Review Article

The Current Status of Predictive Genetic Testing for Cancer in Humans: Scientific, Clinical and Ethical Issues surrounding the p53 gene.

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Our current understanding of the molecular basis of human cancers has raised a very critical issue which is that of predictive genetic testing for cancer in humans. Over the past few years so much data has been forthcoming that it is timely to review the situation.

For many years it has been hypothesized that cancer must have a genetic component. As long ago as 1914, Boveri suggested that an aberration in the genome might be responsible for malignant transformation. Subsequent work has supported this theory and we now define cancer in humans as being a genetic disease at cellular level. Evidence supporting the observation that cancer or the risk of cancer could be inherited comes from the work of Mullvihil et al (1997) and Li et al (1988) on familial cancers.

Almost every form of cancer in humans has been reported to cluster in families. This can be explained either by the inheritance of a mutated susceptibility gene, or by chance association and shared exposures to environmental carcinogens (Knudson, 1989).

Since the early 1980s, extensive research world-wide has been undertaken in order to identify the genes responsible for malignant transformation of morphologically normal cells through their subsequent mutations. Some of these genes have been identified. These include the hereditary retinoblastoma (Rb) gene, the Wilms' tumour (WT1) gene, the neurofibromatosis type 1 gene, the familial polyposis APC gene, the Li-Fraumeni Syndrome (TP53) gene, the male breast cancer *(AR)* gene, the deleted colon cancer (DCC) gene and the recently discovered familial breast/ovarian cancer (BRCA-1) gene, and the familial breast cancer (BRCA2) gene (Knudson, 1989; Wooster et al. 1995; Miki, 1994: Stratton, 1995). Two recent studies have shown that mutations in the BRCA-1 gene which predisposes women to breast and ovarian cancer may also be associated with an increased risk of prostate cancer in men (Hall et al. 1990: Miki et al, 1994: Easton et al. 1995).

Mapping and identification of these cancer predisposing genes on different chromosomes have been facilitated in recent years by the application of new molecular biology techniques. The polymerase chain reaction has in fact revolutionized the approach to genetic research through its ability to cyclically amplify the genomic regions of interest. As a result of these technical advances we have a situation where many genes have been identified and others mapped so rapidly, that our understanding of their biological significance has not kept pace.

There is evidence to indicate that for many types of cancer, including the most common forms such as breast, lung, colon and bladder, there exists not only an environmental influence but also a hereditary predisposition to the development of cancer. This can now be clearly illustrated by the classical example of lung cancer as it is related to cigarette smoking. While appreciating the evidence that cigarette smoking is closely linked to the development of lung cancer in most instances, not all smokers necessarily develop lung cancer. Also, the mortality rate from lung cancer among non-smoking relatives of lung cancer patients (smokers) has been shown to be higher than that of non-smoking relatives of non-smokers used as controls (Garfinkel et al, 1985). Similar results were obtained when comparing the mortality rates from lung cancer of smoking relatives of lung cancer patients to that of smokers with no family history of lung cancer. So it appears that genetic influences contribute to the development of cancer, even where clearly defined environmental factors.

A genetic predisposition to breast cancer has also been shown (Adami et al. 1980: Bain et al, 1980). The exact role that heredity plays in the predisposition to particular breast cancers cannot be quantified. Although (1971) states that approximately 10-15% of breast cancers have a hereditary background. Clearly, women who have no family history of breast cancer may also develop the disease, but those individuals from families with a history of breast cancer are at some increased risk, as shown by Anderson (1972, 1974, 1977). In general, the risk of the same neoplasm developing in close relatives of a cancer patient is approximately three times greater than in control populations (Knudson, 1989).

A frequently asked question concerning both the cancer patients and their relatives is:-
"My mother or my father, or possibly both, died of cancer. Does this mean that I will certainly develop cancer? Under these circumstances, what are my percentage risks and what can be done to prevent the disease from developing?" This brings us to the very essence of the subject of predictive genetic testing for cancer in humans.

Genes predisposing to cancer

At molecular level, it is thought that cancer is the end result of an accumulation of genetic lesions occuring in key regulatory molecules. This widely held concept is gaining in importance as more information on growth arrest and cell death in the regulation of cell number becomes understood. The identification and functional role of these molecules are the subject of intense research. Positional cloning technology has begun to accelerate identification of genes that are responsible for familial cancers (Ruddon, 1994; Symonds et al, 1994). Over these last two years we have seen the closing off two very important cancer predisposing genes. BRCA-1 (Miki, 1994) and BRCA-2 (Stratton, 1995; Tavtigian 1995).

Genes that slow down cellular turnover, in other words growth inhibitors, are termed tumour suppressor genes (Knudson, 1989; Li, 1988; Weinberg, 1991). Seventeen years have passed since the original discovery of a nuclear phosphoprotein with a molecular mass of 53-kd that reacted with antiserum from animals with tumours induced by simian virus 40 (SV 40) (Lane et all, 1979; Lane and Crawford, 1979).

The p53 gene is the most widely altered gene in human cancer (Hollstein et al, 1991; De Fromental and Soussi, 1992). It is a tumour suppressor gene which in its normal form codes for a 53-kd protein which binds to DNA and acts as a transcription factor to halt cells in the G1 to S transition of the cell cycle (Clarke et al, 1993). Mutant forms lack this DNA binding activity and therefore allows for abnormal proteins formed during malignant cell transformation to proceed in the cell cycle. The p53 gene spans a moderately sized segment of DNA (20 Kilobases long), located on the short arm of human chromosome 17, that is ultimately translated to a protein consisting of 393 amino acids contained in 11 exons, the first of which is non-coding. Five evolutionary conserved domains within the coding regions are regarded as essential to the functional activity of p53 (Malkin et al, 1990).

In the presence of DNA damage induced by gamma irradiation or chemotherapeutic drugs, intracellular levels of p53 rise and prompt the expression of a downstream gene WAF/CIP 1, whose protein product p21 binds to cyclin-dependent kinases and inhibits their activity (Harper et al, 1993; El-Deiry et al, 1993). In this manner cell cycle is arrested prior to DNA synthesis and the cell is given the opportunity to repair the damaged DNA. If such repair does not occur, the presence of normal p53 induces the cell through a pathway of apoptosis or programmed cell death (Harris and Hollstein, 1993). The apoptotic pathway is still poorly understood (Yonish, 1992; Stewart, 1994). The early chemical events that cause apoptosis have been so far hypothetical and these include: increases in ionisable calcium in the cytoplasm, drops in pH, generation of free radicals, and phosphorylation cascades. That p53 plays a cardinal role in the early events of apoptosis has been shown by the work of Stewart, (1994).

During the past seventeen years some 1300 mutations have been reported in more than 55% of all sporadically occurring tumours (Nigro et al, 1989). In 1992, the p53 gene was given the honour of being the second most significant scientific trend of the year in the Time Magazine (Time 1992). In 1993, p53 was named Molecule of the Year in Science (1993).

Understanding the role of p53 as a cancer predisposing gene comes from the clinical and scientific work on the Li-Fraumeni Fandlial Cancer Syndrome, first described as a clinical entity in 1969 by Li and Fraumeni, who noted the association between young onset sarcoma and other tumours in close relatives (Li, 1988). This syndrome is an autosomal dominant disorder that predisposes individuals to multiple forms of cancers occuring at a young age and in close relatives. It consists of a sarcoma developing in a first degree relative before the age of 45 and a second first degree relative who has developed any type of cancer under the age of 45 years or a sarcoma at any age Malkin (1993). Other characteristic features of the syndrome include the occurance of multiple primary cancers in affected individuals, the early age of the patient at onset of most tumours and the autosomal pattern of inheritance of the disorder as determined by classical segregation analysis Malkin. (1992).

Component tumours of the syndrome include breast cancers, leukaemias, brain tumours and adrenocortical tumours. A recent study by Kyritsis et al (1994) reporting on germline mutations in the p53 gene on a set of glioma patients is important in that it sustains the recent observations that germline p53 mutations may occur outside the classically defined LFS families (Frebourg et al, 1992; Malkin et al, 1992; Toguchida et al, 1992). This observation complicates the scene of predictive genetic testing for the classical Li-Fraumeni Syndrome (Malkin et al, 1993).

Other cancer predisposing genes whose function is that of growth inhibition include: the retinoblastoma Rb gene, Wilms Tumour Gene WT1, WT2, the adeno polyposis coli gene ***APC*** and BRCA-1/ BRCA-2 genes.

Studies on the retinoblastoma gene demonstrate the correlation between hereditary mutation in tumour suppressor genes and genetic predisposition to develop cancer. Patients with the hereditary form (about 40%) have a high risk of multiple retinoblastoma and other tumours in their family members and they may pass the disease to their progeny as an autosomal trait. The same features of hereditary cases of Rb can also occur in patients with no family history of the disease and are due to new mutations in the germline. The non-hereditary cases are unifocal, with an older average age of onset (Vogel, 1979; Knudson et al, 1989). By analogy with retinoblastoma, some patients with sarcomas of bone and soft tissues and no family history of cancer may be carriers of new germline mutations at the p53 locus (Malkin et al, 1990).

Implications of Germline Mutations

Observational studies in the mutation spectrum of the p53 gene have been going on for quite some time (Baker et al, 1992). We are now at a stage were the focus of current work is to correlate the significance of these mutations with clinical outcome (Harris et al, 1993). The frequency of cancers among carriers varies from 50% to 90% up to the age of 60. Above the age of 60 years the risk of developing cancer is said to be the same as that of the general population of the same age who do not carry a mutation in the p53 gene (Garber et al, 1991; Srivastava et al, 1990; Holstein et al, 1991).

This may be explained by considering the fact that the presence of a particular mutation might just be a rare polymorphism and so there would be no biological significance of this mutation on cell growth. Therefore, any genetic tendency to develop cancer would manifest itself early in those individuals whose mutations are not just a rare variant of DNA, but would not do so in those individuals whose mutations are of no significant functional activity (Lynch and Kursh, 1971; Ory, 1993). When discussing the relative risk for development of early onset breast cancer, the overall penetrance of gene carriers in the Li-Fraumeni Syndrome is 90% by the age of 50 years and the majority of cancers after childhood are breast cancers. Outside the Li-Fraumeni Syndrome families, germ-line p53 mutations have also been reported in patients who develop multiple primary cancers and in patients with a strong family history of cancer affecting multiple tissues (Frebourg and Friend, 1992; Malkin et al, 1992; Toguchida et al, 1992).

Biological and statistical issues also surround surveys for germ-line p53 mutations in population studies (Shapiro, 1989). The predictive power of a positive test for p53 is determined by three factors:

1. the prevalence of p53 mutations in the study population.
2. the sensitivity (the probability of detecting a true positive) of the test.
3. the specificity (probability of detecting a true negative) of the test.

Even when sensitivity and specificity are very high (99%), the predictive power of a positive test is only 50% when the prevalence of p53 mutations in the study population is 1%; i.e., only one half of those with a positive p53 test actually are cancer-prone individuals. The power of the test is increased substantially by studying populations with a high prevalence, preferably greater than 10%. In predictive testing of siblings and offspring of cancer patients with a germ-line p53 mutation, the prevalence of mutation is as high as 50%. Available data suggest that the prevalence of this germline mutation might be 0.01% in the general population, 0.1-1% among various cancer patients, and 5-10 %A among young patients with multiple primary cancers (Li et al, 1991).

Mutation-screening Techniques

The p53 protein can be detected immunohistochemically using monoclonal antibodies against this protein. During 13 years of work on this protein, it has been demonstrated that its overexpression can be detected in a wide variety of human malignancies including cancer of the breast, colon, lung, bladder, prostate and brain (Niggo, 1989).

The immunohistochemical technique has been shown to fail to stain both preneoplastic and neoplastic cells carrying a mutation of the p53 gene. Conversely, it has been shown to stain cells in a cancer family in which the p53 gene is normal (Barnes et al, 1992; Eeles et al, 1993). Normally, the p53 protein occurs at a very low concentration in cells because it is rapidly degraded by cellular proteases. However, using monoclonal antibodies against the mutant p53 protein, cancer cells often demonstrate high levels of the abnormal protein which accumulates in the cells. In transitional cell carcinoma of the urinary bladder, detection of p53 protein accumulation has been reported in up to 61% of invasive tumours (Sidransky et al, 1991; 1992). The immunohistochemical technique still remains useful for detecting p53 overexpression. It can be performed on biopsy material as well as on exfoliated cells such as cervical smears, serous effusions and sputum. Morphologically normal cells, overexpressing the p53 protein, are presumed to indicate a preneoplastic stage of cellular differentiation.

There is no question that as far as testing for p53 gene mutation is concerned, the primary tools are those of molecular genetic techniques. Mutations within the gene are widely dispersed mainly between codons 130 and 290 and most of them involve the evolutionary conserved domains. In particular, at least three mutational hot-spots at codons 173, 248 and 273 have emerged. Mutations at these hot-spots are characteristically transitions at CpG dinucleotides. Cancers originating from various specific tissue sites differ with respect to the distribution and frequency of mutations at these hot-spots (Hollstein et al, 1991; Caron de Fromental and Soussi, 1992). Predictive testing for p53 gene mutation involves testing of the whole gene. A number of screening techniques for the detection of point mutations are available and provide the approximate location of the mutation.

Current methodologies use the polymerase chain reaction (PCR) to amplify a particular segment of the gene being investigated. The most commonly used mutation screening techniques are: single strand conformational polymorphism (SSCP) (Orita et al, 1989), denaturing gel electrophoresis (DGGE or a variant CDGE) (Fisher et al, 1983; Borresen et al, 1991) and with chemical mismatch cleavage (CMC/HOT) (Montandon et al, 1989; Curie11, 1990). The basic principles are as follows. In SSCP, single strands of DNA have a different secondary conformation depending on their base composition. In DGGE, double stranded DNA denatures at different

temperatures or concentrations of denaturant dependent upon the base pair composition. The CMC/HOT technique uses normal DNA with teH mutant and allows single strands from each sample to reanneal. At the site of a base mutation a mismatch occurs and can be identified by a chemical which binds to the mismatch and acts as a cleavage site for piperidine.

Each technique has its advantages and disadvantages. SSCP and CDGE are rapid, but each exon (or at the most two exons together) of the **p53** has to be analysed separately. Both have a sensitivity of nearly 80%. However, it is unlikely to be a long term solution for population screening in sporadic cancer because it is not so useful for analysing large PCR products where conformational differences become insignificant. CMC/HOT can analyse larger areas but is laborious and uses hazardous chemicals. This latter method showed a high sensitivity when compared to the other methods in a blind study of samples (Condie et al. 1993) but has been reported to miss G to T mutations.

Newer methods are now being sought, such as the analysis of Duplex DNA by triple helix formation and is applied to the detection of p53 microdeletions to facilitate DNA screening procedures (Olivas and Maher, 1993). This method exploits the ability of certain oligonucleotides to recognise DNA sequences in the major groove without requiring denaturation of the double helical DNA target and might be directly applied to general screening of mutations affecting homopurine sequences.

All the above screening techniques indicate the approximate site of a mutation. The gold standard is direct sequencing and this will probably be the method of choice if clients wish to have a 100% reassurance that their p53 gene is normal.

It is recommended that once a mutation is found it should always be sequenced and also confirmed by at least one other technique, such as restriction enzyme or allele-specific hybridization.

Once a mutation is identified, tests can show with 100% certainty whether a relative is a carrier of the mutated gene or not (Eeles et al. 1993).

Early detection and prevention

The goal of predictive genetic testing in human cancer is to be able to predict the inheritance of a disease gene that is going to lead to a malignancy, and to initiate preventive measures before a person actually develops cancer. The best example so far of early detection and prevention is in the field of inherited cancer syndromes.

Since the localization of the multiple endocrine neoplasia type 2A (Mole et al. 1993), it has been possible to develop a genetic test to screen for mutation in multiple endocrine neoplasia type 2A (MEN 2A) in the real proto-oncogene on chromosome 10, (Donis-Keller et al. 1993). Multiple endocrine neoplasia (MEN 2A) is an autosomal dominantly inherited cancer syndrome comprising medullary thyroid cancer (MTC): adrenal gland phaeochromocytomas and hyperparathyroidism. Almost all patients with MEN 2A develop MTC during childhood or early adolescence. Genetic tests have been applied in the preclinical state to screen for MEN 2A, permitting early treatment (early curative thyroidectomy)) in children predisposed to the disease ((Telenius et al, 1992: Marsh et al. 1994). This approach is now being performed at several centres, including Washington University and Cambridge University.

A different scenario is set up when discussing the problem of individuals carrying p53 mutations. There is lack of association between specific mutations and tumour histopathology. A situation is created whereby due to our current limitations in clinical diagnostic techniques, tumours cannot be effectively screened. In the case of the Li-Fraumeni Syndrome where familial inherited spectrum of cancers namely sarcomas, breast, brain, acute leukaemia, melanoma, germ-cell tumours, bladder cancers and adrenocortical carcinoma, current screening measures have shown to be ineffective in predicting disease in the preclinical state.

Proposed blood screening for leukaemias and magnetic resonance imaging for brain tumours have all proved to be unsuccessful for early detection. Mammography screening for breast cancer has been shown to decrease mortality in the over 50 years age group (Shapiro et al.1988: Shapiro, 1989), but its efficacy in women under 50 is unknown. With the recent identification of the breast cancer gene BRCA1 (Miki et al, 1994), this approach to screening for predisposition to develop breast cancer can change completely.

Preventative measures such as chemoprevention may be of some value in certain cancers but, there is no evidence that it is of universal benefit. Chemoprevention studies should also include hormonal therapy such as the use of tamoxifen in the tamoxifen prevention trial for women at high risk of breast cancer (Cuzick and Baum, 1985; Nayfield, 1991).

The inclusion of vitamins such as retinoids must also be given due consideration in chemoprevention studies. In women who are carriers of a mutated p53 gene, the risk of developing breast cancer before the age of 45 is 18 fold over the general population (Birch, 1992; Easton et al, 1993; Sidransky et al, 1992: Eeles et al,1993). Prophylactic subcutaneous mastectomy may not be an unreasonable preventive measure for breast cancer in those patients carrying p53 mutations.

Therefore, it may be concluded that so far, detecting individuals carrying germline p53 mutations is not technically impossible. However, monitoring these

individuals. for early detection of the different tumours which may develop, is not yet possible (Garber et al. 1991).

Gene Therapy

Gene therapy is the stable insertion of a functional gene into the genomic of a host cell to alter the functional capabilities of the cell or to correct a specific genetic defect. This technique gives researchers the possibility to understand more about the regulation of gene function and at the same time find its applicability as a therapeutic approach in the treatment of cancer (Foa and Guarini. 1993: Miller. 1992; Gottesman. 1995). Optimization of both efficiency and safety of the ways in which a gene is transferred. is the crucial feature of all strategies seeking to exploit this technology.

The p53 tumour suppressor gene is a prime candidate for gene therapy (Takahashi et al. 1989: D'Amico et al. 1992: Chiba et al. 1990). Genetic lesions in the p53 gene are the most commonly occuring changes found in all human cancers (Vogelstein, 1990). Several groups of scientists were able to show that the stable transfection (Takahashi et al, 1992), or retroviral transduction (Fujiwara et al. 1993) of wild type p53 gene into cancer cells with a mutant p53 dramatically inhibits cell growth in cultured cells despite the possible presence of other genetic lesions. The significance of this observation is that any other genetic lesion need not be corrected before an anti-tumour effect could be seen (Fujiwara et al, 1994).

In-vitro gene therapy experiments started in the late 1980s and it is only now that we are seeing the possible application of in-vivo gene therapy using wild type p53 gene (Carbone and Minna, 1994). News of the first proposed gene therapy for lung cancer to enter human trials has been reported in the (Journal of the National Cancer Institute, Vol. 86 No5 March 2. 1994). This trial is still pending approval by the U.S. Food and Drug Administration on the safety of the retroviral vectors being used (Anderson. 1992). In oncology, research into gene therapy is mainly concentrated on lung cancer. Mutations of the p53 tumour suppressor gene are the genetic abnormalities most frequently identified in non-small cell lung cancer (Takahashi et al. 1989).

Conventional methods of treatment have not resulted in a significant decrease in mortality from lung cancer and therefore this creates a political and economic power to assist researchers pursuing this novel therapy.

The immediate problem with application of gene transfer technology in patients is the delivery of the therapeutic gene to sufficient numbers of tumour cells to produce a clinically observable effect. There is also the consideration of safety of vectors. When a retrovirus infects a cell, its viral RNA is copied by the enzyme reverse transcriptase into DNA that enters the nucleus and integrates randomly into the genome of the host. These natural events are exploited for gene transfer by construction of retroviruses that do not contain the replication genes. and in which the viral structural genes are replaced by the new genes to be inserted into the cells. A very plausable biological model system is being currently promoted. This includes the direct administration of a retroviral wild-type p53 expression vector in orthotopic human lung cancer model in nude mice (Fujiwara et al. 1994: Miller et al. 1989) resulting in growth inhibition of cancer cells.

As is true of interesting studies, these data raise a series of questions that should be considered in future experiments. Although the use of a retroviral vector favours integration in rapidly dividing cells. can all the growth supression be attributed to transfected cells only? Since it is likely that all cancer cells are transfected, could the supression of growth also be due to a bystander effect" (Freeman et al. 1993). Does the growth suppression observed in transfected cells result from the induction of apoptosis (programmed cell death)? Do the bystander cells undergo the same growth suppression due to induction of apoptosis? Is there a bystander effect in metastatic cells? The bystander effect is an observation whereby transduced cells have been shown to inhibit the growth of nontransduced neighbouring cells in culture (Cai et al. 1993; Freeman et al. 1993). The molecular basis of this bystander effect is under investigation. Does this possible therapeutic tool work in other sites of the body for other p53 mutations"!

It is apparent that there are still some fundamental practical and clinical problems to be addressed. Lung cancers are rarely one cell layer thick and they are rarely confined to a closed space. Fujiwara and co-workers (1993) have shown that wild-type p53 is capable of multilayer penetration into the three-dimensional structure of multicellular tumour spheroids. Of clinical concern is the size of the tumour and the accessibility to metastatic sites. The potential toxic effects also need to be addressed. Retroviruses integrate stably into the genome of replicating cells. Therefore, it is important to consider the outcome of genetically altered normal epithelial cells.

Taking into consideration all the available results so far, it is being proposed that in the case of lung cancer. microscopically established tumours in the bronchial epithelium can be efficiently infected with a retroviral vector expressing wild-type p53 gene and that *in-situ* retrovirus-mediated gene transfer may be a useful strategy for manipulating genetic abnormalities of cancer cells in vivo (Roth et al, 1994). Using current molecular techniques it is possible to identify pre-neoplastic as well as microscopical neoplastic cells before these cells display the cytological and histological features of invasive cancers (Esson et al.1991: Sozzi et al. 1992; Kastan et al, 1992).

Much research still needs to be done. At present there are over 100 protocols accepted or under consideration by various advisory committees for gene targeted therapies

world wide, the majority being in the United States. Most are for cancers in which the ethics are perhaps simplest with the lowest risk benefit ratio.

Ethics of Predictive Genetic Testing

Issues regarding ethics of predictive genetic testing are emerging as themes of great concern. Over the past five years scientific publications have presented data ranging from screening for cancer predisposition (Markham et al, 1994) to screening for specific cancers (Kodish et al, 1994), genetic intervention studies (Roth, 1994) and recently pre-implantation diagnosis of inherited predisposition to cancer (Kogan et al, 1987; Handyside, 1993; Harper et al, 1994).

Testing young cancer patients and their unaffected relatives for p53 germline mutations presents a number of difficult clinical and ethical questions (Li et al, 1991; Prosser et al, 1991). As far as clinical management is concerned, the first set of problems arises because of the uncertainties about the risks conferred by germline p53 mutations. The spectrum of cancers so far reported in families with germline p53 mutations have been discussed previously (Li et al, 1988; Birch, 1992; Frebourg et al, 1992). The range of cancers include bone and soft tissue sarcomas, breast cancer, brain cancers, acute leukaemias, melanoma, germ-cell tumours, bladder cancer, adrenocortical carcinoma and prostate cancers. As more families are screened this list of associated cancers will probably increase even further.

Therefore, considering the limited potential for screening and early detection of cancers in carriers of p53 germline mutations, the question of whether it is ethical to test asymptomatic members of cancer families in whom such mutations have been found, must be addressed. What are the social, economic and psychological consequences resulting from such testing? What effective measures are available to carriers of the p53 mutations? At present the greatest benefit that can be derived from testing is reassurance and relief from anxiety in those family members found not to be carriers of a mutation. There are other benefits including ability to plan education, future careers and decisions on marriage and child bearing, taking into account the knowledge of cancer predisposition.

There are concerns that predictive testing in this particular setting will increase people's anxiety and may have a negative effect on psychological and economic issues, raising the question of selection of individuals for predictive testing (Kash et al, 1991). The effect on life insurance premiums is unclear, but individuals with a strong family history would have their premiums weighted and these would be reduced to a mid-range value if a person with a known mutation was shown not to carry the gene (Eeles et al, 1993).

Privacy and confidentiality of test results identified carriers of germline p53 mutations have both social and economic impact. Employers for example may be reluctant to appoint persons at high risk of developing cancer. The psychological effects of belonging to a family with high risk of cancer have not been studied and are not understood (Murray, 1991; Sujansky et al, 1990; U.S. President's commission for the study of ethics, 1990). One way to resolve this conflation of issues is to gain more insight into the biological significance of these mutations in correlation with particular patterns of cancer, i.e. specific mutations causing specific cancers. At present, testing for p53 germline mutations is performed only within the setting of research protocols but it is expected that predictive testing will become more widely available. Predictive testing should be preceded by thorough counselling which should include psychological assessment and potential impact caused by a positive result. There should also be informed consent. A carefully planned long-term follow up is also needed in order to obtain data on the life experiences of carriers of mutations, as well as on cancer incidence.

Testing on children at risk is another contentious issue and it should be reserved only for cases in which a distinct and immediate benefit can be obtained. Such testing is usually postponed until adolescence, when the individual can make their own informed decisions as to whether or not they wish to be tested, (Edwards and Hill, 1992; Wald and Law, 1992; Wald, 1993).

Advisory committees involved in the design of p53 testing programs, relate their recommendations based on their experience with Huntington's Disease (Went, 1990; Ruggins et al, 1990; Lam et al, 1988; Bloch and Hyaden, 1990; Ford et al, 1994; Tyler et al, 1992). Predictive testing for Huntington's Disease involves an area where prevention is not possible and by using a set protocol, individuals having predictive testing for this disease helps to minimise the problems experienced and allows the individuals to have time to decide if they really want the test and for what reason. There may be many reasons why individuals may wish to have a predictive test. In the case of Huntington's Disease, 50% of individuals at risk said they wanted the test for planning their future and their family, and to relieve anxiety.

This experience has a significant relevance to the design of p53 testing programs. We cannot assume that the impact of testing for germline p53 mutations would have the same favourable outcome but there is definitely growing support in favour of such testing (Siegel, 1993; Berg, 1991; Li et al, 1992).

Conclusion

The concerted efforts from the work of the Human Genome Project will soon lead to the identification of many more genes responsible for hereditary diseases, including cancer (Watson, 1990). The genetic data that is presently available and that will be made available, in the near future, on populations and individuals is the subject of debate by all involved in this line of research. Issues such as confidentiality, the right to know or not to know, non-discrimination and/or carriers, insurance, disease specificity, availability of treatment, inheritance pattern

and genc penetrancc and cspressivitj,. fenture prominantly in the ethics of any genetic scrccning program (Huggins ct al. 1990).

The aim of this rcview was to update the present sccnc of canccr genetics and to promotc thc intcrest scen over the past few ywrs on the concept of canccr genetics clinics. At prscnt genc markcrs for the most contmonly occurirg cancers have been idcntrilicd. i.c. bo\vel. breast and ovarian carlcers (Fishcl ct al. 1993: Brouncr ct a1. 1994: Miki. 1994: Woostcr. 1995). This has gcncratcd a particular inkrest both from the general public and from clinicians dcaling with cancer patients. Morc information is bcirig dcmanded on thc availability of gcnctic tcsts. cancer risks. screening nlcasurcs. prcvention and treatment.

Sincc 1989 the concept of canccr genetics clinics was alrcady being proposed (Hoskins. 1989). To datc there arc more than 20 cancer genctics clinics sct up in Europe. In thc United Kingdom alonc rhcrc arc about 6 ccntres. One such centrc is at the Royal Marsdcn Hospital wherc a genetic cancer clinic is hcld which also offers a cancer genctics screcning servicc (personal communication. Eelcs RA). Clients attending these clinics havc accass to information on their own gcnetic risk for canccn as wc11 as to highly spccialised screcning tcsts availablc to datc.

Ths clinical significanc of being either a BRCA1 genc carrier or a BRCA2 genc carrier is at present 11 poorly undcrstcd. Large epidemiological studies have to be carried out to really assess thc contribution of these gcncs to canccr dwelopmcnt in farnitid and sporadic cases (Claus clc. 1994). At prescnt, 10% of breast cancers hat a strong family history and it is only possible to identify a definitc do-minanl pattern of inheritana: in approximately 1% of individuals. However. it is also possible that thesc genes could account for as little as 1-IS% of breast cancers. Since brcast cancer is the commonest tumour occurring in women worldwide, one can appra-iate the potenlid burdcn that individuals can place on 11 cancer genctics clinics, givcn thc current statc of information.

There are as many questions as answers in thc area of p53 cancer gene predisposition. in particulnr, the at risk groups need to bc bettcr dcfincd and follow-up of known carriers is needed. Thc p53 gcnc is offering thc most pronlising openings in the field of corrcctive genc therapy but it is unrealistic to think that their effectivcness would be immediatc.

The advances in science and medicine have brought about yet another clinical issuc to the scenc. This is the ethics of preimplantation diagnosis of inherited predisposition to cancer. It is very likely that couples will seek prenatal diagnosis to prevent passing a mutant genc on to their children. Is the idea of terminating a pregnancy after a diagnosis by conventional means (chorion villus sampling) acceptable? Methods for diagnosing genetic defects in early embryos before implantation are being developed and heavily supported by investments (Harper et al, 1994).

The challcngc which we now facc is how to relate all the information we have so far on cancer predisposing gencs into effcctivc scrccning and intcrventional programmes (Hawdrd ct al. 1991). Effcctive studies also havc to bc undertaken to dcfine the cost effectiveness of' population screening and thc health gain to bc anticipated from cancer predisposition screening.

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