The Fourth American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention

Phenotypes, Genotypes, and Interventions for Hereditary Cancers

Frederick P. Li[1]

Dana-Farber Cancer Institute and Harvard School of Public Health, Boston, Massachusetts 02115

On March 20, 1995, at the 85th annual meeting of the American Association for Cancer Research in Toronto, Ontario, Canada, Frederick P. Li, M.D., was honored with the Fourth American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention. In the epidemiology and cancer research communities, the consensus was that no one was more deserving of this award.

Dr. Li's research career spans more than 25 years. What is it that distinguishes his work from that of his cohort of cancer epidemiologists? The answer, in my view, is that Dr. Li, more than anyone else, perceived both the epidemiological importance of complete, precise, clinical descriptions of family clusters of cancers, and the necessity of applying each succeeding technological advance to the study of the affected and unaffected members of these families. By steadily maintaining this approach, Dr. Li was able to not only describe in 1969, with Joseph Fraumeni, the multiple neoplasm syndrome that bears their names, but also to participate in the identification and chromosome localization of the mutant gene 20 years later. There are several other familial cancers that bear the Fred Li stamp—clinical description, cytogenetic abnormality, identification, and chromosome localization of the mutant gene, with familial renal cancer being a prime example. The Award Committee stated that "his work has become a model for collaborative research leading to new approaches for diagnosis and treatment because it bridges clinical, epidemiological, and cytogenetic or molecular studies."

Dr. Li was born in Guangzhou (Canton), China and emigrated to the United States when he was 6 years old. In China, he is known and revered as Li Pei. He and his wife, Elaine Shiang, introduced the Western world to the maps of cancer mortality in China that had been so painstakingly developed by the Chinese health authorities. His concern for the health and, particularly, the cancer problems of the Chinese population continue to occupy a share of his diverse interests.

Fred Li received his M.D. from the University of Rochester School of Medicine, Rochester, NY, and a Master's degree in Demography from Georgetown University, Washington, DC. He was trained in Internal Medicine at Strong Memorial Hospital in Rochester, Bellevue Hospital in New York City, and at the Peter Bent Brigham Hospital in Boston, MA. In 1967, Dr. Li joined Joseph Fraumeni at the Clinical Epidemiology Branch of the National Cancer Institute for what would prove to be a career's worth of fruitful collaborations. Then, in 1971, he moved to Boston to establish a one-person field station of the National Cancer Institute's Epidemiology Branch. There, with the use of his five senses plus his extraordinary powers of persuasion, Dr. Li combined his clinical observations with epidemiological insights and collaborations with superb bench scientists to greatly advance our knowledge of the genetic basis of many cancers. Since 1991, he has been Chief of the Division of Cancer Epidemiology and Control at the Dana-Farber Cancer Institute and Professor of Epidemiology at the Harvard School of Public Health, Boston, MA.

The Editors of Cancer Epidemiology, Biomarkers & Prevention *are especially proud that one of our Associate Editors and a member of both the American Association for Cancer Research and the American Society of Preventive Oncology was chosen for this richly deserved award.*

W. Thomas London
Fox Chase Cancer Center
Philadelphia, PA

Biological complexities of human carcinogenesis have impeded the efforts of epidemiologists to identify causation *(1–6)*. Cancer is a large family of disorders; each needs to be individually investigated for etiological influences. The interval between carcinogenic exposures and cancer diagnosis (latent period) is typically several decades, and faulty patient recall can lead to inaccurate estimation of exposure dose. In addition, cancer development is a multistep process in which many factors can contribute to disease occurrence *(2, 4–6)*. An etiological factor acting at the single step in the cascade of tumor initiation, promotion, and progression might elevate cancer risk by a minimal amount that is difficult to measure accurately. Data show that the strength of association is weak for most risk factors in epidemiological studies, yielding RRs in the range of 1.5–3. Consequently, inconsistent results often emerge from repeated studies that differ in study design, sample size and other features *(2)*. For many neoplasms such as carcinomas of the kidney, prostate and

Received 5/5/95; accepted 6/15/95.
[1] To whom requests for reprints should be addressed, at Dana-Farber Cancer Institute, Mayer 3A.31, 44 Binney Street, Boston, MA 02115.
[2] The abbreviation used is: RR, relative risk.

pancreas, knowledge of etiology remains fragmentary and uncertain.

At the start of my career at the Epidemiology Branch, National Cancer Institute, Robert W. Miller and Joseph F. Fraumeni, Jr., suggested that I and other trainees seek clues to cancer etiology at the bedside *(7)*. They noted that discoveries of carcinogens in humans were often triggered by anecdotal observations of unusual cancer patients or case clusters *(8, 9)*. These etiological hypotheses were then examined in larger descriptive and analytical epidemiology studies that established a causal relationship *(2)*.

The use of bedside observations to study cancer epidemiology is unconventional, particularly in the present era of powerful statistical methodologies and computer technologies. A valid criticism is that anecdotal clinical observations often identify misleading chance associations. Few epidemiologists are trained clinicians who can discern etiological influences hidden within the medical history, physical examination, and laboratory results. In addition, bedside observations of rare events conferring high cancer risk have little public health impact, unless the knowledge reveals more general principles of human carcinogenesis *(5, 6, 10, 11)*.

Hereditary cancers account for a small fraction of the cancer burden in the population *(11, 12)*. However, highly penetrant single-gene traits can produce striking family aggregates of cancer. Compared with the general population, members of these kindreds often have RR = 1000 or higher for specific cancers *(13)*. The corresponding lifetime occurrence rates for specific cancers approach 80–100% for carriers of dominant traits, such as the multiple endocrine neoplasia syndromes and adenomatous polyposis coli *(14–16)*. Susceptible family members also develop cancer at unusually early ages and multiple primary tumors in one or more organ sites.

Through clinical observations, case referrals, and medical chart reviews, we and other investigators have identified unusual family aggregates of site-specific carcinomas, as well as familial sarcomas, melanoma, hematologic neoplasms, or brain tumors *(12)*. These observations foster the generalization that virtually every form of cancer tends to aggregate in families *(17,18)*. For increasing numbers of familial cancers, the inherited susceptibility genes have recently been cloned *(15, 19–22)*. Despite the rarity of inherited mutations in these genes, corresponding somatic mutations occur frequently during the process of neoplastic transformation *(5, 18)*.

Inherited cancer susceptibility genes are often thought to be organ- or tissue-specific, *e.g.*, hereditary retinoblastoma *(11)*. However, most susceptibility genes can predispose to cancer in multiple organs. Recent studies of a large cohort of survivors of hereditary retinoblastoma show excess occurrence (RR = 25–400) of diverse forms of second tumors, including osteosarcoma, soft tissue sarcoma, brain tumors, cutaneous melanoma, pinealoma, and perhaps other neoplasms *(23)*. In addition, germline mutations in the mismatch repair genes predispose to not only colon cancer but also to other neoplasms described in Lynch Syndrome II (carcinomas of the endometrium, pancreas, ovary, stomach, and other sites; Ref. *24*). Another phenotype of inherited mismatch repair mutations, Muir-Torre syndrome, features multiple colorectal carcinomas associated with sebaceous gland tumors and cancers of the bladder, uterus, and other sites *(25–27)*. Carriers of *BRCA1* mutations develop both breast and ovarian cancers and may have a moderate increase in risk of colon and prostate cancers *(28)*.

In 1969, Fraumeni and I described four families with an autosomal dominant pattern of breast cancers in young women and diverse forms of childhood cancer in their offspring and other blood relatives *(29)*. In the study, we questioned whether these families were afflicted with a previously unrecognized inherited cancer syndrome. To pursue the hypothesis, additional families were collected. A descriptive epidemiological study of a larger series of 24 kindreds revealed an excess of at least 6 forms of cancers: breast cancer, soft tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, and acute leukemia *(30)*. All forms, excluding the breast cancer, tended to develop in children and adolescents. However, the hypothesis of an inherited cancer susceptibility remained to be formally tested. Thus, an analytical study was made of cancer occurrence during follow-up observation of previously cancer-free members of these families. The study design required an estimation of the carrier likelihood of each unaffected relative, under assumptions of an autosomal dominant model with high penetrance and variable ages at cancer diagnosis. Observed and expected numbers of cancers during follow-up were determined for subjects in each carrier-likelihood level and age strata. Results showed a 20-fold relative risk (95% confidence interval, 14–35) of cancer development among blood relatives who were under age 45 years and had a >10% likelihood of inheriting a dominant susceptibility gene *(31)*. The excess cancers on follow-up consisted of the same six tumor types found previously in the families *(31)*. These epidemiological studies, which spanned more than 2 decades, eventually demonstrated dominant transmission in these families of a susceptibility gene for diverse cancers.

In 1990, a collaboration with Stephen Friend (Fred Hutchinson Cancer Center, Seattle, WA), David Malkin (The Hospital for Sick Children, Toronto, Ontario), Louise Strong (M. D. Anderson Cancer Center, Houston, TX), and others led to the identification of germline *p53* mutations in a high proportion of Li-Fraumeni families; the finding was promptly confirmed by other groups *(32, 33)*. In addition to families with this syndrome, inherited *p53* mutations have been found in other subsets of cancer patients: nonfamilial cases with early onset multiple primary cancers, adrenocortical carcinoma, sarcomas, multifocal brain tumors, or premenopausal breast cancer *(34–36)*. Some of these patients have new germline *p53* mutations. In a fraction of Li-Fraumeni families, germline mutations in the coding regions of *p53* have not been found. *p53* linkage has also been excluded in a Li-Fraumeni family, indicating that other inherited defects might produce the syndrome *(37)*.

When germline *p53* mutations were identified, the technical capability became available to identify cancer prone individuals among unaffected relatives in Li-Fraumeni families. These high-risk relatives might be advised to undergo periodic medical surveillance to detect cancer at an earlier, more curable stage. In addition, reduced exposure to environmental carcinogens and use of chemopreventive agents might delay or prevent cancer development. Relatives with no germline *p53* mutation could also be reassured that their cancer risk approximates that of the general population, despite the strong family history of cancer. However, primary and secondary prevention is problematical for a syndrome with multiple forms of cancer that are of unknown etiology and are difficult to diagnose and treat. Additionally, genetic data might expose gene carriers to psychological stress, social stigmatization, job loss, and exclusion from health and life insurance *(38–40)*. It remains unknown whether the knowledge of *p53* genetic status yields a net benefit or harm to at-risk but unaffected relatives. For these reasons, *p53* predisposition testing was not offered to

family members until a research program was established to examine risks and benefits.

To plan for *p53* predisposition testing, two workshops were organized with support from the National Center for Human Genome Research and the National Cancer Institute *(41)*. A series of recommendations were developed for *p53* predisposition testing in Li-Fraumeni families, and we now offer a testing program that is limited to adult subjects *(42)*. The goal of the program is to evaluate outcomes of *p53* predisposition testing, with expectations that the knowledge might be applicable to future predisposition testing for inherited mutations in *BRCA1*, *p16*, and mismatch repair genes that increase risk for common forms of cancer *(20, 21, 43, 44)*.

Mapping and cloning of inherited susceptibility genes have received much attention from clinicians and the public. However, identification of carriers of cancer susceptibility genes provides no direct benefit unless the discoveries are used in interventions that successfully reduce cancer morbidity and mortality *(45, 46)*. Predisposition testing programs are needed that maximize benefits and minimize risks through education, counseling, and psychological and medical support. These services should be available throughout the phases of informed consent to participate, of disclosure, and of follow-up *(43)*. Cancer predisposition testing should be a research activity before being made available as a service to large segments of the population *(39, 47)*.

Intervention strategies for carriers of susceptibility genes might include reducing exposure to environmental carcinogens, periodic surveillance, and early detection of disease at a curable stage *(48–51)*. For example, sunlight avoidance in patients with xeroderma pigmentosum or hereditary melanoma might delay onset or prevent cutaneous neoplasms *(44)*. In patients with inherited mutations in the mismatch repair genes, colonoscopy and excision of precancerous colonic adenomas might interrupt progression to carcinoma *(52)*. However, the optimal age at initiation of colonoscopies and the frequency of surveillance in gene carriers is uncertain *(51)*. The frequencies of missed polyps and flat adenomas are likely to vary considerably among endoscopists. The effectiveness of dietary interventions among gene carriers is also unknown *(49)*. Some carriers of mismatch repair genes with Lynch Syndrome II develop extra colonic cancers; optimal screening for these neoplasms needs to be determined. For breast cancer, mammography and physical examinations can detect early lesions *(50)*. Mammography has been demonstrated to reduce breast cancer mortality among women over age 50 years. Unfortunately, *BRCA1* carriers often develop premenopausal breast cancer, and the effectiveness of mammography screening among younger women is being hotly debated *(50)*. Many risk factors for breast cancer are related to hormonal factors that are difficult to modify *(53, 54)*.

An area of increasing research interest is cancer chemoprevention, the use of pharmaceuticals, foodstuffs, and other agents to delay or prevent cancer occurrence. Chemoprevention trials with diverse agents are in progress *(49, 53, 54)*. If tamoxifen were eventually shown to prevent breast cancer among women in general, its effectiveness among *BRCA1* carriers will need to be independently assessed. A number of colon cancer chemoprevention trials are also in progress *(49)*. Some studies suggest a possible benefit of aspirin, calcium, nonsteroidal anti-inflammatory agents, vitamins, or other micronutrients *(49, 55, 56)*. However, definitive findings on colon cancer chemoprevention are anticipated, including studies of genetically susceptible subgroups.

Remarkably, the modern era of research on cancer families and identification of inherited susceptibility genes spans only a few brief decades *(11)*. Additional work in progress can be expected to identify inherited susceptibility genes for prostate, lung, pancreas, and other common cancers in the years ahead. The challenge is to apply the new genetic information to clinical practice. Prospective studies will be needed to define the lifelong consequences of personal knowledge regarding susceptibility to cancer and other diseases *(39, 57)*. Eventually, predisposition testing for at least some cancer-predisposing genes should prove cost effective, and patients will be empowered with knowledge and tools to reduce their disease risk.

An estimated 5% of all cancers might be due to a highly penetrant single-gene mutation. For the remaining 95% of cancers, determinants of disease risk likely include inherited traits that modify carcinogen absorption, transport, activation, detoxification, and excretion *(58)*. An obvious example is the genes for skin pigmentation that determine susceptibility to sunlight-induced skin cancers, the most common neoplasms in humans. To date, studies of metabolic pathways have focused on families of genes such as the cytochrome P-450 system *(49)*. Much of the available results are preliminary, and discordant findings among studies are not rare. Unlike the highly penetrant single-gene disorders, the excess risks associated with these genes are smaller, creating the usual difficulties associated with measuring modest differences in human populations. Nevertheless, additional knowledge of these genes should strengthen epidemiological and carcinogenesis studies and identify susceptible populations for targeted interventions *(58)*.

References

1. Brugge, J., Curran, T., Harow, E., and McCormick, F. (eds.). Origins of Human Cancer: A Comprehensive Review. Plainview, NY: Cold Spring Harbor Laboratory, 1991.

2. Doll, R., and Peto, R. The cause of cancer: quantitiative estimates of avoidable risks of cancer in the United States today. J. Natl. Cancer Inst., *66:* 1191, 1981.

3. Seventh Annual Report on Carcinogens—Summary: United States Department of Health and Human Services Public Health Service. Rockville, MD: United States Government Printing Office, 1994.

4. Sugimura, T. Multistep carcinogenesis: a 1992 perspective. Science (Washington DC), *258:* 603–607, 1992.

5. Weinberg, R. A. Tumor suppressor genes. Science (Washington DC), *254:* 1138–1146, 1991.

6. Aaronson, S. A. Growth factors and cancer. Science (Washington DC), *254:* 1146–1153, 1991.

7. Miller, R. W., Watanabe, S., Fraumeni, J. F., Jr., Sugimura, T., Takayama, S., and Sugano, H. (eds.). Unusual Occurrences as Clues to Cancer Etiology. Tokyo: Japan Scientific Societies Press, 1987.

8. Miller, R. W. Neoplasia and Down's syndrome. Ann. NY Acad. Sci., *171:* 637–644, 1970.

9. Miller, R. W. How environmental effects on child health are recognized. Pediatrics, *53:* 792–796, 1974.

10. Li, F. P. Molecular epidemiology of familial cancers. Br. J. Cancer, *68:* 217–219, 1993.

11. Knudson, A. G., Jr. Hereditary cancers disclose a class of cancer genes. Cancer Res., *63:* 1888–1891, 1989.

12. Li, F. P. Familial cancer syndromes and clusters. Curr. Probl. Cancer, *14:* 75–106, 1990.

13. Li, F. P. Cancer families: human models of susceptibility to neoplasia—the Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res., *48:* 5381–5386, 1988.

14. Kinzler, K. W., Nilbert, M. C., Su, L. K., Vogelstein, B., Bryan, T. M., Levy, D. B., Smith, K. J., Preisinger, A. C., Hedge, P., McKechnie, D., Finniear, R., Markham, A., Groefeen, J., Boguski, M. S., Altschul, S. F., Horii, A., Ando, H., Miyoshi, Y., Miki, Y., Nishisho, I., and Nakamura, Y. Identification of *FAP* locus genes from chromosome 5q21. Science (Washington DC), *253:* 661–665, 1991.

15. Eng, C., Smith, D. P., Mulligan, L. M., Nagai, M. A., Healey, C. S., Ponder, M. A., Gardner, E., Scheumann, F. W., Jackson, C. E., Tunnacliffe, A., and Ponder, B. A. Point mutation within the tyrosine kinase domain of the RET proto-oncogene in multiple endocrine neoplasia type 2B and related sporadic tumours. Hum. Mol. Genet., *3:* 237–241, 1994.

16. Morita, R., Ishikawa, J., Tsutsumi, M., Hikiji, K., Tsukada, Y., Kamidono, S., Maeda, S., and Nakamura, Y. Identification of *FAP* locus genes from chromosome 5q21. Science (Washington DC), *250:* 1233–1238, 1991.

17. Knudson, A. G., Jr. Hereditary cancers of man. Cancer Invest., *45:* 1437–1443, 1983.

18. Knudson, A. G., Jr. All in the (cancer) family. Nature Genet., *5:* 103–104, 1993.

19. Liu, B., Parsons, R. E., Hamilton, S. R., Petersen, G. M., Lynch, H. T., Watson, P., Markowitz, S., Willson, J. K., Green, J., de la Cahpelle, A., Kinzler, K. W., and Vogelstein, B. hMSH2 mutations in hereditary nonpolyposis colorectal cancer kindreds. Cancer Res., *54:* 4590–4594, 1994.

20. Miki, Y., Swensen, J., Shattuck-Eldens, D., Futreal, P. A., Harshman, K., Tavtigian, S., Liu, Q., Cochran, C., Bennett, L. M., Ding, W., Bell, R. J. R., 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, P. K., Norris, F. H., Helvering, L., Morrison, P., Rosteck, P., Lai, M., Barrett, J. C., Lewis, C., Neuhausen, S., Cannon-Albright, L., Goldgar, D., Wiseman, R., Kamb, A., and Skolnik, M. H. A strong candidate for the breast and ovarian cancer susceptibility gene. Science (Washington DC), *266:* 66–71, 1994.

21. Fishel, R., Lescoe, M. K., Rao, R. S., Copland, N., Jenkins, N., Garber, J., Kane, M., and Kolodner, R. The human mutator gene homolog *MSH2* and its association with hereditary nonpolyposis colon cancer. Cell, *75:* 1027–1038, 1993.

22. Papadopoulos, N., Nicolaides, N. C., Wei, Y. F., Ruben, S. M., Carter, K. C., Rosen, C. A., Haseltine, W. A., Fleischmann, R. D., Fraser, C. M., Adams, M. D., Venter, J. C., Hamilton, S. R., Petersen, G. M., Watson, P., Lynch, H. T., Peltomaki, P., Mecklin, J. P., de la Chapelle, A., Kinzler, K. W., and Vogelstein, B. Mutation of a mutL homolog in hereditary colon cancer. Science (Washington DC), *263:* 1625–1629, 1994.

23. Eng, C., Li, F. P., Abramson, D. H., Ellsworth, R. M., Wong, F. L., Goldman, M. B., Seddon, J., Tarbell, N., and Boice, J. D. Mortality from second tumors among long-term survivors of retinoblastoma. J. Natl. Cancer Inst., *85:* 1121–1128, 1993.

24. Lynch, H. T., Lanspa, S., Smyrk, T., and Boman, B. Hereditary nonpolyposis colorectal cancer (Lynch Syndromes I and II). Cancer Genet. Cytogenet., *53:* 143–160, 1991.

25. Cohen, P. R., and Kohn, S. R. Association of sebaceous gland tumors and internal malignancy: the Muir-Torre syndrome. Am. J. Med., *90:* 606–613, 1991.

26. Li, F. P., and Eng, C. The familial Muir-Torre syndrome. Ann. Intern. Med., *119(6):* 539, 1993.

27. Honchel, R., Halling, K. C., Schaid, D. J., Pittelkow, M., and Thibodeau, S. N. Microsatellite instability in Muir-Torre Syndrome. Cancer Res., *54:* 1159–1163, 1994.

28. Ford D., Easton, D. F., Bishop, D. T., Narod, S. A., and Goldgar, D. E., and the Breast Cancer Linkage Consortium. Risks of cancer in *BRCA1*-mutation carriers. Lancet, *343:* 692–695, 1994.

29. Li, F. P., and Fraumeni, J. F., Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann. Intern. Med., *71:* 747–752, 1969.

30. Li, F. P., Fraumeni, J. F., Jr., and Mulvihill, J. J. A cancer family syndrome in twenty-four kindreds. Cancer Res., *48:* 5358–5362, 1988.

31. Garber, J. E., Goldstein, A. M., and Kanton, A. F. Follow-up study of twenty-four families with Li-Fraumeni syndrome. Cancer Res., *51:* 6094–6097, 1991.

32. Malkin, D., Li, F. P., Strong, L. C., Fraumeni, J. F., Jr., Nelson, C. E., Kim, D. H., Kassel, J., Gryka, M. A., Bischoff, F., Tainsky, M., and Friend, S. Germline *p53* mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science (Washington DC), *250:* 1233–1238, 1990.

33. Birch, J. M., Hartley, A. L., Tricker, K. J., Prosser, J., Condle, A., Kelsey, A. M., Harris, M., Morris-Jones, P. H., Binchy, A., Crowther, D., Craft, A. W., Eden, O. B., Evans, G. R., Thompson, E., Mann, J. R., Martin, J., Mitchell E. L., and Santibanez-Koref, M. F. Prevalence and diversity of constitutional mutations in the *p53* gene among 21 Li-Fraumeni families. Cancer Res., *54:* 1298–1304, 1994.

34. Malkin, D., Jolly, K. W., Barbier, N., Look, A. T., Friend, S. H., Gebhardt, M. C., Andersen, T. I., Borresen, A. L., Li, F. P., Garber, J., and Strong, L. C. Germline mutations of the *p53* tumor-suppressor gene in children and young adults with second malignant neoplasms. N. Engl. J. Med., *326:* 1309–1315, 1992.

35. Li, F. P., and Fraumeni, J. F., Jr. Meeting Report: Collaborative interdisciplinary studies of *p53* and other predisposing genes in Li-Fraumeni syndrome. Cancer Epidemiol., Biomarkers & Prev., *3:* 1–3, 1994.

36. Strong, L. C., Williams, W. R., and Tainsky, M. A. The Li-Fraumeni syndrome: from clinical epidemiology to molecular genetics. Am. J. Epidemiol., *135:* 190–199, 1992.

37. Birch, J. M., Heighway, J., Teare, M. D., Kelsey, A. M., Hartley, A. L., Tricker, K. J., Crowther, D., Lane, D. P., and Santibanez-Koref, M. F. Linkage studies in a Li-Fraumeni family with increased expression of p53 protein but no germline mutation in p53. Br. J. Cancer, *70:* 1176–1181, 1994.

38. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Screening and Counseling for Genetic Conditions. Washington, DC: United States Government Printing Office, 1983.

39. National Advisory Council of the Human Genome Program: Statement on use of DNA testing for presymptomatic identification of cancer risk. JAMA, *271:* 785, 1994.

40. Juengst, E. T. Priorities in professional ethics and social policy for human genetics. JAMA, *266:* 1835–1836, 1991.

41. Li, F. P., Garber, J. G., Friend, S. H., Strong, L. C., Patenaude, A. F., Juengst, E. T., Reilly, P. R., Correa, P., and Fraumeni, J. F., Jr. Recommendations on predictive testing for germ line *p53* mutations among cancer prone individuals. J. Natl. Cancer Inst., *84:* 1156–1160, 1992.

42. Department of Health and Human Services. Additional protections for children involved as subjects in research. Fed. Register, *48:* 9814–9820, 1983.

43. Lerman, C., Daly, M., Masny, A., and Balshem, A. Attitudes about genetic testing for breast-ovarian cancer susceptibility. J. Clin. Oncol., *12:* 843–850, 1994.

44. Cannon-Albright, L. A., Meyer, L. J., Goldgar, D. E., Lewis, C. M., McWhorter, W. P., Jost, M., Harrison, D., Anderson, D. E., Zone, J. J., and Skolnick, M. H. Penetrance and expressivity of the chromosome 9p melanoma susceptibility locus (MLM). Cancer Res., *54:* 6041–6044, 1994.

45. Caskey, C. T. Molecular medicine: A spin-off from the helix. JAMA, *269:* 1986–1992, 1993.

46. Parry, D. M., Mulvihill, J. J., and Miller, R. W. Strategies for controlling cancer through genetics. Cancer Res., *47:* 6814–6817, 1987.

47. 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.

48. Lynch, H. T., and Lynch, J. F. Familial predisposition and cancer management. Contemp. Oncol., 12–25, 1993.

49. Wattenberg, L. W. Prevention-therapy-basic science and the resolution of the cancer problem. Cancer Res., *53:* 5890–5896, 1993.

50. Kerlikowske, K., Grady, D., Rubin, S. M., Sandrock, C., and Ernster, V. L. Efficacy of screening mammography. JAMA, *273:* 149–154, 1995.

51. Meagher, A. P., and Stuart, M. Colonoscopy in patients with a family history of colorectal cancer. Dis. Colon Rectum, *35:* 314–321, 1992.

52. Lieberman, D. A. Targeted colon cancer screening: a concept whose time has almost come. Am. J. Gastroenterol., *87:* 1085–1093, 1992.

53. Rutquist, L. E., Cedermark, B., and Glas, V. Contralateral primary tumors in breast cancer patients with a randomized trial adjuvant tamoxifen therapy. J. Natl. Cancer Inst., *83:* 1299–1306, 1991.

54. Nayfield, S. G., Karp, J. E., and Ford, L. G. Potential role of tamoxifen in prevention of breast cancer. J. Natl. Cancer Inst., *83:* 1450–1459, 1991.

55. Thun, M. J., Namboodiri, B. S., and Heath, C. W. Aspirin use and reduced risk of fatal colon cancer. N. Engl. J. Med., *325:* 1593–1596, 1991.

56. Rigau, J., Pique, J. M., Rubio, E., and Planas, R. Effects of long-term sulidac therapy on colonic polyposis. Ann. Intern. Med., *115:* 952–954, 1991.

57. Wiggins, S., Whyte, P., Huggins, M., Adam, S., Theilmann, J., Bloch, M., Sheps, S. B., Schechter, M. T., and Hayden, M. R. The psychological consequences of predictive testing for Huntington's Disease. N. Engl. J. Med., *327:* 1401–1405, 1992.

58. Shields, P. G., and Harris, C. C. Molecular epidemiology and the genetics of environmental cancer. JAMA, *266:* 681–687, 1991.

The 4th American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention. Phenotypes, Genotypes, and Interventions for Hereditary Cancers.

F P Li

Cancer Epidemiol Biomarkers Prev 1995;4:579-582.