

Null Results in Brief

Variation in Genes Related to Obesity, Weight, and Weight Change and Risk of Contralateral Breast Cancer in the WECARE Study Population

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Abstract

Background: Body mass index (BMI), a known breast cancer risk factor, could influence breast risk through mechanistic pathways related to sex hormones, insulin resistance, chronic inflammation, and altered levels of adipose-derived hormones. Results from studies of the relationship between BMI and second primary breast cancer have been mixed. To explore the relationship between BMI and asynchronous contralateral breast cancer (CBC), we examined whether variants in genes related to obesity, weight, and weight change are associated with CBC risk.

Methods: Variants in 20 genes [182 single-nucleotide polymorphisms (SNP)] involved in adipose tissue metabolism, energy balance, insulin resistance, and inflammation, as well as those identified through genome-wide association studies (GWAS) of BMI and type II-diabetes were evaluated. We examined the association between variants in these genes and the risk of CBC among Caucasian participants [643 cases with CBC and 1,271 controls with unilateral breast cancer (UBC)] in the population-based Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study using conditional logistic regression.

Results: After adjustment for multiple comparisons, no statistically significant associations between any variant and CBC risk were seen. Stratification by menopausal or estrogen receptor (ER) status did not alter these findings.

Conclusion: Among women with early-onset disease who survive a first breast cancer diagnosis, there was no association between variation in obesity-related genes and risk of CBC.

Impact: Genetic variants in genes related to obesity are not likely to strongly influence subsequent risk of developing a second primary breast cancer. *Cancer Epidemiol Biomarkers Prev*; 21(12); 2261–7. ©2012 AACR.

Introduction

Studies examining the relationship between body mass index (BMI) and second primary breast cancer have produced mixed results (1, 2). We recently showed that in a

population of women with early-onset disease (diagnosed before age of 55 years), obese (BMI ≥ 30 kg/m²) postmenopausal women with estrogen receptor (ER)-negative breast cancer had more than 5-fold greater risk of asynchronous contralateral breast cancer risk (CBC) than women of normal weight (BMI < 25 kg/m²) with ER-negative first tumors [rate ratio (RR) = 5.64, 95% confidence interval (CI) 1.76, 18.1; ref. 2]. BMI could influence CBC risk through mechanistic pathways related to sex hormones, insulin resistance, chronic inflammation, and altered levels of adipose-derived hormones (3). The impact of variation in obesity-related genes on CBC risk and breast cancer risk in general is not well known. To further explore the relationship between BMI and risk of CBC, we examined the association between variants in genes related to obesity (weight, weight change, type II-diabetes, and adipose tissue metabolism) and CBC risk in a population-based study of breast cancer survivors.

Materials and Methods

The Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study is a multicenter, case-

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Table 1. Association between obesity-related variants and risk of contralateral breast cancer in the WECARE Study

SNP	Gene	Chr	Coordinate	Alleles	MAF ^a	HWE ^b	RR ^c	95% CI	P value
rs182052	ADIPOQ	3	188043475	G>A	0.35	0.88	1.0	0.8, 1.1	0.59
rs16861205	ADIPOQ	3	188044327	G>A	0.07	0.62	0.9	0.7, 1.2	0.61
rs822391	ADIPOQ	3	188046496	T>C	0.2	0.42	1.0	0.8, 1.2	0.83
rs16861210	ADIPOQ	3	188049191	G>A	0.09	0.16	1.0	0.8, 1.3	0.97
rs822394	ADIPOQ	3	188049421	C>A	0.19	0.35	1.0	0.9, 1.3	0.75
rs12495941	ADIPOQ	3	188050873	G>T	0.34	0.68	1.1	0.9, 1.3	0.16
rs7649121	ADIPOQ	3	188051478	A>T	0.18	0.55	1.0	0.8, 1.2	0.77
rs9877202	ADIPOQ	3	188052300	A>G	0.001	0.97	0.5	0.1, 5.1	0.54
rs17366568	ADIPOQ	3	188053146	G>A	0.13	0.31	0.9	0.7, 1.1	0.39
rs1501299	ADIPOQ	3	188053816	C>A	0.27	0.79	1.1	0.9, 1.3	0.18
rs3821799	ADIPOQ	3	188054179	C>T	0.47	0.56	0.9	0.8, 1.1	0.19
rs3774261	ADIPOQ	3	188054252	G>A	0.4	0.28	1.0	0.9, 1.2	0.80
rs17366743	ADIPOQ	3	188054782	T>C	0.03	0.14	0.8	0.5, 1.2	0.28
rs1063539	ADIPOQ	3	188058085	G>C	0.13	0.24	0.9	0.8, 1.2	0.57
rs7539542	ADIPOR1	1	201176596	C>G	0.33	0.22	1.1	0.9, 1.2	0.51
rs2275735	ADIPOR1	1	201182177	G>A	0.04	0.67	0.8	0.5, 1.2	0.30
rs12045862	ADIPOR1	1	201183428	C>T	0.28	0.34	1.0	0.8, 1.2	0.90
rs12733285	ADIPOR1	1	201188662	C>T	0.3	0.39	1.0	0.9, 1.2	0.90
rs10494839	ADIPOR1	1	201188816	T>C	0.29	0.92	1.0	0.8, 1.1	0.65
rs10753929	ADIPOR1	1	201189800	C>T	0.12	0.70	1.1	0.9, 1.4	0.31
rs12132093	ADIPOR1	1	201192735	G>A	0.009	0.76	1.4	0.7, 3.0	0.34
rs7514221	ADIPOR1	1	201193135	T>C	0.42	0.66	1.1	0.9, 1.3	0.39
rs11061925	ADIPOR2	12	1673494	C>T	0.32	0.49	1.0	0.8, 1.1	0.71
rs11061935	ADIPOR2	12	1684034	A>G	0.15	0.62	1.0	0.8, 1.2	0.69
rs7975600	ADIPOR2	12	1685512	A>T	0.16	0.90	1.0	0.8, 1.2	0.81
rs12826079	ADIPOR2	12	1696816	C>T	0.08	0.57	0.8	0.6, 1.1	0.27
rs11061946	ADIPOR2	12	1698787	C>T	0.07	0.33	1.1	0.8, 1.5	0.54
rs10773984	ADIPOR2	12	1701553	G>A	0.02	0.08	1.2	0.7, 1.9	0.49
rs11612383	ADIPOR2	12	1701615	G>A	0.32	0.91	1.0	0.8, 1.1	0.62
rs1058322	ADIPOR2	12	1707239	C>T	0.33	0.82	1.0	0.9, 1.2	0.95
rs9300298	ADIPOR2	12	1736455	T>A	0.5	0.11	1.0	0.8, 1.1	0.68
rs7967137	ADIPOR2	12	1740785	T>C	0.14	0.46	1.1	0.8, 1.3	0.69
rs12828908	ADIPOR2	12	1749645	A>G	0.33	0.02	1.0	0.8, 1.1	0.52
rs11061979	ADIPOR2	12	1752849	T>G	0.02	0.77	0.7	0.4, 1.1	0.13
rs12829901	ADIPOR2	12	1753638	G>A	0.02	0.47	0.6	0.3, 1.1	0.09
rs4140993	ADIPOR2	12	1759542	A>C	0.006	0.83	0.4	0.1, 1.3	0.14
rs12824519	ADIPOR2	12	1761788	G>A	0.02	0.47	0.6	0.3, 1.1	0.08
rs1044471	ADIPOR2	12	1767216	C>T	0.47	0.00	1.0	0.9, 1.2	0.70
rs9532558	FOXO1	13	40031014	T>C	0.02	0.37	0.5	0.3, 0.9	0.03
rs2755209	FOXO1	13	40035803	A>C	0.39	0.97	1.1	0.9, 1.3	0.33
rs2721068	FOXO1	13	40037711	T>C	0.26	0.82	1.0	0.9, 1.2	0.73
rs2180961	FOXO1	13	40038043	T>A	0.16	0.11	1.1	0.9, 1.3	0.47
rs2755212	FOXO1	13	40041147	T>C	0.01	0.69	1.0	0.5, 2.1	0.98
rs2755213	FOXO1	13	40044300	T>C	0.1	0.31	0.9	0.7, 1.2	0.49
rs2701870	FOXO1	13	40053775	G>C	0.07	0.84	0.9	0.7, 1.3	0.70
rs2951787	FOXO1	13	40059769	C>T	0.4	0.17	0.9	0.8, 1.1	0.46
rs2984121	FOXO1	13	40059978	C>G	0.18	0.74	1.0	0.8, 1.2	0.75
rs4429172	FOXO1	13	40087142	C>A	0.31	0.79	1.0	0.9, 1.2	0.74
rs12876443	FOXO1	13	40094876	T>C	0.1	0.00	1.1	0.9, 1.4	0.48
rs12866643	FOXO1	13	40110731	A>C	0.01	0.60	1.3	0.7, 2.4	0.36
rs12874490	FOXO1	13	40115733	G>C	0.01	0.72	2.1	1.1, 3.8	0.02

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Table 1. Association between obesity-related variants and risk of contralateral breast cancer in the WECARE Study (Cont'd)

SNP	Gene	Chr	Coordinate	Alleles	MAF ^a	HWE ^b	RR ^c	95% CI	P value
rs1334241	FOXO1	13	40121109	G>A	0.21	0.34	1.1	0.9, 1.3	0.44
rs9549248	FOXO1	13	40121395	A>G	0.002	0.93	0.0		0.98
rs9603776	FOXO1	13	40121885	C>T	0.03	0.01	1.1	0.7, 1.8	0.74
rs2297627	FOXO1	13	40131930	T>C	0.31	0.80	1.0	0.9, 1.2	0.63
rs6499640	FTO	16	52327177	A>G	0.41	0.31	0.9	0.8, 1.1	0.24
rs9940646	FTO	16	52358129	C>G	0.42	0.81	1.1	0.9, 1.3	0.34
rs1421085	FTO	16	52358454	T>C	0.39	0.94	1.1	0.9, 1.3	0.31
rs1121980	FTO	16	52366747	C>T	0.42	0.93	1.1	0.9, 1.3	0.35
rs8050136	FTO	16	52373775	C>A	0.39	0.75	1.1	0.9, 1.3	0.33
rs9939609	FTO	16	52378027	T>A	0.39	0.70	1.1	0.9, 1.3	0.31
rs16952624	FTO	16	52480338	C>T	0.004	0.99	0.0		0.98
rs7190492	FTO	16	53828752	G>A	0.37	0.51	1.0	0.9, 1.2	0.94
rs1111875	HHEX	10	94452861	G>A	0.41	0.94	1.0	0.8, 1.1	0.61
rs5015480	HHEX	10	94455538	C>T	0.41	0.99	1.0	0.8, 1.1	0.63
rs1951795	HIF1A	14	61241178	C>A	0.18	0.65	1.0	0.8, 1.2	0.82
rs10135579	HIF1A	14	61242939	A>G	0.05	0.01	0.8	0.6, 1.1	0.21
rs10129270	HIF1A	14	61251706	G>A	0.06	0.17	1.0	0.7, 1.4	0.98
rs4899056	HIF1A	14	61259283	C>T	0.1	0.37	1.0	0.8, 1.2	0.79
rs17099141	HIF1A	14	61263991	G>A	0.02	0.45	0.7	0.4, 1.2	0.23
rs2301111	HIF1A	14	61269953	C>G	0.2	0.54	1.0	0.9, 1.3	0.69
rs966824	HIF1A	14	61270270	C>T	0.04	0.47	1.0	0.7, 1.5	0.98
rs8012370	HIF1A	14	61274047	G>C	0.006	0.83	0.8	0.3, 2.1	0.57
rs10138153	HIF1A	14	61274927	C>T	0.006	0.83	0.8	0.3, 2.1	0.57
rs2301113	HIF1A	14	61276300	A>C	0.22	0.65	1.0	0.8, 1.2	0.99
rs11549465	HIF1A	14	61277309	C>T	0.1	0.63	1.1	0.9, 1.4	0.36
rs7143164	HIF1A	14	62166755	G>C	0.09	0.38	0.9	0.7, 1.2	0.63
rs9912108	IGF2BP1	17	44437242	T>C	0.0004	0.99	1.5	0.1, 26.0	0.76
rs17635703	IGF2BP1	17	44443154	A>C	0.05	0.81	1.0	0.7, 1.3	0.77
rs6504592	IGF2BP1	17	44445296	C>G	0.06	0.01	0.8	0.6, 1.1	0.24
rs9906710	IGF2BP1	17	44446281	C>A	0.36	0.36	1.1	0.9, 1.3	0.34
rs17708997	IGF2BP1	17	44457036	A>G	0.09	0.34	1.2	0.9, 1.6	0.13
rs8073244	IGF2BP1	17	44470036	C>T	0.15	0.68	1.1	0.9, 1.3	0.63
rs11872073	IGF2BP1	17	44474133	G>A	0.03	0.22	0.6	0.4, 1.1	0.10
rs4265867	IGF2BP1	17	44478822	G>A	0.02	0.40	1.2	0.7, 1.9	0.54
rs2969	IGF2BP1	17	44483245	C>T	0.26	0.70	0.9	0.8, 1.1	0.50
rs11655950	IGF2BP1	17	44484119	G>A	0.32	0.98	1.1	0.9, 1.3	0.43
rs3744085	IGF2BP1	17	44486899	T>C	0.49	0.10	1.1	0.9, 1.2	0.45
rs4402960	IGF2BP2	3	186994380	G>T	0.33	0.06	1.0	0.9, 1.2	0.88
rs9515119	IRS2	13	109207336	A>C	0.33	0.08	0.9	0.8, 1.1	0.28
rs7996317	IRS2	13	109207931	A>C	0.0008	0.98	1.0	0.1, 6.4	0.96
rs754204	IRS2	13	109209568	C>T	0.48	0.72	1.0	0.9, 1.2	0.65
rs913949	IRS2	13	109209796	A>G	0.19	0.78	1.1	0.9, 1.3	0.60
rs12583454	IRS2	13	109214505	G>A	0.02	0.59	0.6	0.4, 1.1	0.12
rs2241745	IRS2	13	109220531	A>G	0.14	0.46	1.1	0.9, 1.4	0.43
rs9559648	IRS2	13	109221795	C>T	0.31	0.71	1.0	0.9, 1.2	0.82
rs7323191	IRS2	13	109222075	A>T	0.15	0.07	1.1	0.8, 1.3	0.66
rs7999797	IRS2	13	109224000	A>G	0.46	0.32	1.0	0.8, 1.1	0.69
rs11841502	IRS2	13	109225988	G>A	0.34	0.31	1.0	0.9, 1.2	0.79
rs7997595	IRS2	13	109228768	C>G	0.15	0.55	1.1	0.9, 1.3	0.56
rs11618950	IRS2	13	109232310	G>A	0.17	0.20	1.0	0.8, 1.2	0.88
rs4773092	IRS2	13	109233953	G>A	0.4	0.79	1.1	0.9, 1.3	0.19

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Table 1. Association between obesity-related variants and risk of contralateral breast cancer in the WECARE Study (Cont'd)

SNP	Gene	Chr	Coordinate	Alleles	MAF ^a	HWE ^b	RR ^c	95% CI	P value
rs4731426	LEP	7	127669305	C>G	0.47	0.62	0.9	0.8, 1.1	0.34
rs11763517	LEP	7	127677297	T>C	0.5	0.74	1.0	0.9, 1.2	0.98
rs11760956	LEP	7	127678322	G>A	0.39	0.12	1.0	0.8, 1.1	0.54
rs3828942	LEP	7	127681540	G>A	0.42	0.69	1.0	0.9, 1.15	0.91
rs17151919	LEP	7	127681827	G>A	0.0008	0.98	0.0		0.98
rs12145690	LEPR	1	65659600	A>C	0.45	0.26	1.1	0.9, 1.2	0.54
rs4655802	LEPR	1	65660818	A>G	0.41	0.10	1.0	0.8, 1.1	0.69
rs9436739	LEPR	1	65663286	T>A	0.13	0.79	1.0	0.8, 1.2	0.81
rs9436298	LEPR	1	65663770	T>A	0.007	0.81	0.6	0.2, 1.9	0.41
rs9436740	LEPR	1	65664488	A>T	0.28	0.43	1.1	0.9, 1.3	0.49
rs3790433	LEPR	1	65666929	G>A	0.26	0.48	1.1	0.9, 1.3	0.33
rs9436303	LEPR	1	65669261	A>G	0.25	0.27	1.0	0.8, 1.2	0.94
rs1045895	LEPR	1	65670568	G>A	0.4	0.45	0.8	0.7, 1.0	0.01
rs1536466	LEPR	1	65671559	T>C	0.005	0.85	0.3	0.1, 1.2	0.09
rs10889552	LEPR	1	65678760	C>T	0.05	0.15	1.2	0.9, 1.7	0.25
rs970468	LEPR	1	65679077	T>G	0.36	0.66	1.2	1.0, 1.4	0.07
rs970467	LEPR	1	65679349	G>A	0.12	0.92	1.0	0.8, 1.3	0.73
rs17127652	LEPR	1	65707730	A>G	0.02	0.55	1.4	0.8, 2.4	0.24
rs6704167	LEPR	1	65710467	A>T	0.45	0.62	0.8	0.7, 1.0	0.01
rs7518849	LEPR	1	65721378	T>C	0.07	0.28	1.2	0.9, 1.6	0.17
rs6694528	LEPR	1	65735603	C>T	0.13	0.19	1.1	0.9, 1.4	0.25
rs7537093	LEPR	1	65739151	A>G	0.49	0.28	0.8	0.7, 1.0	0.02
rs6672331	LEPR	1	65748434	G>C	0.03	0.28	1.2	0.7, 1.8	0.54
rs11208659	LEPR	1	65751867	T>C	0.09	0.86	1.2	0.9, 1.5	0.16
rs1627238	LEPR	1	65758666	C>T	0.18	0.95	1.0	0.8, 1.2	0.93
rs1171279	LEPR	1	65761080	C>T	0.27	0.75	1.1	0.9, 1.3	0.43
rs1171267	LEPR	1	65776441	G>T	0.34	0.42	1.2	1.0, 1.4	0.03
rs1137100	LEPR	1	65809028	A>G	0.25	0.59	1.1	1.0, 1.4	0.13
rs3790429	LEPR	1	65809363	A>T	0.18	0.04	1.0	0.8, 1.2	0.70
rs13306519	LEPR	1	65810516	C>G	0.004	0.88	1.4	0.4, 4.3	0.59
rs6588152	LEPR	1	65811585	T>A	0.22	0.76	1.0	0.8, 1.2	0.69
rs6673591	LEPR	1	65820976	G>A	0.52	0.20	0.9	0.8, 1.1	0.21
rs1137101	LEPR	1	65831100	A>G	0.43	0.29	1.1	0.9, 1.3	0.32
rs4655537	LEPR	1	65831388	G>A	0.37	0.01	0.9	0.8, 1.1	0.47
rs3762274	LEPR	1	65836700	A>G	0.38	0.38	1.1	0.9, 1.2	0.56
rs17097193	LEPR	1	65839983	T>C	0.03	0.08	1.1	0.7, 1.7	0.58
rs11585329	LEPR	1	65846401	G>T	0.16	0.01	1.0	0.8, 1.3	0.78
rs8179183	LEPR	1	65848539	G>C	0.18	0.59	1.0	0.8, 1.2	0.68
rs12040007	LEPR	1	65852747	G>A	0.18	0.60	1.1	0.9, 1.3	0.43
rs4655557	LEPR	1	65853374	T>C	0.38	0.12	1.1	0.9, 1.2	0.52
rs17127832	LEPR	1	65869512	T>C	0.19	0.16	1.0	0.8, 1.2	0.91
rs17700144	MC4R	18	55962961	G>A	0.2	0.78	1.1	0.9, 1.3	0.43
rs17782313	MC4R	18	56002076	T>C	0.21	0.40	1.1	0.9, 1.3	0.47
rs12970134	MC4R	18	56035729	G>A	0.24	0.97	1.1	0.9, 1.3	0.51
rs17700633	MC4R	18	56080411	G>A	0.28	0.50	1.0	0.9, 1.2	0.80
rs2229616	MC4R	18	56190255	G>A	0.02	0.07	1.1	0.7, 1.8	0.66
rs8087522	MC4R	18	56191457	G>A	0.31	0.45	1.2	1.0, 1.4	0.03
rs3101336	NEGR1	1	72523772	G>A	0.38	0.48	1.1	0.9, 1.2	0.49
rs2568958	NEGR1	1	72537703	A>G	0.38	0.52	1.1	0.9, 1.2	0.44
rs2815752	NEGR1	1	72585027	T>C	0.38	0.46	1.1	0.9, 1.2	0.49
rs2227562	PLAU	10	75342966	G>A	0.15	0.41	1.2	1.0, 1.5	0.04

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Table 1. Association between obesity-related variants and risk of contralateral breast cancer in the WECARE Study (Cont'd)

SNP	Gene	Chr	Coordinate	Alleles	MAF ^a	HWE ^b	RR ^c	95% CI	P value
rs2227564	PLAU	10	75343106	C>T	0.24	0.53	1.1	0.9, 1.3	0.21
rs4065	PLAU	10	75346469	T>C	0.43	0.53	1.2	1.1, 1.4	0.01
rs344783	PLAUR	19	34997734	C>T	0.48	0.15	1.0	0.9, 1.2	0.93
rs4251938	PLAUR	19	48843460	A>G	0.12	0.04	0.9	0.7, 1.2	0.43
rs2302524	PLAUR	19	48848311	T>C	0.16	0.09	1.0	0.8, 1.2	0.75
rs4251871	PLAUR	19	48853337	G>C	0.05	0.52	1.0	0.7, 1.4	0.96
rs4251864	PLAUR	19	48854072	T>C	0.09	0.94	1.1	0.8, 1.4	0.60
rs2239372	PLAUR	19	48854793	G>A	0.5	0.76	1.0	0.9, 1.1	0.83
rs2283628	PLAUR	19	48854900	T>C	0.18	0.31	1.1	0.9, 1.3	0.32
rs397374	PLAUR	19	48855620	A>T	0.22	0.76	1.1	0.9, 1.3	0.30
rs2283632	PLAUR	19	48856930	G>A	0.11	0.11	1.1	0.8, 1.3	0.68
rs4251831	PLAUR	19	48861577	G>C	0.29	0.96	0.9	0.8, 1.1	0.18
rs2286960	PLAUR	19	48863864	C>T	0.24	0.70	1.0	0.9, 1.2	0.83
rs1801282	PPARG	3	12368124	C>G	0.12	0.13	1.0	0.8, 1.3	0.97
rs6092	SERPINE1	7	100558436	G>A	0.11	0.34	0.9	0.7, 1.2	0.61
rs2227666	SERPINE1	7	100561424	G>A	0.05	0.77	1.3	0.9, 1.8	0.18
rs2227712	SERPINE1	7	100563672	G>A	0.003	0.91	0.8	0.2, 3.1	0.78
rs2070682	SERPINE1	7	100563986	T>C	0.44	0.52	1.0	0.9, 1.2	0.61
rs2227692	SERPINE1	7	100565963	C>T	0.08	0.12	0.8	0.6, 1.1	0.22
rs1050813	SERPINE1	7	100568334	G>A	0.21	0.09	1.0	0.9, 1.2	0.83
rs2227714	SERPINE1	7	100568628	C>T	0.05	0.82	1.1	0.8, 1.6	0.51
rs7903146	TCF7L2	10	114748338	C>T	0.29	0.87	0.9	0.8, 1.1	0.42
rs2867125	TMEM18	2	612826	G>A	0.19	0.81	0.9	0.8, 1.1	0.53
rs6548238	TMEM18	2	624904	C>T	0.19	0.67	1.0	0.8, 1.2	0.83
rs4854344	TMEM18	2	628143	T>G	0.19	0.73	1.0	0.8, 1.2	0.85
rs7561317	TMEM18	2	634952	G>A	0.19	0.81	1.0	0.8, 1.2	0.81
rs10168696	TMEM18	2	662495	T>C	0.14	0.88	1.0	0.8, 1.2	0.76
rs2293084	TMEM18	2	665830	C>A	0.46	0.42	1.1	0.9, 1.2	0.50
rs2293083	TMEM18	2	666176	C>G	0.26	0.44	0.9	0.7, 1.0	0.07

Abbreviations: Chr, chromosome; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency.

^aMAF in UBC controls.

^bHWE in UBC controls, $P < 0.001$.

^cPer allele RR (log-additive model) adjusting for age at diagnosis and the counter-matching offset term.

control study in which cases are women with asynchronous CBC and controls are women with unilateral breast cancer (UBC). Recruitment, eligibility criteria, data and biospecimen collection, and genotype methods have been described (2, 4).

Eight genes were selected for evaluation based on genome-wide association studies (GWAS) of BMI, weight change, waist circumference, and type II-diabetes (*FTO*, *TCF7L2*, *TMEM18*, *NEGR1*, *MC4R*, *HHEX*, *IGF2BP2*, and *PPARG*; refs. 5–7). Twelve candidate genes were selected on the basis of biologic plausibility and known involvement with adipose tissue metabolism and obesity (*LEP*, *LEPR*, *ADIPOQ*, *ADIPOR1*, *ADIPOR2*, *HIF1A*, *PLAU*, *PLAUR*, *SERPINE1*, and *IGF2BP1*; ref. 3) or a functional relationship with both obesity and DNA repair (*IRS2* and *FOXO1*; ref. 8). Single-nucleotide polymorphisms (SNP) identified from GWAS were genotyped directly, whereas

SNPs in candidate genes were selected using a tagSNP approach, supplemented with potentially functionally relevant SNPs from dbSNP (4). A total of 194 SNPs in 20 genes was genotyped.

Of the 2,107 WECARE Study participants, 4 were excluded because they did not consent to genotyping. We further excluded from analysis 10 SNPs with less than 95% call rate, 1 monomorphic SNP, 1 SNP deviating from Hardy–Weinberg equilibrium ($P < 0.001$), and 20 subjects with more than 10% missing genotypes. To minimize the potential influence of ancestral differences in genotype frequencies, analyses were restricted to Caucasian women ($n = 169$ excluded). After quality control, analyses were conducted for 182 SNPs in 643 CBC cases and 1,271 UBC controls. Using HapMap Phase II release 24, these remaining variants captured 55% of the SNPs in *LEP*, 97% in *LEPR*, 100% in *ADIPOQ*, 93% in *ADIPOR1*, 96% in

ADIPOR2, 96% in *HIF1A*, 75% in *PLAU*, 75% in *PLAUR*, 72% in *SERPINE1*, 87% in *IGFBP1*, 82% in *IRS2*, and 84% in *FOXO1* ($r^2 > 0.80$).

Statistical Analysis

RRs and 95% CIs were estimated using conditional logistic regression by fitting a log-additive model, adjusting for age at first breast cancer diagnosis and accounting for the sampling probabilities of the UBC controls (described previously in ref. 9). A conservative Bonferroni correction was used to determine the multiple comparison cut-point [$\alpha = 0.0003$, obtained from $(0.05/182 \text{ SNPs})$], for example, the value for which results were considered statistically significant. The P_{ACT} method of adjusting for multiple comparisons, which takes into account linkage disequilibrium between nearby markers was also applied (10). We also conducted analyses stratified by menopausal status at first diagnosis, reference date (date of CBC diagnosis in cases and corresponding date in matched controls), and ER status of the first primary tumor.

Results

After adjustment for multiple comparisons, no statistically significant association between any genetic variant and risk of CBC was seen (Table 1). Similarly, no associations were seen in analyses stratified by menopausal status at first diagnosis or at reference date, or ER-status of the first primary breast cancer (results not shown).

Discussion

The risk of CBC was not associated with any of the variants of the 20 selected genes involved in adipose tissue metabolism, energy balance, insulin resistance, and inflammation or those identified through GWAS of BMI and type II-diabetes. The primary limitation of the analysis is the limited sample size available for subgroup analyses (e.g., when stratifying by ER-status). We also had limited information on the ER status of second cancers in cases, and therefore were unable to take this into account. A tagSNP approach was not taken for the genes identified by GWAS, and the coverage of some candidate genes was reduced after quality control. Thus, it is possible that untyped variants are associated with risk. Furthermore, other genes in these candidate pathways might be associated with CBC risk. Nonetheless, the results of this study suggest that among women, who survive a first breast cancer diagnosed before age of 55 years, genetic variation in obesity-related genes is not likely to influence subsequent risk of second primary breast cancer.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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