Review

Is the Association between Cigarette Smoking and Breast Cancer Modified by Genotype? A Review of Epidemiologic Studies and Meta-analysis

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Abstract

Epidemiologic studies have examined the association between cigarette smoking and breast cancer risk according to genotype with increasing frequency, commensurate with the growing awareness of the roles genes play in detoxifying or activating chemicals found in cigarette smoke and in preventing or repairing the damage caused by those compounds. To date, ~50 epidemiologic studies have examined the association between smoking and breast cancer risk according to variation in genes related to carcinogen metabolism, modulation of oxidative damage, and DNA repair. Some of the findings presented here suggest possible effect modification by genotype. In particular, 14 epidemiologic studies have tended to show positive associations with long-term smoking among *NAT2* slow acetylators, especially among postmenopausal women. Summary analyses produced overall meta–relative risk (RR) estimates for smoking of 1.2 [95% confidence interval (95% CI), 1.0-1.5] for rapid acetylators and 1.5 (95% CI, 1.2-1.8) for slow acetylators. After stratification by menopausal status, the meta-RR for postmenopausal slow acetylators was 2.4 (95% CI, 1.7-3.3), whereas similar analyses for the other categories showed no association. In addition, summary analyses produced meta-RRs for smoking of 1.1 (95% CI, 0.8-1.4) when *GSTM1* was present and 1.5 (95% CI, 1.1-2.1) when the gene was deleted. Overall, however, interpretation of the available literature is complicated by methodologic limitations, including small sample sizes, varying definitions of smoking, and difficulties involving single nucleotide polymorphism selection, which likely have contributed to the inconsistent findings. These methodologic issues should be addressed in future studies to help clarify the association between smoking and breast cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(4):602–11)

Introduction

Animal experiments and *in vitro* studies have shown that compounds found in tobacco smoke, such as polycyclic hydrocarbons, aromatic amines, and *N*-nitrosamines, may induce mammary tumors (1-3). The finding of smoking-specific DNA adducts (4-7) and p53 gene mutations (8) in the breast tissue of smokers also support the biological plausibility of a positive association between cigarette smoking and breast cancer. Nonetheless, >100 epidemiologic studies on smoking and breast cancer have shown inconsistent results, and the association remains the focus of debate (1-3). Epidemiologic studies have examined the association between smoking and breast cancer risk according to genotype with increasing frequency, commensurate with the growing awareness of the roles genes play in detoxifying or activating chemicals found in cigarette smoke and in preventing or repairing the damage caused by those compounds. Whether studies that considered genotype have helped to clarify the association is unclear. Our aim here is to summarize the results of epidemiologic studies of smoking and breast cancer risk that considered genotype and discuss their implications for future investigations.

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Materials and Methods

We obtained relevant articles through searches of Medline and by cross-matching the references of relevant articles. The review of literature is organized by gene category and by individual gene. The presentation of epidemiologic findings in each section is preceded by a brief description of gene function. Results of individual studies are presented for the highest category of smoking duration compared with never smokers. If estimates for smoking duration were not available in a study, then results are presented for pack-years, cigarettes per day, current smokers, or ever smokers, in that order of priority. Nearly all of these studies have been of case-control design, including those nested within a cohort. Nine studies (9-17) did not report the association between smoking and breast cancer within strata of certain genotypes but provided the necessary counts of cases and controls so that crude odds ratios (OR) and corresponding 95% confidence intervals (95% CI) could be calculated by the authors of this review. Nearly all of these studies evaluated interaction between smoking and genotype on a multiplicative scale (e.g., using likelihood ratio tests); some studies also evaluated interactions on an additive scale (refs. 16, 18-25; e.g., using interaction contrast ratios). The results of two case-only studies (26, 27) are discussed in the text but are not shown in the tables.

Whenever possible, we examined each study with respect to its power to detect a relative risk (RR) estimate (main effect) of at least 2.0 (or 0.5 in one cohort study, where the frequency of disease among of nonexposed participants was 58%) and present these calculations in the tables. Power calculations were not done when necessary data were not available. All power calculations were conducted using statistical software Epi Info (Centers for Disease Control and Prevention, Atlanta,

GA) for cohort studies and unmatched case-control studies and statistical software Quanto version 0.5 (University of Southern California, Los Angeles, CA) for matched case-control studies.

A summary meta-RR estimate for the association between smoking and breast cancer risk was calculated for genotypes for which estimates were available from three or more studies with nonoverlapping samples (*NAT2, NAT1, CYP1A1, GST, SOD2*, and *XRCC1*). We calculated meta-RRs as weighted averages of the individual study results using inverse variances as the weights (28). These summary analyses were based on random effects models, which assume that study-specific effect sizes arise from a random distribution of effect sizes with a certain mean and variance. Where the variability among studies is negligible (high levels of homogeneity), the random effects model reduces to a fixed effects model, which attributes all observed variations among results to sampling error alone (29). Because these studies examined different smoking measures and included a mixture of ages and ethnicities, the meta-RRs are intended to serve only as one possible summary of the available data. In instances where the meta-RR estimates were significantly different from null, we evaluated the potential role of publication bias by calculating the weighed fail-safe n as described by Rosenberg (30). The fail-safe n is equivalent to the number of studies of null effect and mean weight necessary to change the observed type I error from <0.05 to 0.05. These calculations were done using the Fail Safe Number Calculator software (Arizona State University, Tempe, AZ).

Results

Epidemiologic Studies of Smoking and Breast Cancer Risk according to Carcinogen-Metabolizing Genotype. Cancer risk is, at least in part, an integrated function of carcinogen exposure and polymorphisms in genes involved in carcinogen metabolism, including cytochrome *P*450s (CYP), glutathione *S*-transferases (GST), *N*-acetyltransferases (NAT), and sulfotransferases (SULT; ref. 31). Studies that examined the association between smoking and breast cancer according to variation in carcinogen metabolism genes are discussed in the next four subsections (Tables 1-4).

N-*acetyltransferases.* Aromatic and possibly heterocyclic amines, constituents of tobacco smoke, may be detoxified or activated by NATs, including NAT1 and NAT2 (32). Regarding *NAT2* genotype, individuals carrying homozygous wild-type, homozygous variant, and heterozygous genotypes are considered to be rapid, slow, or intermediate acetylators, respectively. These genotypes can determine the rate of metabolism or activation of carcinogenic aryl or heterocyclic amine substrates (32). For example, most studies indicate that slow acetylators, particularly individuals homozygous for *NAT2* slow acetylator alleles, have an increased risk of arylamine-induced bladder cancer (33). However, whether this is true for breast cancer is unclear.

Effect modification by *NAT2* genotype has been evaluated in 14 epidemiologic studies of smoking and breast cancer risk (Table 1). These studies tend to show increased risks due to smoking among postmenopausal slow acetylators. This suggests that rapid acetylators more efficiently detoxify the carcinogenic compounds in tobacco smoke and that greater exposure of breast tissue to activated compounds is likely in slow acetylators. Among all subjects combined, summary analyses produced meta-RR estimates of 1.2 (95% CI, 1.0-1.5) for rapid acetylators and 1.5 (95% CI, 1.2-1.8; fail-safe n = 54) for slow acetylators. After stratification by menopausal status, the meta-RR for postmenopausal slow acetylators was 2.4 (95% CI, 1.7-3.3; fail-safe n = 57), whereas similar analyses for the other categories showed no association (Table 1). However, these studies generally did not find the *NAT2* genotype itself to be independently associated with breast cancer risk, and a recent case-only study of breast cancer (n = 502; ref. 26) found little evidence of interaction between smoking and *NAT2* genotype. In addition, seven of these studies considered passive smoking in analyses according to *NAT2* status (21, 26, 34-38), showing no clear pattern of effect modification of the association by genotype.

Five studies have examined the association between cigarette smoking and breast cancer risk according to *NAT1* genotypes (Table 2). The *NAT1*10* allele was considered in most of these studies, because it has been associated with elevated NAT1 activity (39). However, there has been no clear effect modification by this or any of the *NAT1* alleles examined in epidemiologic studies of smoking and breast cancer risk. Summary analyses showed no association between smoking and breast cancer irrespective of *NAT1* genotype (Table 2).

Cytochrome P450. Unlike aromatic and heterocyclic amines, polycyclic aromatic hydrocarbons (PAH) are metabolized primarily by enzymes in the CYP family and by GSTs, a process that can produce highly reactive DNA-damaging metabolites (40). The *CYP1A1* gene encodes microsomal CYP1A1, a phase I enzyme that contributes to aryl hydrocarbon hydroxylase activity, catalyzing the metabolism of PAHs and other carcinogens (41). Four *CYP1A1* polymorphisms have been studied in relation to breast cancer: 3801T→C (M1, a *Msp*I RFLP in the 3′-noncoding region), Ile^{462}Val (M2), 3205T→C (M3, a *Msp*I RFLP in the 3′-noncoding region), and Thr^{461}Asp (M4). These polymorphisms generally have not been shown to alter breast cancer risk and their functional significance remains unclear (41). Regarding the M1 polymorphism, some studies have shown higher levels of DNA adduct levels in breast tissue, or urinary biomarkers of PAH exposure, among individuals with the variant allele (41). However, the results of these studies, and similar studies of the Ile^{462}Val polymorphism, have been largely inconsistent (41).

Four studies have examined the association between smoking and breast cancer risk according to *CYP1A1* genotypes to date (Table 3). There seems to be no clear effect modification by *CYP1A1* generally, although the results of two studies (42, 43) suggest that long-term smoking may increase risk among women with *CYP1A1-M1* variant genotype. Summary analyses produced meta-RR estimates for smoking of 1.3 (95% CI, 1.0-1.6) for women with M2 wild-type and 1.2 (95% CI, 0.6-2.1) for carriers of the variant allele.

The association between smoking and breast cancer risk has also been examined according to polymorphisms of other genes in the *CYP* family. In an early case-control study (272 cases and 334 controls, a subset of a larger study with information on genotype), Shields et al. (44) showed smoking increased breast cancer risk among premenopausal but not postmenopausal women with 6*CYP2E1* variant (a *Dra*I restriction enzyme site in intron 6). Because CYP2E1 enzyme is involved in the metabolic activation of *N*-nitrosamines, which are contained in tobacco smoke, it is possible that the polymorphism will modify susceptibility to breast cancer due to smoking. However, these findings were based on small numbers of subjects in some of the exposure categories and remain to be replicated. More recently, a case-only analysis (282 cases; ref. 27) suggested that *CYP1B1* polymorphism (Val^{432}Leu) may increase breast cancer susceptibility among smokers. CYP1B1 activates a variety of procarcinogens, including those found in tobacco smoke (45). This study also examined the association between smoking and breast cancer risk according to a polymorphism in *SULT1A1* (see below).

Glutathione S-transferases. The GSTs are phase II enzymes that play key roles in detoxification of many potentially carcinogenic compounds, including PAHs, which are

Table 1. Cigarette smoking and breast cancer risk according to NAT2 genotypes

First author, year (ref.)	No. cases/ controls	Comparison	All subjects			
			NAT2 rapid		NAT2 slow	
			OR (95% CI)	Power (%)	OR (95% CI)	Power (%)
Ambrosone, 1996 (84)	304/327	>365 pack-years vs never				
Hunter, 1997 (85)	466/466*	30+ pack-years vs never	0.8 (0.5-1.5)	73	1.4 (0.8-2.3)	86
Millikan, 1998 (38)	498/473	>20 y smoking vs never				
Morabia, 2000 (21)	177/170	Ever active vs never	4.2 (1.5-12.0)	24	2.7 (1.1-6.6)	28
Delfino, 2000 (86)	113/278	Interaction with smoking			No interaction	
Krajinovic, 2001 (87)	149/207	Ever smoked vs never	2.6 (0.8-8.2)	24		
Chang-Claude, 2002 (35)	422/887	Duration 20+ y vs never	1.2 (0.6-2.4)	86	1.8 (1.1-3.2)	94
Egan, 2003 (88)	791/797	Ever smoked vs never	1.2 (0.9-1.7)	>99	1.5 (1.1-2.0)	>99
		>25 pack-years vs never				
van der Hel, 2003 (24)	229/264*	Duration 30+ y vs never	1.3 (0.6-2.9)	35	1.7 (0.8-3.4)	51
		20+ cigarettes/d vs never				
Alberg, 2004 (36)	110/113*	>15 pack-years vs never	1.5 (0.3-6.6)	8	2.0 (0.7-5.8)	18
Sillanpaa, 2005 (37)	483/482	5+ pack-years vs never	1.0 (0.6-1.9)‡	70	0.8 (0.4-1.4)‡	70
Lilla, 2005 (34)	419/884	11+ pack-years vs never	1.2 (0.6-2.5)	34	1.9 (1.0-3.3)§	88
van der Hel, 2005 (25)	676/669*	>20 cigarettes/d vs never	1.3 (0.6-2.7)	84	1.1 (0.6-2.0)	92
Meta-RR estimate			1.2 (1.0-1.5)		1.5 (1.2-1.8); FSN = 54 †	

NOTE: Power calculations for each study show the probability of detecting an OR (or RR for cohort studies) of at least 2.0 with the type I error of 0.05.
Abbreviations: N/A, not available, FSN, fail-safe *n*.
*A nested case-control study.
†Fail-safe *n* is the number of studies of null effect and mean weight necessary to change the observed type I error to 0.05, calculated only for meta-RR estimates with type I error of <0.05.
‡Estimates were calculated by the authors of this review.
§Lilla et al. (34) separately reported an OR for very slow acetylators (*NAT2*5*) of 2.3 (1.1-4.9).

contained in tobacco smoke. There are eight distinct gene families encoding GSTs in humans: α, μ, θ, π, ζ, σ, κ, and χ (also called ω; ref. 46). Polymorphisms have been described in several *GST* genes, although mostly in the μ, θ, and π families (46). A recent pooled analysis showed no association between several of these polymorphisms and breast cancer risk (47).

Seven studies have examined the association between smoking and breast cancer risk according to *GST* genotypes (Table 4). These studies tend to show positive associations with smoking among women with *GSTM1-null* genotype. Individuals with this genotype express no protein (46), a protein that has been shown to modulate cytogenetic damage in smokers (48). Summary analyses produced meta-RR estimates for smoking of 1.1 (95% CI, 0.8-1.4) when the *GSTM1* gene was present and 1.5 (95% CI, 1.1-2.1; fail-safe $n = 11$) when the gene was deleted (Table 4). Similar analyses for *GSTT1* produced meta-RRs of 1.3 (95% CI, 1.1-1.6; fail-safe $n = 7$) and 1.2 (95% CI, 0.9-1.7) for *GSTT1-present* and *GSTT1-null*, respectively. An increased risk due to smoking among individuals with the *GSTT1-present* genotype is not necessarily inconsistent with similar findings for *GSTM-null* because GSTT1 may not only detoxify but may also metabolically activate carcinogens (49). Nonetheless, our findings for smoking according to *GST* genotypes differ from those of a recent analysis of data pooled from seven previous studies (2,048 cases and 1,969 controls)[1] that showed no clear effect modification in the association between *GST* genotypes and smoking (47). In addition, one study did not support effect modification by *GSTP1* genotypes (50).

Sulfotransferase 1A1. SULTs are enzymes involved in the metabolism of several classes of compounds through sulfonate conjugation, including the activation and inactivation of PAHs and heterocyclic amines found in cigarette smoke. A common polymorphism, a G→A transition ($Arg^{213}His$) in *SULT1A1*, results in reductions in enzyme activity, particularly among individuals homozygous for the His allele (51). A case-only analysis (282 cases; ref. 27) showed that carrying any His allele may increase breast cancer susceptibility among smokers, suggesting increased exposure to unsulfated tobacco carcinogens among His allele carriers. However, two case-control studies that examined the association between smoking and breast cancer risk according to this polymorphism found no clear evidence of effect modification (34, 52). A population-based case-control study in Finland (483 cases and 482 controls) reported no interaction between smoking status and $Arg^{213}His$ polymorphism (ref. 52; relevant ORs were not reported). A population-based case-control study in Germany (419 cases and 884 controls) showed women who smoked ≥16 years had ~50% increased breast cancer risk compared with nonsmokers, again with no clear effect modification by the *SULT1A1* polymorphism (34). The latter study further examined the association between smoking and breast cancer by *SULT1A1* after additional stratification by *NAT2* genotype, also showing no clear effect modification when *NAT2* was considered. Although that study had >90% power to detect ORs of at least 2.0 among strata of the *SULT1A1* polymorphism, power fell to <35% for all analyses that were further stratified according to *NAT2* genotype.

Epidemiologic Studies of Smoking and Breast Cancer Risk according to Oxidative Metabolism Genotypes

Superoxide dismutase 2. SOD2 encodes manganese superoxide dismutase (MnSOD), a mitochondrial enzyme that protects the cell against damage from superoxide free radicals. A common polymorphism, a T→C transition ($Val^{16}Ala$), was shown to alter the MnSOD mitochondrial targeting sequence (53), and animal studies have linked reduction in MnSOD activity to increased DNA damage and higher incidence of cancer (54). Increased expression of MnSOD was found to suppress the malignant phenotype of human breast cancer cells *in vitro* (55).

Four epidemiologic studies have examined the association between smoking and breast cancer risk according to this

[1] Unpublished data included in the analyses.

Table 1. Cigarette smoking and breast cancer risk according to NAT2 genotypesn (Cont'd)

Premenopausal				Postmenopausal			
NAT2 rapid		NAT2 slow		NAT2 rapid		NAT2 slow	
OR (95% CI)	Power (%)	OR (95% CI)	Power (%)	OR (95% CI)	Power (%)	OR (95% CI)	Power (%)
2.1 (0.5-7.9)	15	1.2 (0.4-3.8)	22	0.9 (0.4-2.1)	41	2.8 (1.4-5.5)	48
1.7 (0.7-4.2)	29	1.3 (0.6-2.8)	38	1.8 (1.0-3.2)	61	1.9 (0.7-5.5)	64
3.0 (0.7-11.8)	N/A	2.9 (0.8-10.3)	N/A	8.2 (1.4-46.0)	N/A	2.9 (0.8-11.2)	N/A
1.1 (0.5-2.5)	36	1.7 (0.8-3.8)	44	1.3 (0.8-2.1)	82	2.0 (1.3-3.2)	89
1.1 (0.3-3.5)	16	1.0 (0.4-2.5)	29	1.1 (0.3-3.7)	13	4.2 (1.3-13.2)	20
Not significant				0.6 (0.1-1.3)†	8	2.9 (0.9-9.3)	15
1.5 (0.9-2.4)		1.4 (0.9-2.2)		1.3 (0.8-2.0)		2.4 (1.7-3.3); FSN = 57	

SOD2 genotype (Table 5). These studies suggest that long-term smoking may increase risk in women homozygous for the Ala allele. Summary analyses produced meta-RR estimates for smoking of 0.8 (95% CI, 0.2-2.8) for the Val/Val genotype and 1.5 (95% CI, 1.1-2.1; fail-safe $n = 3$) for Ala/Ala.

Epidemiologic Studies of Smoking and Breast Cancer Risk according to DNA Repair Genotypes. The genes discussed above work in several ways to modulate the dose of carcinogens experienced by individuals and, consequently, the amount and type of DNA damage. Once DNA damage occurs, however, cells have ways of minimizing long-term damage that may result, including repair of the damage through several pathways. DNA repair capacity seems to play an important role in disease susceptibility (56).

XRCC1. X-ray repair cross-complementing group 1 (*XRCC1*) acts as the central scaffolding protein for POLB and ligase III in the base excision repair of oxidative damage, participates in the removal of nonbulky DNA adducts caused by exogenous agents, including several compounds in tobacco smoke, and interacts with poly(ADP-ribose) polymerase in the detection of single-strand breaks (56). Three polymorphisms resulting in nonconservative amino acid substitutions ($Arg^{194}Trp$, $Arg^{280}His$, and $Arg^{399}Gln$) have been identified in the *XRCC1* gene (23). The $Arg^{280}His$ and $Arg^{399}Gln$ polymorphisms have recently been characterized as ''possibly damaging'' based on protein conservation analyses (Sorting Intolerant from Tolerant) that identify amino acids that are likely important for the function and structure of protein families (57).

Five epidemiologic studies have examined the association between smoking and breast cancer risk according to *XRCC1* polymorphisms (Table 6). In an early report using data from the Carolina Breast Cancer Study (18), smoking duration of >20 years was positively associated with breast cancer risk among African American women homozygous for the Gln allele (OR, 2.9; 95% CI, 1.6-5.2), but no clear association was found among those with a wild-type allele, among women with or without $Arg^{194}Trp$ polymorphism, or among White women. However, an updated analysis of Carolina Breast Cancer Study data using more cases subsequently showed a positive association with smoking among White women with the Gln/Gln genotype (1).

The latter findings are consistent with those of a recent case-control study nested in the American Cancer Society Cancer Prevention Study II (White women only; ref. 13), which showed women homozygous for the Gln allele (compared

Table 2. Cigarette smoking and breast cancer risk according to NAT1 genotypes

First author, year (ref.)	No. cases/ controls	Comparison	Strata definition	Stratum-specific OR (95% CI)	Stratum-specific power (%)
Zheng, 1999 (22)	154/330*	Duration 25+ y and 15+ cigarettes/d vs nonsmokers	NAT1*4/*4, *3/*4, *3/*3	0.8 (0.3-1.6)	48
			NAT1*10/any genotype	0.6 (0.2-1.8)	30
Millikan, 2000 (16)	639/647†	Ever smoked vs never	African Americans		
			NAT1*4/*4, *3/*4, *3/*3	1.3 (0.6-3.0)	34
			NAT1*10/any genotype	1.2 (0.7-1.9)	80
			Whites		
			NAT1*4/*4, *3/*4, *3/*3	1.1 (0.7-1.8)	85
			NAT1*10/any genotype	1.1 (0.6-1.9)	64
			NAT1*11/any genotype	0.4 (0.03-4.7)	3
Krajinovic, 2001 (87)	149/207	Ever smoked vs never	NAT1*10	0.4 (0.1-1.6)	12
van der Hel, 2003 (24)	229/264*	Interaction smoking × genotype	NAT1 genotype	No interaction	N/A
van der Hel, 2005 (25)	676/669*	>20 cigarettes/d vs never	NAT1*10	1.2 (0.5-3.2)	65
			Non-NAT1*10	1.5 (0.8-2.9)	89
Meta-RR estimate			NAT1*4/*4, *3/*4, *3/*3	1.0 (0.7-1.5)	
			NAT1*10	1.0 (0.8-1.4)	

NOTE: Power calculations for each study show the probability of detecting an OR (or RR for cohort studies) of at least 2.0 with the type I error of 0.05.
*A nested case-control study.
†African American women (253/266) + White women (386/381).

Table 3. Cigarette smoking and breast cancer risk according to CYP 1A1 genotypes

First author, year (ref.)	No. cases/controls (or no. cohort)	Smoking comparison	Genotypes examined	Wild-type		Any variant	
				OR (95% CI)	Power (%)	OR (95% CI)	Power (%)
Ambrosone, 1995 (17)	216/282	20+ pack years vs never	CYP1A1-M2	1.2 (0.7-2.2)*	67	0.8 (0.2-3.4)*	14
Ishibe, 1998 (43)	466/466†	30+ pack-years vs never	CYP1A1-M1	1.1 (0.7-1.6)	96	2.0 (0.9-4.4)	36
			CYP1A1-M2	1.2 (0.8-1.8)	97	1.2 (0.5-2.7)	25
Basham, 2001 (89)	1,873/712	Interaction with genotype	CYP1A1-M4	No interaction	N/A	No interaction	N/A
	1,948/1,355	CYP1A1-M2	No interaction	N/A	No interaction	N/A	
Li, 2004 (42)	688/722	Duration >20 y vs never	CYP1A1-M1	1.2 (0.9-1.6)	>99	2.1 (1.2-3.5)	72
			CYP1A1-M2	1.3 (0.9-1.8)	97	1.4 (0.4-4.8)	14
			CYP1A1-M3	1.3 (0.8-2.2)	77	2.4 (0.9-7.1)	19
			CYP1A1-M4	0.2 (0.1-0.9)	97	1.5 (1.0-2.1)	17
Meta-RR estimate			CYP1A1-M2	1.3 (1.0-1.6)		1.2 (0.6-2.1)	

NOTE: Power calculations for each study show the probability of detecting an OR (or RR for cohort studies) of at least 2.0 with the type I error of 0.05.
*Estimates were calculated by the authors of this review.
†A nested case-control study.

with those homozygous for Arg) had ORs of 2.8 (1.4-5.6) and 0.6 (0.3-1.3) for smokers and nonsmokers, respectively ($P_{interaction}$ = 0.01). These findings are also consistent with those of a recent population-based case-control study in Finland (10) that examined the association according to $Arg^{399}Gln$ and $Arg^{280}His$, showing smoking (>5 pack-years versus less) increased risk among carriers of the ^{399}Gln allele (OR, 4.1; 95% CI, 1.7-12.0) but not clearly among carriers of ^{280}His (OR, 2.0; 95% CI, 0.6-7.0). However, the most recent analysis of the Carolina Breast Cancer Study data showed positive associations between smoking and breast cancer risk among women with *XRCC1* codon 194 Arg/Arg, 399 Arg/Arg, and 280 His/His genotypes (58).

Thus far, there has been little consistency among studies of smoking and breast cancer risk according to *XRCC1* genotype. Summary analyses produced meta-RR estimates for smoking of 1.2 (95% CI, 1.0-1.5) for the 194 Arg/Arg genotype and 1.0 (95% CI, 0.7-1.5) for any Trp (Table 6). Summary analyses also produced meta-RR estimates for smoking of 1.1 (95% CI, 0.7-1.7) for the 399 Arg/Arg genotype and 1.1 (95% CI, 0.9-1.4) for any Gln.

XPD (ERCC2). Xeroderma pigmentosum D (*XPD*), also known as *excision repair cross-complementing rodent repair deficiency, complementation group 2* (*ERCC2*), encodes a protein that plays a role in nucleotide excision repair of bulky DNA adducts (59), including those that may be caused by tobacco carcinogens. Several polymorphisms have been described in *XPD*, although relatively few epidemiologic studies have investigated *XPD* polymorphisms and cancer risk and the results of these studies have been inconsistent (60). Effect modification by a

Table 4. Cigarette smoking and breast cancer risk according to *GST* genotypes

First author, year (ref.)	No. cases/controls	Comparison	Strata definition	Strata OR (95% CI)	Power (%)
Ambrosone, 1995 (17)	216/282	20+ pack-years vs none	GSTM1-present	1.1 (0.5-2.6)*	39
			GSTM1-null	1.0 (0.5-2.1)*	48
Garcia-Closas, 1999 (19)	466/466†	20+ pack-years vs none	GSTT1-present	1.2 (0.8-1.7)‡	98
			GSTT1-deleted	1.5 (0.8-2.6)‡	37
			GSTM1 × smoking	No interaction	NA
Millikan, 2000 (50)	688/663	Duration >20 y vs never	GSTM1-null	1.7 (1.0-2.8)	N/A
			GSTM1-present	1.1 (0.7-1.7)	N/A
			GSTT1-null	0.9 (0.4-2.2)	N/A
			GSTT1-present	1.3 (0.9-1.8)	N/A
			GSTP1 Ile/Val + Val/Val	1.3 (0.9-2.0)	N/A
			GSTP1 Ile/Ile	1.4 (0.8-2.3)	N/A
Zheng, 2002 (14)	338/345	Duration >30 y vs never smoked	GSTM1-A	0.7 (0.3-1.7)	39
			GSTM1-B	1.6 (0.4-7.1)	12
			GSTM1-present	1.0 (0.5-2.0)*	53
			GSTM1-null	1.6 (0.8-2.9)	59
			GSTT1-present	1.4 (0.8-2.3)	77
			GSTT1-null	1.3 (0.5-3.6)	24
van der Hel, 2003 (24)	229/264†	Duration 30+ y vs never smoked	GSTM1-present	1.5 (0.7-3.4)	34
			GSTM1-null	2.5 (1.2-5.2)	51
van der Hel, 2005 (25)	676/669‡	>20 cigarettes/d vs never	GSTM1-present	1.0 (0.6-1.5)	73
			GSTM1-null	1.3 (0.6-2.8)	82
			GSTT1-present	2.0 (1.0-3.9)	86
			GSTT1-null	1.1 (0.5-2.2)	82
Zheng, 2002 (90)	202/481†	Current smokers vs nonsmokers	GSTM1-present	1.1 (0.5-2.5)*	45
			GSTM1-null	0.8 (0.4-1.7)*	55
			GSTT1-present	0.9 (0.4-1.9)*	54
			GSTT1-null	1.0 (0.2-3.7)*	19
Meta-RR estimate			GSTT1-present	1.3 (1.1-1.6); FSN = 7	
			GSTT1-null	1.2 (0.9-1.7)	
			GSTM1-present	1.1 (0.8-1.4)	
			GSTM1-null	1.4 (1.1-1.9); FSN = 11	

NOTE: Power calculations for each study show the probability of detecting an OR (or RR for cohort studies) of at least 2.0 with the type I error of 0.05.
*Estimates were calculated by the authors of this review.
†A nested case-control study.
‡A case-cohort study (rate ratios were reported).

Table 5. Cigarette smoking and breast cancer risk according to MnSOD2 genotypes

First author, year (ref.)	No. cases/ controls	Comparison	Gene/SNP	Strata definition	Strata OR (95% CI)	Power (%)
Mitrunen, 2001 (11)	483/482	Ever smokers vs nonsmokers	SOD2/Val^{16}Ala	Val/Val	0.6 (0.3-1.5)*	52
				Val/Ala	1.1 (0.6-2.0)*	62
				Ala/Ala	1.2 (0.4-3.5)*	25
Millikan, 2004 (20)	462/380	Duration >20 y vs no active or passive	SOD2/Val^{16}Ala	Val/Val or Val/Ala	1.2 (0.9-1.5)	>99
				Ala/Ala	1.5 (1.0-2.2)	87
Tamimi, 2004 (91)	968/1,205†	Duration 40+ y (current) vs never	SOD2/Val^{16}Ala	Val/Val	0.3 (0.1-0.9)	50
				Val/Ala	0.9 (0.5-1.6)	72
				Ala/Ala	1.6 (0.7-3.5)	36
Gaudet, 2005 (12)	1,034/1,084	Ever smokers vs nonsmokers	SOD2/Val^{16}Ala	Val/Val	2.6 (1.1-6.3)*	29
				Val/Ala or Ala/Ala	1.3 (0.8-2.1)*	89
Meta-RR estimate				Val/Val	0.8 (0.2-2.8)	
				Ala/Ala	1.5 (1.1-2.1); FSN = 3	

NOTE: Power calculations for each study show the probability of detecting an OR (or RR for cohort studies) of at least 2.0 with the type I error of 0.05. SNP, single nucleotide polymorphism.
*Estimates were calculated by the authors of this review.
†A nested case-control study.

polymorphism in this gene (Lys^{751}Gln) has been examined in two recent population-based case-control studies of smoking and breast cancer risk, the Long Island Breast Cancer Study (15) and a study in Finland that also examined polymorphisms in *XRCC1* (ref. 10; Table 6). This polymorphism has been shown to change the electronic configuration of the amino acid (61) and hence may have important consequences to DNA repair capacity (60). In both of these studies (10, 15), an increased breast cancer risk among smokers was limited to women who had both copies of the Gln allele. In the Finnish study, women who had ever smoked and were homozygous for the *XPD* Gln allele and also carried the *XRCC1* ^{399}Gln or the *XRCC1* ^{280}His allele had the highest breast cancer risk (10).

MGMT. *O^6-methylguanine DNA methyltransferase* (*MGMT*) encodes a protein involved in the direct reversal repair of DNA damage at the *O*^{6}-position of guanine, which can be caused by various exogenous alkylating agents, including tobacco-specific nitrosamines (62). Genetic alterations in the *MGMT* gene may impair the protein's ability to remove alkyl groups from this position and, through this mechanism, may possibly increase the risk of cancer (63). Three polymorphisms resulting in nonconservative amino acid substitutions (Leu^{84}Phe, Ile^{143}Val, and Lys^{178}Arg) have been identified in the *MGMT* gene (63). The results of epidemiologic studies of these polymorphisms in relation to cancer risk have been inconsistent (23), although the Leu^{84}Phe and Ile^{143}Val polymorphisms have recently been shown to modify chromosome aberration frequencies in human leukocytes exposed *in vitro* to the tobacco-specific nitrosamine carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-buyanone (64). Only one epidemiologic study has examined the association between smoking and breast cancer risk according to *MGMT* polymorphisms (23), a recent study from the Long Island Breast Cancer Study that showed heavy smoking (>31 pack-years) increased breast cancer risk particularly among women with the Leu^{84}Phe polymorphism. There was no effect modification according to Ile^{143}Val or Lys^{178}Arg in that study (Table 6).

BRCA1. Women carrying a deleterious mutation of the *BRCA1* gene have an increased risk of developing breast cancer (65). Inherited mutations of *BRCA1* play a role in ~40% to 45% of hereditary breast cancers but in only 2% to 3% of all breast cancers (65). Multiple functions of *BRCA1* may contribute to its tumor suppressor activity, including roles in cell cycle progression, specialized DNA repair processes, DNA damage-responsive cell cycle checkpoints, regulation of a set of specific transcriptional pathways, and apoptosis (65).

There have been four studies of smoking and breast cancer among *BRCA1* mutation carriers (Table 6). A matched case-control study (186 cases and 186 controls) that first examined the association between smoking and breast cancer risk in women with *BRCA1* and *BRCA2* mutations showed an inverse association with smoking (66), although this finding was not confirmed in a later report from this group (67) using data from a greater number of subjects (1,097 cases and 1,097 controls). More recently, data from 316 female *BRCA1* mutation carriers, including a subset of women who participated in the previous case-control studies (66, 67), were analyzed using a retrospective cohort design (176 cases and 140 noncases), showing a reduced risk of cancer among women who had ever smoked. An inverse association was dose-response with increasing pack-years of consumption. In this latter study, a reduced breast cancer risk was particularly prominent in *BRCA1* mutation carriers who smoked and also had a 28 repeat allele for *amplified in breast cancer 1* (*AIB1*) genotype. AIB1 is an estrogen receptor coactivator (68), although exactly how *AIB1* CAG allele repeat lengths affect the function of this protein remains unclear (69). Given these associations, it is possible that *BRCA1* and *AIB1* genotypes and cigarette smoking will decrease breast cancer risk (e.g., through synergistic modulations of estrogen receptor activity and estrogen potency). However, smoking was not associated with breast cancer risk in a recent matched case-control study (348 cases and 348 controls) of *BRCA1* mutation carriers (Table 6). To date, there seems to be no consistent association between smoking and breast cancer risk among *BRCA1* mutation carriers.

Comments

The association between smoking and breast cancer risk remains controversial despite >100 epidemiologic studies conducted over the past three decades. The results of these studies overall suggest that smoking probably does not decrease risk and indeed suggest that there may be an increased risk with smoking, particularly heavy smoking of long duration (1). Some authors have suggested that any positive association is likely driven by confounding (or residual confounding) from alcohol consumption (70). Although confounding by alcohol may have occurred in some studies, two recent cohort studies (71, 72) found statistically significant positive associations between smoking of long duration and breast cancer risk among nondrinkers in their populations. The RR estimates among nondrinkers in these cohort studies were similar in magnitude to those among

drinkers and in the entire cohort with statistical adjustment for alcohol consumption.

The results of studies of smoking and breast cancer stratified by genotype have also been largely inconsistent. Foremost among several possible explanations for this are inadequate sample size and lack of statistical power and precision. Our review of the available studies indicates that most were severely underpowered (Tables 1-6). Approximately 68% of the stratum-specific analyses shown in the tables had <80% power to detect an OR of at least 2.0. As with the studies reviewed here, small sample sizes have contributed to inconsistent findings more generally in studies of genetic variation and complex diseases (73). Another difficulty of comparing the results across studies is the lack of uniform methods of smoking characterization. The various smoking measures used in epidemiologic studies are often highly correlated, yet they may have distinct implications regarding disease etiology (1, 74).

Table 6. Cigarette smoking and breast cancer risk according to DNA repair genotypes

First author, year (ref.)	No. cases/controls or noncases	Comparison	Gene/SNP	Strata definition	Strata OR (95% CI)	Power (%)
Duell, 2001 (18)	639/647	Duration >20 y vs never	XRCC1/Arg^{399}Gln	African Americans		
				Any Gln	0.7 (0.3-1.5)	38
				Arg/Arg	2.9 (1.6-5.2)	58
				Whites		
				Any Gln	1.2 (0.8-2.0)	82
				Arg/Arg	1.3 (0.7-2.2)	70
		Interaction with genotype	XRCC1/Arg^{194}Trp	—	No interaction	N/A
Patel, 2005 (13)	502/502†	Ever smokers vs nonsmokers	*XRCC1*/Arg^{194}Trp	Arg/Arg	1.3 (1.0-1.8)*	>99
				Any Trp	0.9 (0.4-2.1)*	36
			XRCC1/Arg^{399}Gln	Arg/Arg	1.0 (0.6-1.5)*	91
				Arg/Gln	1.2 (0.8-1.8)*	91
				Gln/Gln	2.9 (1.3-6.6)*	38
				Any Gln	1.4 (1.0-2.1)*	97
Shen, 2005 (9)	1,067/1,110	Ever smoked vs never	*XRCC1*/Arg^{194}Trp	Arg/Arg	1.0 (0.8-1.3)*	>99
				Any Trp	1.2 (0.7-2.0)*	69
			XRCC1/Arg^{399}Gln	Arg/Arg	1.4 (1.0-1.9)*	>99
				Any Gln	0.9 (0.7-1.1)*	>99
Pachkoswki, 2006 (58)	2,077/1,818‡	Duration 20 y vs never	*XRCC1*/Arg^{399}Gln	Arg/Arg	1.7 (1.2-2.3)	>99
				Any Gln	1.0 (0.7-1.4)	>99
			XRCC1/Arg^{194}Trp	Arg/Arg	1.4 (1.1-1.7)	>99
				Any Trp	0.9 (0.5-1.7)	60
			XRCC1/Arg^{280}His	Arg/Arg	1.2 (1.0-1.6)	>99
				Any His	2.7 (1.2-6.1)	45
Metsola, 2005 (10)	483/482	>5 pack-years vs never	XRCC1/Arg^{280}His	Arg/Arg	0.8 (0.5-1.3)*	92
				Any His	1.3 (0.3-4.3)*	18
			XRCC1/Arg^{399}Gln	Arg/Arg	0.5 (0.3-0.9)*	75
				Arg/Gln	1.5 (0.7-2.9)*	53
				Gln/Gln	1.9 (0.5-7.7)*	12
				Any Gln	1.6 (0.9-2.8)*	65
			XPD/Lys^{751}Gln	Lys/Lys	1.0 (0.7-1.4)*	48
				Lys/Gln	0.5 (0.3-0.9)*	72
				Gln/Gln	2.8 (0.9-6.8)*	24
Terry, 2004 (15)	1,053/1,102	Current smokers vs nonsmokers	*XPD*/Lys^{751}Gln	Lys/Lys	0.8 (0.6-1.2)*	97
				Lys/Gln	1.0 (0.0-1.4)*	99
				Gln/Gln	1.6 (0.8-3.3)*	53
Shen, 2005 (23)	1,067/1,110	>31 pack-years vs nonsmoker	MGMT/Leu^{84}Phe	Leu/Leu	1.4 (0.9-2.2)	92
				Any Phe	3.0 (1.4-6.2)	34
			MGMT/Ile^{143}Val	Ile/Ile	2.0 (1.3-3.1)	88
				Any Val	1.2 (0.6-2.3)	53
Brunet, 1998 (66)	186/186	>4 pack-years vs never	BRCA1/2 mutation carriers	—	0.5 (0.3-0.8)	N/A
Ghadirian, 2004 (67)	1,097/1,097§	20+ packs per year vs never	BRCA1/2 mutation carriers	—	0.8 (0.6-1.2)	>99
Gronwald, 2005 (92)	348/348	Ever smoked vs never	BRCA1 mutation carriers	—	1.1 (0.8-1.5)	>99
Colilla, 2005 (69)	176/140§	20+ pack-years (heavy) vs never	BRCA1 mutation carriers	Entire sample	0.4 (0.2-0.7)	76
		Joint effect smoking *AIB1 genotype		With a 28 repeat allele for AIB1	0.2 (0.1-0.5)	N/A
Meta-RR estimate				XRCC1 194 Arg/Arg	1.2 (1.0-1.5)	
				XRCC1 194 Any Trp	1.0 (0.7-1.5)	
				XRCC1 399 Arg/Arg	1.1 (0.7-1.7)	
				XRCC1 399 Any Gln	1.1 (0.9-1.4)	

NOTE: Power calculations for each study [except Colilla et al. (69)] show the probability of detecting an OR (or RR for cohort studies) of at least 2.0 with the type I error of 0.05. Power calculations for Colilla et al. (69) examine the probability of detecting a RR of 0.5 because the frequency of disease among of nonexposed participants in this study is 58%.

*Estimates were calculated by the authors of this review.

†A nested case-control study.

‡Data from the same study as Duell et al. (18).

§The study by Ghadirian et al. (67) contains a subset of women in the study by Brunet et al. (66). The study by Colilla et al. (69), a retrospective cohort study, also contains a subset of these women.

Interpretation of the current literature is also complicated by the fact that many studies provide only a perfunctory rationale for selection of genes and gene polymorphisms. Whereas most studies have considered the role of selected genes in a given etiologic pathway and perhaps also the functional significance of a particular single nucleotide polymorphism, few have considered the known level of gene expression in breast tissue (75), the frequency of variant alleles and their differences among groups with known differences in disease incidence (73), or whether disease susceptibility may be conferred by a particular single nucleotide polymorphism, a haplotype, or by a specific combination of variants in several genes (76, 77). For example, two recent studies of breast cancer (that did not consider smoking) showed stronger positive associations with variants in carcinogen metabolism genes when considered jointly than individually (25, 78). Three studies reviewed here examined the association between smoking and breast cancer risk according to two genotypes (10, 34, 69), in each case examining different sets of genotypes in underpowered analyses. Thus, whether the association between smoking and breast cancer risk is modified by two or more interacting genotypes remains virtually unexplored.

Our summary analyses produced several statistically significant associations between smoking and breast cancer, and these results need to be viewed with caution. Meta-analyses, by virtue of their large sample sizes, can show relatively small statistically significant departures from null. Seemingly precise meta-RR estimates are not necessarily ''true'' or ''noteworthy,'' however, and the possibility of false-positive findings due to systematic error or chance requires careful consideration (79), particularly when effect sizes are modest. The relatively small number of relevant publications available for some genotypes also warrants caution given the possibility of publication bias (80). Our fail-safe *n* calculations indicate that the ''file drawer problem,'' the omission of negative unpublished results (81), may explain some of the statistically significant meta-RR estimates, such as those we observed in analyses according to *GST* and *SOD2* genotypes.

These methodologic issues notwithstanding, some of the findings presented here suggest possible effect modification by genotype. For example, 14 epidemiologic studies to date have tended to show positive associations with long-term smoking among *NAT2* slow acetylators, particularly among postmenopausal women, who are more likely than premenopausal women to be very long-term smokers. Considering that our fail-safe *n* estimates were in the 50 to 60 range, it seems unlikely that these findings can be explained by publication bias alone. Firozi et al. (82) showed that breast tissue from *NAT2* slow acetylators had significantly higher levels of the diagonal radioactive zone (smoking-related) DNA adduct pattern than that from fast acetylators, supporting the hypothesis that women with *NAT2* slow genotypes may suffer greater exposure to tobacco carcinogens and consequent higher risk of breast cancer. There was also a suggestion in two studies (42, 43) that long-term smoking increases breast cancer risk among women with *CYP1A1-M1* variant genotype. That variant has also been linked to levels of a smoking-related benzo[*a*]pyrene-like adduct in breast tissue (82), an association that was particularly evident among women who also had the *GSTM1-null* genotype. These same genotypes, particularly when considered together, were also associated with higher levels of benzo[*a*]pyrene diol epoxide adduct in lung tissue (40) and leukocytes (83) of smokers.

That cigarette smoking can cause breast cancer in genetically susceptible women remains a reasonable hypothesis and an important public health concern. Studies that examined potentially effect-modifying effects of genotype suggest promising avenues for future studies. However, methodologic limitations, such as small sample sizes, varying definitions of smoking, and difficulties involving single nucleotide polymorphism selection, likely have contributed to the inconsistent findings. These methodologic issues should be addressed in future studies to help clarify the association between smoking and breast cancer.

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