Misclassification of Genetic Susceptibility Biomarkers: Implications for Case-Control Studies and Cross-Population Comparisons[1]

Nathaniel Rothman,[2] Walter F. Stewart, Neil E. Caporaso, and Richard B. Hayes

Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, NIH, Bethesda, Maryland 20892 [N. R., N. E. C., R. B. H.]; and Department of Epidemiology [W. F. S.], The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland 21205

Abstract

Phenotype and genotype markers of genetic susceptibility are of increasing interest in case-control studies of cancer. It is well established that bias to the odds ratio is caused by less-than-perfect assay sensitivity and specificity and varies with risk factor prevalence. As such, the observed variation in odds ratio between studies of genetic markers and cancer risk may be real, or may be attributed, in part, to variation in assay accuracy or in risk factor prevalence (e.g., prevalence differences between racial groups). The latter can be a particular concern when the prevalence of the "at risk" polymorphism in one or more populations is either very high (e.g., >85%) or very low (e.g., <15%). For example, even very high sensitivity (e.g., 98%) can produce substantial bias to the odds ratio when the risk factor prevalence is high. Under some prevalence conditions, however, assays with only moderate accuracy are sufficient and result in minimal bias to the odds ratio. Understanding misclassification in the context of marker prevalence may help to explain disparate findings in the literature and should assist investigators in selecting markers that are appropriate for future studies.

Introduction

Genetic risk factors are of increasing interest in cancer causation. Genetic markers that have come under study in epidemiological investigations include polymorphisms for enzymes which activate and detoxify xenobiotics, such as NAT2 (1), CYP1A1 (2), CYP1A2 (3), CYP2D6 (4), CYP2E1 (5), and GST1 (6), and polymorphisms in genes of uncertain function, such as *HRAS-1* rare alleles (7).

Although laboratory assay accuracy generally improves with time, some degree of misclassification is almost inevitable, especially during the initial application of an assay in human populations. In addition, under field conditions common to epidemiological research, factors outside of the laboratory can introduce further misclassification, such as variation in subject compliance with phenotype protocols and variation in sample collection, processing, time-to-storage, and shipment conditions. Potential sources of error for metabolic phenotype assays include drug, dietary, or other exposures which inhibit or induce enzyme activity (8–12) and which may cause individuals who have a "rapid" phenotype to be misclassified as "slow," and *vice versa*. Genotype can be misclassified due to failure to recognize a variant that contributes to the genotype of interest, false priming in polymerase chain reaction-based assays (13), and erroneous recognition of a pseudogene. Finally, coding errors at any point during sample collection, laboratory analysis, or data processing are almost inevitable and accumulate in the data.

The influence of misclassification on estimates of risk has been extensively addressed in the epidemiological literature (14–19). In particular, Flegal *et al.* (20) have described bias to the odds ratio as a function of sensitivity and specificity of risk factor categorization, risk factor prevalence, and the magnitude of the true risk. The purpose of this article is to apply these principles to case-control studies of genetic susceptibility biomarkers and cancer.

Methods

In case-control studies, the odds ratio is derived as a measure of the strength of an association between disease status and genetic risk factor status. Errors in defining genetic susceptibility will produce an observed odds ratio that is a biased estimate of the true odds ratio. To simplify the discussion, genetic risk factor status is defined as a binary variable (susceptible *versus* nonsusceptible). Assay accuracy is defined by Se,[3] the proportion of susceptibles correctly classified, and Sp, the proportion of nonsusceptibles correctly classified as such.

Using the formula derived by Flegal *et al.* (20) we calculate values of the observed odds ratio (*OOR*) as a function of the true odds ratio (*TOR*), the true prevalence

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[2] To whom requests for reprints should be addressed, at NIH, NCI, Epidemiology and Biostatistics Program, Executive Plaza North, Rm. 418, Bethesda, MD 20892.

[3] The abbreviations used are: Se, sensitivity; Sp, specificity.

(*Prev*) of the risk factor, and the assay *Se* and *Sp*.[4] Bias to the true odds ratio is defined in terms of excess relative risk (*i.e.*, TOR − 1) and can be expressed as a simple ratio:

$$\text{Bias} = \frac{OOR - TOR}{TOR - 1}$$

When the true odds ratio is greater than 1, bias is negative if the true odds ratio is underestimated and is positive if the true odds ratio is overestimated. We assume that misclassification is nondifferential, *i.e.*, errors occur similarly for cases and controls. Under the range of misclassification considered in this article, the true odds ratio is always underestimated for categorical variables and bias will, therefore, be expressed as a negative value.

The true odds ratio has been set at 10 in our examples. The relative amount of bias would be more substantial at higher odds ratios and of smaller magnitude at lower odds ratios (20) for most scenarios. Although observed odds ratios are generally less than 10 in epidemiological studies that report significant positive associations, these estimates of risk are based upon exposure and biomarker measures that are likely to be reported with some error. We show that under conditions common in case-control studies, even small degrees of misclassification can reduce observed estimates of a true odds ratio of 10 to levels more commonly found in epidemiological research.

In this article, we examine how bias varies for selected assay values of Se and Sp as the prevalence of the susceptible genetic risk factor in the controls ranges from 1 to 99%. For Se and Sp, we have selected a range of values from 100 to 70%, which are consistent with our experience, and that of other investigators, in the evaluation of several phenotype and genotype assays and cancer risk (11, 12, 21–26).[5] The calculation of Se and Sp assumes the existence of a gold standard. When perfect gold standards do not exist, which is often the case with newly developed phenotype and genotype assays, values of Se and Sp are generally underestimated.

Results

Given a Se or Sp which is less than perfect, the degree of bias to the true odds ratio will depend on the prevalence of the genetic risk factor. In Fig. 1, we first consider a scenario where the true odds ratio is 10, Sp is perfect (100%), and Se varies from 70 to 99%. Under these conditions, an assay with a Se of 90% results in a small degree of bias when the prevalence of the risk factor is low (prevalence, 5%; bias, −0.05; observed odds ratio, 9.6) but substantial bias when the prevalence is higher (prevalence, 50%; bias, −0.5; observed odds ratio, 5.5).

Fig. 1 also shows that substantial variability in assay Se produces little difference in bias when the prevalence of the risk factor is low but substantial differences in bias as prevalence increases. For example, at 10% prevalence, assay Se of 99, 90, and 70% yield observed odds ratio of 9.9 (bias, −0.01), 9.1 (bias, −0.10) and 7.75 (bias, −0.25), respectively. In contrast, at 50% prevalence, assay Se over the same values results in observed odds ratio of 9.2 (bias, −0.09), 5.5 (bias, −0.50), and 3.25 (bias, −0.75).

As previously mentioned, the magnitude of this bias is generally smaller as the true odds ratio decreases (20). Consider a scenario where the genetic risk factor prevalence is 50%, and the assay Se = 90% and Sp = 100%. As the true odds ratio ranges over 20, 10, 5, and 2, the observed odds ratios are 7.3 (bias, −0.67), 5.5 (bias, −0.50), 3.6 (bias, −0.33), and 1.83 (bias, −0.17), respectively.

In Fig. 2, we consider bias when the assay Se is perfect and the assay Sp varies from 70 to 99%. Under these conditions, less than perfect assay Sp results in substantial bias to the true odds ratio when the prevalence of the risk factor is low and smaller degrees of bias as the prevalence increases. For example, when risk factor prevalence ranges from 1, 5, 10, and 50%, and the true odds ratio is 10, an assay with a Sp of 98% results in observed odds ratio of 4.0 (bias, −0.66), 7.5 (bias, −0.28), 8.6 (bias, −0.15), and 9.8 (bias, −0.02), respectively.

Fig. 2 also shows that variability in assay Sp produces substantially different degrees of bias when the prevalence of the genetic risk factor is low and negligible differences in bias at high prevalence. For example, at a 5% prevalence of the risk factor in controls, assay Sp of 99 and 90% yields observed odds ratio of 8.5 (bias, −0.16) and 4.1 (bias, −0.66), respectively. In contrast, at a prevalence of 50%, assay Sp over the same values would result in similar observed odds ratio of 9.9 (bias, −0.01) and 9.2 (bias, −0.09).

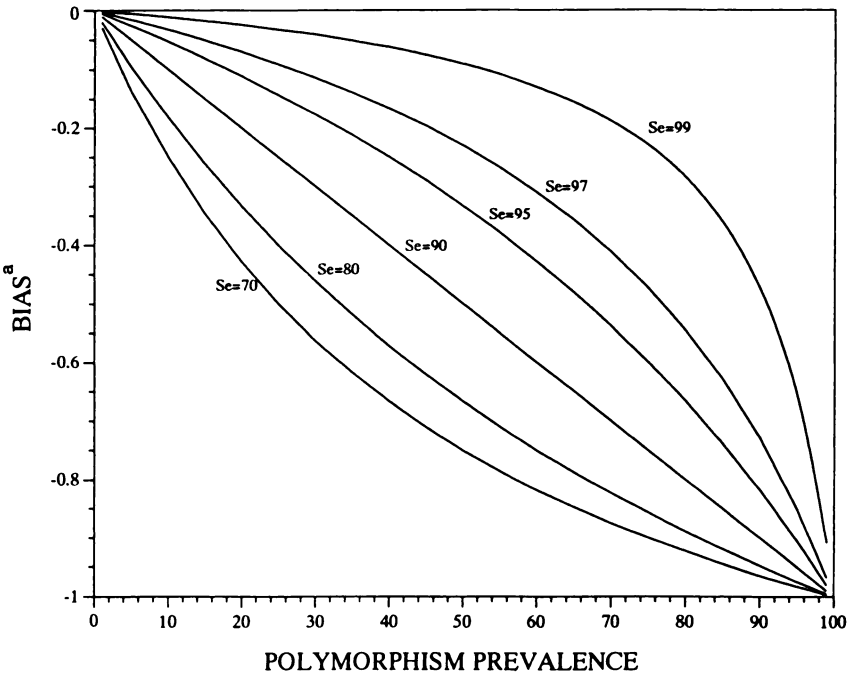
Discussion

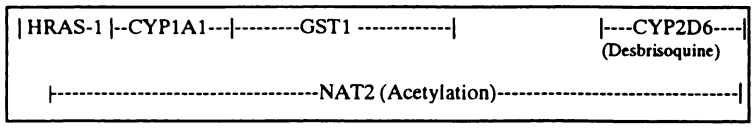
The prevalence of the genetic risk factor should be considered when assessing the bias caused by risk factor misclassification. Nearly perfect Sp is critical when the risk factor prevalence is very low (e.g., <15%) (27) while nearly perfect Se is important when the risk factor is very high (e.g., >85%) (20). In contrast, relatively poor assay Se produces only a modest bias to the true odds ratio at low prevalence, while relatively poor assay Sp produces little bias at high prevalence. Several applications of these observations follow.

Small differences in genetic marker misclassification may lead to discrepant findings between studies if marker prevalence is either very high or very low. For example, substantial variation has been reported for the association of the extensive/intermediate debrisoquine metabolizing phenotype (prevalence, ~92%) and risk of lung cancer. Reported odds ratios have ranged from 13.2 (28), 5.9 (29), and 4.8 (30), to 1.6 (26), 1.5 (31), and 1.4 (32). It is possible that the variation in risk estimates may be explained, in part, by small degrees of marker misclassification. For example, one source of assay inaccuracy is unrecognized intake of quinidine class drugs in study subjects, which can cause extensive metabolizers to be misclassified as poor metabolizers due to enzyme inhibition (11, 12). Table 1 portrays a hypothetical case-control study of 200 lung cancer cases and 200 controls where the true odds ratio of developing lung cancer for extensive/intermediate metabolizers is 8.6. A phenotype

[4] $$OOR = \frac{[Se \times TOR \times Prev + (1 - Sp)(1 - Prev)] \times [(1 - Se)Prev + Sp\ (1 - Prev)]}{[Se \times Prev + (1 - Sp)(1 - Prev)] \times [(1 - Se)TOR \times Prev + Sp\ (1 - Prev)]}$$

[5] Unpublished data.





Prevalence Range for Selected Polymorphisms

Fig. 1. Bias to a true odds ratio (*OR*) of 10 and genetic marker prevalence, given assay specificity = 100% and varying levels of sensitivity (Se). [a] Bias = $\frac{\text{(Observed OR} - \text{True OR)}}{\text{(True OR} - 1)}$. Observed OR calculated with formula presented in footnote 4. Genetic biomarker prevalence values (Refs. 2, 33–37).

assay with a Se of 99% and a Sp of 100% would bias the odds ratio to 4.8 by mislabeling only 4 of 382 true extensive/intermediate metabolizers as poor metabolizers (Table 1). If the 4 misclassified subjects were all cases the odds ratio would decrease to 2.8, a plausible scenario since lung cancer patients would tend to use more medication than would controls (Table 1). By comparison, if all 4 misclassified subjects were controls the odds ratio would be elevated to 11.

It is increasingly recognized that the prevalence of many genetic risk factors differ by race (33–37) which has implications for cross-population comparisons. An observed difference in risk between racially distinct populations which also differ by prevalence of the genetic risk factor may be due to true racial differences in risk (attributable to other unmeasured factors) or to the impact of the same assay misclassification in populations which differ in risk factor prevalence. Consider the example of a case-control study of the association of the slow acetylation polymorphism and bladder cancer. If the true risk was 10, an assay with a Se of 90% would produce an observed odds ratio of 9.1 in a Japanese population (prevalence, 10%), 5.5 in a European Caucasian population (prevalence, 50%), and 1.9 in a Moroccan population [prevalence, 90%; prevalence estimates from Weber (28)]. This phenomenon should be excluded as a competing explanation for differences in risk before attributing such differences to race.

The slow acetylator phenotype is a risk factor for bladder cancer in populations with occupational exposure to aromatic amines (1), while the rapid acetylator phenotype may be a risk factor for colon cancer (3, 38–40). A genotype assay for NAT2 which detects 90% of slow acetylator genotypes and correctly identifies all subjects with wildtype alleles would have Se = 90% and Sp = 100% in a study of bladder cancer. At a slow acetylator genotype prevalence of 50%, this assay would produce a substantial bias of −0.50 to a true odds ratio of 10. In contrast, the identical assay, used in a study of colon cancer, would have an Se of 100% and an Sp of 90%, producing a bias of only −0.09. Thus, the same assay applied to the same population with the same prevalence of NAT2 alleles would be appropriate to use in studies of colon cancer, but would be of marginal use in studies of bladder cancer under these conditions.

Polymerase chain reaction-based techniques have recently become available (13) to analyze genomic DNA samples for CYP2D6 alleles, the gene which codes for

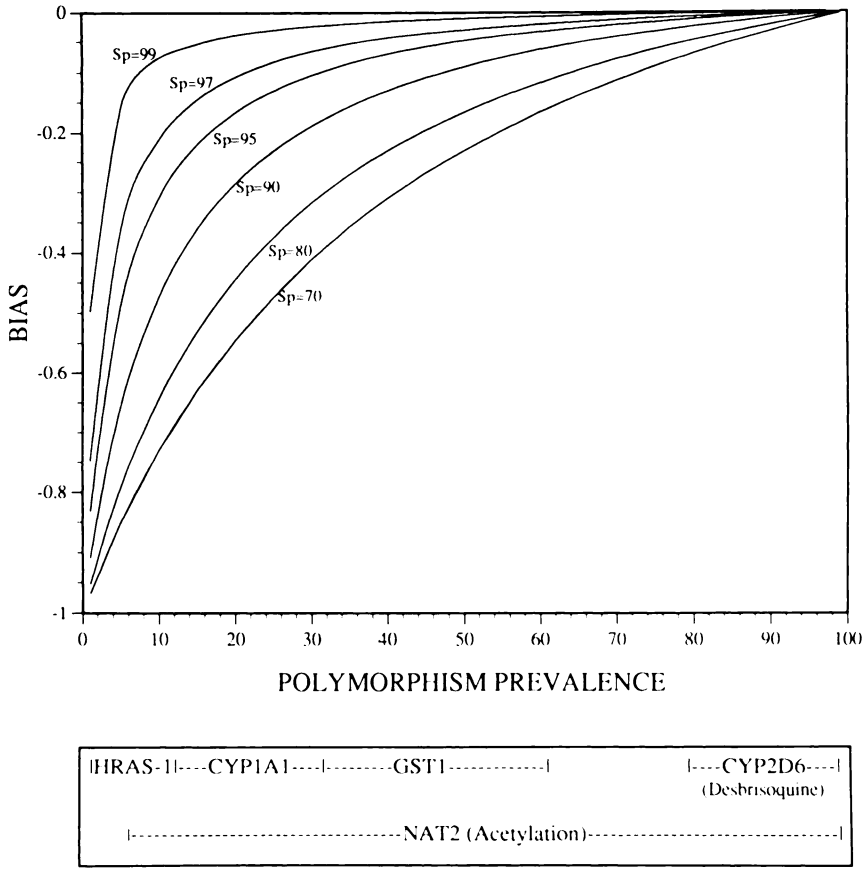


Fig. 2. Bias to a true odds ratio of 10 and genetic marker prevalence, given assay sensitivity = 100% and varying levels of specificity (Sp).

the debrisoquine metabolizing phenotype. Assay Sp (proportion of poor metabolizers, the protective phenotype, correctly identified) ranges from 95 (23) to 75% (25), while Se is essentially 100% (23, 25). While the debrisoquine phenotype assay described in Table 1 (Se, 99%; Sp, 100%) would bias a true odds ratio of 8.6 to 4.8, a genotype assay with an Se of 100% and Sp as low as 50% would bias the odds ratio to only 8.3 under conditions of nondifferential misclassification. These results suggest that for this case-control study, assays with only moderate specificity would be adequate, while only assays with essentially perfect sensitivity would be acceptable.

Table 1 Impact of misclassifying the debrisoquine phenotype in a hypothetical case-control study of lung cancer (n = 200 cases, 200 controls)[a]

Classification	EM/IM	PM	Se (%)	Sp (%)	OR	Bias
Risk factor perfectly classified						
Case	198	2	100	100	8.6	0
Control	184	16	100	100		
Nondifferential misclassification						
Case	196	4	99	100	4.8	−0.50
Control	182	18	99	100		
Differential misclassification						
Case	194	6	98	100	2.8	−0.76
Control	184	16	100	100		

[a] EM/IM, extensive/intermediate metabolizers; PM, poor metabolizers; OR, odds ratio.

Epidemiological studies should attempt to minimize biomarker misclassification (reviewed in Ref. 41). In general, however, some degree of genetic risk factor misclassification will almost inevitably occur in population-based studies. Evaluating this phenomena in the context of marker prevalence and true risk may help to explain disparate findings in the literature and should assist investigators in selecting markers that are appropriate for future studies.

References

1. Hein, D. W. Acetylator genotype and arylamine-induced carcinogenesis. Biochim. Biophys. Acta, *984:* 37–66, 1988.

2. Kawajiri, K., Nakachi, K., Imai, K., Yoshii, A., Shinoda, N., and Watanabe, J. Identification of genetically high risk individuals to lung cancer by DNA polymorphisms of the cytochrome P450IA1 gene. FEBS Lett., *263:* 131–133, 1990.

3. Lang, N. P., Butler, M. A., Massengill, J., Lawson, M., Pollack, M., and Kadlubar, F. F. Aromatic amine acetylation and *N*-oxidation phenotype in colorectal cancer, colorectal polyp and control patients. *In:* Biomonitoring and Susceptibility Markers in Human Cancer: Applications in Molecular Epidemiology and Risk Assessment. Kailua-Kona, HI: IARC, 1991.

4. Caporaso, N., Landi, M. T., and Vineis, P. Relevance of metabolic polymorphisms to human carcinogenesis: evaluation of epidemiologic evidence. Pharmacogenetics, *1:* 4-19, 1991.

5. Uematsu, F., Kikuchi, H., Motomiya, M., Abe, T., Sagami, I., Ohmachi, T., Wakui, A., Kanamaru, R., and Watanabe, M. Association between restriction fragment length polymorphism of the human cytochrome P450IIE1 gene and susceptibility to lung cancer. Jpn. J. Cancer Res., *82:* 254-256, 1991.

6. Zhong, S., Howie, A. F., Ketterer, B., Taylor, J., Hayes, J. D., Beckett, G. J., Wathen, C. G., Wolf, C. R., and Spurr, N. K. Glutathione *S*-transferase mu locus: use of genotyping and phenotyping assays to assess association with lung cancer susceptibility. Carcinogenesis (Lond.), *12:* 1533-1537, 1991.

7. Sugimura, H., Caporaso, N. E., Modali, R. V., Hoover, R. N., Resau, J. H., Trump, B. F., Lonergan, J. A., Krontiris, T. G., Mann, D. L., Weston, A., and Harris, C. C. Association of rare alleles of the harvey *ras* protooncogene locus with lung cancer. Cancer Res., *50:* 1857-1862, 1990.

8. Anderson, K. E., Conney, A. H., and Kappas, A. Nutrition as an environmental influence on chemical metabolism in man. *In:* W. Kalow *et al.* (ed.), Ethnic Differences in Reactions to Drugs and Xenobiotics, pp. 39-54. New York: Alan R. Liss, 1986.

9. Butler, M. A., Lang, N. P., Young, J. F., Caporaso, N. E., Vineis, P., Hayes, R. B., Teitel, C. H., Massengill, J. P., Lawsen, M. F., and Kadlubar, F. F. Determination of CYP1A2 and NAT2 phenotypes in human populations by analysis of caffeine urinary metabolites. Pharmacogenetics, *2:* 116-127, 1992.

10. Olsen, H., and Mørland, J. Ethanol-induced increase in drug acetylation in man and isolated rat liver cells. Br. Med. J., *2:* 1260-1262, 1978.

11. Speirs, C. J., Murray, S., Boobis, A. R., Seddon, C. E., and Davies, D. S. Quinidine and the identification of drugs whose elimination is impaired in subjects classified as poor metabolizers of debrisoquine. Br. J. Clin. Pharmacol., *22:* 739-743, 1986.

12. Brøsen, K., Gram, L. F., Haghfelt, T., and Bertilsson, L. Extensive metabolizers of debrisoquine become poor metabolizers during quinidine treatment. Pharmacol. Toxicol., *60:* 312-314, 1987.

13. Heim, M. H., and Meyer, U. A. Genetic polymorphism of debrisoquine oxidation: restriction fragment analysis and allele-specific amplification of mutant alleles of CYP2D6. Methods Enzymol., *206:* 173-183, 1991.

14. Bross, I. Misclassification in 2 × 2 tables. Biometrics, *10:* 478-486, 1954.

15. Diamond, E. L., and Lilienfield, A. M. Effects of errors in classification and diagnosis in various types of epidemiological studies. Am. J. Public Health, *52:* 1137-1144, 1962.

16. Copeland, K. T., Checkoway, H., McMichael, A. J., and Holbrook, R. H. Bias due to misclassification in the estimation of relative risk. Am. J. Epidemiol., *105:* 488-495, 1977.

17. Shy, C. M., Kleinbaum, D. G., and Morgenstern, H. The effect of misclassification of exposure in epidemiologic studies of air pollution health effects. Bull. NY Acad. Med., *54:* 1155-1165, 1978.

18. Gladen, B., and Rogan, W. J. Misclassification and the design of environmental studies. Am. J. Epidemiol., *109:* 607-616, 1979.

19. Greenland, S. The effect of misclassification in the presence of covariates. Am. J. Epidemiol., *112:* 564-569, 1980.

20. Flegal, K. M., Brownie, C., and Haas, J. D. The effects of exposure misclassification on estimates of relative risk. Am. J. Epidemiol., *123:* 736-751, 1986.

21. Hardy, B. G., Lemioux, C., Walker, S. E., and Bartle, W. R. Interindividual and intraindividual variability in acetylation: characterization with caffeine. Clin. Pharmacol. Ther., *44:* 152-157, 1988.

22. Deguchi, T., Mashimo, M., and Suzuki, T. Correlation between acetylator phenotypes and genotypes of polymorphic arylamine *N*-acetyltransferase in human liver. J. Biol. Chem., *265:* 12757-12760, 1990.

23. Daly, A. K., Armstrong, M., Monkman, S. C., Idle, M. E., and Idle, J. R. Genetic and metabolic criteria for the assignment of debrisoquine 4-hydroxylation (cytochrome P4502D6) phenotypes. Pharmacogenetics, *1:* 33-41, 1991.

24. Gonzalez, F. J., and Meyer, U. A. Molecular genetics of the debrisoquine-sparteine polymorphism. Clin. Pharmacol. Ther., *50:* 233-238, 1991.

25. Graf, T., Broly, F., Hoffmann, F., Probst, M., Meyer, U. A., and Howald, H. Prediction of phenotype for acetylation and for debrisoquine hydroxylation by DNA-tests in healthy human volunteers. Eur. J. Clin. Pharmacol., *43:* 399-403, 1992.

26. Roots, I., Drakoulis, N., Ploch, M., Heinemeyer, G., Loddenkemper, R., Minks, T., Nitz, M., Otte, F., and Koch, M. Debrisoquine hydroxylation phenotype, acetylation phenotype, and ABO blood groups as genetic host factors of lung cancer risk. Klin. Wochenschr., *66:* (Suppl. XI)87-97, 1988.

27. Stewart, W. F., and Correa-Villasenor, A. False positive exposure errors and low exposure prevalence in community-based case-control studies. Appl. Occup. Environ. Hyg., *6:* 534-535, 1991.

28. Caporaso, N. E., Tucker, M. A., Hoover, R. N., Hayes, R. B., Pickle, L. W., Issaq, H. J., Muschik, G. M., Green-Gallo, L., Buivys, D., Aisner, S., Resau, J. H., Trump, B. F., Tollerud, D., Weston, A., and Harris, C. C. Lung cancer and the debrisoquine metabolic phenotype. J. Natl. Cancer Inst., *82:* 1264-1272, 1990.

29. Ayesh, R., Idle, J. R., Ritchie, J. C., Crothers, M. J., and Hetzel, M. R. Metabolic oxidation phenotypes as markers for susceptibility to lung cancer. Nature (Lond.), *312:* 169-170, 1984.

30. Law, M. R., Hetzel, M. R., and Idle, J. R. Debrisoquine metabolism and genetic predisposition to lung cancer. Br. J. Cancer, *59:* 686-687, 1989.

31. Benitez, J., Ladero, J. M., Jara, C., Carrillo, J. A., Cobaleda, J., Llerena, A., Vargas, E., and Munoz, J. J. Polymorphic oxidation of debrisoquine in lung cancer patients. Eur. J. Cancer, *27:* 161-166, 1991.

32. Duche, J. C., Joanne, C., Barre, J., Cremoux, H. de., Dalphin, J. C., Depierre, A., Brochard, P., Tillement, J. P., and Bechtel, P. Lack of a relationship between the polymorphism of debrisoquine oxidation and lung cancer. Br. J. Clin. Pharmacol., *31:* 533-536, 1991.

33. Weber, W. W. The Acetylator Genes and Drug Response, pp. 65, 161, 164-165. New York: Oxford University Press, 1987.

34. Tefre, T., Ryberg, D., Haugen, A., Nebert, D. W., Skaug, V., Brøgger, A., and Børresen, A. L. Human CYP1A1 (cytochrome $P_1$450) gene: lack of association between the *Msp*I restriction fragment length polymorphism and the incidence of lung cancer in a Norwegian population. Pharmacogenetics, *1:* 20-25, 1991.

35. Bell, D. A., Thompson, C. L., Taylor, J., Miller, C. R., Perera, F., Hsieh, L. L., and Lucier, G. W. Genetic monitoring of human polymorphic cancer susceptibility genes by polymerase chain reaction: application to glutathione transferase μ. Environ. Health Perspect., *98:* 113-117, 1992.

36. Nakamura, K., Goto, F., Ray, W. A., McAllister, C. B., Jacqz, E., Wilkinson, G. R., and Branch, R. A. Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian populations. Clin. Pharmacol., Ther., *38:* 402-408, 1985.

37. Weston, A., Vineis, P., Caporaso, N. E., Krontiris, T. G., Lonergan, J. A., and Sugimura, H. Racial variation in the distribution of Ha-*ras*-1 alleles. Mol. Carcinogenesis (Lond.), *4:* 265-268, 1991.

38. Lang, N. P., Chu, D. Z. J., Hunter, C. F., Kendall, D. C., Flammang, T. J., and Kadlubar, F. F. Role of aromatic amine acetyltransferase in human colorectal cancer. Arch. Surg., *121:* 1259-1261, 1986.

39. Ilett, K. F., David, B. M., Detchon, P., Castleden, W. M., and Kwa, R. Acetylation phenotype in colorectal carcinoma. Cancer Res., *47:* 1466-1469, 1987.

40. Wohlleb, J. C., Hunter, C. F., Blass, B., Kadlubar, F. F., Chu, D. Z. J., and Lang, N. P. Aromatic amine acetyltransferase as a marker for colorectal cancer: environmental and demographic associations. Int. J. Cancer, *46:* 22-30, 1990.

41. Vineis, P., Schulte, P. A., and Vogt, R. F. Technical variability in laboratory data. *In:* P. A. Schulte and F. P. Perera (eds.), Molecular Epidemiology: Principles and Practices, pp. 109-135. San Diego: Academic Press, 1993.

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