Commentary

Utilization of human tissue in breast cancer research

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Abstract

The use of human tissue, and material derived from such tissue, for research purposes is currently the subject of much debate. This debate needs to address several issues, including: the principle of abandonment; the distinction between identified and unidentified specimens; general versus specific informed consent; and, with the improvement in biotechnology and medical informatics, the design and security of research databases. The outcome of this debate will shape the way in which research studies using human biological materials are designed and executed.

Keywords: anonymized, coded, research, sample, tissue

Introduction

There is currently considerable debate regarding the retention and use of human tissue for research purposes. This debate has arisen partly because of the increase in public concern about this issue, but also because of the significant advances in both biotechnology and medical informatics that have taken place in recent years. Thus, potentially significant information regarding individuals is being increasingly generated in research laboratories, and these data are often stored on computerized databases with varying degrees of security. These factors raise issues of patient confidentiality, and the balance between this confidentiality and the need for progress in biomedical science must be carefully considered.

Principles

One of the fundamental issues in the retention of human tissue for research purposes is the principle of abandonment. Until recently, most biomedical researchers have viewed excess tissue that has been removed for a diagnostic or therapeutic procedure as 'abandoned', and therefore such surplus material has been often used for research purposes without specific patient consent. This approach has recently been called into question [1,2], and it is likely that informed consent will be required in the future for a broader range of research involving human biological material than has been the case thus far. This has significant implications for research on human tissue and will necessitate alterations in the way that routine consent is obtained from patients. The central concept in this approach is that patients are asked to 'gift' their tissue for research.

An important distinction when considering individual specimens is whether they can be viewed as 'identified' or 'unidentified'. Unidentified specimens, which can still be associated with clinically relevant data, are either anonymous (ie no individual identifiers were recorded at the time of collection) or anonymized (ie all specific patient identifiers have been irreversibly removed from previously identified samples). The fundamental principle is that a link cannot be made under any circumstances between the specimen and the individual from whom the specimen was obtained. Thus, there is no prospect of patient confidentiality being breached. Conversely, identified specimens

NBAC = National Bioethics Advisory Committee; OPRR = Office for Protection from Research Risks.

are associated with specific patient identifiers, and therefore can be linked to the patient of origin.

Between these two extremes, there are coded or linked specimens. For these, the specific patient identifiers are separated from the other information about the specimen, as well as research data derived from the specimen, such that no immediate link can be made with the patient. However, a mechanism still exists, through the use of coding systems, by which the patient can be identified. Many tissue collections fall into the category of coded/linked samples, and it is this category that is currently causing concern.

Where the specimen is specifically identified, specific informed consent must be obtained. Where the specimen is anonymous or anonymized there is usually no issue of confidentiality, but there is also no possibility of obtaining further information about the patient, particularly clinical follow-up data. This may significantly reduce the research value of the specimen. Coded or linked specimens provide the opportunity to protect patient confidentiality while maintaining a possible link such that clinical follow-up information can be obtained. One way of achieving this is to introduce a firewall between the specific patient identifiers and the rest of the clinical and biological information. The use of encryption techniques has been suggested for this purpose. A further complication is the realization that, on rare occasions, especially with very small sample populations, an accumulation of nonspecific identifiers may theoretically lead to identification of an individual through an otherwise 'anonymized' sample that has no associated name or chart number [2]. This is an important consideration when designing databases.

The issue of consent is intimately involved with the types of samples that may be used in a research study. Clearly, if the principle of abandonment is rejected, the logical consequence is that consent will be required in most cases when human biological materials are to be used for research purposes, and not necessarily only for identified or coded samples. At the very least, use of identified samples will require informed consent, involving providing the patient with sufficient information to make an informed decision regarding whether to participate in a particular research project.

A distinction can be made between general versus specific informed consent. With the former, patients give blanket or unspecified consent to use their material for research purposes without identification of a specific project. The validity of blanket or general consent has recently been questioned [2]. Specific informed consent, on the other hand, governs the situation in which consent is provided for a specific project with known risks and benefits. However, it is clearly not always possible to anticipate potential research projects or technical advances that might make more sophisticated investigation possible in the future. It has been suggested [2] that when a clinical sample is obtained, the patient's willingness to be recontacted in the future for a possible research study should be determined. Clearly, this has time and cost implications and may limit the availability of samples for future studies. For both forms of consent, there is a need to consider the detail with which consent is obtained, for example with regard to custodianship of tissue and issues of commercialization. The more detailed and unwieldy consent forms become, the less likely patients will be to give their consent, thereby potentially inhibiting research activity. Conversely, care must be taken to ensure that sufficient information is provided for consent to be 'informed'.

Agreement by a patient to participate in a research study should not be linked to availability of clinical care. Participation in research should be voluntary and not coerced. It is also important to note that internationally agreed principles of human subjects research state that consent is not irreversible. Thus, it should be made clear to patients that they have the right to opt out of a study and remove their samples at any time.

Another important issue to be considered is the nature of the information that is to be derived from the research activity. Although many groups have stressed that all biomedical research is potentially sensitive [3], some people are particularly concerned about the generation of genetic information [1,2], which may have implications for propensity of disease development, not only for the patient, but also for the patient's family. This is particularly relevant in cancer research, where an individual gene mutation or polymorphism may be associated with elevation or reduction in the risk of developing a particular tumour or group of tumours.

Furthermore, the issue of whether patients should be informed of the results of research investigations is not a simple one. For example, it is important that research data are reliable, valid and relevant to the disease process. In the USA, it has been suggested that before being used to make clinical decisions, genetic information generated in research studies should be independently validated by accredited laboratories. However, this may not be possible during test development of rare disorders. Again, this issue represents a balance between the harm that could be done to individuals if confidentiality is violated on the one hand, and on the other the potential impairment of generation of new knowledge if overly stringent measures are taken to protect patient confidentiality that result in an inability to conduct the research study at all. Careful attention to confidentiality and privacy policies, and the security of research data, should be a hallmark of all research on human biological materials to prevent misuse of research information.

Current status

UK

Several government and professional bodies have recently considered the issue of using human biological materials in research [4–7]. The Medical Research Council [4] has published interim operational and ethical guidelines for the use of human tissue and biological samples in research, including their use by commercial companies. These guidelines explore many of the issues touched on above and, in particular, put forward the suggestion that the principle of abandonment is no longer valid.

Thus, in the UK it is likely that ethical approval and specific patient consent will be required for the use of biological materials in research. This specifically includes archival material in pathology departments that, traditionally, has not required such approval and consent. Although it is suggested that this should not operate in retrospect, in view of the tremendous difficulties there would be in obtaining patient consent for material currently being stored in tissue archives, it does mean that hospital consent forms will have to be altered in order to obtain informed consent from all patients undergoing interventional or operative procedures. Moreover, it is recommended that such consent be obtained separately from the consent to operation so that it is clear to patients what is being asked of them. The principle of informed consent also requires that patients be given sufficient information to make an informed decision and also be given sufficient time to assimilate this information. This has significant implications for the time that will need to be invested in obtaining patient consent, and therefore for manpower. The design and funding of research will therefore need to take these issues into account.

USA

In the USA, federally funded research involving human subjects (including the use of their tissues) is overseen by the Office for Protection from Research Risks (OPRR). Nonfederally funded research is not regulated in the USA except at the local level, although research conducted in institutions that accept federal funds, even when not specifically federally funded, is usually subject to federal regulations by agreements between the OPRR and the medical institutions. For the most part, research conducted on excess human biological materials has been covered by a general statement within the clinical consent form that permits use of such samples for research and education. Also, in practice many biomedical researchers have not appreciated that the informed consent requirement applies to their work on coded human samples.

Recently, President Clinton's National Bioethics Advisory Commission (NBAC) released a report [2] recommending guidelines for the use of human biological materials in research. To a large extent, the NBAC supports the current OPRR interpretation of regulations, including the consideration of coded samples as identified. Therefore, research utilizing coded human biological materials requires informed consent and review by a local institutional review board. The board can waive the informed consent requirement under specific circumstances that include assessment of minimal risk to the patient, of patient personal autonomy, and of the practicability of obtaining consent (eg for use of archived samples). Unidentified samples (eg anonymous and anonymized samples) are exempt from the regulations, as are samples from patients who are no longer living. The NBAC report [2] recommended that the exemption of samples from deceased individuals be reconsidered, and also strongly urged an improved consent process, including separation of consent for research from consent for the clinical procedure.

The National Action Plan for Breast Cancer recently formulated new consent forms and procedures [8], and these are under investigation for feasibility. Although the NBAC recommendations do not have legal standing, it is generally presumed that institutional review boards and regulators will use them as a guide pending further legislative changes. There is no doubt, however, that the new sensitivity to the use of coded samples and the consequent requirement for informed consent will impact on the design and execution of research studies using human biological materials.

Conclusion

In conclusion, the debate regarding the use of human tissue for research purposes needs to address several issues, including: the principle of abandonment; the distinction between identified and unidentified specimens; general versus specific informed consent; and, with the improvement in biotechnology and medical informatics, the design and security of research databases. The outcome of this debate will shape the way in which research studies using human biological materials are designed and executed.

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