 (2.8)	N/A
Menin et al., 2001 (99)	Northern Italy	N/A		Ovarian cancer cases from "high-risk" breast/ovarian cancer families (defined as having three or more cases of breast and/or ovarian cancer on the same parental branch among first-degree relatives); age unreported	50	19 (2.5)	N/A	23 (2.7)	N/A	N/A	N/A
				Case-control studies							
Spurdle et al., 2000 (97)	Australia	Control group 1: unrelated monozygotic female twins of European descent voluntarily registered in the Australian Twin Registry and participating in a study of the genetics of alcoholism, 1992–1996; controls were frequency-matched to cases by date of birth; age range, 30–90 years; mean age, 50.9 years	300	Incident cases of ovarian adenocarcinoma identified at a single hospital from 1985 to 1996; age range, 21–95 years; mean age, 59.8 years	319	20.5 (20.2, 20.8)	20.3 (20.1, 20.5)	23.4 (23.1, 3.7)	23.6 (23.4, 23.8)	22.0 (21.8, 22.2)	22.1 (21.9, 22.1)
		Control group 2: women without breast or ovarian cancer selected from the electoral roll by stratified random sampling and participating in a study of breast cancer; age range, 20–69 years; mean age not reported	553								
Santarosa et al., 2002 (40)	Italy	Healthy female blood donors recruited from the same hospital as the cases; age range, 20–76 years; mean age, 40.1 years	100	Women with cases of ovarian cancer consecutively diagnosed at a single hospital from 1989 to 1996 (100 women)		20.3 (19.8, 20.9)	20.3 (19.9, 20.7)	23.4 (23.0, 23.8)	22.8 (22.3, 23.3)	21.9 (21.5, 22.3)	21.5 (21.2, 21.9)
				Women with consecutively diagnosed cases of ovarian cancer participating in a study of high-risk families (21 women); age range, 21–78 years; mean age, 54.2 years							

TABLE 3. Association of the progesterone receptor gene *PROGINS* polymorphism with epithelial ovarian cancer in various studies

Polymorphism and study	Subject population	Genotype			
Alu repeat insertion in intron G		T1/T1	T1/T2	T2/T2	T2/*
McKenna et al., 1995 (66)	Pooled data				
	No. of cases	43	23	1	24
	No. of controls	146	33	5	38
	OR† (95% CI†)		2.4 (1.3, 4.5)	0.7 (0.1, 6.0)	2.1 (1.2, 4.0)
	Irish women				
	No. of cases	26	15	0	21
	No. of controls	58	21	4	25
	OR (95% CI)		1.6 (0.7, 3.6)		1.3 (0.6, 2.9)
	German women				
	No. of cases	17	8	1	9
	No. of controls	88	12	1	13
	OR (95% CI)		3.5 (1.2, 9.7)	5.2 (0.3, 86.8)	3.6 (1.3, 9.7)
Manolitsas et al., 1997 (192)	No. of cases	173	52	6	58
	No. of controls	162	54	4	58
	OR (95% CI)		0.9 (0.6, 1.4)	1.4 (0.4, 2.6)	0.9 (0.6, 1.4)
Lancaster et al., 1998 (85)	No. of cases	76	15	5	20
	No. of controls	79	18	4	22
	OR (95% CI)		0.9 (0.4, 1.8)	1.3 (0.3, 5.0)	0.9 (0.5, 1.9)
Runnebaum et al., 2001 (186)	All *BRCA1/2*†-positive women				
	No. of cases	101	60	6	66
	No. of controls	328	153	15	168
	OR (95% CI)		1.3 (0.9, 1.8)	1.3 (0.5, 3.4)	1.3 (0.9, 1.8)
	OC† users				
	No. of cases	54	23	1	24
	No. of controls	236	122	12	134
	OR (95% CI)		0.8 (0.5, 1.4)	0.4 (0.05, 2.9)	0.8 (0.5, 1.3)
	OC nonusers				
	No. of cases	47	37	5	42
	No. of controls	92	31	3	34
	OR (95% CI)		2.3 (1.3, 4.2)	3.3 (0.7, 14.2)	2.4 (1.4, 4.3)

Table continues

Asians/Pacific Islanders, African Americans, and Native Americans/Alaskans were 18.1, 13.5, 12.6, 12.2, and 10.2 per 100,000, respectively (104). From 1989 to 1999, incidence rates declined by 0.7 percent per year (102). Although the rates among Asians and Hispanics in the United States are greater than the rates among women in Asia and Central/South America, they do not reach the rate of US Caucasians.

The lifetime risk of ovarian cancer in the population as a whole is approximately 1.4 percent. For women with a mutated *BRCA1* gene, population-based studies estimate the risk to be 16–30 percent (105). Approximately 75 percent of women have advanced-stage disease at the time of diagnosis (102). Despite aggressive surgery and chemotherapy, the prognosis for these women is poor, with a 5-year survival rate of less than 40 percent (102). This outcome is due, in large part, to a lack of effective prevention and early detection strategies; with current treatment modalities, the survival rate is approximately 95 percent when this cancer is diagnosed at an early stage (102).

Ovarian cancer is surpassed only by cervical cancer as the leading cause of death from gynecologic malignancy worldwide, with a mortality rate of 114.2 per 100,000 women (100). In the United States, ovarian cancer accounts for 5 percent of cancer deaths among women and is the leading cause of death from gynecologic malignancy (106). In 2003, approximately 14,300 US women will die from the disease. The overall age-adjusted mortality rate in the United States is 9.1 per 100,000 (104), with the highest mortality rates being observed among Whites (9.4/100,000), African Americans (7.7/100,000), and Hispanics (5.8/100,000).

TABLE 3. Continued

Polymorphism and study	Subject population	Genotype			
Lancaster et al., 2003 (84)	All women				
	No. of cases	219	80	10	90
	No. of controls	285	95	17	112
	OR (95% CI)		1.1 (0.8, 1.5)	0.8 (0.3, 1.7)	1.0 (0.8, 1.5)
	Adjusted‡ OR (95% CI)		1.1 (0.7, 1.5)	0.7 (0.3, 1.6)	1.0 (0.7, 1.4)
	OC users				
	No. of cases	146	51	5	56
	No. of controls	180	70	14	84
	OR (95% CI)		0.9 (0.6, 1.4)	0.4 (0.2, 1.3)	0.8 (0.6, 1.2)
	Adjusted§ OR (95% CI)		0.9 (0.6, 1.3)	0.4 (0.2, 1.2)	0.8 (0.5, 1.2)
	OC nonusers				
	No. of cases	73	29	5	34
	No. of controls	105	25	3	28
	OR (95% CI)		1.7 (0.9, 3.1)	2.4 (0.6, 10.3)	1.7 (1.0, 3.1)
	Adjusted§ OR (95% CI)		1.7 (0.9, 3.4)	2.2 (0.5, 9.9)	1.8 (1.0, 3.3)
Exon 5 C→T Hist770Hist or exon 4 G→T Val660Leu polymorphism		A1/A1	A1/A2	A2/A2	A2/*
Tong et al., 2001 (187)	Austrian women				
	No. of cases	167	50	9	59
	No. of controls	141	52	1	53
	OR (95% CI)		0.8 (0.5, 1.3)	7.6 (1.0, 60.7)	0.9 (0.6, 1.5)
Exon 4 G→T polymorphism		Val/Val	Val/Leu	Leu/Leu	Leu/*
Spurdle et al., 2001 (185)	Australian women				
	No. of cases	395	144	12	156
	No. of controls	203	90	5	95
	OR (95% CI)		0.8 (0.6, 1.1)	1.2 (0.4, 3.5)	0.8 (0.6, 1.1)
	Adjusted¶ OR (95% CI)		0.8 (0.6, 1.1)	1.4 (0.5, 4.1)	

† OR, odds ratio; CI, confidence interval; *BRCA1/2*, breast cancer gene 1 or 2; OC, oral contraceptive.
‡ Adjusted for age, race, and menopausal status.
§ Adjusted for age, race, and tubal ligation.
¶ Adjusted for age.

Descriptive epidemiology

The most consistent protective factors for ovarian cancer are bearing children (107–126) and using oral contraceptives (107–114, 126–139). Tubal ligation and breastfeeding also appear to reduce risk (126, 140–142). Other factors shown to lower risk include physical activity (143), twinning (144), and the use of antiinflammatory agents, such as aspirin and the newer nonsteroidal antiinflammatory drugs (145), although data on these factors are inconsistent (145–154).

Age is an important risk factor for ovarian cancer. The disease is uncommon before age 35 years, and incidence steadily increases until about age 80 years (103). The most consistent risk factor for ovarian cancer is family history. Women with one affected first-degree relative have a 5 percent lifetime risk (1 in 20, versus 1 in 70 for the general population). Those with two affected first-degree relatives have a 7 percent risk (155). Three hereditary syndromes have been defined: the very rare Lynch Syndrome II, which is associated with defects in DNA mismatch repair genes and hereditary nonpolyposis colorectal cancer; and hereditary site-specific ovarian cancer and hereditary breast/ovarian cancer, both of which are associated with mutations in breast cancer genes 1 and 2 (*BRCA1/2*).

Other risk factors that have been less consistently associated with ovarian cancer include talc use (156), infertility (157), endometriosis (72), pelvic inflammatory disease (158), polycystic ovary syndrome (20), hormone replacement therapy (159), and central obesity (increased waist-to-hip ratio) (24). Cigarette smoking has also been shown to be a risk factor, but only for tumors of the mucinous subtype (160–163).

Genetic epidemiology

Approximately 5–10 percent of malignant epithelial tumors contain germline *BRCA1/2* mutations (164–166),

most of which are found in *BRCA1*. Compared with sporadic disease, *BRCA1/2*-associated ovarian cancer is often diagnosed at a later stage (167, 168), although survival for *BRCA1/2*-associated disease appears to be better than survival for sporadic disease (167–169).

Approximately 1 in 800 women carries a *BRCA1/2* mutation. In Ashkenazi Jewish women, the prevalence is about 1 in 50 (170–172). Among the Ashkenazim, approximately 45 percent of ovarian cancers arise from two *BRCA1* mutations (185delAG and 5382insC) and a single *BRCA2* mutation (6174delT) (173–176). These three mutations are commonly found in other ethnic groups. The penetrance of *BRCA1* mutations for ovarian cancer is 36 percent by age 80 years (177) and may depend on the location of the mutation (178, 179). In general, the penetrance of *BRCA2* mutations is lower than that of *BRCA1* mutations (177), and an ovarian cancer cluster region has been identified (180, 181).

Among women carrying a mutated *BRCA1/2* gene, childbearing (182) and tubal ligation (182) appear to be protective against the disease. Whether oral contraceptives afford the same degree of protection to carriers as they do to noncarriers remains controversial (182–184).

ASSOCIATIONS AND INTERACTIONS

PGR polymorphisms and ovarian cancer risk

Table 3 shows the reported associations of *PGR* polymorphisms with epithelial ovarian cancer in the seven studies identified in the literature. The first study (66), comprising a small convenience sample, suggested a possible increase in ovarian cancer risk associated with the *PROGINS* allele. However, more recent studies using larger data sets (84, 185) have failed to establish any statistically significant associations, and no consistent pattern of increased risk has emerged. Only one population-based study has addressed the question (84), with a modest association of borderline significance found only among women who had never used oral contraceptives (OR = 1.8, 95 percent CI: 1.0, 3.3; adjusted for age, tubal ligation, and race). A similar finding was reported among women with *BRCA1/2* mutations (186).

There are several reasons for the negative findings. Small sample sizes limit the power of any one study; convenience samples may introduce bias into the study results; and selection of controls who are not representative of the population from which the cases were ascertained may generate selection bias. Data on other important factors, such as the response rates of cases and controls, were not reported in most of the published articles. This made it difficult to adequately assess other biases or flaws that may have been introduced into individual studies.

Several studies have examined the association of *PROGINS* with tumor behavior (84, 185, 187). No significant associations have been reported for tumor grade, stage, histologic subtype, invasiveness, or age at onset. Again, the small sample sizes and the limited details provided by the reports make it difficult to assess the validity of these findings.

PGR polymorphisms, oral contraceptive use, and ovarian cancer risk

No studies have investigated formal interactions between *PROGINS* and ovarian cancer risk factors. However, Runnebaum et al. (186) examined the association of *PROGINS* with oral contraceptive use and ovarian cancer risk among women with a *BRCA1/2* mutation. They reported no association overall between disease status and the presence of the *PROGINS* allele and no modifying effect of *PROGINS* in women who reported ever using oral contraceptives. However, in women who had never been exposed to oral contraceptives, the presence of at least one *PROGINS* allele was associated with increased risk of ovarian cancer (unadjusted OR = 2.4, 95 percent CI: 1.4, 4.3). The association was even stronger (though not statistically significant) when the analysis was limited to women carrying two *PROGINS* alleles (unadjusted OR = 3.3, 95 percent CI: 0.7, 14.2). The authors reported a similar association after adjustment for year of birth and ethnicity. No other adjustments were mentioned.

Lancaster et al. (84) recently reported no association between *PROGINS* and ovarian cancer risk in general or among oral contraceptive users and nonusers. However, in their data set, the *PROGINS* allele was less common among cases who had ever used oral contraceptives in comparison with controls (OR = 0.8, 95 percent CI: 0.5, 1.2; adjusted for age, race, and tubal ligation) but more common among cases who had never used oral contraceptives in comparison with controls (adjusted OR = 1.8, 95 percent CI: 1.0, 3.3). This difference between ever users and never users of oral contraceptives was even stronger when the analysis was limited to women carrying two *PROGINS* alleles: The adjusted odds ratio was 0.4 for oral contraceptive users and 2.2 for never users. Together, the data of Runnebaum et al. (186) and Lancaster et al. (84) suggest a possible interaction between oral contraceptive use and carriage of the *PROGINS* allele.

AR CAG repeat length and ovarian cancer risk

Two case series (98, 99) examined the association of repeat length with age of disease onset. Levine and Boyd (98) studied 179 Ashkenazi Jewish ovarian cancer patients consecutively diagnosed at a single hospital in New York City (85 *BRCA1/2* mutation carriers, 94 sporadic cases). Independent of *BRCA1/2* carriage, women who carried a short *AR* allele, defined as fewer than 20 repeats, were diagnosed an average of 7.2 years (95 percent CI: 2.3, 12.1) earlier than patients who did not carry a short allele (p = 0.0004). In contrast, Menin et al. (99) reported that among 50 women from high-risk families (14 of whom were *BRCA1/2* carriers), cases with fewer than 19 repeats had a median age at diagnosis of 58 years, as compared with 52 years for cases with 19 or more repeats (p = 0.03).

Two case-control studies have examined the association of CAG repeat length with ovarian cancer risk (table 4). Spurdle et al. (97) found no association between ovarian cancer risk and *AR* CAG repeat length in a population-based case-control study. When CAG repeat length was analyzed as a continuous variable, there were no differences between

TABLE 4. Association of the androgen receptor gene CAG repeat with epithelial ovarian cancer in two studies

Study	CAGn cutpoint	No. of alleles	No. of cases	No. of controls	Age-adjusted odds ratio	95% confidence interval
Spurdle et al., 2000 (97)	22	0	75	194		
		4	149	437	0.86	0.59, 1.25
		2	95	222	1.18	0.78, 1.78
		1 or 2	244	659	0.96	0.68, 1.37
	29	0	308	820		
		1 or 2	11	33	1.06	0.47, 2.38
Santarosa et al., 2002 (40)	22	0	27	35		
		1	57	47	1.7	0.82, 3.53
		2	37	21	3.45	1.42, 8.37
		1 or 2	94	66	2.17	1.10, 4.27

incident cases and either population controls or controls from a study of monozygotic twins (in which only one twin from each pair was included in the control group) for smaller, larger, and average allele sizes of CAG repeat length, before or after adjustment for age. Moreover, no differences between cases and controls were found when repeat length was analyzed as a dichotomous variable based on median length (22 or more repeats) or based on the length reported to act as a modifier of breast cancer risk (29 or more repeats) (188). However, there was a borderline-significant suggestion that alleles of at least 27 repeats may be weakly protective against ovarian cancer (for cases versus the pooled control group, unadjusted OR = 0.64, 95 percent CI: 0.41, 0.99). This latter finding is consistent with the hypothesis that increased androgen exposure is a risk factor for ovarian cancer (1), because functional studies suggest that longer CAG repeat alleles are associated with decreased AR hormone action (189).

In contrast, in a hospital-based case-control study, Santarosa et al. (40) observed an increase in ovarian cancer risk among women carrying at least one allele with 22 or more CAG repeats (OR = 2.17, 95 percent CI: 1.10, 4.27; adjusted for age). This association was more pronounced in women with a family history of the disease (adjusted OR = 3.52, 95 percent CI: 1.18, 10.47) and in women carrying at least two alleles with 22 or more repeats (adjusted OR = 3.45, 95 percent CI: 1.42, 8.37) (40). Interestingly, 18 of the 27 tumors (six hereditary and 21 sporadic) examined showed preferential expression of the long *AR* allele, with five of the six hereditary tumors expressing the long allele. Thus, while these data do not support a role for androgens in the etiology of ovarian cancer, they do support the hypothesis that the *AR* gene may serve as a tumor suppressor gene.

Although the contradictory findings of these two studies might be attributed to ethnic or environmental differences in ovarian cancer etiology between the two populations, it is likely that the differing study designs contributed to the differing results. In particular, although both studies employed a case-control design, in one study, controls were recruited from the general population (97), while in the other, controls were recruited from women donating blood at the hospital from which the cases were identified (40). However, in both studies, the mean age of the controls was significantly lower than that of the cases. Thus, it is possible that the contrasting findings of the two studies can be attributed to differences in the control populations. In particular, while the distribution of allele lengths was almost identical for both studies' case groups, the distribution of allele lengths between the two studies' control groups differed substantially (table 4). Hence, because the biology of ovarian carcinogenesis is likely to be independent of ethnic origin, the differences in allele distributions in the control groups may represent a bias in one of the studies rather than a true ethnic difference in allele frequency.

AR CAG repeat length, *BRCA1/2* carriage, and ovarian cancer risk

Only one study (98) has examined the interaction between *BRCA1/2* carriage and *AR* CAG repeat length. Among the 179 consecutive Ashkenazi Jewish cases, no differences in short, long, or average allele length were found between women with one of the three Ashkenazi founder mutations and women without any founder mutations. This result contrasts with results that have been reported for breast cancer (188), in which *AR* CAG repeat length modified the age at onset and the risk associated with *BRCA1/2* carriage. The finding also does not support in vitro studies showing that in breast and prostate cancer cell lines, *BRCA1* binds to the AR in the N-terminal region (where the CAG repeat is found) and serves as a coactivator for the gene (190), possibly playing a role in androgen-induced apoptosis (191).

LABORATORY TESTING

PGR gene

Early genotyping studies (66) used Southern blot analysis of *Taq*I-digested genomic DNA hybridized with a *PGR* cDNA probe. In more recent studies, undigested genomic DNA from peripheral blood leukocytes or banked tissue specimens has been amplified by polymerase chain reaction (PCR). In several studies (66, 84, 85, 186, 192), the region flanking the *Alu* insertion was amplified. Alleles lacking the insertion appear as smaller bands compared with alleles with the insertion (175 base pair fragments vs. 481) when resolved on agarose gel. Spurdle et al. (185) used the Sequence Detection System allelic discrimination assay (PE Applied Biosystems, Foster City, California) to detect the G and T alleles of the exon 4 Val660Leu polymorphism. Tong et al. (187) used fluorescein-labeled PCR primers to amplify DNA fragments containing the polymorphic sites in exons 4 and 5. They then designed 5-biotin-labeled probes to hybridize either to the wild-type PCR product or the polymorphic PCR product. Allele detection was performed with the ViennaLab Universal Gene Mutation Detection Kit (ViennaLab Labordiagnostika GmbH, Vienna, Austria), in which denatured PCR product is added to oligonucleotide-specific streptavidin-coated wells. The captured oligonucleotides for the polymorphisms in exons 4 and 5 hybridize specifically with either wild-type or polymorphic PCR products, generating genotype-specific color signals. No data on the sensitivity, specificity, or positive and negative predictive values of any of the *PROGINS* assays have been presented. Moreover, there are no data on the clinical validity of any of these assays.

AR gene

Molecular methods for determining *AR* CAG repeat length were summarized by Nelson and Witte (89). Briefly, PCR is utilized to amplify the CAG trinucleotide repeat in exon 1 using primers that are labeled with [γ^{33}P]-adenosine triphosphate. The amplified products are then size-separated and analyzed on a denaturing polyacrylamide sequencing gel. The number of repeats can be determined by comparing the gel band to a series of CAG size standards. More recently, fluorescein-labeled primers have been used and the sizes of the PCR products have been determined automatically (97). No data on the sensitivity, specificity, or positive and negative predictive values of the CAG repeat assays have been presented, although Nelson and Witte stated that because "the primers for this test are designed specifically for the CAG repeat,… the sensitivity and specificity are extremely high" (89, p. 888). No data on the clinical validity of the CAG repeat assay have been presented.

POPULATION TESTING

There is insufficient evidence to justify testing for the *PROGINS*, the +44C/T and +331G/A *PGR* polymorphisms, or the *AR* CAG trinucleotide repeat in a screening program for ovarian cancer in the general population. Neither is there sufficient evidence to justify testing for these polymorphisms in a screening program for high-risk women, including *BRCA1/2* mutation carriers.

OTHER POTENTIAL PUBLIC HEALTH APPLICATIONS

At this time, the data are insufficient to support any public health recommendations.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

The mounting evidence for a role of both progestins and androgens in ovarian cancer supports the hypothesis that polymorphisms in the *PGR* and *AR* genes may act as risk factors for ovarian cancer and/or as modifiers of risk associated with exposure to hormonal factors. However, the data thus far have been inconclusive. Only two studies have examined the association of the *AR* CAG repeat with ovarian cancer, with contradictory findings. As was discussed above, differences in the study designs may explain these disparate findings. This suggests a need for large, well-designed studies specifically aimed at addressing the association of the polymorphism with ovarian cancer. Additionally, more research is needed to understand the *AR* CAG polymorphism and its interaction with known risk factors and protective factors, including oral contraceptive use, parity, hormone replacement therapy, and *BRCA1/2* mutation status.

While there have been a greater number of studies on *PROGINS* and ovarian cancer, the results thus far have been predominantly negative. Although the lack of an association may be real, it is possible that methodological issues, such as small sample sizes, may be obscuring any true association. In addition, the association of *PROGINS* with a subset of women not using oral contraceptives and with those carrying a *BRCA1/2* mutation is intriguing and underscores the need for further investigation into the gene-gene and gene-environment interactions that may partially explain the etiology of ovarian cancer.

In addition to large-scale, population-based studies examining the *AR* CAG repeat and *PROGINS* as independent risk factors and as risk-modifying factors for ovarian cancer, studies of emerging polymorphisms in these genes are also needed. Notably, the four recently identified *PGR* polymorphisms (S344T, G393G, +44C/T, and +331G/A) (65) warrant further investigation, especially because the S344T and G393G polymorphisms are located in the coding region of the gene and the +331G/A polymorphism, which has been found to be associated with an almost twofold increase in risk of endometrial cancer (65), favors increased receptor transcription. In particular, the +331G/A polymorphism is 3′ of the *PGR*-A and -B transcriptional start sites and favors production of the B isoform (65). Highly malignant forms of ovarian cancer have been correlated with overexpression of *PGR*-B (193). An association with the +331G/A polymorphism is therefore plausible.

This review has focused on common polymorphisms in the *AR* and *PGR* genes. However, polymorphisms in genes along the sex steroid biosynthesis and metabolism pathways also warrant investigation as ovarian cancer risk factors, either alone or, more likely, in combination with lifestyle/

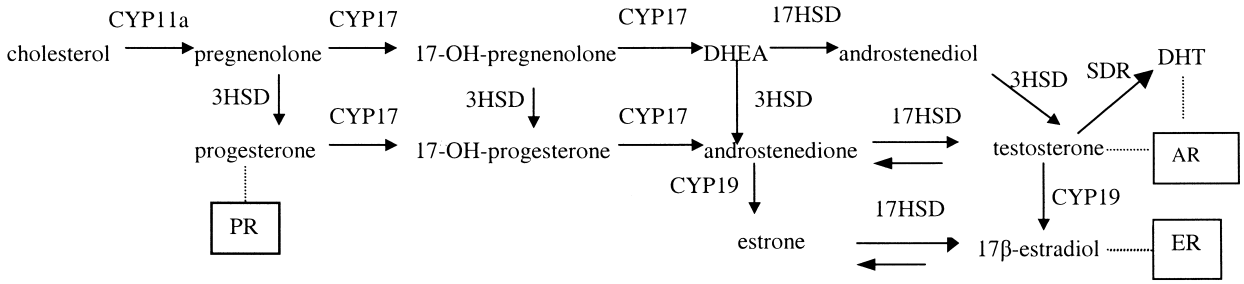

FIGURE 1. General scheme of the sex steroid synthesis pathway and the associated hormone receptors. For simplicity, only some of the enzymes and some of the potential receptor-hormone complexes are shown. CYP, cytochrome P-450; 17HSD, 17β-hydroxysteroid dehydrogenase; OH, hydroxy; DHEA, dehydroepiandrosterone; 3HSD, 3α-hydroxysteroid dehydrogenase; SDR, steroid 5α-reductase II; DHT, dihydroxytestosterone; PR, progesterone receptor; AR, androgen receptor; ER, estrogen receptor. Solid arrows indicate conversion pathways; dotted lines represent potential hormone-receptor complexes; boxes represent hormone receptors.

environmental exposures and other genetic polymorphisms. In particular, polymorphisms in the estrogen receptor gene as well as in enzymes involved in the conversion of cholesterol to progesterone, androgens, and estrogens must be considered (figure 1). To date, only a handful of studies have examined the association of ovarian cancer with single polymorphisms in enzymes involved in this pathway (194–197), and no studies have examined the interaction of several of these polymorphisms together or between these polymorphisms and environmental exposures. Moreover, only one study has examined the association of genotypes with specific histologic subtypes of ovarian cancer (197). The results of these few studies have been mostly negative; only one study reported a significant association between carriage of the cytochrome P-450 17 A2 variant and ovarian cancer (OR = 1.86, 95 percent CI: 1.26, 2.75) (197). The increased risk was most apparent in women over age 50 years and in women with invasive serous carcinoma. The same investigators reported an inverse association with carriage of a valine/methionine variant of the catechol-*O*-methyltransferase gene, especially for women with mucinous tumors (197).

Investigations of multiple polymorphisms in the steroid metabolism pathway are critical, because the high degree of interaction among these gene products, such as the cross-talk between the estrogen receptor and both AR (198) and PGR (199), makes it is unlikely that any one polymorphism alone will confer a substantial individual risk of ovarian cancer. As an example of the effect of multiple polymorphisms in this pathway on cancer risk, one recent study showed that although a polymorphism in the estrogen receptor gene was not a risk factor for prostate cancer, it substantially modified the risk of prostate cancer associated with a short *AR* CAG repeat (200).

Because the steroid hormone system both influences and is influenced by the insulin and insulin-like growth factor pathways (201–204), these latter pathways and the factors affecting them must also be considered. For example, polymorphisms in insulin-like growth factor I and its binding proteins may alter the availability of insulin-like growth factors (205, 206), which in turn can alter steroid hormone levels (202–204).

Hence, researchers must consider not only the individual effects of genetic polymorphisms but also the joint effects of several genes interacting. Moreover, because an environmental and lifestyle factor, such as alcohol drinking, may exert its effect on both the sex steroid and insulin-like growth factor pathways, genotype combinations must also be considered in conjunction with such factors.

These studies should include ethnically diverse populations in order to capture data on potential lifestyle and cultural factors, as well as other genetic factors, that may modify risk. For identification of specific risk modifiers, the *PGR* and *AR* polymorphisms should be examined in combination with specific hormonal exposures, such as oral contraceptive use and hormone replacement therapy regimens. Additional putative risk modifiers include hormone-altering host and dietary/lifestyle factors. Examples of such host factors include body mass index and central obesity, which correlate with hormone levels, especially androgen levels (25). Lifestyle factors that may alter circulating hormone levels include the use of alcohol and certain supplements (such as soy). Alcohol intake has been shown to alter progestin and androgen levels in both oral contraceptive users and nonusers (207).

In addition, detailed data on the timing of host and lifestyle factors, such as weight throughout the life span, should be obtained in order to identify critical time periods in which exposure to certain factors could modify the risk of ovarian cancer associated with the *AR* or *PROGINS* polymorphisms. Similarly, detailed data on exposure levels should be recorded in order to identify potential threshold effects.

More advanced approaches to identifying those polymorphisms involved in ovarian cancer are also warranted. In particular, knowledge of the haplotype map will enable researchers to focus on identifying those functional polymorphisms that influence risk, age at onset, clinical course, and response to treatment. In addition, more advanced analytical techniques aimed at uncovering higher-order interactions (208) will prove useful in increasing our knowl-

edge and understanding of the complex interactions between multiple genes along a single pathway, such as the steroid synthesis pathway, or along related pathways, such as the insulin and insulin-like growth factor pathways. These techniques will probably apply to interactions with environmental and lifestyle exposures as well.

In conclusion, although currently the data do not support a definite role for the *AR* CAG and *PROGINS* polymorphisms in ovarian cancer etiology, there is sufficient evidence of a possible association to warrant further investigation. Studies collecting detailed data on lifestyle and host factors throughout the life span, together with additional genetic data on not only the steroid hormone pathways but also related pathways such as those of the insulin-like growth factors, are needed. Collection of such detailed data in large, diverse populations will enable scientists to identify more precisely the individual and joint roles of genetic factors and environmental exposures in the etiology of ovarian cancer.

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APPENDIX

Internet Sites

Ovarian cancer

American Cancer Society: http://www.cancer.org
National Ovarian Cancer Coalition: http://www.ovarian.org/
Ovarian Cancer National Alliance: http://www.ovariancancer.org/
National Ovarian Cancer Association: http://www.ovariancanada.org/
National Cancer Institute (Cancer.gov): http://www.cancer.gov/cancerinfo/types/ovarian
Gilda Radner Familial Ovarian Cancer Registry: http://www.ovariancancer.com/default.asp

Genetic databases

The Androgen Receptor Gene Mutations Database: http://www.mcgill.ca/androgendb
Human Gene Mutation Database: http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html
OMIM—Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/Omim
GenAtlas: http://www.dsi.univ-paris5.fr/genatlas/
UniGene: http://www.ncbi.nlm.nih.gov/UniGene
GeneCards: http://bioinfo.weizmann.ac.il/cards/
National Center for Biotechnology Information Single Nucleotide Polymorphism Database: http://www.ncbi.nlm.nih.gov/SNP/