Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

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

Jennifer D. Brooks[1], Leslie Bernstein[2], Sharon N. Teraoka[5,6], Julia A. Knight[7], Lene Mellemkjær[8], Esther M. John[3], Kathleen E. Malone[9], Anne S. Reiner[1], Charles F. Lynch[10], Patrick Concannon[5,6], Robert W. Haile[4], and Jonine L. Bernstein[1] for the WECARE Study Collaborative Group

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 $\geq$ 30 kg/m^2) 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/m^2) 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–

Authors' Affiliations: [1]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York; [2]Department of Population Sciences, Beckman Research Institute of the City of Hope, Duarte; [3]Cancer Prevention Institute of California, Fremont; [4]Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine at the University of Southern California, Los Angeles, California; [5]Center for Public Health Genomics, [6]Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, Virginia; [7]Prosserman Centre for Health Research Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada; [8]Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark; [9]Program in Epidemiology, Division of Public Health Science, Fred Hutchinson Cancer Research Center, Seattle, Washington; and [10]Department of Epidemiology, The University of Iowa College of Public Health, Iowa City, Iowa

Corresponding Author: Jennifer D. Brooks, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 E 63rd Street, 2nd floor, New York 10065. Phone: 646-735-8068; Fax: 646-735-0010; E-mail: brooksj@mskcc.org

doi: 10.1158/1055-9965.EPI-12-1036

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

(Continued on the following page)

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

(Continued on the following page)

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

(Continued on the following page)

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.

[a]MAF in UBC controls.

[b]HWE in UBC controls, $P < 0.001$.

[c]Per 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 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.D. Brooks, L. Bernstein, P. Concannon, J.L. Bernstein
Development of methodology: J.D. Brooks, L. Bernstein, J.L. Bernstein
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Bernstein, S.N. Teraoka, L. Mellemkjær, K.E. Malone, C.F. Lynch, P. Concannon, J.L. Bernstein
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.D. Brooks, L. Bernstein, J.A. Knight, L. Mellemkjær, A.S. Reiner, J.L. Bernstein
Writing, review, and/or revision of the manuscript: J.D. Brooks, L. Bernstein, S.N. Teraoka, J.A. Knight, L. Mellemkjær, E.M. John, K.E. Malone, A.S. Reiner, C.F. Lynch, P. Concannon, R.W. Haile, J.L. Bernstein
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.D. Brooks, L. Bernstein, J.L. Bernstein
Study supervision: L. Bernstein, K.E. Malone, J.L. Bernstein

Acknowledgments

The authors thank the women who participated in the WECARE Study.

The WECARE Study Collaborative Group:
Memorial Sloan Kettering Cancer Center (New York): J.L. Bernstein (WECARE Study Principal Investigator), C. Begg, J.D. Brooks, M. Capanu, X. Liang, A.S. Reiner, I. Orlow, R. Klein (co-investigator), K. Offit (co-investigator), M. Woods
Beckman Research Institute, City of Hope National Medical Center (Duarte, CA): L. Bernstein (sub-contract Principal Investigator)
Cancer Prevention Institute of California (Fremont, CA): E.M. John (sub-contract Principal Investigator)
Danish Cancer Society (Copenhagen, Denmark): J.H. Olsen (sub-contract Principal Investigator), L. Mellemkjær
Fred Hutchinson Cancer Research Center (Seattle, WA): K.E. Malone (sub-contract Principal Investigator)
International Epidemiology Institute (Rockville, MD) and Vanderbilt University (Nashville, TN): J.D. Boice Jr (sub-contract Principal Investigator)
National Cancer Institute (Bethesda, MD): D. Seminara
New York University (New York): R.E. Shore (sub-contract Principal Investigator)
Samuel Lunenfeld Research Institute, Mount Sinai Hospital (Toronto, Canada): J. Knight (sub-contract Principal Investigator), A. Chiarelli (co-investigator)
Translational Genomics Research Institute (TGen; Phoenix, AZ): D. Duggan (sub-contract Principal Investigator)
University of Iowa (Iowa City, IA): C.F. Lynch (sub-contract Principal Investigator), J. DeWall
University of Southern California (Los Angeles, CA): R.W. Haile (sub-contract Principal Investigator), D. Stram (co-investigator), D.C. Thomas (co-investigator), A.T. Diep (co-investigator), S. Xue, N. Zhou, E. Ter-Karapetova
University of Texas, MD Anderson Cancer Center (Houston, TX): M. Stovall (sub-contract Principal Investigator), S. Smith (co-investigator)
University of Virginia (Charlottesville, VA): P. Concannon (sub-contract Principal Investigator), S. Teraoka (co-investigator)

Grant Support

This research was funded by the National Cancer Institute at the NIH (R01CA114236, U01CA083178, and R01CA129639).

Received September 7, 2012; revised August 20, 2012; accepted September 12, 2012; published OnlineFirst October 2, 2012.

References

1. Li CI, Daling JR, Porter PL, Tang M-TC, Malone KE. Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. J Clin Oncol 2009;27:5312–8.
2. Brooks J, John E, Mellemkjær L, Reiner A, Malone K, Lynch C, et al. Body mass index and risk of second primary breast cancer: the WECARE Study. Breast Cancer Res Treat 2012;131:571–80.
3. Neilson HK, Friedenreich CM, Brockton NT, Millikan RC. Physical activity and postmenopausal breast cancer: proposed biologic

mechanisms and areas for future research. Cancer Epidemiol Biomarkers Prev 2009;18:11–27.
4. Brooks JD, Teraoka SN, Reiner AS, Satagopan JM, Bernstein L, Thomas DC, et al. Variants in activators and downstream targets of ATM, radiation exposure, and contralateral breast cancer risk in the WECARE Study. Hum Mutat 2012;33:158–64.
5. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 2009; 41:25–34.
6. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40:638–45.
7. Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 2009;41:18–24.
8. Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER III, Hurov KE, Luo J, et al. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science 2007;316:1160–6.
9. Bernstein J, Langholz B, Haile R, Bernstein L, Thomas D, Stovall M, et al. Study design: evaluating gene-environment interactions in the etiology of breast cancer—the WECARE Study. Breast Cancer Res 2004;6:R199–214.
10. Conneely KN, Boehnke M. So many correlated tests, so little time! Rapid adjustment of *P* values for multiple correlated tests. Am J Hum Genet 2007;81:1158–68.