Identification and Management of Inherited Cancer Susceptibility

Frederick P. Li

Dana-Farber Cancer Institute, Harvard School of Public Health, Boston, Massachusetts

Identification of inherited cancer-predisposing genes offers opportunities for cancer prevention. Inherited susceptibility genes have been identified, primarily through studies of unusual cancer cases and families but also through general population studies. Examples include the *RB1* gene for retinoblastoma; the *WT1* gene for Wilms' tumor; germline *p53* mutations in families with the Li-Fraumeni syndrome; the *NF1* and *NF2* genes for neuroblastomatosis, types 1 and 2; the *VHL* gene for renal cancer and other tumors associated with Von Hippel-Lindau disease; the *APC* gene for adenomatous polyposis coli; the *BRCA1* gene for hereditary breast and ovarian cancer; and the mismatch repair genes for colon and other common cancers. For some cancers, identification of gene carriers might be beneficial for targeting screening and chemopreventive interventions. On the other hand, predisposition testing for cancer has the potential for harm from loss of insurability and employability, psychological distress, social stigmatization and other adverse effects. Research is needed to identify predisposition testing procedures that maximize benefits while minimizing harm to subjects. Chemoprevention trials in genetically susceptible populations offer the prospect of finding effective methods of reducing future cancer risk. — Environ Health Perspect 103(Suppl 8):297–300 (1995)

Key words: germline mutations, inherited cancer susceptibility, tumor suppressor genes, cancer genetics, chemoprevention

Introduction

Speakers at this meeting have summarized current knowledge of cancer etiology and considered opportunities for prevention. Epidemiological studies of human populations have demonstrated the carcinogenic effects of ionizing and ultraviolet radiation, tobacco, alcoholic beverages, viral and bacterial agents, and chemical compounds (*1,2*). In the *1994 Annual Report on Carcinogens* (*3*), nearly two dozen substances, occupational exposures, and medical treatments were classified as carcinogenic in humans. Many more substances were said to be "reasonably anticipated to be carcinogens," but uncertainties remain. Presently, known carcinogens account for perhaps half the incident cancers in the United States. For many common forms of cancer, such as cancers of the breast, prostate, and gastrointestinal tract, lifestyle factors have been implicated, although specific causes have been difficult to pinpoint.

A constant challenge to cancer epidemiologists is the relatively small excess risk associated with exposures to many suspected carcinogens (*4*). To overcome the problem, researchers are utilizing laboratory tools to refine dose–response relationships and to reinforce the biological plausibility of hypotheses (*5*). Molecular biomarkers also can be applied to classify patients and strengthen associations in study subgroups (*6*). In this emerging era of molecular epidemiology, substantial progress has been made in the identification of inherited single-gene traits that markedly increase cancer risk (*7*). In the future, the knowledge of the more complex genetic systems involved in the activation and detoxification of carcinogens should further enhance the power of cancer epidemiology, as described in Rothman's paper (*8*). This overview will explore opportunities for cancer prevention based on recent discoveries of inherited cancer-predisposing genes.

Cancer Families and Cancer Susceptibility Genes

Historically, the effects of inherited cancer susceptibility genes were discerned through studies of cancer occurrence in families. More recent advances in cytogenetics provided the first glimpses of inherited genetic changes that confer susceptibility to cancer. In 1986, the first inherited cancer susceptibility gene, the *RB1* gene for retinoblastoma, was cloned (9). Since then, a dozen such genes have been identified, mostly through studies of unusual cases and families.

Epidemiological studies have consistently shown that a family history of cancer is a risk factor for virtually all forms of neoplasia in humans (*10*). The relative risk is typically 1.5- to 3-fold for the forms of cancer that have occurred in close relatives. In some instances, the elevated risk extends to multiple organ sites, as in the multiple endocrine neoplasia syndromes (*11*). Familial aggregation of cancers is usually attributed to inherited susceptibility, although shared exposures to environmental hazard among close relatives often cannot be excluded. For the common forms of cancers, chance aggregation among blood relatives is a third explanation. Historically, inherited susceptibility factors seldom were the focus of epidemiological research, in part because laboratory tools for genetic analyses were rudimentary. Inherited predisposition was also viewed as immutable, whereas environmental carcinogens should be avoidable. The attributable risk of individual genes seems trivial compared with the effects of tobacco and sunlight exposure. However, the relative risk is exceptionally high among carriers of many inherited cancer susceptibility genes. The lifetime risk of specific cancers is 80 to 90% among carriers of certain susceptibility genes. These persons often are prone to early onset disease and multiple primary cancers.

Cancer in certain families appears to be transmitted as an autosomal dominant trait with high penetrance. Clinical observations at the bedside have helped to identify inherited susceptibility genes, and affected families. Epidemiological studies of these kindreds have quantitated their excess risk. Laboratory studies have helped clarify the biological basis of susceptibility,

This paper was presented at the President's Cancer Panel Conference on Avoidable Causes of Cancer held 7–8 April 1994 in Bethesda, Maryland. Manuscript received 9 March 1995; manuscript accepted 24 March 1995.

Address correspondence to Dr. Frederick P. Li, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115. Telephone: (617) 632-3158. Fax: (617) 632-3161. E-mail: frederick_li@dfci.harvard.edu

including identification of inherited cancer-predisposing genes. Genes found to date include tumor suppressor genes, an oncogene (*RET*), and more recently, mismatch repair genes (*11,12*). In these studies, clinicians and epidemiologists provided the tissue specimens essential to the molecular discoveries by laboratory scientists. Identification of inherited susceptibility genes has, in turn created new clinical opportunities to reduce cancer morbidity and mortality.

Retinoblastoma is a prototypic hereditary cancer in humans (*13*). Mutations in the retinoblastoma gene, even single-nucleotide alterations, can confer a 90% likelihood of development of cancer (*9*). Based on studies of retinoblastoma, Knudson developed a 2-mutation model that, provided the conceptual framework for studying rare family aggregates of cancer to gain new understanding of human carcinogenesis (*14*). The model postulates that at least two mutations are required to transform a normal cell into a cancer cell. At the molecular level, the same mutant genes are involved in both familial and sporadic (nonfamilial) forms of a cancer. Patients with hereditary retinoblastoma have inherited a germinal mutation and subsequently acquired another in the second *RB1* allele, whereas those with sporadic cancers had to acquire both *RB1* mutations within one retinal cell. Despite the rarity of retinoblastoma as a clinical diagnosis, recent studies have shown that acquired mutations in *RB1* can occur in most forms of cancer (*15*). Thus, studies of a rare hereditary cancer led to the identification of a gene that is commonly mutated during neoplastic transformation. Knowledge of the structure and functions of *RB1* might yield novel approaches to therapy of cancer in the future.

Most known tumor suppressor genes have been discovered through studies of families with hereditary cancers: the *WT1* gene for Wilms' tumor; germline *p53* mutations in families with diverse childhood cancers, and early onset breast cancer (Li-Fraumeni syndrome); the *NF1* and *NF2* genes for neurofibromatosis, types 1 and 2; the *VHL* gene for renal cancer and other tumors associated with von Hippel-Lindau disease; and the *APC* gene for adenomatous polyposis coli (*12*). Mapping and cloning of these genes have been facilitated by finding large affected families and rare cases with constitutional chromosome markers, particularly translocations and deletions.

Major discoveries in the last year include identification of the *BRCA1* gene for hereditary breast and ovarian cancer and the mismatch repair genes *(MSH2, MLH1,* and *PMS1* and *PMS2*) for colon and other common cancers (*16–18*). Discovery of these genes has vastly increased the numbers of cancer susceptibility gene carriers who can be identified. In contrast to the rarity of carriers of *RB1, WT1, p53, APC,* and *RET,* approximately 5% of breast or colon cancer patients might carry an inherited susceptibility gene. Carriers of susceptibility genes may account for more than 10,000 cases of breast cancer and 10,000 cases of colon cancer diagnosed annually in the United States. Up to 1 to 2 million Americans are estimated to carry a breast or colon cancer susceptibility gene. Because survival from these cancers depends largely on disease stage, identification of carriers for targeted interventions might be beneficial. However, seeking gene carriers in cancer-free populations (genetic predisposition testing or predictive testing) is new (*19*). Benefits of predisposition testing are determined largely by the availability of prevention and early detection measures. On the other hand, predisposition testing for cancer or other hereditary disease runs the risk of harm from loss of insurability and employability, psychological distress, social stigmatization, and other adverse affects. Research is needed to identify predisposition testing procedures that maximize benefits while minimizing harm to subjects (*20*). Investigators, clinicians, governmental agencies, and institutional review boards are working to set guidelines to protect subjects who volunteer for testing (*21*). The social and ethical issues of offering commercial testing to the general population are drawing headlines in both the lay and professional press.

Genetic research on human cancers is not new. Until inherited cancer susceptibility genes were cloned, however, genetic studies were limited to analyses of somatic mutations acquired during neoplastic transformation. The results had no relevance to future cancer risks among relatives of the patient. In marked contrast, cancer predisposition testing is conducted in cancer-free individuals with the goal of disclosing results that might sharply elevate estimates of future risk.

The potential for adverse effects of disclosure of inherited cancer susceptibility requires that adequate safeguards be provided to test subjects (*22,23*). There must be freedom from coercion to be tested. Informed consent is imperative, with provisions for freedom to withdraw or postpone disclosure. Before testing begins, discussions are necessary regarding disclosure of results to persons other than the subject, including physicians, relatives, and third parties. Providers of predisposition testing should assess the mental and emotional competence of test subjects. Counseling and education should include interpretation and limitations of test results. The investigators should be prepared to manage complications of testing and to follow up to assess long-term outcomes.

After new inherited susceptibility genes such as *BRCA1* and the colon cancer genes are cloned, population surveys often are conducted to assess population frequency of inherited mutations. A dilemma is whether to disclose individual or aggregate results from these surveys to the participants. Surveys for mutations in large numbers of specimens in research laboratories may not be as accurate as those conducted by clinical laboratories where government agencies monitor quality control. Considering the profound adverse effects of reporting erroneous results, survey findings probably should be considered preliminary and not disclosed to individuals without confirmation. In these survey studies, most subjects do not show inherited mutations, but the clinical significance of a negative finding is problematical. Multiple inherited susceptibility genes, some still unknown, can predispose a person to breast, colon, and other cancers. A negative test may simply mean that the mutation is in another susceptibility gene. Thus, the absence of a germline mutation is meaningless unless a germline mutation was previously identified in an affected relative.

A common misconception is that a positive genetic test predicts that cancer will develop, whereas a negative test is associated with the baseline population frequency for that cancer (*23*). This view disregards data on risk conveyed by the family and personal medical history. Cancer predisposition testing modifies clinical risk estimates but does not predict with certainty when, where (organ site), and if cancer will develop. To convey these concepts, counseling about cancer risk should begin even before specimens are collected for laboratory testing. Individuals should be counseled on the basis of family history of cancer, personal history of antecedent diseases, and known risk factors such as hormonal and reproductive factors for breast cancer. Risk estimates associated

with family history can be refined further on the basis of number of affected relatives, ages at diagnosis, relationship to the test subject, and cases of multiple primary neoplasms. In this context, subsequent DNA test results further refine risk estimates.

Identification of an inherited susceptibility gene per se provides no benefit to the subject. Benefit from cancer predisposition testing accrues when primary prevention, targeted screening, and more effective treatments lead to reduced morbidity and mortality (*24*). Finding carriers of inherited susceptibility genes creates an obligation to develop strategies for the care of these cancer-prone individuals. Increased medical surveillance might detect early cancers in at-risk organs and tissues. For example, identification of an inherited *RB1* mutation in an at-risk infant can lead to surveillance and curative treatments with minimal loss of eyesight. Benefits of targeted screening might also accrue to carriers of colon and breast cancer susceptibility genes (*25*). Targeted colonoscopies can lead to excision of pre-cancerous polyps, but the procedure is neither inexpensive nor free of morbidity. An alternative is primary prevention through reducing exposures to carcinogens among those with inherited susceptibility to cancer. Avoidance of sunlight exposure in patients with xeroderma pigmentosum or hereditary melanoma can reduce the risk of skin neoplasms. Dietary modification might reduce the risk of colon and other cancers in gene carriers, but sustained change in dietary practices is difficult to achieve. There are a few indications at present to perform prophylactic surgery to remove the target organs in genetically susceptible individuals. Prophylactic total colectomy is standard treatment for patients with adenomatous polyposis coli due to the *APC* gene. However, morbidity of the procedure is high, and deaths from dismoid tumors arising at the surgical site are frequent. A few patients in breast–ovarian cancer families have undergone prophylactic mastectomy, oophorectomy, or both. Unfortunately, abdominal carcinomatosis have developed subsequent to prophylactic oophorectomy in rare cases, and the extent of risk reduction after prophylactic mastectomy is not known

A new and exciting area of research is chemoprevention (*26*). The goal of chemoprevention is to prevent or delay cancer occurrence through the use of chemical agents. Chemopreventive agents under study include natural and synthetic products including vitamin micronutrients, natural compounds, and pharmaceutical agents. A growing number of clinical chemoprevention trials are in progress, and early results from several studies have been encouraging. Target populations in these studies include cancer patients at high risk of second cancers, those with precancerous lesions, and carriers of cancer susceptibility genes. The latter are an attractive group for chemoprevention trials, in part because their risk of future cancer development is exceptionally high. In these groups, chemopreventive agents with some toxicity might be acceptable. Chemoprevention trials require large numbers of subjects. When cancer prevention is the end point, studies should be extended over many years; their cost is high. Intermediate biomarkers of efficacy could give early indications of benefit. Unfortunately, validated biomarkers have been difficult to identify and their predictive power is difficult to measure. Problems notwithstanding, chemoprevention trials in genetically susceptible populations offer the prospect of finding effective methods of reducing future cancer risk.

REFERENCES

1. Doll R, Peto R. The cause of cancer: quantitiative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 66:1191–1308 (1981).
2. Willett WC, Stampfer MJ, Colditz GA. Dietary fat and the risk of breast cancer. N Engl J Med 316:22–28 (1987).
3. U.S. Department of Health and Human Services. Public Health Service. Seventh Annual Report on Carcinogens—Summary. Rockville, MD: Technical Resources, 1994.
4. Hennekens CH, Buring JE, Mayrent SL, eds. Epidemiology in Medicine. Boston/Toronto:Little Brown and Company, 1987.
5. Shields PG, Harris CC. Molecular epidemiology and the genetics of environmental cancer. JAMA 266:681–687 (1991).
6. Jones PA, Buckley JD, Henderson BE, Ross RK, Pike MC. From gene to carcinogen: a rapidly evolving field in molecular epidemiology. Cancer Res 51:3617–3620 (1991).
7. Li FP. Cancer families: human models of susceptibility to neoplasia, the Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res 48:5381–5386 (1988).
8. Rothman N, Hayes RB. Using biomarkers of genetic suseptibility to enhance the study of canccer etiology. Environ Health Perspect 103(Suppl 8):291–295 (1995).
9. Friend SH, Bernard R, Rogelj S, Weinberg RA, Rapport JM, Albert DM, Dryja TP. Identification of a human DNA segment having properties of the gene that predisposes to retinoblastoma and osterosarcoma. Nature 323:643–646 (1986).
10. Knudson AG Jr. Hereditary cancers of man. Cancer Invest 45:1437–1443 (1983).
11. Mulligan LM, Eng C, Healey CS, Clayton D, Kwok JB, Gardner E, Ponder MA, Frilling A, Jackson CE, Lehnert H, Neumann HPH, Thibodeau SN, Ponder BAJ. Specific mutations of the RET protooncogene are related to disease phenotype in MEN 2A and FMTC. Nature Genet 6:70–74 (1994).
12. Li FP. Molecular epidemiology studies of cancer in families. Br J Cancer 68:217–219 (1993).
13. Knudson AG Jr. Hereditary cancers disclose a class of cancer genes. Cancer Res 63:1888–1891 (1989).
14. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 68:820–823 (1971).
15. Harbour JW, Lai SL, Whang-Peng J. Abnormalities in structure and expression of the human retinoblastoma gene in SCLC. Science 24:353–357 (1988).
16. Miki Y, Swensen J, Shattuck-Eldens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholamo Z, Shaffer D, Stone S, Bayer S, Wray C, Bodgen R, Dayananth P, Ward J, Tonin P, Narod S, Bristow PK, Norris FH, Helvering L, Morrison P, Rosteck P, Lai M, Barrett JC, Lewis C, Neuhausen S, Cannon-Albright L, Goldgar D, Wiseman R, Kamb A, Skolnik MH. A strong candidate for the breast and ovarian cancer susceptibility gene BRCAI. Science 266:66–71 (1994).
17. Bronner CE, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, Kane M, Earabino C, Lipford J, Lindblom A, Tannergard P, Bollag RJ, Godwin AR, Ward DC, Nordenskjold M, Fishel R, Kolodner R, Liskay RM. Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary nonpolyposis colon cancer. Nature 368:258–261 (1994).
18. Leach FS, Nicolaides N, Papadopoulos N, Liu B, Jen J, Parsons R, Peltomaki P, Sistonen P, Aaltonen LA, Nystrom-Lahti M, Guan XY, Zhang J, Meltzer PS, Yu J, Kao FT, Chen DJ, Cerosaletti KM, Fournier REK, Todd S, Lewis T, Leach RJ, Naylor SL, Weissenbach J, Mecklin JP, Jarvinen P, Petersen H,

Hamilton SR, Green J, Jass J, Watson P, Lynch HT, Trent JM, de la Chapelle A, Kinzler KW, Vogelstein B. Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. Cell 75:1215–1215 (1993).
19. Lieberman DA. Targeted colon cancer screening: a concept whose time has almost come. Am J Gastroenterol 87:1085–1093 (1992).
20. Statement of the American Society of Human Genetics on Genetic Testing for Breast and Ovarian Cancer Predisposition. Am J Hum Genet 55:1–5 (1994).
21. OPRR. Protecting Human Research Subjects. Institutional Review Board Guidebook. Bethesda, MD:Office of Protection from Research Risks, 1993; 42–63.
22. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Screening and Counseling for Genetic Conditions. Washington:U.S. Government Printing Office, 1983.
23 Li FP, Garber JG, Friend SH, Strong LC, Patenaude AF, Juengst ET, Reilly PR, Correa P, Fraumeni JF Jr. Recommendations on predictive testing for germ line p53 mutations among cancer prone individuals. J Natl Cancer Inst 84:1156–1160 (1992).
24. Parry DM, Mulvihill JJ, Miller RW. Strategies for controlling cancer through genetics. Cancer Res 47:6814–6817 (1987).
25. Wattenberg LW. Prevention-therapy-basic science and the resolution of the cancer problem. Cancer Res 53:5890–5896 (1993).
26. Benner SE, Hong WK. Clinical chemoprevention: developing a cancer prevention strategy. J Natl Cancer Inst 85:1446–1447 (1993).