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A BRIEF ORIGINAL CONTRIBUTION

Problems Ascertaining Friend Controls in a Case-Control Study of Lung Cancer

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Willingness of newly diagnosed lung cancer patients to volunteer names of friends as potential control subjects was assessed from August through December 1988 in a case-control study at the National Cancer Institute and Naval Hospital, Bethesda, Maryland. Friend controls appeared ideal to examine a genetically determined metabolic characteristic and lung cancer risk, since potentially confounding characteristics could be matched and cooperation should be high. Only 11 of 23 cases named at least one friend. Cases interviewed during the second study month were most likely to volunteer names. Either the recency of the diagnosis of a highly fatal disease or the referral to a tertiary care research hospital may have contributed to the reluctance of cases to volunteer names. No characteristic was identified that might offer a means to increase referral of friend controls. *Am J Epidemiol* 1991;133:63-6.

case-control studies; epidemiologic methods; lung neoplasms; research design

In the design of a multiinstitutional case-control study, a control is frequently selected for each case matched on one or more potentially confounding factors such as age, sex, race, and geographic area or institution. Matched controls may be drawn from hospitalized patients, from the neighborhood of cases, from among family members, or from friends of cases. We planned to examine the relation of a genetically determined metabolic characteristic with lung cancer risk in a case-control study of incident lung cancer. Identifying a control population for a study involving administration of a drug and the collection of biologic material was a challenge. Neighborhood controls were not felt to be a viable option, since it would be

physically and logistically difficult to conduct the metabolic portion of the study in the multiple geographic areas. Matching on friendship may effectively match on many of the potentially confounding characteristics of age, race, and socioeconomic status. Friend controls may also be easier and less costly to identify than matched controls obtained by other means (1). Other investigators have reported response rates from 94 to 100 percent with the use of friend controls in telephone interview studies (2-4). The potential disadvantages of friend controls include overmatching or the introduction of bias if the study exposure is a determinant of friendship (1). While occupation, alcohol consumption, or other social habits may be determinants of friendship, genetically determined metabolic rates should be independent of friendship.

MATERIALS AND METHODS

Previous studies reporting an association between debrisoquine metabolic phenotype

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and lung cancer risk have used control groups of either chronic obstructive pulmonary disease patients and/or cancer patients with cancers other than lung (5). While hospitalized patients may be more available for the biologic component of a study, their illness, medications, or reason for hospitalization may make it difficult for them to participate in the study and limit generalizability. These studies require the subject to take debrisoquine, which is considered an investigational drug in the United States, and to collect the subsequent 8-hour urine sample. Thus, control response rates may be low (30 percent) as reported in a prior study (6).

We felt that this study represented the ideal circumstance for the use of friend controls. The genetically determined activity of debrisoquine-4-hydroxylase, the P450 debrisoquine-metabolizing isozyme, was unlikely to be a determinant of friendship. The use of friend controls would make available a nondiseased population approximating the general population matching the cases and increase the cooperation in a complex study. In addition, since patients referred to these two hospitals may come from a distance, either due to their military duty station or in search of investigational treatment, matching on residence would be facilitated with friends.

Newly diagnosed cases of lung cancer seen at the National Cancer Institute Clinical Center and Naval Hospital, Bethesda, Maryland, were identified beginning in August 1988. Each case was asked at the completion of the administered study questionnaire to provide names of up to five friends who lived near them and were of the same sex, race, and age within 5 years. These friends would be invited to participate in the study as healthy control subjects. The data from the questionnaire interview and medical abstract were examined in an attempt to determine the characteristics distinguishing cases who volunteered friend names from those who refused. Logistic regression analysis was used to evaluate possible factors influencing willingness to volunteer names of friends for control selection.

RESULTS

During the first year of the study, 45 cases completed data collection activities. All were requested to volunteer names of friends to serve as control subjects by the same study nurse. Those cases who initially offered no names were reassured of confidentiality and recontacted at later times to volunteer friends' names. However, after the first 5 months of the study, when only 11 of 23 cases completing data collection activities volunteered names, the decision was made to recruit controls from outpatient appointment logs at the Naval Hospital, Bethesda, MD. Although all subsequent cases were still asked to name friends, the diligence with which names were sought definitely decreased after this time; i.e., only two of the subsequent 22 cases volunteered at least one name in contrast to 11 of the first 23 cases. Of those volunteering names, 69 percent gave two or more names. Because of the difference in recruiting efforts, only the cases that accumulated during the first 5 months were examined. Variables examined included age; sex; race; height; weight; smoking (ever/never, amount, current status, pack-years of cigarette smoking); use of multiple vitamins; prior diagnosis of chronic bronchitis, emphysema, asthma, or malignant tumor; education; religion; month of study interview; family history of cancer; and institutional subgroup. Sixty-seven percent of subjects under 55 years, 56 percent of heavy smokers, 71 percent of subjects interviewed in the second month of the study, and 63 percent of non-Department of Defense subjects referred to the National Cancer Institute-Navy Medical Oncology protocols volunteered names (table 1). Cases interviewed during the second study month were more likely to volunteer names. Data from the medical abstracts revealed that 63 percent of patients with adenocarcinoma gave names compared with 33 percent of small cell lung cancer patients. Stage was not important, although 15 of 21 (71 percent) cases had advanced stage disease (table 1); two cases were not staged since they were found not to have lung cancer. Ninety-five

TABLE 1. Characteristics of lung cancer patients by willingness to volunteer names of friends as potential control subjects

	Control names given	
	No	Yes
Sex		
Male	8	7
Female	4	4
Age		
<55 years	3	6
≥55 years	9	5
Education		
<12 years	3	0
12 years	3	5
>12 years	6	6
Study month		
1	5	1
2	2	5
3	2	1
4	2	2
5	1	2
Institutional affiliation		
NCI-NMOB*	3	5
DOD* beneficiary	7	5
NIH*	2	1
Smoking history		
≤50 pkyr*	8	6
>50 pkyr	4	5
Histologic type		
Squamous cell	1	0
Small cell	6	3
Adenocarcinoma	3	5
Other	2	3
Stage		
Non-small cell		
I, II	1	0
IIIA	1	1
IIIB	2	3
IV	1	3
Small cell		
Limited	3	2
Extensive	3	1
Other	1	1

* NCI-NMOB, National Cancer Institute-Navy Medical Oncology Branch; DOD, Department of Defense; NIH, National Institutes of Health; pkyr, pack-years of cigarette smoking.

percent of cases were fully ambulatory despite symptoms referable to lung cancer.

DISCUSSION

An unexpected problem in this study was the unwillingness of lung cancer cases to give names of friends as potential controls. Sub-

jects referred to the National Cancer Institute-Navy Medical Oncology protocols may reflect referral bias, since these subjects were referred specifically for protocol therapy, which may affect their willingness to participate in other research studies compared with an unselected group. Most small cell lung cancer patients are offered protocol therapy, and only 33 percent of this group volunteered friends' names. Reluctance to acknowledge illness may have decreased willingness to volunteer friends' names. Reasons offered by the cases for not volunteering names included not having living friends of the appropriate age, not wanting to bother their friends, and wanting to speak to their friends before giving their name, which seemed to serve as a surrogate for refusal. While assurances of protection of privacy and nondisclosure of the case's diagnosis were not questioned by the cases, fear that friends would discover the diagnosis before the case was ready to disclose it may explain the reluctance in large part. Among the names given for control subjects who were contacted before this method was abandoned, four refused to answer the telephone-screening questions, five were ineligible, and all six friend controls determined to be eligible participated. Unfortunately, this method had to be abandoned, since having control subjects for less than 50 percent of the cases was unacceptable. No variable could be identified that might have been used to improve control referral, although the sample size was small.

Our experience with friend controls differs from that reported in the literature. Edmondson et al. (4) used friend controls in the evaluation of hepatic adenomas and oral contraceptives, enrolling 34 controls for the 36 cases. Schlech et al. (2) and Shands et al. (3), who also used friend controls in their studies of toxic shock syndrome, apparently obtained the desired number of names from the cases and had 100 percent participation with the telephone interviews. While an acceptable response rate was anticipated and observed despite the biologic component, the refusal at the case level was unexpected. The reason for the differences may include

part of the study, 45 cases participated in telephone screening activities. All were offered names of friends to volunteer by the same study who initially offered no names of friends to volunteer. However, after the first 5 months, when only 11 of 23 cases participated in telephone screening activities, the decision was made to continue outpatient appointments at the National Cancer Institute Hospital, Bethesda, Maryland. Subsequent cases were still offered names of friends, but the diligence with which names were sought definitely decreased; i.e., only two of the 11 cases volunteered at least one name of a friend. Of the 11 of the first 23 cases who volunteered names, 69 percent volunteered names. Because of the diligent efforts, only the cases who volunteered names during the first 5 months were included in the analysis of variables examined in this study: sex; height; weight; smoking history; current status; use of multiple diagnostic tests; diagnosis of chronic disease; asthma, or malignancy; religion; month of family history of cancer; and age group. Sixty-seven percent of cases were under 55 years, 56 percent were 55-74 years, and 71 percent of subjects were in the second month of the study. The number of non-Department of Defense cases referred to the National Cancer Institute-Navy Medical Oncology Branch is shown in table 1. Cases who volunteered names (table 1). Cases who did not volunteer names in the second study month are shown in table 2. Data abstracts revealed that 63 percent of cases with adenocarcinoma volunteered names, and 33 percent of cases with small cell lung cancer volunteered names. Stage was not known in 15 of 21 (71 percent) cases who volunteered names and 15 of 21 (71 percent) cases who did not volunteer names (table 1); the remaining 6 cases were unstaged since they were referred to the National Cancer Institute-Navy Medical Oncology Branch for lung cancer. Ninety-five

the older population in this study, contact at the time of diagnosis of a highly fatal disease compared with contact after cure of an acute illness, and the stigma many people still associate with the diagnosis of cancer.

Friend controls were expected to be extremely useful in studying biochemical and genetic markers of cancer susceptibility, since these were unlikely to be determinants of friendship. Although the lack of cooperation of the cases limited the use of friend controls in this study, friend controls appeared willing to participate. This may be a useful group to consider as controls in studies of less lethal diseases.

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