Application of Biomarkers in Cancer Epidemiology
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Ethical and social issues in the use of biomarkers in epidemiological research

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The use of biomarkers in epidemiological research may raise ethical and social issues. These issues stem from the belief that research participants have 'rights' to appropriate information before, during and after studies so that they can make informed decisions. Ethical issues can arise during protocol development, obtaining participation, and in the interpretation and notification of text and study results. Additionally, there are ethical considerations concerning the use of biological specimens collected and stored for one purpose and subsequently used for other research purposes. A major ethical issue is the maintenance of participants' privacy and the confidentiality of their test and study results. Ethics committees need to be well-informed about the scope, limitations and expectations of biomarker research in order to be able to respond to social and scientific developments in the use of biomarkers.

Epidemiological research potentially raises many ethical questions and issues. The use of biomarkers in such research may raise further issues, because biomarkers are obtained from the individual person and have the potential for providing important information about exposures, biological effects of exposures and susceptibility to disease for that individual (Grandjean, 1991; Schulte, 1992; Van Damme *et al.*, 1995). At the same time, there is the widespread misconception that biological information is always more valid than other information, such as that obtained from questionnaires, environmental monitoring or record review. None the less, the potential contribution of biomarkers to enhancing determination of carcinogen exposure–disease associations, identifying disease earlier, or identifying particular etiological subgroups makes the use of biomarkers desirable and inevitable.

There is increasing recognition that many of the issues related to recruiting and informing subjects of test and study results have varied depending on study design. Consider three examples: (1) a cross-sectional study involving occupational exposure and a biomarker of early effect (e.g. cytogenetic effects); (2) a cancer case–control study evaluating the impact of common polymorphisms of metabolizing enzymes; and (3) a prospective cohort study with banked biological specimens. In general, cross-sectional studies of healthy workers are completed in a short period of time, with the expectation that the biomarkers under study may provide some insight into the potential risk of an exposed group as a whole, or possibly into an individual's risk of subsequent cancer development. Notifying workers of their results in these studies is common. By contrast, the case–control study involves subjects who are already sick, along with randomly selected controls who are not definable in an *a priori* sense to be at risk. These subjects are generally not notified of results. Finally, in the third example, everyone is healthy and samples are provided with the expectation that results will not be available for a relatively long time.

In the following pages, we will generalize about these issues, but the appropriateness may vary by study design or detail and the ethical issues should be addressed on a case-by-case basis.

In this paper, we will use the steps in the research process as the organizing theme and discuss ethical and social issues for each step. Where there are issues that differ according to the type of marker or the use of a marker, these aspects will be identified. Finally, we will discuss the use of stored specimens in biomarker research.

A premise of this paper is that ethical use of biomarkers in research involves attention to the 'rights' of subjects to appropriate information

before, during and after studies, so that they can make informed decisions. Failure to plan or budget adequately for these efforts can lead to these rights not being met. We would note, however, that there is some difference of opinion about when and what to tell research participants, and this will be discussed in later sections.

Protocol development and study design

Ethical issues come into play from the moment biomarkers are considered for a study. Why is the biomarker being considered? Biomarkers are usually more resource- and labour-intensive than other measures of exposure, outcome or risk. The use of scarce resources to develop, validate or apply a biomarker can be wasteful or inefficient if there is not a good rationale. Essential to the design of transitional, etiological or applied studies is the need to identify the driving scientific or public health questions and to determine whether they could be answered by some other approach (Rothman, 1993; Rothman *et al.*, 1995). This may be less of an issue for laboratory studies where biomarker work is the defining activity. It may be more critical when considering using biomarkers as independent or dependent variables in epidemiological studies or for public health applications such as screening, monitoring or in risk assessment (Office of Technology Assessment, 1990; Perera, 1987; Schulte & Halperin, 1987; Rüdiger, 1994).

Ethical and social problems may also arise from a failure of researchers to anticipate and plan the actions required for dealing with the more extreme biomarker assay results. This may include repeat testing, counselling or diagnostic evaluations. For transitional studies in which the characteristics of a marker are being determined, and where there are clearly no associated clinical findings, prognostic significance or meaning, the needs of subjects may be different from those situations, such as screening or biological monitoring, where a marker can have implications for individual risk or for disease. With markers of susceptibility, it may be important to consider the impact of the research not only on individual participants, but also on their families.

Obtaining participation

How subjects are recruited into studies can involve serious ethical and social issues (Schulte & Sweeney, 1995). These issues hinge on what potential subjects are told about the study and whether they can truly give informed consent. If subjects are deceived or coerced into participating in a study, or are given false expectations (e.g. 'we can tell if you are sick or well') with respect to the value of the study to the participant, ethical principles are violated. For example, a researcher could coerce a potential subject directly (e.g. 'you may lose your job if you don't participate') or by implication. Communicating false expectations or using pressure is patently dishonest and unethical. It is unlikely that such deception or coercion would be overt; rather, it would be more subtle and difficult to detect. A broad spectrum of opinion exists about what obtaining informed consent entails and when it is achieved. Some believe that for markers whose meaning is not known at the time of the study, a subject or worker in an occupational study cannot give truly informed consent (Samuels, 1994). This implies a much higher standard of interpretation for biomarker information than for other information routinely obtained by questionnaires, environment monitoring or record linkage. In studies to validate markers of exposure, the level of understanding of the meaning of the marker is similar to that from classical exposure sources. Frequently, airborne exposure, levels in blood, or frequency of DNA or protein adducts are part of the same exposure paradigm. Markers of effect or susceptibility are different. Until there is determination of predictive value and course in the natural history, such markers are clearly only research variables with no clinical meaning, and participants should be made aware of this. If a marker has been validated (i.e. quantitatively linked to risk of disease at the group or individual level), then a clear description of it should be given to potential research participants. With regard to informing participants of risks, general practice has been to identify only medical risks; however, it has been argued that truly informed consent should include reference to non-medical risks that might affect participants. For example, a study subject may be informed that they carry a genetic mutation that puts them at a high risk of subsequently developing cancer. In the extreme case, the mere acknowledgement on an employment or insurance application that they have had a biological or genetic test may result in denial of employment or insurance. Another variation on this scenario is that

misinterpretation of a biomarker assay result could occur and have the same impact.

Participants consent to provide the specimens and corollary demographic and risk factor information, and hence cooperate in the specified research. The subject generally does not consent or imply consent to distribution of the data in a way that identifies him or her individually to any other parties, such as employers, unions, insurers, credit agencies, lawyers, family members, public health agencies, etc.

Dissemination or revelation of results beyond the explicit purposes for which specimens were collected intrudes on subjects' privacy. Studies where biological specimens and DNA are banked for future use may require informed consent about this future use. In this respect, questions are raised about whether specimens collected for one purpose can be used for different research purposes and about the responsibility for conveying results back to the subjects (Schulte & Sweeney, 1995). Also related to this is the ownership of specimens. Who owns them—the subject, the researcher, the sponsoring agency or others? Although this has been adjudicated in the case of a clinician who profited from a hairy cell leukaemia line derived from cells taken from a patient (Cooper, 1985; Office of Technology Assessment, 1987), we have found no references (except Clayton *et al.*, 1995, see later discussion) to the issue as it pertains to epidemiological research with stored specimens.

Interpretation and notification of test and study results

Biomarker research yields individual test (assay) and study results (Schulte & Singal, 1989). Research participants may want, or have, a right to these results and an interpretation of them. Interpretation of these results is the responsibility of investigators. Some institutions require investigators to provide individual test results to subjects as well as overall study results, while others may advise them not to communicate results of assays that have no clinical relevance. Attendant to these efforts is the provision of an interpretation as far as is possible. Even though participants are told that tests may be purely for research purposes and have no clinical value, they still ultimately want to know if they are 'all right'. Investigators and practitioners face ethical issues in interpreting tests and in deciding when biomarkers indicate that early warning steps should be taken. These may include efforts to control exposures (in occupational or environmental settings), the need for subsequent testing, ongoing monitoring, or simply, and often most importantly, counselling and a demonstration of caring.

Interpretation of biomarker data can be difficult. For example, in cross-sectional studies of populations with occupational or environmental exposure, evaluating the relationship between exposure and markers of early biological effect, biomarkers will not be indicators of risk *per se*, but of exposure, susceptibility given exposure, or biological changes that could be homeostatic responses to an exposure (Ashford, 1986). The investigator needs to sort out these changes against a background of extensive intra-individual and interindividual variability in biomarkers. The current technological capabilities offer investigators and practitioners the opportunity to utilize techniques with heightened sensitivity for detecting changes at cellular and molecular levels, and for detecting exposures to minute amounts of a xenobiotic. At the same time, at these levels, inherited and acquired host factors and other confounding factors can be strong causes of wide variability in biomarker results unrelated to the exposure of interest.

The results of studies of biomarkers of susceptibility can lead to findings that might be misunderstood or abused (Lappe, 1983; Ashford, 1986; Nelkin & Tancredi, 1989). For example, some genes (such as those that are commonly occurring, that confer low relative risk and that require a specific exposure or other genes to increase risk of disease) (see Caporaso & Goldstein, this volume) do not provide unambiguous information, but various groups in society may start using such genotype information as if it represented 'diagnoses' rather than risk factors (Wagener, 1995).

In some studies, multiple biomarkers will be assessed, and researchers have a responsibility to consider whether issues of multiple comparisons can lead to inappropriate selection of significance levels. Association of biomarkers not included in original hypotheses should be evaluated at more rigorous levels of statistical significance, and subsequent interpretations should be considered in that light.

One area of interpretation that is problematic is what is called 'individual risk assessment'.

Generally, epidemiological studies (with or without biomarkers) yield group results. The risk pertains to the group as a whole and not necessarily to individual members of the group. It is possible to compute an individual risk using a risk function equation (Truett *et al.*, 1969); however, if the marker being used has not been validated for disease, the calculation will be meaningless. Thus far, for the current generation of molecular biomarkers used in cancer research, there are practically no markers, with the exception of a few genetic mutations linked to high risk of disease in cancer family syndromes, for which an individual risk can be determined based on the level of the marker.

All of these characteristics of biomarker data may lead an investigator to conclude that a particular biomarker is of uncertain meaning with regard to risk. None the less, the investigator has the obligation to portray accurately the degree of uncertainty in test and study results. There are a range of opinions about communicating results of biomarker tests on individuals or groups if there is no clinical meaning, such as usually occurs in transitional studies to validate markers. Some believe the autonomy of participants is not honoured if they do not receive the information, while others believe that the information is meaningless to participants. The latter view has the appearance of being paternalistic, but may be viewed as doing no harm.

Other ethical issues involved in notification are the importance of communicating information in a timely fashion and the evaluation of the impact of notification efforts. The timeliness of notification is mainly an issue when results indicate an action that could reduce exposure or risk, or effect timely treatment. Evaluating the impact of notifications may not need to be a routine matter, but since the impact of notification cannot always be anticipated, it may be useful to have included in the notification an opportunity for the participant to obtain more information or provide feedback about the results.

Use of stored specimens in biomarker research

Biomarker research is qualitatively different from most other epidemiological research, because technical developments make new assays feasible on stored specimens long after the original consent is obtained. Unlike questionnaire-based research, in which the response to a new hypothesis is usually to start a new study and ask the relevant questions, a new hypothesis using a biomarker can often be tested using specimens from previous studies. If it is desirable to have prospectively collected specimens, for instance if the biomarker level may be biased by disease, then available specimen banks with follow-up data will be the preferred resource for testing the new hypothesis. Otherwise, it might take many years to develop a new specimen bank with sufficient outcomes and follow-up to test a hypothesis.

Ethical issues for stored specimens relate to (1) whether consent for use of the specimens in research was originally given, and (2) whether this consent was generic or specific to the hypothesis to be tested, and whether the consent obtained when the specimens were collected still meets the standards of informed consent.

Many specimens stored for research purposes would have been collected after informed consent to research was given; however, some types of specimens, particularly clinical specimens initially used for diagnostic or prognostic purposes, may have been stored without consent or even without the patient's knowledge. Frequently in clinical settings, a wide variety of tests are ordered without any consultation with the patient, although clear exceptions exist, such as HIV testing, for which consent is usually mandatory. It has long been held as ethically acceptable practice to conduct some types of research on 'discarded' blood or tissues, i.e. specimens left over after the clinical tests are performed. Access to these tissues has been critical to the development of new clinical markers such as histological or immunochemical markers of cancer prognosis, in which hundreds or thousands of uniformly collected specimens are frequently needed to establish a new test as being informative. It would seem a natural extension of this tradition that new biomarkers of genetic susceptibility or prognosis would also be evaluated in this way. However, because of the potential high predictive value of some of these tests, as well as the implications for family members, this tradition is being challenged, and a lively debate is currently underway about the ethics of using these tissues. A recent statement from a working group of the Ethical, Legal, and Social Implications of the Human Genome Project suggested that informed consent should usually be obtained before testing for genetic susceptibility on clinical specimens

(Clayton *et al.*, 1995), although the statement acknowledged that research involving 'minimal risk', and for which re-consenting subjects would be impracticable, could be exempted. The definition of 'minimal risk' and the determination of what constitutes 'impracticability' are at the centre of much of the current uncertainty and debate.

Even in a research study, the original consent form can only be as thorough as the original aims of the study and the state of knowledge at the time permit. Samples from participants in a study of cancer risk factors, for instance, may subsequently be useful in a study of cardiovascular disease or psychiatric illness. Even the best designed and informed consent process in a study of genetic susceptibility to cancer may be outdated with the discovery of a new susceptibility gene or a new prognostic implication of an 'old' gene. A major dilemma in current biomarker research is whether the generic consent originally given by a participant to do research on a specimen is adequate consent to conduct a specific test which may not even have been envisaged at the start of the study. The obvious strategy of obtaining fresh consent has at least three major problems: (1) subjects may be very difficult to contact if follow-up has not been maintained, or they may have died; (2) a high proportion of non-consent, due either to inability to re-contact or to refusal, may bias the study; (3) for certain especially valuable specimens, such as those from cohort studies, multiple genes may be of interest and a process of very specific informed consent would generate an almost continuous stream of consent requests to the participant. Failure to obtain a new informed consent may expose the researcher to allegations of unethical behaviour, or may create a difficult situation if the biomarker information is of clinical relevance to the participant and yet the participant was not pre-test counselled about the test. The nature and force of these problems will be very different according to the predictive quality of the biomarker and its clinical implications, and the social and cultural setting of the research.

Owing to the heterogeneity of study settings, and of social norms and responses, it is likely to be impossible to draft uniform rules on what constitutes ethical behaviour in every application of biomarker research and every situation. This is currently the case with research involving human subjects, in which the first rule is that virtually all such research must be approved and reviewed by an appropriate ethics committee but relatively few types of research are absolutely proscribed or highly regulated. Some have proposed that research involving genetic susceptibility is qualitatively different from other research, and that much stricter standards of informed consent should apply (Annas, 1995); while others have argued that the level of consent or notification should be commensurate with the degree of risk involved, and thus less stringent procedures may be appropriate for low risk, relatively common polymorphisms (e.g. *P450* genes) than for high-risk genotypes (e.g. *BRCA1, BRCA2*). In the USA, the possibility that biomarkers of susceptibility could be used to discriminate in the context of health insurance or employment is a major concern, which may expose research participants to potential economic harm. On the other hand, epidemiology has a good track record in protecting participants from loss of confidentiality in many studies over many years which have included highly sensitive questionnaire-based data. Although some unique issues are raised by biomarker research, most issues are similar to those encountered in other types of research, and can be overseen by appropriately constituted ethics committees who are in the best position to be aware of the local and particular aspects of any proposed biomarker research. Especially close scrutiny should be given to any proposal using a biomarker with likely high predictive value. Ethics committees also need to be well informed about the scope, limitations and implications of biomarker research, as the ethical climate in this field may change quite rapidly as scientific developments occur and society responds to these developments.

Confidentiality of data

Investigators need to maintain the confidentiality of biomarker data because of the potential for misuse or abuse leading to discrimination, labelling and stigmatization. This can be increasingly difficult because ownership of stored specimens may be in question and various investigators may request the use of specimens for research, litigation or commercial enterprise. In some cases, where specimens are identifiable or are capable of being linked to databases where identification is possible, it may be difficult to assure confidentiality.

Informatics and the ability to link disparate databases are progressing at a rapid pace. In some countries, there may be a need for further legislation to prohibit unauthorized access to, or use of, specimen results. The challenge will be to assure the rights of study participants while providing for a broad range of research opportunities.

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