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POLYMORPHISMS IN ESTROGEN BIOSYNTHESIS AND METABOLISM-RELATED GENES, IONIZING RADIATION EXPOSURE, AND RISK OF BREAST CANCER AMONG U.S. RADIOLOGIC TECHNOLOGISTS

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Abstract

Ionizing radiation-associated breast cancer risk appears to be modified by timing of reproductive events such as age at radiation exposure, parity, age at first live birth, and age at menopause. However, potential breast cancer risk modification of low- to moderate radiation dose by polymorphic estrogen metabolism-related gene variants has not been routinely investigated. We assessed breast cancer risk of 12 candidate variants in 12 genes involved in steroid metabolism, catabolism, binding, or receptor functions in a study of 859 cases and 1083 controls within the US Radiologic Technologists (USRT) cohort. Using cumulative breast dose estimates from a detailed assessment of occupational and personal diagnostic ionizing radiation exposure, we investigated the joint effects of genotype on the risk of breast cancer. In multivariate analyses, we observed a significantly decreased risk of breast cancer associated with the *CYP3A4* M445T minor allele

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(rs4986910, OR=0.3; 95% CI 0.1–0.9). We found a borderline increased breast cancer risk with having both minor alleles of *CYP1B1* V432L (rs1056836, CC vs. GG, OR=1.2; 95% CI 0.9–1.6). Assuming a recessive model, the minor allele of *CYP1B1* V432L significantly increased the dose-response relationship between personal diagnostic x-ray exposure and breast cancer risk, adjusted for cumulative occupational radiation dose ($p_{\text{interaction}}=0.03$) and had a similar joint effect for cumulative occupational radiation dose adjusted for personal diagnostic x-ray exposure ($p_{\text{interaction}}=0.06$). We found suggestive evidence that common variants in selected estrogen metabolizing genes may modify the association between ionizing radiation exposure and breast cancer risk.

Introduction

Higher cumulative exposures to endogenous and exogenous sex hormones increase the risk of breast cancer (reviewed in [1]). Biologically, estrogens and other steroid hormones increase proliferation and are thought to damage DNA by oxidative processes (reviewed in [2,3]) and exert a promotional effect on mammary tumors [4]. Radiation-associated breast cancer risk appears to be modified by factors related to timing of reproductive events, such as age at radiation exposure, parity, age at first live birth, and age at menopause (reviewed in [5,6]). To our knowledge no human studies of quantitative breast cancer risks associated with ionizing radiation exposure and polymorphic variation in estrogen biosynthesis and catabolism genes have been reported. Since the mid-1980s, we have followed a large nationwide cohort of US radiologic technologists (USRT) who were exposed to low levels of ionizing radiation from occupational sources and from personal medical diagnostic and therapeutic procedures. Here we report the analysis of effect modification of occupational and personal medical diagnostic ionizing radiation exposure on breast cancer risk by single nucleotide polymorphisms (SNPs) in genes involved in steroid hormone metabolism.

Materials and Methods

The study population, radiation dosimetry and blood specimen collection have been described in detail elsewhere [7–10]. Study methods are briefly summarized below.

Study population

In 1982, the U. S. National Cancer Institute, in collaboration with the University of Minnesota and the American Registry of Radiologic Technologists, initiated a study of cancer incidence and mortality among 146,022 (106,953 female) U.S. radiologic technologists who were certified for at least two years between 1926 and 1982. During the years 1984–1989 and 1993–1998, surveys were mailed to all eligible cohort members to collect detailed information on work history as a radiologic technologist, family history of cancer, reproductive history, height, weight, other cancer risk factors (such as alcohol and tobacco use), and information regarding health outcomes, including breast cancer. 69,524 of 98,233 (71%) and 69,998 of 94,508 (74%) female technologists known to be alive at the time of each survey responded, respectively (for questionnaires, see <http://radtechstudy.nci.nih.gov>; for other study participation details, see [11]). This study has been approved annually by the human subjects review boards of the National Cancer Institute and the University of Minnesota.

Case and control recruitment

All living female technologists reporting a primary breast cancer (ductal carcinoma *in situ* or invasive breast cancer) that was confirmed by pathology or medical records were eligible for inclusion. In December, 1999, when biospecimen collection began, there were 1386 living

prevalent breast cancer cases that were diagnosed between 1955 and 1998. By the end of December 2003, 874 (63 %) breast cancer cases had provided informed consent, a blood sample, and completed a telephone interview which provided data on cancer risk factors and family cancer history information as well as selected work history information. Female controls identified from the USRT cohort were frequency matched to cases (ratio 1.5:1) by birth year in 5 year strata. Of 2268 living controls identified, 1,094 (48 %) provided informed consent, a blood sample, and completed a telephone interview. Participation details, non-responder and responder characteristics, and comparisons with decedents have been previously published [8,10], and did not reveal any meaningful differences.

Sample handling

After venipuncture, whole blood samples were shipped on ice overnight to the processing laboratory in Frederick, MD. Blood components were separated and DNA was extracted using Qiagen Kits (Qiagen, Valencia, CA). Samples were tracked by a unique ID code, and laboratory investigators were blinded to case-control status. After exclusion of samples with biospecimen contamination (n = 12), inadequate biospecimen quantity (n = 12), and incomplete survey data (n = 2), the final sample size consisted of 859 cases and 1083 controls.

Selection of candidate SNPs and sample genotyping

Candidate SNPs in the estrogen biosynthesis and metabolizing pathway were selected based on a minor allele frequency > 0.05, potential function based on amino acid substitution or location in promoter regions or splice sites, and results of previous epidemiologic studies. We chose 12 candidate variants in 12 genes: *COMT* (rs4680), *CYP17A1* (rs743572), *CYP19A1* (rs28757184), *CYP11B1* (rs1056836), *CYP3A4* (rs4986910), *ESR1* (rs3020314), *HSD17B3* (rs2066479), *HSD3B1* (rs4986952), *PGR* (rs1042838), *SHBG* (rs6259) and *SRD5A2* (rs523349). Samples were genotyped using standard TaqMan or MGB Eclipse assays. Genotyping methods can be found at <http://www.snp500cancer.nci.nih.gov> [12] and in Stredrick *et al.* [13].

Occupational and Personal Diagnostic Ionizing Radiation Exposure

The occupational dosimetry system used to estimate absorbed dose to the breast (in units of Gy) has been described in detail elsewhere [7], with some significant refinements [9] introduced for this work. Individuals without archival monitoring badge readings were assigned yearly badge doses and organ doses using simulation techniques from probability distributions that described the plausible range of exposures. For the current study, the probability distributions that describe the variability in doses received in a given year were partitioned, where possible, into narrower distributions based on work history data. Annual breast doses were based on the badge doses and organ dose conversion coefficients that accounted for energy range, and protection by lead aprons (where applicable) and were summed to derive a cumulative occupational breast dose for each person. Doses up to 10 years prior to breast cancer diagnosis for cases and for an equivalent time point for controls were excluded. A 10 year lag for exposure was chosen because this is a generally accepted latency period for solid cancers, including breast cancer [5,14,15]. The occupational radiation dose distributions to the breast are shown in Table 1.

Cumulative personal medical radiation exposure was estimated using data from the two surveys mailed to the cohort. Self-reported numbers and calendar time periods of the diagnostic x-ray procedures were used to calculate a cumulative breast dose score as an approximation of breast dose as previously described [8]. Procedures occurring 10 years prior to breast cancer diagnosis for cases and an equivalent time point for controls were excluded from the cumulative score as a lag period to minimize potential bias from

procedures performed because of pre-clinical disease symptoms. Personal medical radiation score distributions to the breast are shown in Table 1.

Statistical Analyses

We assessed Hardy-Weinberg equilibrium (HWE) among controls using chi-square or Fisher's exact tests. Associations between SNPs and breast cancer were evaluated using unconditional logistic regression. For each SNP, the rare allele among controls was considered the variant allele. When less than 2% of the controls were homozygous variant, homozygous variant and heterozygous subjects were combined. Tests for trend were conducted assuming a log additive model for genotype.

Main effects of occupational breast dose and personal diagnostic radiation breast dose score were assessed by modeling the odds ratio as a linear function in logistic regression models:

$$OR=1+\beta*D$$

where D is continuous radiation dose and β is the excess odds ratio (EOR) per unit dose (Gy) or dose score. Occupational radiation dose and personal diagnostic radiation dose score were adjusted for each other. Adjusting for exposure from radiation and radionuclide therapies had little effect on the estimated risks from occupational and personal diagnostic x-ray exposures.

To evaluate whether SNPs modified the relation between radiation and breast cancer risk, we allowed the radiation-related EOR to vary by genotype while adjusting for the genotype effect. EOR heterogeneity across genotype categories was assessed using likelihood ratio tests (LRT). Since some genotype categories contained small numbers of individuals, dose-response estimates were sometimes less than zero and are denoted as “<0”. Based on genotype main effect associations from the present study, we also analyzed selected SNPs assuming a dominant or recessive mode of inheritance.

All regression models were adjusted for year of birth, and occupational radiation dose and personal diagnostic radiation dose score were adjusted for each other. Since adjustment for age at menarche, number of live births, age at first birth, family history of breast cancer, history of benign breast disease, oral contraceptive use, menopausal status, hormonal replacement therapy, body mass index, height, alcohol consumption and cigarette smoking did not substantially change genotype or radiation main effect estimates or radiation effect estimates stratified by genotype, these variables were not included in the final models. We were unable to examine genotype-radiation interactions by reproductive factors because of small numbers that resulted in unstable models.

Confidence intervals for genotype risk estimates were Wald-based while confidence intervals for radiation risk estimates were derived from the profile likelihood method. We used EPICURE software (Hirosoft, Seattle, WA) for linear dose-response analyses and SAS software (SAS Institute, Cary, North Carolina, Release 8.02) for all other analyses.

Results

Selected demographic and ionizing radiation exposure variables are summarized in Table 1. Cases were more likely than controls to have had a previous history of radiation therapy. An increased risk of breast cancer was significantly associated with cumulative occupational radiation absorbed dose to the breast after adjustment for age and personal diagnostic radiation exposure (EOR/Gy = 3.0, 95% CI = 0.04–7.8, $p = 0.046$), but not with personal

diagnostic radiation breast dose score (EOR/Gy = 1.3, 95% CI = -0.4–4.0, $p = 0.3$). The two sources of radiation exposure were uncorrelated ($r^2 = 0.02$).

Allele frequencies in controls did not deviate from expectation based on HWE except for a borderline finding for rs6259 in the *SHBG* gene ($p=0.05$). In multivariate analyses (Table 2), the minor allele of *CYP3A4* M445T (rs4986910) was associated with a decreased risk of breast cancer (OR=0.3; 95% CI 0.1–0.9). Interactions with ionizing radiation associated breast cancer risk by genotype are shown in Table 3. There was a borderline increase in breast cancer risk with having both minor alleles of *CYP1B1* V432L (rs1056836). In a co-dominant model, *CYP1B1* V432L showed suggestive ionizing radiation interaction LRT p -values of 0.05 and 0.07. The increased breast cancer risk pattern appeared most consistent with a recessive mode of inheritance. In analyses using a recessive genetic model, *CYP1B1* V432L increased the dose-response relationship between medical diagnostic radiation and cumulative occupational radiation dose and breast cancer risk ($p_{\text{interaction}} = 0.03$ and 0.06, respectively). While effect modification was observed for *CYP17A1* (rs743572), *CYP19A1* (rs28757184), and *HSD17B3* (rs2066479), the magnitude of the effect was opposite for the two sources of radiation exposure.

Discussion

In this nested breast cancer case-control study of common variants in estrogen biosynthesis and metabolism-related genes, we found a significant decrease in risk of breast cancer associated with the *CYP3A4* M445T minor allele (rs4986910, alias *CYP3A4* *3). The *CYP3A4* gene is important in the oxidation of testosterone and estrogen (4- and 16 α -hydroxylation) and polymorphic variants have been evaluated due to the possible relationship of *CYP3A4* overexpression and breast cancer risk (reviewed in [16]). Subsequent candidate genotyping and genome-wide studies have not identified variants in *CYP3A4* as strong candidates for increased risk of breast cancer, however interaction between a different *CYP3A4* variant and combined hormone replacement therapy was suggested [17].

We observed a slight, but not statistically significant, increase in breast cancer risk with both minor alleles of *CYP1B1* V432L (rs1056836, CC vs GG), suggesting that a recessive model fit the data better. In the co-dominant interaction model, the pattern of risk over genotype strata also suggested a recessive model, with the highest risks associated with the minor alleles. In a recessive model, having the two minor alleles of *CYP1B1* V432L significantly increased the dose-response relationship between both cumulative occupational radiation and personal diagnostic radiation exposure. If oxidative damage to DNA from radiation or estrogen hormones is handled equivalently by mammary epithelial cells, then the recent report of significant interaction between the *CYP1B1* V432L variant and years of estrogen and progesterone use [18] supports our present observation. In a related study of low-dose medical radiation exposure among women diagnosed with breast cancer under the age of 50 years, no effect modification between estrogen/progesterone receptor status and x-ray examinations was found [19] suggesting teasing apart the inferred effect of genotypes vs. tumor characteristics will be complicated.

The significant interactions observed for *CYP17A1* (rs743572), *CYP19A1* (rs28757184), and *HSD17B3* (rs2066479) were inconsistent across the two sources of radiation exposure. Given the lack of a genotype main effect and the relatively low frequency of some alleles, these interaction results may well be due to chance.

Our study has several unique features including the detailed assessment of breast radiation dose from occupational exposure [7], cumulative questionnaire-based diagnostic radiation

breast dose scores [8], and the availability of detailed information about reproductive, demographic and lifestyle factors derived from interviews of all subjects. Our risk estimates for both occupational and personal diagnostic radiation exposure were consistent with studies of radiation effects on breast cancer risk (reviewed in [6,20]). The radiation dose estimates and large sample size uniquely positioned us to evaluate gene-radiation effects. This is the first study to our knowledge to evaluate the joint effects of polymorphisms in the estrogen biosynthesis and metabolism pathway and low-dose exposure to radiation.

Limitations of the present study include the use of prevalent cases and the modest participation rates. However, analysis of allele frequencies over time were relatively static (data not shown) and comparison of demographic characteristics did not reveal any significant differences between participants and non-participants (results not shown). It is possible that the associations we observed between personal diagnostic radiation dose score and breast cancer risk were confounded by other breast cancer risk factors that are associated with increased screening for breast cancer, such as family history of breast cancer and history of benign breast disease. Inclusion of these variables, however, did not appreciably alter the regression point estimate (results not shown).

In summary, we identified one polymorphism, *CYP1B1* V432L, that may modify the radiation-associated breast cancer risk. The findings observed here need to be confirmed in other studies [21] with well-characterized exposure to radiation. Future studies should include more genes in the estrogen metabolism pathway related to oxidative DNA damage and denser coverage of these genes.

Abbreviations

EOR	excess odds ratio
Gy	Gray
HWE	Hardy-Weinberg Equilibrium
LRT	likelihood ratio test
SNP	single-nucleotide polymorphism
USRT	U.S. Radiologic Technologists

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Demographic and ionizing radiation exposure variable distributions among breast cancer cases and controls, US Radiologic Technologists study

Table 1

Characteristic	Cases (%) (n = 859)	Controls (%) (n = 1083)	p- value*	p- trend†
<i>Ethnicity</i>				
Caucasian	842 (98)	1048 (97)	0.2	N/A‡
African American	9 (1)	18 (2)		
Other	8 (1)	17 (2)		
<i>Year of Birth</i>				
≤ 1925	120 (14)	138 (13)	0.9	0.7
1926 – 1935	195 (23)	249 (23)		
1936 – 1945	292 (34)	382 (35)		
> 1945	252 (29)	314 (29)		
<i>Occupational Ionizing Radiation Breast Dose (Gy)</i>				
0 to 0.05	687 (80)	894 (83)	0.2	0.1
>0.05 to 0.1	90 (10)	100 (9)		
>0.1 to 0.2	63 (7)	76 (7)		
>0.2	19 (2)	13 (1)		
<i>Personal Diagnostic Radiation Breast Dose Score</i>				
0 to 0.05	686 (80)	908 (84)	0.1	0.05
>0.05 to 0.1	106 (12)	104 (10)		
>0.1 to 0.2	46 (5)	51 (5)		
>0.2	21 (2)	20 (2)		
<i>Radionuclide Procedures</i>				
Never	721 (84)	937 (87)	0.3	NA
Ever	65 (8)	71 (7)		
Unknown	73 (9)	75 (7)		
<i>Radiation Therapy</i>				
Never	803 (94)	1021 (94)	0.01	NA
Ever	24 (3)	14 (1)		
Unknown	32 (4)	48 (4)		

* Chi-square test

[†] Mantel-Haenszel trend test

[‡] Not Applicable

Table 2

Age-adjusted associations between estrogen and hormone-related polymorphisms and breast cancer risk in US Radiologic Technologists

Gene	Entrez SNP ID *	AA or nt variant ID †	Genotype	Cases (%) (n=859)	Controls (%) (n=1083)	OR ‡	95% CI	P- value	P- trend §
<i>COMT</i>	rs4680	V158M	AA	231 (28)	293 (27)	1.0			0.7
			GA	416 (51)	542 (50)	1.0	0.8, 1.2	0.8	
			GG	184 (22)	245 (23)	1.0	0.7, 1.2	0.7	
<i>CYP17A1</i>	rs743572	Ex1+27T>C	TT	302 (36)	397 (37)	1.0			0.7
			CT	388 (47)	512 (47)	1.0	0.8, 1.2	0.9	
			CC	139 (17)	170 (16)	1.1	0.8, 1.4	0.6	
<i>CYP19A1</i>	rs28757184	T201M	CC	761 (93)	1016 (94)	1.0			
			TC/TT	58 (7)	60 (6)	1.3	0.9, 1.9	0.2	
<i>CYP11A1</i>	rs1048943	I462V	AA	774 (93)	1002 (93)	1.0			
			AG/GG	60 (7)	79 (7)	1.0	0.7, 1.4	0.9	
<i>CYP11B1</i>	rs1056836	V432L	CC	253 (31)	354 (33)	1.0			0.1
			GC	403 (49)	539 (50)	1.0	0.9, 1.3	0.6	
			GG	163 (20)	185 (17)	1.2	0.9, 1.6	0.1	
<i>CYP3A4</i>	rs4986910	M445T	TT	840 (99)	1045 (98)	1.0			
			TC	5 (<1)	18 (2)	0.3	0.1, 0.9	0.04	
<i>ESR1</i>	rs3020314	IVS4+5029C>T	TT	373 (45)	489 (46)	1.0			0.5
			CT	356 (43)	453 (43)	1.0	0.8, 1.3	0.8	
			CC	103 (12)	123 (12)	1.1	0.8, 1.5	0.5	
<i>HSD17B3</i>	rs2066479	G289S	GG	767 (90)	976 (91)	1.0			
			GA/AA	81 (10)	101 (9)	1.0	0.7, 1.4	0.9	
<i>HSD3B1</i>	rs4986952	R71I	GG	824 (98)	1057 (99)	1.0			
			TG	18 (2)	11 (1)	2.1	1.0, 4.4	0.06	
<i>PGR</i>	rs1042838	V660L	GG	569 (69)	766 (72)	1.0			0.3
			GT	237 (29)	263 (25)	1.2	1.0, 1.5	0.07	
			TT	19 (2)	33 (3)	0.8	0.4, 1.4	0.4	
<i>SHBG**</i>	rs6259	D356N	GG	664 (80)	846 (78)	1.0			0.4
			GA	158 (19)	213 (20)	0.9	0.8, 1.2	0.6	

Gene	Entrez SNP ID *	AA or nt variant ID †	Genotype	Cases (%) (n=859)	Controls (%) (n=1083)	OR ‡	95% CI	P- value	P- trend §
SRD5A2	rs523349	V89L	AA	12 (1)	22 (2)	0.7	0.3, 1.4	0.3	0.2
			GG	412 (50)	554 (51)	1.0			
			GC	342 (41)	445 (41)	1.0	0.9, 1.2	0.7	
			CC	77 (9)	80 (7)	1.3	0.9, 1.8	0.1	

* Entrez SNP reference ID number (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=snp>)

† Amino acid sequence variation (regular font), nucleotide sequence variation (*italics*)

‡ Adjusted for year of birth

§ 1 df test across genotypes

** Genotype frequencies in controls were borderline for Hardy-Weinberg expectation, $p = 0.05$

Analysis of interaction between estrogen and hormone-related SNPs, breast radiation dose from occupation and dose score from personal diagnostic x-rays, and breast cancer risk in US Radiologic Technologists

Table 3

Gene	Entrez SNP ID (rs)	AA or nt variant ID [†]	Geno- type	Cases (n=859)	Controls (n=1083)	Occupational radiation effect modification			Diagnostic radiation effect modification		
						EOB/ Gy [‡]	95% Confidence Interval	p- value [§]	EOB/unit breast dose score [‡]	95% Confidence Interval	p- value [§]
<i>COMT</i>	4680	V158M	AA	231 (28)	293 (27)	3.8	<0, 13.8	0.2	2.7	<0, 11.6	0.4
			GA	416 (51)	542 (50)	4.5	0.3, 11.5	1.9	<0, 6.5		
			GG	184 (22)	245 (23)	<0	<0, 4.1		<0	<0, 3.4	
<i>CYP17A1</i>	743572	<i>Ex1</i> +27T>C	TT	302 (36)	397 (37)	2.3	<0, 8.7	>0.5	<0	<0, 1.7	0.04
			CT	388 (47)	512 (47)	3.0	<0, 10.1		2.7	<0, 7.9	
			CC	139 (17)	170 (16)	2.5	<0, 14.0		9.6	0.1, 32.3	
<i>CYP19A1</i>	28757184	T201M	CC	761 (93)	1016 (94)	3.0	0.06, 7.9	0.003	1.1	<0, 3.9	0.2
			TC/TT	58 (7)	60 (6)	<0	<0, <0		14.0	<0, 65	
			AA	774 (93)	1002 (93)	3.3	0.2, 8.5	>0.5	1.3	<0, 4.3	>0.5
<i>CYP11A1</i>	1048943	I462V	AG/GG	60 (7)	79 (7)	1.9	<0, 20.1		3.5	<0, 32.4	
			CC	253 (31)	354 (33)	4.9	<0, 15.1	0.05	<0	<0, 2.0	0.07
			GC	403 (49)	539 (50)	<0	<0, 4.3		1.1	<0, 5.1	
<i>CYP11B1</i>	1056836	V432L	GG	163 (20)	185 (17)	10.2	2.0, 28.5		11.3	2.0, 29.8	
			CC/GC	253 (31)	354 (33)	1.4	<0, 6.0	0.06	0.6	<0, 3.2	0.03
			GG	163 (20)	185 (17)	10.1	1.6, 28.3		11.3	1.7, 29.9	
<i>CYP3A4</i>	4986910	M445T	TT	840 (99)	1045 (98)	2.7	<0, 7.4	>0.5	1.1	<0, 3.9	>0.5
			TC	5 (<1)	18 (2)	2.4	<0, >100		13.1	<0, >100	
			TT	373 (45)	489 (46)	1.7	<0, 7.2	>0.5	1.1	<0, 5.3	>0.5
<i>ESR1</i>	3020314	<i>IVS4</i> +5029C>T	CT	356 (43)	453 (43)	4.5	<0, 13.2		1.2	<0, 6.8	
			CC	103 (12)	123 (12)	3.7	<0, 17.8		2.1	<0, 12.6	
			GG	767 (90)	976 (91)	2.9	<0, 7.7	0.4	0.6	<0, 3.1	0.02
<i>HSD17B3</i>	2066479	G289S	GA/AA	81 (10)	101 (9)	<0	<0, 15.9		18.9	2.6, 59.7	
			GG	824 (98)	1057 (99)	3.0	0.03, 7.9	0.3	0.9	<0, 3.6	0.3
			TG	18 (2)	11 (1)	30.0	<0, >100		18.2	<0, >100	

Gene	Entrez SNP ID (rs)	AA or nt variant ID [†]	Geno- type	Cases (%) (n=859)	Controls (%) (n=1083)	Occupational radiation effect modification			Diagnostic radiation effect modification		
						EOR/ Gy [‡]	95% Confidence Interval	p- value [§]	EOR/unit breast dose score [‡]	95% Confidence Interval	p- value [§]
<i>PGR</i> ^{**}	1042838	V660L	GG	569 (69)	766 (72)	4.7	0.7, 11.4	0.08	2.0	<0, 5.7	0.4
			GT/TT	256 (31)	296 (28)	<0	<0, 5.1		0.08	<0, 5.8	
<i>SHBG</i> ^{**}	6259	D356N	GG	664 (80)	846 (78)	2.3	<0, 7.2	0.5	1.9	<0, 5.7	0.4
			GA/AA	170 (20)	235 (22)	5.5	<0, 19.1		<0	<0, 4.9	
<i>SRD5A2</i>	523349	V89L	GG	412 (50)	554 (51)	2.9	<0, 8.7	>0.5	1.0	<0, 4.4	0.4
			GC	342 (41)	445 (41)	2.0	<0, 9.6		2.9	<0, 9.7	
			CC	77 (9)	80 (7)	4.6	<0, 28		<0	<0, 5.5	

* Entrez SNP reference ID number (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=snp>)

[†] Amino acid sequence variation (regular font), nucleotide sequence variation (italics)

[‡] Excess Odds Ratio adjusted for year of birth and occupational or personal diagnostic radiation dose; significance of EOR/Gy is denoted when the 95% CI (profile likelihood bounds) exclude the null value of zero

[§] Likelihood ratio test comparing the genotype-specific EORs

^{**} Dominant mode of inheritance assumed due to small numbers of rare homozygotes