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THE EPIDEMIOLOGIC BASIS FOR THE NOTIFICATION OF SUBJECTS OF COHORT STUDIES

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The issue of whether to notify surviving subjects of the positive results of retrospective cohort mortality studies has been raised by the United States Congress (1) and by the media (2), but has not so far been debated in the epidemiologic literature. At issue is the question of whether or not investigators have failed to inform subjects of studies about risk information that might be of concern to them. The general practice of epidemiologists has been not to individually notify surviving subjects comprising study cohorts, the publication of study results not withstanding. It has, however, been argued (3–9) that the subjects of epidemiologic studies have a right to know of results indicative of excess risk, that investigators have a duty to inform them of such results, and that these rights and duties are consistent with the legislative and public policies of the last 20 years. Still, the unanswered scientific question is whether there is an epidemiologic basis for notifying surviving subjects of cohort studies. If so, what assumptions are made in the process, and what issues and criteria should be considered prior to notification?

The fundamental premise of this commentary is that subjects of retrospective cohort mortality studies should be notified of results if the results contain risk information about them, and if that information is held by an investigator who is a member of an institution with public responsibility such as a government agency, corporation, university, or labor union. This obligation derives from the fact that investigators have both the names and addresses of cohort members, as well as risk information about them (4). Although the issues discussed herein pertain to cohort studies, in general, the focus will be restricted to occupational retrospective cohort mortality studies.

Retrospective cohort mortality studies are based on an evaluation of the experience of the deceased members of the cohort compared with what would be expected if the experience of some standard comparison population, such as the US population, was applied to them. These studies involve identification of cohort members, usually through personnel records. Vital status of each study participant is determined using company records, and by cross checking with such agencies as the Social Security Administration, the Internal Revenue Service, Bureau of Motor Vehicles, and private locators. If a cohort member is deceased, the death certificate is sought and the cause of death is determined by a nosologist. Statistical comparisons of the mortality experience are then conducted. Nowhere are individuals in the cohort contacted or subject to the requirements of "informed consent."

METHODOLOGIC FEATURES OF COHORT MORTALITY STUDIES

Demonstration of excess deaths

If the ratio of observed to expected for a particular cause of death, as summarized

Abbreviation: SMR, standardized mortality ratio.

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by the cause-specific standardized mortality ratio (SMR), is greater than 100 and is statistically significant (usually at the 0.05 level), then a study is considered to have demonstrated excess cause-specific deaths (10). Before declaring such findings truly positive, an investigator typically evaluates whether the apparent association is consistent with other findings, is biologically plausible, indicates a dose-response relationship, and is generally in conformity with a number of commonly recognized criteria (10). In short, the investigator asks if the findings make sense and are consistent with other work. If the findings of a study are novel, they will generally require additional studies for confirmation.

Inherent limitations

Given a duly derived positive finding that adheres to these criteria, are the results pertinent to cohort members? That is, for example, would a person who understands epidemiology want to know if he or she was a subject of a positive cohort study or are there inherent or conceptual aspects of the cohort mortality study methodology that produce results that have no relevance for surviving cohort members?

Numerous cohort mortality studies have been performed. The methodology is classically exemplified in the study by Doll and Hill (11) of smoking in physicians, and that by Lloyd and Ciocco (12) of the long-term mortality of steelworkers. Critiques of the method and discussions of its limitations also have been adduced. Greenland (13) demonstrated the problems of inadequate follow-up. Wang and Miettinen (14) criticized the use of the general population as a valid reference population due to lack of comparability of effects, populations, and information. A standardized mortality ratio (SMR) has been shown to be affected by differences in the age distribution between an occupational cohort and a reference population. Gaffey (15) has shown that age-specific SMRs may vary even if the relative risk is the same at all ages. This results because an SMR and a relative risk are not the same. Fleiss (16) has defined a relative risk in terms of the probability of death (i.e., the proportion of persons who die in an interval), while an SMR is defined in terms of mortality rates (i.e., the number of deaths per person-years of observation). Enterline (17) has described how overlap between exposure and follow-up can hinder the determination of a dose-response relationship in cohort studies. Through all of this examination, the conceptual basis of the retrospective cohort mortality study has not, however, been repudiated, and such studies continue to be performed by researchers in private and public organizations (18–22).

The findings of cohort mortality studies are usually presented for publication, and for occupational investigations are often disseminated to workers by their unions or management, and sometimes by the media. There are no studies of the extent to which study results reach cohort members, but my experience indicates that various occupational cohorts contain large numbers of subjects who may not learn of results because of their relocation, retirement, or termination of employment.

Pertinency of study results to cohort members

Do cohort mortality studies contain information that warrants proceeding beyond general dissemination of results to notifying individuals? Positive epidemiologic studies in general, and cohort mortality studies in particular, produce results that indicate an excess of cause-specific deaths compared with some standard. It is not specious to interpret these results as indicating an excess risk, even though, to be precise, this excess is a ratio of observed to expected deaths. A risk is a probability of developing or dying from a disease in a given interval, conditional on not dying from any other causes during that interval. It is a dimensionless quantity that can vary between one and zero (23). It is customary

to use the term risk or its derivatives (e.g., risky, at-risk, risk factor, etc.) in a much broader sense than suggested by the narrower definition (23). The notification of study subjects would accentuate the broader definition of risk indicating that the probability of a cause-specific death in a cohort is more than would be expected if the mortality rates of a standard population were applied.

In a positive study, the risk of cause-specific death is greater than in the standard population. The risk, however, is applicable to the cohort as a whole and does not pertain to individual members in a way that would allow one to inform an individual worker that he or she is at risk of a certain disease. This strict interpretation is not violated in individual notification if the individual is informed of the cohort risk concept and of the fact that risk is a probabilistic rather than a deterministic phenomenon.

The issue is portrayed by the following example. In 1974, a mortality study (24) was performed on a cohort of workers at a vinyl chloride production plant. The study demonstrated an excess of deaths due to angiosarcoma of the liver (SMR = 1,155). Put another way, the chances that the cohort would experience more angiosarcoma deaths than in a similar, but not exposed cohort, were approximately 11 to 1. If you are a member of that cohort, your risk would not necessarily be 11 times "normal" but, as part of such a group, if you were exposed to vinyl chloride you probably would have some increased risk of angiosarcoma. There appear to be no inherent limitations that mitigate against the logic in that statement of risk. Excess deaths can be used as an indicator of risk.

Risk to survivors

The next question that arises is whether the surviving members of a cohort have the same risk of a specific disease or death as the deceased, or if the excess risk is restricted to the deceased. It is possible that those who died of the cause in question had some greater exposure, were more sensitive, or had some other characteristics not shared by the remainder of the cohort. This is particularly likely if the deceased workers were employed at an earlier date than the survivors since exposures to occupational toxins were typically greater in the past than today (42). The assumption that risks for surviving members are similar to those of the deceased needs to be evaluated, as part of the consideration for notification, on a cohort-specific basis. Some of the survivors are likely to have the same occupational characteristics as the decedents, and probably share similar risks. Follow-up mortality studies on cohorts previously evaluated generally still show excess risks, even if they are somewhat lower than in the initial evaluation (25). However, in some cases, risks are actually increased (26).

Simultaneous inferences

As with most comparative studies, differences between observed and expected mortality in retrospective mortality studies are evaluated with regard to the likelihood that they are related to the hypothesis in question (i.e., reject the null hypothesis) rather than to chance. In this regard and assuming statistical independence, a certain percentage of studies or standardized mortality ratios within studies, typically five in 100, will appear to be positive when, in fact, they are not. A notification should not be based on a chance positive finding.

In a cohort mortality study, usually one or a few causes of death (expressed as standardized mortality ratios) are identified in a priori hypotheses to be in excess. In addition to evaluating the hypothesized causes, the investigator usually looks at all other specific causes. These other causes that are not part of the a priori hypothesis can be considered as a posteriori hypotheses. Formal hypothesis testing of these findings may not be appropriate, but if a posteriori hypotheses are generated the

implications of simultaneous inferences need to be considered (27, 28).

Weighing the decision to notify

Despite the ascertainment of a "true" excess risk, notification may conflict with the medical maxim "primum non nocere"—"above all, or first, do no harm" (29). There are two salient manifestations of this conflict. First, within a cohort or in a series of cohorts, there will most likely be false notifications. These may be categorized in a 2×2 characterization of notification decisions and risk status (figure 1) which contains two cells where there will be false notifications, that is, notifying when there is no risk (false positive) or failing to notify when there is a risk (false negative). Epidemiologic data may be used to differentiate subcohorts at risk and reduce many false positive notifications. False negatives are less likely, in as much as the whole process of notification may be viewed as an effort to reduce false negatives. However, false negatives will result when faulty data are used for risk differentiation and subsequent notification.

The second manifestation is whether there should be notification when there are no effective methods of intervention (early detection or treatment). It is a premise of this commentary that this is a public policy consideration but that a person has a right to risk information regardless of whether there are intervention possibilities. The epidemiologic questions with regard to the effectiveness of early detection and treatment are secondary to this consideration. This is an arguable premise that merits discussion but the discussion should not be limited to epidemiologists.

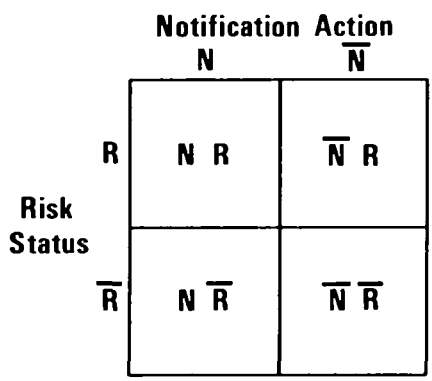

FIGURE 1. Classification of notification decisions with notification action and risk status considered as dichotomous variables. $N\overline{R}$ = false positive notifications; $\overline{N}R$ = false negative notifications.

PROPOSED CRITERIA

There appear to be no strong inherent limitations in the design and interpretation of cohort mortality studies that are contraindications for notification when excess risk is evident. Notification, however, is a powerful action that has an impact on many individuals and groups (4, 8). The potential for these impacts to be debilitating and costly demands that notifications be accurately targeted and based on sound research. There are no explicit criteria for what constitutes a risk of which a subject should be notified.

This absence of criteria for what constitutes a notifiable risk could lead to many false notifications. The burden of such false notifications can be substantial not only for individuals but also for their families and for many other sectors of society (4, 8, 30). A person notified of a risk, but who does not develop the disease, has many of the same needs as one who does. The establishment of explicit criteria for notification is critical to the orderly evaluation of research results as they pertain to surviving subjects. This proposal for establishing criteria for notification is not meant to be a final statement on this important subject, but, rather, a starting point to begin discussion of the matter.

Methodologic integrity

Studies that are candidates for notification should not be evaluated merely on their adherence to some decision algorithm. Each study needs to be assessed for methodologic integrity, consistency with other findings, and for specific cohort exposure and disease characteristics that might mitigate a decision concerning notification.

The same criteria that apply to evaluation of disease-exposure associations may be used for deciding whether there is a notifiable high risk, although there can be notifiable risks even if the cause is not known. Monson (10) has elaborated on the criteria and has included consistency, specificity, strength of association, dose-response relationship, biologic plausibility, temporal relationship, and statistical significance. Complete adherence to all these criteria is not necessary for notification to be indicated. Rather, there needs to be a sense that the study was methodologically sound and the excess risk is not spurious.

Since many retrospective cohort mortality studies do not address all confounding influences, it is possible that an excess risk of disease may be related to some nonoccupational factor or to some occupational exposure other than that under study. In such cases, the finding of an excess may not be in error, but the identity of the cause could be in question; this may not relieve the need to notify since the risk is apparently real. For example, 10,000 automobile and agricultural-implement pattern and model makers were notified of a two-fold risk of colon and rectal cancer as a result of three epidemiologic studies (31–33). Although the employees' work involved numerous toxic and carcinogenic substances, none was imputed as causal, and in fact, there is a strong likelihood that there is a socioeconomic component to the etiology. Nonetheless, this group appears to have an excess risk and its union, the Pattern Makers League of North America, felt that notification was warranted (4). On the other hand, if, upon subsequent review, some strong comparison or other type of bias is found, a risk might be considered specious and should be rejected as a subject for notification.

Adjusted statistical significance

The problem of simultaneous inferences is acutely evident in retrospective mortality studies where, in addition to hypothesized cause-specific SMRs, often all possible cause-specific SMRs are evaluated. For notification purposes, such studies should be considered positive only if they meet a level of statistical significance that is adjusted for simultaneous inferences. Jones and Rushton (27) have reviewed some of the adjustment methods appropriate for epidemiologic studies and indicate that the effort to adjust is more important than the actual approach selected. They support the use of a Bonferroni-type adjustment because of its wide use. Another method, described by Sidak (28), is similar to this but allows for a calculation of an exact adjusted α level.

The exact adjusted α level for each of k independent SMRs can be determined from the formula

$$(\text{adjusted } \alpha) = 1 - (1 - \alpha)^{1/k}$$

where α is usually 0.05 (28).

This adjustment assumes a worst-case scenario (independent tests) and therefore is a lower bound to the exact adjusted α level. Causes of death are mutually exclusive events but not independent. However, despite the lack of independence, the issue is still valid because the probability of finding at least one standardized mortality ratio that is significant (given that there are actually none) would be greater than 0.05 in most mortality studies. This procedure provides a way of reducing the number of spuriously significant standardized mortality ratios in a cohort mortality study. It represents a conservative measure that would apply to the extreme case of total independence. In the condition of partially dependent events, it still provides a lower bound on the individual significance levels. This conservative approach is justified when a notification action might be triggered by a significant finding. It is suggested that this adjustment method be applied to a priori and a posteriori analyses separately. In this way, the power of the study would not be sacrificed because typically, only one to five causes of death are

hypothesized prior to the study, k would be relatively small, and hence the individual significance levels would not be reduced appreciably. In contrast, where there are a posteriori evaluations, as many as 80 causes of death might be surveyed, k would be large, and the power would be reduced. Loss of power in a posteriori evaluations is considered justifiable in the interest of a rigorous testing procedure considering the unexpected nature of a positive result.

Magnitude of absolute lifetime risk

The previous discussion has been about standardized mortality ratios which are relative risks. The magnitude of the absolute risks also needs to be considered, when deciding whether to notify, in order to define where risks are so small as to be insignificant subjects for notification.

Absolute lifetime risks may be defined as the sum of background risks for a given disease and any incremental risks associated with a specific exposure. To illustrate how a criterion for absolute risk magnitude would operate with regard to notification, cancer risks will be considered. Cancers represent the cause of death of interest in many mortality studies and they have often been considered in discussions of risk assessment methods.

The background risk component of absolute risk has been calculated as probabilities of developing site-specific cancers. For purposes of this discussion, the probabilities calculated by Zdeb (34) using a life table approach, will be considered. They range from risks of the order of 10^{-2} for lung cancer to 10^{-4} for monocytic leukemia (in males).

The incremental component of absolute risk has been discussed by the Office of Technology Assessment in a document on carcinogen risk determination as a basis for regulation (35) in which a framework for decision-making about incremental risks was suggested:

> . . . risks above a certain level (10^{-3} to 10^{-2}) might be declared unreasonable no matter what, and risks below a certain level (10^{-6}) might be declared reasonable, acceptable or negligible. In between, the risks that range from 10^{-6} up to 10^{-3} or 10^{-2} would require balancing of the risks and benefits to decide whether or not to regulate.

Both Albert (36) and the Office of Technology Assessment have suggested that "substances associated with individual lifetime risks of 10^{-5} might be considered as presenting risks so low that they require no action to reduce them further." This same level was discussed by a working group at the national conference on Ethical Issues in Worker Notification held in Pacific Grove, CA, June 3–5, 1981, and sponsored by the Western Institute for Occupational and Environmental Science and funded by the National Cancer Institute. The group suggested that risks less than 1 in 100,000 did not need notification. There was no specification, however, of whether this meant a lifetime risk or an annual risk.

For the purposes of identifying notifiable risks, the decision-making framework from the Office of Technology Assessment document is useful and may be applied to the probabilities for developing cancer. Accordingly, if the sum of background risks and incremental risks were such that the absolute lifetime risk is greater than 10^{-3}, notification would be warranted. If the absolute risk was in the range of 10^{-3} to 10^{-5}, other quantitative criteria would need to be applied, and if the risks were less than 10^{-5}, notification would generally not be warranted.

A number of caveats and conditions must be placed on this scheme. 1) The magnitude of risk criterion is only meant to be applied to positive studies after the other criteria of methodologic integrity and adjusted statistical significance are met. 2) It is assumed that the absolute risk will be of the same order of magnitude as the background risk. Therefore, the use of background risks, such as those calculated by Zdeb (34), will be satisfactory as the scale on which to make notification decisions for positive studies. 3) In the categorically non-notifiable range of risks smaller than 10^{-5}, it

might be worthwhile to consider an additional criterion of relativity of risks, so that risks greater than a relative risk of 10 would become notifiable. This may not apply to most chronic occupational diseases, but eventually it could be of concern as rare markers become subjects of investigations. 4) Positive studies with risks within the range 10^{-3} to 10^{-5} would be potentially notifiable, but because of their relative smallness, there is a likelihood that the presence of a significant standardized mortality ratio (SMR) could reflect methodologic factors rather than factors related to disease-exposure associations. These methodologic factors include the use of an external comparison group in the form of national mortality rates, and the fact that "at older ages the SMR is subject to limitations in possible values more or less independent of any hazard to which the study population may be exposed" (15). Since these factors could influence a study outcome with the result being positive for otherwise borderline associations of relatively rare diseases, a fairly restrictive minimum standardized mortality ratio should be used for deciding whether to notify.

It is proposed here that a standardized mortality ratio of 300 for diseases with a lifetime risk between 10^{-3} and 10^{-5} be the minimum acceptable if notification is to take place. The choice of a three-fold elevated standardized mortality ratio for a disease with a lifetime risk of less than 10^{-3} is arbitrary. It was chosen to reflect the concern that an excess of disease found in studies where there is a higher probability of a spurious finding (due to relatively low incidence and small excesses) should be conservatively evaluated because of the negative effects it might cause in people not at risk, but who are falsely notified. Figure 2 displays the three notification decision risk ranges.

The argument for delineating notifiable risks should not be confused with attempts to balance the impact of notifying or not notifying a group truly at risk. Such an exercise repudiates the premise of this commentary, that is, the right of people to know of their own study results and hence their cohort's risks, if some institution or individual has that knowledge. Implied by this right, however, is the understanding that the investigator has some degree of certainty or confidence in the information (within the bounds of the appropriate disciplinary conventions), and that, given that everyone is at some risk, the information is meaningful. Where the risk information is uncertain enough, and indistinguishable enough from the background, the investigator has the responsibility to consider the rights of a group (including not only workers but families, communities, and employers) not at risk, who may be wrongly drawn into the labeling process, and thus suffer undue consequences.

Three studies reported in the literature illustrate the application of these quantitative criteria. Waxweiler et al. (24) reported a standardized mortality ratio (SMR) of 1,155 (seven observed, 0.6 expected) for biliary and liver cancer in a cohort of workers exposed to vinyl chloride. Using Zdeb's (34) calculations, the lifetime risk for liver cancer would be on the order of 10^{-3} (2.1/1,000). Since the study was based on a hypothesis concerning liver cancer and four other cancer sites, there would be need to adjust for simultaneous inferences so that the significance level would be reduced to 0.01. The SMR still was significant at this adjusted level, and, since the SMR was greater than 300, the study results would be subject to notification.

In contrast, in a study of motor vehicle examiners exposed to carbon monoxide, Stern et al. (37) found an SMR of 235 (four observed, 1.7 expected) for brain tumors (classified as malignant gliomas). The probability of developing cancer of the brain is on the order of 10^{-3} (3.4/1,000 in males). However, in this case, brain cancers were not hypothesized prior to the study, and numerous simultaneous inferences were made as part of the a posteriori in-

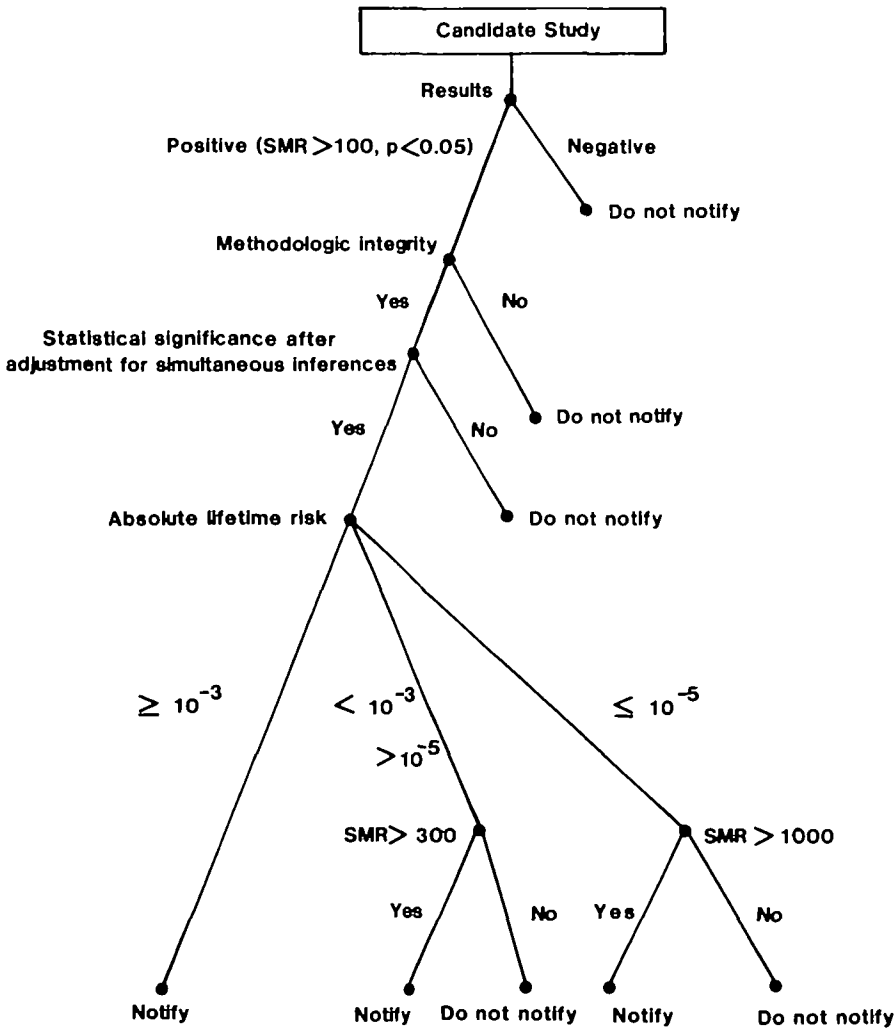

FIGURE 2. Decision logic for notification criteria—a proposed model. SMR, standardized mortality ratio.

spection of the data. Thus the adjusted significance level would be well below the p value (0.03) found for the brain cancers and, since the SMR is less than 300, the findings would be excluded from notification.

The third example demonstrates not only the application of the quantitative criteria, but also one of the previously mentioned premises of this commentary, namely that a risk found in a methodologically sound study is a subject for notification regardless of whether it is occupationally related. Although the foregoing discussions have involved mortality studies, the incidence study of Pell et al. (38) illustrates this premise. The investigators reported an unusually high incidence of cancer of the cervix among women in a chemical company. This finding was not hypothesized before the study, nor is this site usually linked to occupational chemical exposures. The probability of developing cancer of the cervix uteri, according to Zdeb (34), is on the order of 10^{-2}. This would definitely be in the range of a notifiable risk, at least before adjustment for simultaneous inferences. Based on the table of standardized incidence ratios in the paper by Pell et al. (38), it can be assumed that at least 21 sites were

evaluated. Hence, using the formula for adjusted statistical significance, the p value would have to be less than or equal to 0.002 to be statistically significant. In this case, the p value for 141 observed and 60.5 expected cases is less than 0.00001, or highly significant. If the study was found to be methodologically sound, the risk of cancer of the cervix would be a subject for notification even though it could not be explained by occupational factors. On the other hand, as Pell et al. (38) discussed, the unusually high rate may merely reflect early casefinding as a result of the company's cancer screening program. If that could be substantiated, it would show that there may not be an excess risk and notification might not be warranted.

Discussion

Notification is not a single communicative act but, rather, the initiation of a process with far reaching consequences (4). These consequences involve not only those notified, their families, and communities, but include also the medical, legal, business, media, government, and social welfare sectors.

Moreover, the impact on the investigator and institution initiating the notification is significant and long lasting. It may involve subsequent activities ranging from meetings with local medical societies to testifying in litigation proceedings. For these reasons, failure to notify in an instance when the results of a study are positive could leave an epidemiologist in a vulnerable legal and moral position. Speaking on this issue, John Fletcher (38), bioethicist for the National Institutes of Health, has said that epidemiologists performing record-linkage studies may have to join other biomedical scientists who have the obligation to notify study subjects. It is therefore important that criteria be established for this action. Epidemiologic research is not designed to provide risk specifications for individuals, yet the fears and concerns of individuals potentially exposed to deleterious conditions hinder them and others from appreciating the complexities of such research. At the same time, specifying that an individual is part of a group found to have an excess of deaths due to specific or unknown causes does not appear to violate epidemiologic principles and should be considered an obligation of investigators or their sponsoring institutions. In practice, the notification of individuals will involve not just composing and dispatching initial communications, but also may include, in some circumstances, meeting with local physicians and other concerned individuals, assisting in the development of appropriate screening or tertiary prevention programs, and generally responding to the situation.

The goal of establishing the criteria suggested in this paper has been to provide a systematic framework for minimizing false positive notifications. Since frequencies of false positives and false negatives are interrelated, minimizing one will increase the other. Notification, however, is inherently an action for reducing the number of "at risk" people not notified (i.e., reducing the number of false negatives). The question then becomes one of weighing the significance of the resultant increase in false positive notifications. This increase should be guarded against by the application of strict criteria. There has been little study of the effects on those who are not at risk, but who are notified that they are, and hence must go through the rest of their lives thinking and behaving as a group labeled "at risk." This group will have many of the same medical and social needs as those truly at risk. A false positive notification may also affect family members who, realizing that this is an example of "crying wolf", could be skeptical about other health warnings.

Another area of consideration is the issue of negative results. Should the subjects of studies with negative results be told of the findings? There does not appear to be the same ethical duty to disclose negative results as there is with positive results. While

notification about negative results might be consoling or assuring to some people, it is probably not worth the effort involved. Moreover, as Hernberg (40) has noted, "theoretically the negative study requires an infinite number of observations or at least a large number" to test the null hypothesis.

If the notification of subjects of positive retrospective cohort mortality studies is an obligation that has been overlooked by epidemiologists, then the criteria suggested here may be useful in meeting that obligation. Although there are decidedly epidemiologic questions involved, this issue goes beyond the epidemiologic community because it reflects a societal situation that needs a societal solution (41). Such a solution might involve legislation that would mandate such action and provide compensation for those notified.

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