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Ethical and Scientific Considerations for Chemoprevention Research in Cohorts at Genetic Risk for Breast Cancer

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Abstract Identification of cohorts at genetic risk for cancer offers unique research opportunities to explore the steps in carcinogenesis, from the inheritance of a predisposing mutation to the development of preinvasive lesions or overt malignancy, and to evaluate interventions to modulate the carcinogenic process. However, cancer prevention strategies for most inherited cancer predisposition syndromes are of unproven benefit, and the potential for adverse psychosocial effects and employment or insurance discrimination associated with genetic testing is substantial. Thus testing for genetic cancer risk remains highly controversial, and the National Center for Human Genome Research and the American Society of Human Genetics advise DNA testing for presymptomatic identification of cancer risk only in the setting of a carefully monitored research environment.

The commercial availability of predictive genetic testing, particularly for inherited susceptibility to cancer, has focused attention not only on the urgent need for research in cancer prevention for cohorts at genetic cancer risk but also on ethical considerations surrounding clinical prevention research in genetic risk groups. This paper addresses the interrelationship of ethical and scientific issues in conducting chemoprevention research in these cohorts, especially for those studies which require presymptomatic testing for specific gene mutations as a study entry criterion or as a criterion for stratification. Practical approaches to study design and implementation issues for chemoprevention research in genetic risk cohorts are discussed, emphasizing the interactions of ethical and scientific considerations at all levels of the research process. J. Cell. Biochem. 25S:123–130.

Key words: carcinogenesis; predisposing mutation; malignancy; DNA testing

INTRODUCTION

Identification of cohorts at genetic risk for cancer is an appealing concept to scientists because it offers unique research opportunities: to explore the steps in carcinogenesis, from the inheritance of a predisposing mutation through the development of preinvasive lesions or overt malignancy; to investigate the influences of environmental and lifestyle factors on this process; and to evaluate potential interventions to modulate this sequence of events. However, testing for mutations in cancer-associated genes to evaluate cancer risk remains a controversial issue because of limitations in laboratory testing procedures, minimal knowledge about potential prevention strategies, and the likelihood of adverse psychosocial effects associated with identification of genetic risk [1].

The urgent need for cancer prevention research among genetic risk cohorts has been emphasized by the recent identification of BRCA1 and other breast cancer genes among families with frequent occurrence of breast cancer and, often, of cancers at other primary sites [2,3]. Women from kindreds with frequent breast and/or ovarian cancers who carry an inherited mutation in the BRCA1 gene appear to have an 85% risk of developing breast cancer by age 70 and a 63% risk for ovarian cancer [4]. Although identification of a specific BRCA1 mutation within a kindred makes direct DNA testing for carrier status possible for its members, cancer prevention options for mutation carriers are limited. Optimal techniques and schedules for early detection procedures have not been established for this group, and the efficacy of prophylactic surgical procedures is not known despite the frequent use of prophylactic mastec

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tomy [5] and prophylactic oophorectomy [6]. While promising agents for breast and ovarian cancer chemoprevention are under development [7,8], little is known about their ability to modulate the development of preinvasive lesions or invasive cancers or their potential as adjuvant therapies to enhance prophylactic surgical procedures.

Ethical issues surrounding genetic testing become especially linked to scientific considerations when study participation requires formal assessment of genetic risk. This paper attempts to identify important ethical issues associated with genetic testing for breast-ovarian cancer risk, i.e., mutations in BRCA1, and to demonstrate how these interact with scientific considerations at all levels of chemoprevention study planning and implementation.

BREAST CANCER RISK ASSESSMENT

Most breast cancer chemoprevention studies are currently conducted within cohorts at high risk of disease. This approach targets the subgroup at greatest potential benefit; also, the associated increase in expected endpoints (preinvasive lesions or invasive cancers) accommodates a smaller sample size and justifies testing interventions with potential for slight inconvenience or mild side effects.

Traditionally, breast cancer risk for individual participants is estimated from epidemiologic models which consider a variety of risk factors and project a cumulative risk for developing disease over a finite period of time [9–13]. A family history of breast cancer in a first-degree relative (mother or sister) has been associated with a 2–4-fold increase in breast cancer risk [14], and epidemiologic models in clinical use include the number of first degree relatives with breast cancer as a factor for estimating breast cancer risk. Other details of family history (i.e., second degree relatives with breast cancer, early age onset of disease in affected relatives, and bilaterality) may also be strong predictors of breast cancer risk [15].

The extent to which family history factors are incorporated into epidemiologic models varies considerably. The Gail model, based on data from participants in the Breast Cancer Detection Demonstration Project (BCDDP) screening program, includes reproductive and personal medical history factors but limits family history to the number of first degree relatives with breast cancer (0, 1, or 2 or more) [11]. The model derived from breast cancer cases and controls in the population-based Cancer and Steroid Hormone (CASH) study by Claus et al. predicts breast cancer risk based on various combinations of affected first- and second-degree relatives and on the ages at onset of disease for the affected relatives [13], while models by Ottman et al. [9] and by Anderson and Badzioch [10] include bilaterality of disease as well as specific first degree relationships (mother-daughter, sister-sister). Cumulative risk estimates derived from the different models may diverge by as much as 40%, depending on the populations from which the data was derived and the individual factors included in the model [16]. Thus the relevance of the risk factors in the model to the study objectives and population from which the model was derived (i.e., validation of the model for the chemoprevention target population) are important considerations in defining risk criteria by this approach.

The recent recognition of hereditary breast cancer syndromes linked to mutations in specific cancer-associated genes offers greater potential for accurate identification of family members at extremely elevated cancer risk [4]. The use of strict family history criteria (e.g., multiple cases of early onset breast cancer and/or epithelial ovarian cancer), with or without genetic linkage analysis, may provide kindred-based cohorts with a high prevalence of germline mutations in BRCA1. Linkage analysis of 214 breast cancer and breast-ovarian cancer families suggests that up to 50% of site-specific breast cancer families and more that 75% of breast-ovarian cancer families are likely to be linked to BRCA1 [17]. Within families with a high probability of linkage, about one-third of female family members without a prior breast cancer diagnosis may be at extremely high lifetime risk of developing the disease (e.g., 80–90%), while the remaining two-thirds may have an estimated lifetime breast cancer risk similar to that of the general population (10–16%) [18].

LABORATORY TESTING FOR BRCA1 MUTATIONS

Most current knowledge about the clinical significance of BRCA1 mutations is derived from observations of large breast-ovarian cancer families in which mutation carrier status has been determined by genetic linkage analysis [19]. The initial identification of a BRCA1 muta-

tion within a breast cancer kindred, or in unrelated individuals at high risk, is a complex process. The large number of unique mutations that have been identified among breast, breast-ovarian, and ovarian cancer families to date [20] indicates that direct DNA sequencing should be used as the "gold standard" for the laboratory diagnosis of BRCA1 mutations and for the validation of other laboratory testing procedures.[1] However, the size of the gene (24 coding exons over 100 kb of genomic DNA [2] makes testing large numbers of individuals by direct DNA sequencing impractical at the present time and thus limits the use of testing in populations other than breast and ovarian cancer families. Other approaches to the detection of the more common mutations are currently being explored, such as gene scanning techniques (comparing normal and test sequences to detect differences) or identification of a truncated BRCA1 protein [22], but the sensitivity and specificity of these methods are suboptimal.

The rapid evolution of BRCA1 testing from the research setting into clinical and commercial applications has raised unique scientific and ethical considerations. First, the progress in genetic testing technology has quickly outpaced the development of quality assurance and quality control methods for these molecular diagnostics. While preparation of laboratory reagents and conduct of testing procedures are regulated under the Clinical Laboratory Improvement Amendments (1988) [23], specific directives for genetic testing are not included in its requirements. Although standards for laboratory genetics services have been established by the American College of Medical Genetics [24], compliance is voluntary. Thus the accuracy and reliability of BRCA1 test results remain of scientific and ethical concern. Secondly, assuming a valid and reliable test, the clinical implications of carrier status are largely unknown. The risks for breast cancer (and cancers of other sites) currently associated with common BRCA1 mutations have been estimated from disease occurrence in breast and breast-ovarian cancer families and may not apply to different mutations or to individuals with a more limited family history of these diseases. In addition, optimal medical management, effective preventive strategies, and psychosocial implications for gene carriers have not been systematically evaluated, so that clinical decision-making may be confounded (rather than clarified) by BRCA1 testing. For these reasons, the American Society of Human Genetics (ASHG) has cautioned that "Once direct and reliable testing for BRCA1 mutations is available, it may be offered to members of specific types of families with strong breast-ovarian cancer histories. While the cancer risks associated with different BRCA1 mutations are being determined, testing should initially be offered and performed on an investigational basis by appropriately trained health care professionals who have a therapeutic relationship with the patient and are fully aware of the genetic, clinical, and psychosocial implications of testing, as well as of the limitations of existing test procedures [25]." In view of the increasing commercial availability of genetic testing for cancer risk, the American Society of Clinical Oncology (ASCO) recommends genetic testing only when the results will influence the management of the patient or family member [26]. ASCO recognizes BRCA1 as a hereditary syndrome in which the medical benefit of identification of a carrier is presumed but not proven and supports BRCA1 testing only if adequate genetic education and counseling, as well as access to preventive options and surveillance, are provided.

[1]Because extraneous sequencing bands may be generated in glycine-and cystine-rich areas, point mutations (single base pair changes) detected by sequencing may require confirmation by an alternative testing methods [21].

ELIGIBILITY CRITERIA

The implications of genetic testing for breast cancer chemoprevention clinical trials have been discussed in detail recently by Baker and Freedman [27]. Two basic approaches to defining a study population comprise [1] restricting enrollment and randomization to individuals without breast cancer who test positive for the gene, or [2] enrolling and randomizing all individuals who meet clinical/epidemiological risk entry criteria and stratifying by genetic test result in the analysis.

Positive Genetic Test as an Eligibility Requirement

The first approach requires genetic testing and communication of test results to all potential participants but offers enrollment only to those who test positive for the cancer-related mutation. While this approach minimizes the sample size required for adequate statistical

power, recruitment may become cumbersome because of the extensive education and genetic counseling involved in the informed consent process for genetic testing as well as the need for clinical counseling, medical management decisions, and psychological support when test results are provided to the individual [28]. The counseling protocols are complex and resource intensive; multidisicplinary expertise which includes clinical genetics, laboratory aspects of DNA testing, prevention and treatment of breast and ovarian cancers, and psychosocial support is necessary to address the relevant issues identified by ASHG [25] and ASCO [26].

Surveys of first degree relatives of ovarian cancer patients [29] and unaffected members of breast-ovarian cancer families [30] suggest a high level of interest in BRCA1 testing: 75 to 80% anticipated a definite desire for testing, and 15 to 20% reported probable interest. While practical experience in breast-ovarian cancer families confirms this level of initial interest, approximately half of those who express initial interest do not proceed to testing after pretest genetic counseling [31]. Thus actual uptake among breast and ovarian cancer kindreds may be as low as 40% of male and female family members, of whom only about one third may test positive [18]. Decisions for prophylactic surgery among female BRCA1 carriers further depletes the recruitment pool for chemoprevention studies which require BRCA1 carrier status as an eligibility requirement.

The intensity of resources required for genetic counseling and testing of large numbers of potential participants, and the relatively low yield of eligibles (even among breast-ovarian cancer kindreds with relatively high BRCA1 prevalence and penetrance) are significant limitations to the use of this approach. In general, Phase II chemoprevention clinical trials are more appropriate for this recruitment strategy than Phase III studies because of the Phase II focus on intermediate biomarker endpoints and their smaller sample sizes. Affiliation of these chemoprevention studies with ongoing programs in clinical genetics and hereditary cancer prevention services provides an excellent opportunity for recruitment of gene carriers in a setting which assures long-term follow-up of genetic risk.

Genetic Testing for Stratification Purposes Only

An alternative recruitment approach is to define eligibility by clinical criteria or epidemiological risk, requiring genetic testing after enrollment and randomization, and using test results only for stratification in analysis. While the sample size required for adequate statistical power will be larger than that for studies enrolling BRCA1 carriers only, the number of individuals requiring genetic testing is markedly decreased because testing is no longer used to determine eligibility [27].

A critical issue in this study design is the decision whether the high-risk participant will receive the results of her genetic testing. Currently, the decision by investigators to withhold test results can be justified by the limitations of current testing procedures, the lack of information on effective cancer prevention methods, potential psychosocial implications of a positive (or negative) test, lack of information about individual clinical outcomes related to test results (outside the setting of studied kindreds), and the large proportion of members of breast and ovarian cancer families who decide against genetic testing when it is offered in a research setting. However, the intent to withhold test results and the reasons for this decision by investigators must be clearly addressed in the informed consent process. Study participants who later decide they want to receive test results should be offered referral for genetic counseling and retesting; the option for referral should be assured during the consent process and in the informed consent document. This approach of "blinded" testing, without disclosure of test results, has advantages in that it offers research participation to a large high-risk group who would not independently pursue (or complete) formal genetic testing, and it obviates the need for the extensive pre- and post-test counseling required for release of test results.

A potential problem in providing test results following randomization is the concern that knowledge of carrier status may influence compliance with the assigned study regimen or contribute to study drop-out [27]. In randomized chemoprevention clinical trials, persons in the control group who test positive for carrier status need not be changed to the test intervention unless new scientific information suggests

that the intervention is superior because the null hypothesis for randomized clinical trials is that there is no difference in outcomes between the study interventions. One approach to this problem is to collect and store specimens at the time of randomization but to perform genetic testing at completion of the clinical trial.

Recruitment Timing

At what point during the process of genetic testing should potential participants be offered enrollment? For randomized placebo-controlled chemoprevention studies, the chemopreventive intervention is assumed to be no better than placebo, so that study participants are not assured of any advantage over the "standard care" of surveillance alone. Thus when gene carrier status is required as an entry criteria, participation should be offered only after post-test medical management decision-making is complete, and then only to BRCA1 carriers who decide for surveillance as a preventive strategy. Participation in prevention studies should not be presented as an alternative to prophylactic mastectomy for BRCA1 carriers who are uncomfortable with surveillance alone. High-risk individuals who decide against genetic testing for hereditary cancer risk can be offered participation in a study that employs blinded testing (for stratification only, without disclosure of results) as soon as the decision against formal genetic counseling and testing is made.

STUDY DESIGN: AGENT AND ENDPOINTS

A characteristic of genetic risk cohorts that must be considered in chemoprevention research is that many gene mutations confer increased risk for cancers of multiple sites. For example, in addition to dramatically increased risks for breast and ovarian cancers, BRCA1 mutation carriers appear to have a 3-fold increased risk of prostate cancer and a 4-fold increased risk for colon cancer [32]. Chemoprevention agents are often targeted to specific cancer sites on the basis of efficacy in animal models and human experience. The effects of specific agents on tissues other than that of the cancer under study, usually monitored as toxicities or adverse effects, become important considerations in genetic risk cohorts for whom adverse events may be enhanced by the mutation(s) which confer cancer risk.

Tamoxifen, an oral antiestrogen used in the adjuvant therapy of breast cancer, is currently under study for the chemoprevention of breast cancer among women at high risk of disease [33]. While tamoxifen's estrogen-like activity in other reproductive tissues has not been associated with an increase in ovarian cancer, ovarian proliferative effects have been reported in both pre- and postmenopausal women, including a twofold increase in the development of complex ovarian cysts [34]. These ovarian effects may pose a significant diagnostic dilemma in BRCA1 carriers [35], especially for those with a family history of ovarian cancer. In addition, a recent report suggests a 3-fold increase in gastrointestinal cancers among patients receiving tamoxifen in an adjuvant study [36]. Considering the marked increase in risk for breast cancer associated with BRCA1 mutations in cancer families, these considerations may not preclude the use of tamoxifen as a chemopreventive in this cohort. However, these factors must be addressed in obtaining informed consent for tamoxifen chemoprophylaxis and considered in risk-benefit assessments for individual BRCA1 carriers. In addition, investigators are obligated to provide appropriate surveillance for these potentially enhanced adverse effects and to include them as secondary endpoints in the study design.

IMPLEMENTATION

Conducting clinical research among genetic risk cohorts becomes complicated because of the potential psychosocial consequences of genetic testing - loss of privacy, social stigmatization, loss of insurability, and job discrimination. The implications of genetic testing and of participation in clinical research for hereditary risk groups may extend beyond the participant to impact family members, emphasizing the importance of informed consent and confidentiality for research in these cohorts.

Informed Consent

For the studies discussed above, enrollment is based on two separate decisions: 1) Whether to undergo genetic testing and receive test results; and 2) whether to participate in a clinical research project. The decision for genetic testing may be made independent of a clinical research participation, for example, by high risk individuals who seek testing through a clinical

genetics program. Alternatively, when mutation carrier status is an eligibility requirement for study participation, potential candidates for testing may be identified and approached through a "screening" component of the chemoprevention research project. In either situation, obtaining informed consent for genetic testing with disclosure of results requires imparting adequate and comprehensible information on which a participant can base the decision to undergo testing and ensuring that the consent is autonomous [37]. In practice, the extensive educational components of pre-test counseling protocols seek to establish the necessary information base, while the nondirective approach to genetic counseling protects the individual's right to make his/her own decisions [28]. The key components of informed consent for BRCA1 testing include the limitations of the testing procedure, the probabilistic nature of the genetic information and risk estimates, the current limitations of preventive interventions, and the possible psychosocial consequences for the person undergoing testing and for family members [1].

Informed consent for inherited cancer risk is best viewed as a continuous process, with interactive exchange of information taking place throughout the course of the physician-patient relationship [38]. However, current limitations in knowledge about inherited cancer risk, combined with the rapid growth of scientific information in this area, suggest that physician responsibilities in information exchange extend beyond short-term participation in a clinical research study and imply an ethical responsibility to provide or arrange for continued access to new information. Thus appropriate follow-up for individuals who undergo genetic testing as part of a chemoprevention clinical trial should be ensured beyond the completion of the research project.

The information elements required for informed consent for participation in a clinical research study have been defined in the U.S. Department of Health and Human Services (DHSS) Policy for Protection of Human Research Subjects [39]. In the context of genetic risk cohorts, it is important that sections on disclosure of risks, potential benefits, and alternative prevention/treatment approaches are tailored to the specific genetic mutations under study. Specific examples for BRCA1 mutation carriers have been discussed in preceding sections of this paper.

Confidentiality

The need for protecting the confidentiality of personal data generated as a part of clinical research is recognized by the DHSS policy requiring confidentiality assurances as part of informed consent [39]. In both the clinical and research settings, privacy and confidentiality of genetic information is particularly important because of the risks for "social harm" to the individual (and family members) due to loss of insurance, employment discrimination, and social ostracism.

While inherited predisposition for cancer may be a consideration for disability income and life insurances, loss of health insurance coverage has become a major issue for women BRCA1 mutation carriers. As one breast cancer patient explained: "The insurance industry is the enemy...Because I did have a diagnosis of cancer, I was able to get my surgeries reimbursed. But my sisters who have the gene [BRCA1] are still fighting to get approval for prophylactic surgeries. They're in a Catch-22. If they tell the insurer the scientific reason of why they know they are at high risk of cancer - because they have the gene - then our whole family runs the risk of losing its health insurance because we have this genetic defect. Yet, when my sisters tell their insurers about the family history, they're told, "So what? The family history doesn't mean that *you* will get cancer [40]." These concerns are relevant to genetic testing results obtained in investigational studies because most insurers require access to medical records as a condition of coverage, and notations about test results and study participation may be included in the patient's medical record. Issues of insurability may translate to discrimination in employment, since most individuals with group health insurance are covered through employment and many large and small employers are self-insured: employers will avoid hiring persons perceived to be high-cost users of health care, such as persons at inherited cancer risk [41].

Procedures for assuring confidentiality of research records are usually delineated in study protocols. For chemoprevention research in genetic risk cohorts, investigators should review standard procedures carefully and enhance the safeguards for data collection, management,

and storage whenever possible. Research staff should be educated about the potential consequences of breach of confidentiality for this target population, and staff access to research records should be limited. Study information should be excluded from participants' medical records; the use of alphanumeric patient identification codes may make it possible for researchers to quickly recognize information for the individual participant while precluding the filing of laboratory results and clinical notes generated as a part of the research study in the patient's medical records.

Since 1988, Certificates of Confidentiality from DHSS[2] have been available to researchers in biomedical, behavioral, and clinical research [42]. This mechanism, originally developed for research in alcoholism and substance abuse, was designed to protect the identity of research subjects in studies collecting sensitive data which, if released, could be damaging to the individual's financial standing, employability, or reputation within the community, or which could lead to social stigmatization or discrimination. It protects investigators from being compelled to reveal identifying information about a research subject through civil, criminal, or legislative proceedings. The protection remains in place even after the death of the research participant. The limitation of this protection to data collected during the conduct of a research project, not to information that is considered a part of normal medical care, emphasizes the need to segregate research data and to guard against incorporating research data into records of routine patient care. The Certificate of Confidentiality does not prevent voluntary disclosure of information by a study subject or protect the investigator from releasing information with request or consent of the participant.

Legislative efforts to protect against discrimination due to genetic risk status have been undertaken at both state and federal levels. Pre-employment screening for non-job-related genetic conditions is currently prohibited by specific statutes in several states [41] and, nationally, by a recent interpretation of the Americans with Disabilities Act [37]. Proposed federal legislation addressing privacy issues includes S.1360 (The Medical Records Confidentiality Act of 1995) which would protect the privacy of personally identifiable health care information obtained as a part of diagnosis, enrollment, payment, testing, or research processes. S.1416 (The Genetic Privacy and Nondiscrimination Act of 1995) would prohibit disclosure of genetic information without written authorization of the individual, prohibit the use of genetic information by health insurers to deny, limit, or cancel coverage or to increase rates, and prohibit employers from seeking to obtain or use and employee's or prospective employee's genetic information for discrimination. However, the proposed legislation does not obviate the investigator's responsibility for maintaining privacy and confidentiality of research data, especially for participants in clinical research from genetic risk cohorts.

CONCLUSIONS

The identification of specific genes for inherited susceptibility to cancer and the commercial availability of predictive genetic testing for cancer risk have focused scientific attention on the urgent need for clinical research in cancer prevention for cohorts at inherited risk of disease. However, ethical considerations become critical in conducting clinical prevention research within genetic risk groups when study participation requires formal assessment of genetic risks and interact with scientific considerations at all levels of study design and implementation. Investigators conducting chemoprevention research among genetic risk cohorts must be sensitive to the ethical, legal, and psychosocial implications of genetic testing for cancer risk and of the necessity for maintaining privacy and confidentiality of study participants from these cohorts and integrate these considerations throughout their clinical research projects in these cohorts.

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REFERENCES

1. Lerman C, Croyle R (1994): Psychological issues in genetic testing for breast cancer susceptibility. Arch Intern Med 154:609–616.
2. Miki Y, Swenson J, Shattuck-Eidens D, et al. (1994): A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71.
3. Futreal PA, Liu Q, Shattuck-Eidens D, et al. (1994): BRCA1 mutations in breast and ovarian cancers. Science 266:120–122.
4. Easton DF, Ford D, Bishop TD, and the Breast Cancer Linkage Consortium (1995): Breast and ovarian cancer

incidence in BRCA1 mutation carriers. Am J Hum Genet 56:265–271.
5. Stefanek M (1995): Bilateral prophylactic mastectomy: Issues and concerns. Monogr Natl Cancer Inst 17: 37–42.
6. Strewing JP, Watson P, Easton DF, et al. (1995): Prophylactic oophorectomy in inherited breast/ovarian cancer families. Monogr Natl Cancer Inst 17:33–36.
7. El-Bayoumy K (1994): Evaluation of chemopreventive agents against breast cancer and proposed strategies for future clinical interevention trials. Carcinogenesis 15(11):2395–2420.
8. Kelloff GJ, Boone CW, Crowell JA, Nayfield SG, Hawk E, Steele VE, Lubet RA, Sigman CC (1995): Development of breast cancer chemopreventive drugs. Breast J 1(5):271–283.
9. Ottman R, Pike MC, King MC, Henderson BE (1983): Practical guide for estimating risk for familial breast cancer. Lancet ii:556–558.
10. Anderson DE, Badzioch MD (1985): Risk of familial breast cancer. Cancer 56:383–387.
11. Gail MH, Brinton LA, Byar DP, et al. (1989): Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 81:1879–1886.
12. Colditz GA, Willett WC, Hunter DJ, et al. (1993): Family history, age, and risk of breast cancer. JAMA 270:338–343.
13. Claus EB, Risch N, Thompson WD (1994): Autosomal dominant inheritance of early-onset breast cancer. Cancer 73:643–651.
14. Kelsey JL (1993): Breast cancer epidemiology: Summary and future directions. Epidemiol Rev 15:256–263.
15. Claus EB, Risch N, Thompson WD (1990): Age at onset as an indicator of familial risk of breast cancer. Am J Epidemiol 131:961–72.
16. Gail MH, Benichou J (1992): Assessing the risk of breast cancer in individuals. In De Vita, Jr. VT, Hellman S, Rosenberg SA (eds): "Cancer Prevention." Philadelphia: Lippincott, pp 1–15.
17. Easton DF, Bishop DT, Ford D, Crockford GP (1993): Genetic linkage analysis in familiar breast and ovarian cancer — results from 214 families. Am J Human Genet 52:677–700.
18. Porter DE, Steel CM, Cohen BB, et al. (1993): Genetic linkage analysis applied to unaffected women from families with breast cancer can discriminate high- from low-risk individuals. Br J Surg 80:1381–1385.
19. Easton DF, Narod SA, Ford D, et al. (1994): The genetic epidemiology of BRCA1. Lancet 344:761.
20. Shattuck-Eidens D, McClure M, Simard J, et al. (1995): A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene. Implications for presymptomatic testing and screening. JAMA 273:535–41.
21. Eeles RA, Stratton MR, Goldgar DE, Easton DF (1994): The genetics of familial breast cancer and their practical implications. Eur J Cancer 30A:1383–90.
22. Hogervorst FB, Cornelis RS, Bout M, et al (1995): Rapid detection of BRCA1 mutations by the protein truncation test. Nat Genet 10:208–12.
23. Clinical Laboratory Improvement Ammendments of 1988: "Public Health Service Act 42 USC §353."
24. American College of Medical Genetics (1993): "Standards and Guidelines: Clinical Laboratory Genetics." Bethesda, MD: American College of Medical Genetics.
25. American Society of Human Genetics Ad Hoc Committee on Breast and Ovarian Cancer Screening (1994): Statement of the American Society of Human Genetics on genetic testing for breast and ovarian cancer predisposition. Am J Human Genet 55:i–iv.
26. American Society of Clinical Oncology (1996): Statement of the American Society of Clinical Oncology: Genetic testing for cancer susceptibility. J Clin Oncol 14(5):1730–1736.
27. Baker SG, Freedman LS (1995): Potential impact of genetic testing on cancer prevention trials, using breast cancer as an example. J Natl Cancer Inst 87:1137–1144.
28. Biesecker BB, Boehnke M, Calzone K, et al. (1993): Genetic counseling for families with inherited susceptibility to breast and ovarian cancer. JAMA 269:1970–1974.
29. Lerman C, Daly M, Masny A, Balshem A (1994): Attitudes about genetic testing for breast-ovarian cancer susceptibility. J Clin Oncol 12:843–850.
30. Struewing JP, Lerman C, Kase R, et al. (1995): Anticipated uptake and impact of genetic testing in hereditary breast and ovarian cancer families. Cancer Epidem Biomarkers Prev 4:169–173.
31. Watson M, Murday V, Lloyd S, et al. (1995): Genetic testing in breast/ovarian cancer (BRCA1) families. Lancet 346:583.
32. Ford D, Easton DF, Bishop DT, et al. (1994): Risk of cancer in BRCA1 mutation carriers. Lancet 343:692–695.
33. Kramer BS, Brawley OW, Nayfield S, et al. (1993): NCI studies in primary prevention of breast and prostate cancer. Cancer Res Ther Control 3:203–211.
34. Kedar RP, Bourne TH, Powles TJ, et al. (1994): Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomized breast cancer prevention trial. Lancet 343:1318–13321.
35. Hochner-Celnikier D, Anteby E, Yagel S (1995): Ovarian cysts in tamoxifen-treated premenopausal women with breast cancer — A management dilemma. Am J Obstet Gynecol 172:1323–1324.
36. Rutqvist LE, Johansson H, Signomklao T, et al. (1995): Adjuvant tamocifen therapy for early stage breast cancer and second primary malignancies. J Natl Cancer Inst 87:645–651.
37. Holtzman NA (1996): Are we ready to screen for inherited susceptibility to cancer? Oncology 10:57–64.
38. Appelbaum PS, Lidz CW, Meisel JD (1987): Informed Consent in Practice. In: "Informed Consent. Legal Theory and Clinical Practice," Chapter 8. New York: Oxford University Press, pp 151–174
39. Department of Health and Human Services Rules and Regulations, 45 CFR 46
40. Breo DL (1993): Altered fates — Counseling families with inherited breast cancer. JAMA 269:2017–2022.
41. Rothstein MA (1995): Genetic testing: Employability, insurability, and health reform. Monogr Natl Cancer Inst 17:87–90.
42. Earley CL, Strong LC (1995): Certificates of confidentiality: A valuable tool for protecting genetic data. Am J Human Genet 57:727–731.