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Brief Original Contribution

N-Acetyltransferase 2 Polymorphisms, Tobacco Smoking, and Breast Cancer Risk in the Breast and Prostate Cancer Cohort Consortium

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Common polymorphisms in the *N*-acetyltransferase 2 gene (*NAT2*) modify the association between cigarette smoking and bladder cancer and have been hypothesized to determine whether active cigarette smoking increases breast cancer risk. The authors sought to replicate the latter hypothesis in a prospective analysis of 6,900 breast cancer cases and 9,903 matched controls drawn from 6 cohorts (1989–2006) in the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium. Standardized methods were used to genotype the 3 most common polymorphisms that define *NAT2* acetylation phenotype (rs1799930, rs1799931, and rs1801280). In unconditional logistic regression analyses, breast cancer risk was higher in women with more than 20 pack-years of active cigarette smoking than in never smokers (odds ratio (OR) = 1.28, 95% confidence interval (CI): 1.17, 1.39), after controlling for established risk factors other than alcohol consumption and physical inactivity. However, associations were similar for the slow (OR = 1.25, 95% CI: 1.11, 1.39) and rapid/intermediate (OR = 1.24, 95% CI: 1.08, 1.42) acetylation phenotypes, with no evidence of interaction ($P = 0.87$). These results provide some support for the hypothesis that long-term cigarette smoking may be causally associated with breast cancer risk but underscore the need for caution when interpreting sparse data on gene-environment interactions.

arylamine *N*-acetyltransferase; breast neoplasms; NAT2 protein, human; polymorphism, single nucleotide; smoking

Abbreviations: Cal/EPA, California Environmental Protection Agency; IARC, International Agency for Research on Cancer; NAT2, *N*-acetyltransferase 2; SNP, single nucleotide polymorphism.

Tobacco smoke contains over 4,000 chemicals, among which more than 60 are listed as class 1 or class 2 carcinogens by the International Agency for Research on Cancer (IARC) (1). Approximately 20 of the constituents in cigarette smoke designated as definite or probable human carcinogens cause mammary tumors in rodents. However, whether active cigarette smoking increases breast cancer risk in humans has been debated for decades. In its most recent evaluation, the IARC judged the evidence for active smoking as "limited" (2), while both the California Environmental Protection Agency (Cal/EPA) (3) and a panel convened in Canada in May 2009 (4) concluded that "the associations between active smoking and both pre- and postmenopausal breast cancer are consistent with causality" (4, p. 11). Both the IARC and Cal/EPA designations acknowledge that bias, confounding, and chance cannot be excluded with reasonable certainty, even though the Cal/EPA terminology appears to be more definitive.

Part of the controversy surrounding cigarette smoking as a possible cause of breast cancer concerns whether common genetic polymorphisms predispose some female smokers to substantially greater risk. Polymorphisms in the *N*-acetyltransferase 2 gene (*NAT2*) have received the most attention. NAT2 is one of 2 human *N*-acetyltransferases that acetylate and thereby detoxify aromatic amines, an important class of carcinogens in tobacco smoke. The hypothesis that female smokers with the slow acetylation phenotype may have higher risk of breast cancer than those with the intermediate or rapid acetylation phenotype has been examined in case-control studies with retrospectively assessed information on smoking history, as well as in case-control studies nested in

cohorts with prospectively assessed smoking history. The results of individual studies have been inconsistent. Findings have been summarized in a meta-analysis that included 6,758 breast cancer cases and a pooled analysis of 4,264 cases, both carried out by Ambrosone et al. (5). In the pooled analysis, Ambrosone et al. reported a statistically significant 1.4- to 1.5-fold increase in breast cancer risk among premenopausal and postmenopausal women who were slow acetylators and had accrued more than 20 pack-years of cigarette smoking, as compared with slow acetylators who had never smoked (5). The increase in risk was confined to persons with the slow acetylation phenotype; no statistically significant increase in risk was observed among rapid/intermediate acetylators who reported more than 20 pack-years of smoking (*P* for interaction not reported).

We sought to replicate this finding in a consortium of 6 large cohort studies being conducted in the United States and Europe with prospectively collected information on smoking history. Included in our analyses were 6,900 breast cancer cases and 9,903 controls. While the primary aim of our study was to assess interaction between smoking and the relevant *NAT2* polymorphisms, we also assessed whether 2 polymorphisms associated with both nicotine addiction and lung cancer risk in genome-wide association studies were associated with breast cancer in our cohorts.

MATERIALS AND METHODS

Study population

The Breast and Prostate Cancer Cohort Consortium, which includes large, well-established cohorts assembled in the United States and Europe, and the participating cohorts have been described in detail elsewhere (6). Further details regarding the numbers of cases and controls obtained from each cohort, as well as the distributions of age and menopausal status at baseline, are shown in Table 1. Dates ranged from 1989 to 2006. Informed consent was obtained from all subjects, and each cohort study was approved by the relevant appropriate institutional review board. A relatively small number of cases ($n = 392$) from the Nurses' Health Study cohort were included in the previous meta-analysis by Ambrosone et al. (5), and none were included in the prior pooled analyses. Because our main comparisons were with the prior pooled analyses (5), we did not exclude this small number of subjects from the analyses described here. In order to minimize issues of population stratification, we restricted our analyses to Caucasian women.

Breast cancer cases were confirmed by medical records, pathology reports, and/or linkage with population-based tumor registries. Controls were matched to cases by age at study entry (study baseline), and in some cohorts, additional matching criteria were employed (for example, country of residence in the European Prospective Investigation into Cancer and Nutrition).

Using a standardized approach, we genotyped the 3 most common polymorphisms that define NAT2 acetylation phenotype (rs1799930, rs1799931, and rs1801280), as well as 2 polymorphisms related to nicotine addiction and lung cancer risk (rs12914385 (7) and rs8034191 (8)), in 6,900 breast cancer cases and 9,903 matched controls with baseline information on tobacco smoking history and established breast cancer risk factors. All studies included blinded replicate samples for assessment of genotype reproducibility. No quality control discrepancies were detected in genotyping these replicates; genotyping success rates were high in all studies (>95%); and no deviations from Hardy-Weinberg equilibrium were observed.

NAT2 acetylation phenotype was determined using the NAT2PRED Web server (9). While NAT2PRED allows for the use of 6 polymorphisms in *NAT2* to determine acetylation phenotype, linkage disequilibrium is high between the 3 single nucleotide polymorphisms (SNPs) we used and the other 3 SNPs possible ($D' > 0.80$), and these same polymorphisms were used in the majority of the studies in the meta-analysis of Ambrosone et al. (5). Therefore, we included only these SNPs in our analyses.

Duration of cigarette smoking and pack-years of smoking were calculated using smoking data collected at study baseline. Both factors were analyzed as continuous and categorical variables. Smoking duration was stratified into $\leq$15 years and >15 years, and pack-years were stratified into $\leq$20 and >20, as in the study by Ambrosone et al. (5). Where data were available, we also calculated smoking duration and pack-years during the period between menarche and age at first full-term pregnancy (or menopause for nulliparous women). We combined intermediate acetylators with rapid acetylators in order to make our analyses more comparable with prior studies. Power calculations were carried out using QUANTO (10, 11). Unconditional logistic regression analyses controlling for age at baseline, body mass index at baseline, ever use of menopausal hormone therapy at baseline, parity, and cohort were used to estimate associations and 95% confidence intervals, with product terms included to evaluate interactions. All *P* values reported here are 2-sided. Tests for heterogeneity across cohorts were carried out using Cochran's *Q* test. Statistical testing was carried out using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Breast cancer risk was weakly associated with both duration of smoking and pack-years of smoking (for each additional year of smoking and for each additional pack-year, odds ratio = 1.01, 95% confidence interval: 1.00, 1.01; Table 2). No main-effect association was seen between NAT2 acetylation phenotype and breast cancer risk (Table 2). The associations observed between breast cancer and the 2 smoking parameters (for more than 20 pack-years of smoking, odds ratio = 1.28, 95% confidence interval: 1.17, 1.39) were not modified by NAT2 status, irrespective of whether the smoking variables were specified as continuous or categorical (all *P*'s for interaction ≥ 0.03; Table 3). No heterogeneity across the 6 cohorts in the main effects of either NAT2 acetylation phenotype or smoking history was observed (all *P*'s for heterogeneity > 0.30; Table 2). Assuming a null association between NAT2 acetylation phenotype (rapid/intermediate vs. slow acetylators) and breast cancer risk and a 1% increase in breast cancer risk per pack-year or year of cigarette smoking,

Table 1. Contribution of Each Cohort in the Breast and Prostate Cancer Cohort Consortium to an Analysis of Interaction Between Cigarette Smoking and Relevant *N*-Acetyltransferase 2 Polymorphisms in Breast Cancer Risk, 1989–2006

Cohort	Year Blood Collection Began	No. of Cases	No. of Controls	Mean Age, years (SD)[a]		Postmenopausal[a]			
				Cases	Controls	Cases		Controls	
						No.	%	No.	%
Cancer Prevention Study 2	1998	622	862	62.2 (6.2)	62.0 (6.1)	589	94.7	813	94.3
European Prospective Investigation into Cancer and Nutrition	1992	2,456	3,352	54.5 (7.6)	54.6 (8.0)	1,565	63.7	2,099	62.6
Multi-Ethnic Cohort Study	1996	522	574	60.6 (8.3)	59.2 (8.7)	463	88.7	472	82.2
Nurses' Health Study	1989	1,632	2,629	61.5 (8.1)	62.4 (8.2)	1,151	70.5	1,934	73.6
Nurses' Health Study II	1999	469	1,239	45.9 (4.2)	45.6 (4.1)	144	30.7	368	29.7
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	1993	798	1,000	62.3 (5.0)	62.3 (5.1)	789	98.9	992	99.2
Women's Health Study	1993	701	696	56.0 (7.3)	56.0 (7.3)	446	63.6	418	60.1

Abbreviation: SD, standard deviation.
[a] Age and menopausal status as determined at baseline (blood collection).

our study had greater than 85% power to detect an odds ratio of 1.1 for interaction between NAT2 acetylation phenotype and cigarette smoking.

Upon examining smoking duration and pack-years during the period between menarche and first full-term pregnancy (or menopause for nulliparous women), only the pack-years variable was marginally associated with breast cancer risk (odds ratio = 1.01, 95% confidence interval: 1.00, 1.01; Table 3). No differences in this association were observed by NAT2 acetylation phenotype status. Stratifying analyses by menopausal status at baseline did not reveal any differences in the association between smoking and breast cancer risk by NAT2 acetylation phenotype status in either menopausal group (Table 4). Similarly, no associations with breast cancer risk were observed for rs12914385 or rs8034191—SNPs reported to be associated with nicotine addiction and lung cancer risk, respectively, in previous genome-wide association studies on lung cancer (7, 8). In addition, these SNPs did not interact statistically with *NAT2* genotype (Appendix Table 1) to influence breast cancer risk.

DISCUSSION

Active smoking is designated as being causally related to cancer at 17 or more sites or subsites. Our study found a modest association between breast cancer and both duration and pack-years of active cigarette smoking but no evidence of modification of the smoking relation by *NAT2* genotype.

The modest association that we observed between breast cancer and long-term smoking is inconclusive, partly because our study was not sufficiently large to restrict our analyses to nondrinkers. Smoking and alcohol consumption are closely related in terms of both duration and intensity. An influential collaborative analysis restricted to nondrinkers found no association between ever smoking and breast cancer (12), and on the basis of this finding, the investigators proposed

Table 2. Association Between *N*-Acetyltransferase 2 Phenotype and Smoking History in Breast Cancer Risk in the Breast and Prostate Cancer Cohort Consortium, 1989–2006

	Cases			Controls			Odds Ratio[a]	95% Confidence Interval	*P* for Heterogeneity[b]
	No.	%	Mean (SD)	No.	%	Mean (SD)			
NAT2 phenotype[c]									
Rapid acetylator	456	6.6		625	6.3		1	Reference	0.95
Intermediate acetylator	2,369	34.1		3,366	33.8		0.97	0.85, 1.11	0.70
Slow acetylator	4,128	59.4		5,974	60.0		0.96	0.84, 1.09	0.40
Smoking history									
Years (continuous)			24.0 (13.1)			23.2 (13.1)	1.01	1.00, 1.01	0.33
Pack-years (continuous)			20.5 (18.7)			18.8 (17.2)	1.01	1.00, 1.01	0.37

Abbreviations: NAT2, *N*-acetyltransferase 2; SD, standard deviation.
[a] Logistic regression was used to estimate odds ratios and 95% confidence intervals, adjusted for age at baseline, body mass index at baseline, ever use of menopausal hormone therapy at baseline, parity, and cohort.
[b] *P* for heterogeneity across cohorts using Cochran's *Q* test for all odds ratios (including the trend test).
[c] Test of trend from rapid acetylation phenotype to slow acetylation phenotype: $P = 0.52$.

Table 3. Interactions Between *N*-Acetyltransferase 2 Phenotype and Smoking History in Breast Cancer Risk, Breast and Prostate Cancer Cohort Consortium, 1989–2006

Smoking History and NAT2 Phenotype	Cases			Controls			Odds Ratio[a]	95% Confidence Interval	*P* for Interaction[b]
	Mean (SD)	No.	%	Mean (SD)	No.	%			
Duration of smoking (continuous), years									0.98
Rapid + intermediate acetylators	23.9 (13.0)			23 (12.9)			1.01	1.00, 1.01	
Slow acetylators	24.0 (13.2)			23.2 (13.1)			1.01	1.00, 1.01	
Pack-years of smoking (continuous)									0.87
Rapid + intermediate acetylators	20.0 (18.0)			18.7 (17.2)			1.01	1.00, 1.01	
Slow acetylators	20.7 (19.1)			19.0 (17.3)			1.01	1.00, 1.01	
Duration of smoking between menarche and first full-term pregnancy (continuous), years									0.03
Rapid + intermediate acetylators	7.4 (7.7)			7.7 (8.1)			1.00	1.00, 1.00	
Slow acetylators	7.4 (7.7)			7.9 (8.6)			1.00	1.00, 1.00	
Pack-years of smoking between menarche and first full-term pregnancy (continuous)									0.14
Rapid + intermediate acetylators	5.4 (7.5)			5.3 (6.9)			1.01	1.00, 1.02	
Slow acetylators	5.5 (7.4)			5.6 (7.5)			1.00	1.00, 1.01	
Duration of smoking (categorical), years									0.97
Rapid + intermediate acetylators									
Never smoking		1,431	51.7		2,165	55.4	1	Reference	
≤15		410	14.8		559	14.3	1.14	0.98, 1.32	
>15		927	33.5		1,182	30.3	1.17	1.04, 1.30	
Slow acetylators									
Never smoking		2,090	51.5		3,205	54.8	1	Reference	
≤15		606	14.9		865	14.8	1.07	0.95, 1.21	
>15		1,362	33.6		1,775	30.4	1.18	1.07, 1.29	
Pack-years of smoking (categorical)									0.87
Rapid + intermediate acetylators									
Never smoking		1,431	52.7		2,163	56.5	1	Reference	
≤20		772	28.4		1,045	27.3	1.13	1.01, 1.27	
>20		514	18.9		619	16.7	1.24	1.08, 1.42	
Slow acetylators									
Never smoking		2,090	52.8		3,205	56.1	1	Reference	
≤20		1,108	28.0		1,571	27.5	1.08	0.92, 1.19	
>20		757	19.1		936	16.4	1.25	1.11, 1.39	

Abbreviations: NAT2, *N*-acetyltransferase 2; SD, standard deviation.

[a] Logistic regression was used to estimate odds ratios and 95% confidence intervals, adjusted for age at baseline, body mass index at baseline, ever use of menopausal hormone therapy at baseline, parity, and cohort. For continuous variables, persons with no exposure comprised the reference category.

[b] Interaction *P* values were tested using a multiplicative interaction term in the models.

that future analyses of this issue be restricted to nondrinkers to avoid residual confounding by alcohol consumption. However, interpretation of that report's results has been criticized because of the crude definition of smoking used (ever vs. never) and the failure to consider smoking status, duration of smoking, or initiation during periods of potentially greater susceptibility (4). Our analyses also could not control for physical inactivity, which is associated with both long-term smoking and breast cancer risk and could confound the observed association.

Several genetic polymorphisms have been proposed to modify associations between tobacco exposure and cancer risk. The evidence for effect modification by common *NAT2* polymorphisms on the risk of bladder cancer from tobacco exposures is strong (13–17). This association is attributed to incompletely *N*-acetylated (detoxified) aromatic amines from tobacco smoke being held in the bladder before being eliminated. On the basis of these findings for bladder cancer, it has been hypothesized that *NAT2* polymorphisms might also modify the association between tobacco exposure and breast

Table 4. Relation Between Cigarette Smoking and *N*-Acetyltranserase 2 Phenotype in Breast Cancer Risk, According to Menopausal Status at Baseline, Breast and Prostate Cancer Cohort Consortium, 1989–2006

Smoking History, Menopausal Status, and NAT2 Phenotype	Mean (SD)		Odds Ratio[a]	95% Confidence Interval	*P* for Interaction[b]
	Cases	Controls			
Duration of smoking (continuous), years					
Premenopausal					0.99
Rapid + intermediate acetylators	8.2 (11.5)	6.8 (10.1)	1.00	0.99, 1.01	
Slow acetylators	8.0 (11.3)	7.1 (10.5)	1.00	0.99, 1.01	
Postmenopausal					0.71
Rapid + intermediate acetylators	12.6 (15.8)	11.6 (15.1)	1.00	1.00, 1.01	
Slow acetylators	10.8 (13.6)	11.7 (15.6)	1.01	1.00, 1.01	
Pack-years of smoking					
Premenopausal					0.98
Rapid + intermediate acetylators	5.6 (10.4)	4.8 (9.1)	1.00	0.99, 1.01	
Slow acetylators	5.6 (10.3)	5.0 (9.7)	1.00	0.99, 1.01	
Postmenopausal					0.65
Rapid + intermediate acetylators	10.6 (17.3)	9.4 (16.1)	1.01	1.00, 1.01	
Slow acetylators	11.1 (18.3)	9.6 (16.3)	1.01	1.00, 1.01	

Abbreviations: NAT2, *N*-acetyltransferase 2; SD, standard deviation.

[a] Logistic regression was used to estimate odds ratios and 95% confidence intervals, adjusted for age at baseline, body mass index at baseline, ever use of menopausal hormone therapy at baseline, parity, and cohort. Persons with no exposure comprised the reference category.

[b] Interaction *P* values were tested using a multiplicative interaction term in the models.

cancer risk; it would be modified similarly by these same polymorphisms. Furthermore, the inconsistencies observed among studies with respect to an association between cigarette smoking and breast cancer risk may be due to the existence of subpopulations that are more susceptible to the effects of cigarette smoking based on genetic or other environmental exposures.

In a recent meta-analysis including 6,758 breast cancer cases, Ambrosone et al. (5) observed significant associations between cigarette smoking and breast cancer risk only among women carrying the slow acetylation phenotype. However, in our analyses we did not see any modification of the effect of smoking on breast cancer risk by this phenotype. Indeed, the odds ratios for long-term smoking, measured by either duration or pack-years, were almost equivalent in women with the two acetylation phenotypes.

It is not entirely clear why our results differed from those of the pooled analysis by Ambrosone et al. (5). Our analyses included 6,900 breast cancer cases and was therefore slightly larger than the pooled analyses of Ambrosone et al. (4,264 cases). The cohort investigators in our study assessed smoking history prospectively, before the diagnosis of breast cancer, whereas most of the studies included in the pooled analyses of Ambrosone et al. were retrospective case-control studies. It is plausible that recall bias might differentially affect the reporting of smoking histories by cases and controls but not that it would differentially affect the genetic subgroups. The percentages of never smokers were similar among the cases in our study (52%) and in the pooled analysis by Ambrosone et al. (47%), as were the percentages of controls (55% and 50%, respectively, as calculated from Ambrosone et al.'s Table 4 (5)). Sampling variation with respect to *NAT2* polymorphisms may be greater in small, geographically dispersed case-control studies than in a small number of large cohort studies. The most likely explanation for the divergent results, other than chance, is that the studies included by Ambrosone et al. were all drawn from published articles on this issue and were therefore more susceptible to publication bias than were the studies included in our analysis.

Our results do not support the prior reports of effect modification by NAT2 acetylation phenotypes of the association between tobacco exposure and breast cancer risk. Given our large sample size, we can exclude all but very small interaction risk estimates. This study had greater than 85% power to detect an interaction odds ratio of 1.1 for a continuous environmental exposure at a relatively conservative alpha value of 0.01, under the assumption of modest associations with smoking and no overall association between NAT2 acetylation phenotype and breast cancer risk.

It has also been hypothesized that smoking exposure during the period between menarche and first full-term pregnancy, a period of mammary gland development, may be particularly relevant to breast cancer risk and therefore may be modified by NAT2 phenotype. Similar to our overall findings, we did not see any effect modification by NAT2 acetylation phenotype of the risk of breast cancer conferred by tobacco exposures incurred during this critical life period.

Discordance between studies of cigarette smoking and breast cancer risk may still be explained by environmental, lifestyle, or genetic factors. However, we did not observe any modification by NAT2 acetylation phenotype on the putative risk of breast cancer associated with tobacco exposure. Our results suggest that it is not necessary to assess common variations in *NAT2* genotype in order to evaluate whether a

smoking-breast cancer association exists. Despite the lack of modification of risk by NAT2 acetylation phenotype, reducing exposure to cigarette smoke remains of great importance to reducing risks of various diseases, including many cancers.

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Appendix Table 1. Relation Between Single Nucleotide Polymorphisms Previously Found to Be Associated With Lung Cancer[a] and Breast Cancer Risk, Breast and Prostate Cancer Cohort Consortium, 1989–2006

SNP and Genotype	Cases		Controls		Odds Ratio[b]	95% Confidence Interval	*P* for Interaction[c]
	No.	%	No.	%			
rs12914385[d]							0.37
C/C	2,706	39.1	3,766	39.1	1	Reference	
C/T	3,185	46.1	4,607	46.5	0.96	0.90, 1.03	
T/T	1,025	14.8	1,533	15.5	0.93	0.85, 1.02	
rs8034191[e]							0.11
T/T	3,078	44.4	4,311	43.4	1	Reference	
T/C	3,045	43.9	4,372	44.1	0.98	0.91, 1.05	
C/C	809	11.7	1,242	12.1	0.92	0.83, 1.02	

Abbreviations: NAT2, *N*-acetyltransferase 2; SNP, single nucleotide polymorphism.

[a] SNPs reported to be associated with nicotine addiction and lung cancer risk, respectively, in genome-wide association studies (7, 8).

[b] Logistic regression was used to estimate odds ratios and 95% confidence intervals, adjusted for age at baseline, body mass index at baseline, ever use of menopausal hormone therapy at baseline, parity, and cohort.

[c] *P* for interaction between SNP and NAT2 phenotype. Interactions were tested using a multiplicative interaction term in the models.

[d] *P*-trend = 0.11.

[e] *P*-trend = 0.15.