# CANCER GENETICS

*in*

# WOMEN

Volume I

Henry T. Lynch
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# Cancer Genetics in Women

## Volume I

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# PREFACE

Progress in the comprehension of cancer etiology and pathogenesis has been of almost logarithmic proportions during the past decade. These advances have been contributed to in a major way by the dogged persistence of countless scientists throughout the world who have shown an unbridled thirst for understanding those molecular events which drive cells to both normal and abnormal pathways of proliferation. In the therapeutic arena, advances in the control of cancer are likely to evolve through knowledge of the biochemistry of oncogenes and its relationship to carcinogenesis. While we are stymied by problems of heterogeneity in cancer, even to the extent that every single cancer may have its own unique chemical profile, research in such areas as immunological-response modifiers, such as the interleukins and monoclonal antibodies to tumor antigens, or regulation of oncogene products in cellular proliferation control pathways could prove to have therapeutic advantage.

While these glowing predictions give us some solace, we must nevertheless look at the real world, wherein countless patients will die of metastatic cancer. Many of them might have been salvaged through application of knowledge of basic genetic principles. Such information, often readily at hand through an informative family cancer history, coupled with knowledge of hereditary cancer syndrome identification could allow highly organ-targeted predictability of cancer occurrence, thereby enabling the marshaling of forces for primary or secondary prevention.

We addressed the biomolecular advances in carcinogenesis at the outset so that appropriate perspective could be given to the descriptive stream of thought throughout this book; namely, the need for physicians to grasp the significance of family history of cancer in women, thereby enabling hereditary cancer syndromes to be identified. The sequel is the implementation of highly targeted surveillance/management programs which are responsive to the particular hereditary cancer syndrome's natural history. As will be seen, this relatively simplistic matter (when compared to the biomolecular phenomenon we have addressed) has been given short shrift in the usual clinical-practice setting. This is unfortunate, since the price we may pay for this short-sightedness may be economically staggering and emotionally draining. Cancer's morbidity and mortality rates will continue at their present unacceptable, and indeed, tragic proportions.

Needed, of course, is the ultimate linking of knowledge from the biomolecular and carcinogenesis laboratories to the clinical practice arena where prudent cancer-genetic science must be administered. Such orchestration of the basic science and clinical disciplines is our hope. If this book helps to fulfill the needs of the clinical portion of this important equation, then we will consider it to have achieved its purpose.

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Chapter 1

# INTRODUCTION TO CANCER GENETICS IN WOMEN

**Henry T. Lynch and Stig Kullander**

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## I. GENERAL BACKGROUND

Much has been written about the emerging discipline of cancer genetics during the past 2 decades.[1-8] Indeed, at least one medical journal is now devoted exclusively to this problem and is appropriately entitled *Cancer Genetics and Cytogenetics* (Elsevier North Holland, New York). Advances in genetic etiology of cancer have occurred at a virtually explosive rate, mandating its inclusion in any discussion of cancer etiology. Recent advances relating hereditary factors in breast and gynecologic oncology should therefore stimulate an increased interest in identifying families prone to these disorders. This will then aid in signifying those women who are at high risk of cancer so that they might then become candidates for highly targeted screening regimens. Primary prevention (surgical prophylaxis) may be offered to a subset of these high-risk women.

It seemed prudent to provide this treatise on cancer genetics in women in the hope that physicians and geneticists, as well as basic scientists and clinical investigators, would become more responsive to the total cancer-genetic burden affecting women. It is important to comprehend fully all facets of the cancer-genetic problem in women, as opposed to a more fragmentary approach through the study of only a single cancer, such as carcinoma of the breast. This is mandatory since two or more seemingly distinctive forms of cancer may be etiologically related to a common cancer-prone genotype.[8-10] The primary thrust of this book will therefore be concerned with a more eclectic approach to cancer-genetic problems in women through considering all of the potential oncogenic ramifications of the particular cancer-prone genotype which the individual patient might have inherited.

## II. ECOGENETICS

An ecogenetic perspective in cancer etiology has capitalized heavily upon the tremendous advances which have been made in cancer epidemiology and genetics during the past couple of decades and it clearly embraces the entire realm of human carcinogenesis.[11] Such an approach must necessarily consider the extraordinary interhuman variability in susceptibility to carcinogens. This is particularly cogent when considering that the range of susceptibility to many of the common types of cancer may be as high as 100-fold.[12,13] At the biomolecular level, Harris et al.[13] have shown that binding levels of benzo(a)pyrene to DNA vary 50- to 100-fold in cultured-human cells. This enormous variation in carcinogen interaction(s) with human cells may be attributed to the fact that the majority of chemical carcinogens require enzymatic activation, and herein, host factors play a major etiologic role in determining variation in such enzyme capability. This has been clearly documented at the infrahuman level[14] and has also been inferred in humans. It has been postulated that the ratio of metabolic activation to deactivation of carcinogens may determine the individual's cancer risk.[15]

Women should be alerted to specific carcinogenic-environmental agents when appropriate. The changing lifestyle of women has increased, to a remarkable degree, their exposure to environmental as well as therapeutic carcinogens. Menopausal therapy with estrogens among women who are inordinately prone to hereditary cancer should be avoided. Gestagenic hormones would be the treatment of choice. Contraceptive use of gestagenic hormones is also available for genetically cancer-susceptible women. Long-acting gestagenic injections would be an important substitute for intrauterine devices (IUD), which have an increased risk of vaginal and pelvic infections.

Various birth defects or immunologic deficiencies, often determined by interaction of multiple genes and/or environmental factors, have a special importance in correlating etiology of familial occurrence of many forms of cancer. This area needs greater attention in gynecologic and breast cancers. A problem peculiar to women with respect to teratogenesis-carcinogenesis became apparent when DES was used as an antiabortifacient and gave rise

to malformations and cancer sequelae in their progeny. Concerns now exist about the long-term effects in the treated women themselves (Chapter 18).

The problem of sorting out the relative effects of environment vs. primary-genetic effects in cancer causation in relatives at increased cancer risk by virtue of pedigree analysis in hereditary-cancer syndromes represents an area of intensive interest. However, our knowledge base at this genetic/environmental interphase is exceedingly limited.

### A. Cancer Genetic Hypotheses and Clues

The significance of host factors in cancer susceptibility is an important question from both a practical and theoretical point of view. If all individuals who are exposed to specific-oncogenic agents are not equally liable to develop cancers, then the identification of specific genetic-risk factors could provide the basis for an effective cancer-control program. Host factors that contribute to cancer liability include variation in the efficiency of genetic-repair mechanisms, variation in relevant-immune mechanisms, or variation in the metabolism of potentially oncogenic compounds.

A variety of congenital malformations may be antecedents of neoplasms in man, so-called teratologic-neoplastic syndromes. Certain of these problems are associated with chromosomal abnormalities. The "two-hit" theory of carcinogenesis as proposed by Knudson[16] integrates etiologic conceptions of these problems wherein the first hit is expressed as an inherited anomaly. One can always argue that neoplasms have chromosome changes below the level of resolution even with the G-banding method of staining. The association of some constitutional aberrations with neoplasia (Downs' and Klinefelter's syndromes) may also be indirect and due to hormonal imbalance or other physiologic factors.

Cancer occurrence may represent an imbalance between genes concerned with its expression or suppression. There may be nonrandom-chromosomal changes which are etiologic in certain predominantly environmentally induced human tumors. These cytogenetic factors may relate to clinical features such as survival, including response to treatment.

### B. Cytogenetics

A detailed discussion of cytogenetics will not be part of the preview of this book since the subject has received wide attention in the literature during the past couple of decades; the reader is referred to the following selected references for review of the subject.[17-21]

### C. Oncogenes

Extensive-cytogenetic investigations have been performed on virtually every form of cancer occurring in women. The role of oncogenes appears to relate to certain of these cytogenetic aberrations, particularly chromosome-break sites and deletions, a matter discussed at length by Yunis and Soreng[19] and by LeBeau and Rowley.[22]

Progress in understanding mechanisms of oncogene expression in carcinogenesis has been evolving at a rapid rate of discovery during the past decade. New clues about oncogenes are constantly being reported in the literature. These observations frequently cause significant changes in many of the perceptions of oncogenes which, *a priori*, had been considered to be based upon solid evidence. The history of medicine is replete with similar examples of rapid progress once certain hypotheses and/or therapies have been subjected to systematic appraisal; i.e., the field of antibiotics in the 1930s.

The future holds great promise as we learn more about the role of oncogenes in cancer. Priority should be given to the study of the protein products of these genes and their relationship to malignant transformation. Such investigations as these will undoubtedly provide new clues to cell biology and molecular evolution. One of the major insights stemming from this research may contribute to ways in which the protein products of cellular oncogenes might be controlled through a variety of pharmacologic and biomolecular meth-

odologies, with possible production of so-called anti-oncogenes for enhancement of cancer control.[23] Fruits of this oncogene research may soon be applied to the understanding and control of cancer-genetic problems in women.

### D. Hereditary Cancer Syndrome Delineation

Hereditary tumors may be identified by recognizing specific, noncancer-phenotypic features of the trait or syndrome in the patient or his family; i.e., skin signs in the cancer-associated genodermatoses.[4] Thus, the clinician who diagnoses cancer in an individual patient but ignores the hereditary components of the syndrome, of which it is a manifestation, will make an incomplete diagnosis. Failure to recognize an hereditary-cancer syndrome will be a disservice to the patient and his or her relatives who may be deprived of the possible benefits of counseling and surveillance for prevention and early detection of cancer. An opportunity for further research in pathogenesis will be lost.

The characteristics of familial tumors in general are that the tumors tend to be multifocal and, in the case of paired organs, bilateral. They tend to occur at younger ages than the sporadic lesions. In the case of dominantly inherited tumors, incomplete penetrance and variable expressivity may occur as in other nontumorous, dominantly inherited conditions.

It is possible to identify hereditary-cancer syndromes in which a differing spectrum of tumors appear together in certain families. Identifying syndrome (phenotypic) associations may teach us about common cancer susceptibility mechanisms.

Certain remarkable familial occurrences of cancer may, at first glance, suggest genetic susceptibility. However, with such commonly occurring tumors as carcinoma of the breast, the role of chance must always be considered as an explanation for their familial aggregation. This becomes less likely, of course, when families have an exceptional concentration of tumors which show segregation patterns consistent with a Mendelian mode of inheritance and which conform to known hereditary-cancer syndromes. In the absence of these situations, it may be exceedingly difficult to determine if, in a given family, multiple tumors have biologic meaning or represent a coincidence. Hence, the need for genetic biomarkers.

Genetic factors may also contribute to single occurrences of cancer in a family. This is worth emphasizing with the growing trend toward smaller families in our society. In the absence of familial aggregation, genetic predisposition to cancer may be suspected among patients with early onset of cancer or with multiple-primary neoplasms, but diagnosis will not be precise until appropriate biological markers are developed.

Studies of familial cancer at the bedside are essential for purposes of maximizing patient care, research, and teaching. The clinical approach should also lead younger physicians to obtain more detailed family histories and to participate in etiologic studies. Many oncogenic factors in man were first identified by physicians at the bedside. Demonstration of the necessary skills to make etiologic observations should be fostered in clinical training programs.

### E. Problems in Family History Collection

We have been concerned about a general lack of interest in cancer family history collection by physicians as part of the general-medical work-up of patients. Perhaps this deficiency results from the disproportionately increased attention which has been given to environmental causes of cancer during the primary, as well as postgraduate, education of physicians. Soberingly, it has led us to conclude, based upon more than 5 decades of our combined clinical experience, that the cancer family history is probably one of the most sorely neglected areas in the medical work-up of any patient. If our book could in just a small way help to ameliorate this serious problem, we would consider its writing to have been a major triumph.

### F. Need for Population-Based Tumor Registries

Tumor-registry, autopsy, and death-certificate data should be analyzed by anatomic sites as well as specific histologic types. When all cancers are grouped together, important etiologic

differences in occurrence of certain subtypes may be obliterated. Near absence of a particular neoplasm within a given population may suggest genetic resistance. This could arise from stimulation of the immune system that may uniquely suppress certain tumors.

The lack of population-based cancer data precludes an analysis that could indicate incidence of specific varieties of hereditary cancer, as well as better comprehension of mechanism(s) of carcinogenesis. Genetic predisposition to cancer may involve genes that affect the metabolism of potential carcinogens, an otherwise ubiquitous oncogene, the virulence of an oncogenic virus, or a specific transforming gene.

A natural resource for the study of hereditary cancer is an entire population (population-based) where complete genealogical data and accurate medical information for the current generation is compiled. A tumor registry; indicating those individuals who have developed cancer, meticulous details about the nature of the malignancy, its treatment, and the patient's response to the treatment; would be extremely useful. Findings from such a resource may provide answers to questions which twin and kindred studies are unable to do.

Population-based resources can be used to isolate cancer-prone and cancer-free families for biochemical- and chromosome-linkage studies and to attempt to relate gene segregation (HLA, ABO, immunoglobulins, oncogenes, and others) to cancer risk. Risk factors may be calculated for individuals in order to develop more efficient screening programs which are responsive to individual needs.

## III. PREVENTIVE ONCOLOGY

### A. Primary Prevention

The most significant contribution of preventive oncology pertains to primary prevention (see Chapter 8). This involves several clinical entities, most classical of which is familial-multiple adenomatous polyposis coli, wherein prophylactic colectomy can prevent colon-cancer occurrence. The risk of colon cancer in this disease, in the absence of prophylactic-surgical intervention, approaches 100% by age 50. Other examples of primary prevention include subtotal colectomy, as opposed to segmental resection, in patients manifesting colonic cancer in hereditary-*non*polyposis colorectal cancer; prophylactic-total thyroidectomy in patients showing elevated calcitonin and who are at genetic risk for MEN-IIa and MEN-IIb (multiple-mucosal neuroma syndrome); prophylactic mastectomy in highly selected patients at risk for hereditary-breast cancer (see Chapter 5); prophylactic oophorectomy in hereditary ovarian cancer (see Chapter 12); gonadectomy in gonadal dysgenesis where an XO/Y chromosome is present; and orchiopexy in patients with cryptorchism to prevent testicular carcinoma.

### B. Secondary Prevention — Early Detection

Cancer surveillance, when focused intensively upon organs/systems at high risk for hereditary cancer, may lead to early detection, a form of secondary prevention. This matter will be discussed at length in appropriate chapters throughout this book.

### C. Philosophical, Psycho-Socio-Cultural, and Carcinogenic Exposure Problems Peculiar to Some Women

Risk factors and early diagnosis, as well as management of cancer in women, may be influenced in a major way by many societal factors and by problems directly related to their gender. To a greater or lesser degree, a particular woman's response to differing facets of the cancer problem will be influenced by her socioeconomic and educational status, her general emotional health and ego strength, and the societal-cultural setting in which she was raised and/or currently is residing. The following listing of such examples is not complete, but should reflect some of the important considerations which could influence whether a

particular woman will expediently enter into the health-care system, whether she will show compliance to specific recommendations for surveillance/management, and whether cancer family histories can be elicited in sufficient depth to derive meaningful information for hereditary-cancer syndrome identification. These are as follows:

1. Modesty is a problem in certain cultures, particularly in Moslem women. Certain ethnic groups; i.e., Hispanics, harbor old-wive's tales and misconceptions such as "women's pelvic examination will cause loss of virility in male partners." They are, therefore, less likely to come to medical attention for screening or to heed the significance of early symptomatology.
2. In religious groups, such as nuns, cervical cancer screening with Papanicolaou examinations would be of limited value because cervical carcinoma is an extraordinarily rare tumor in these women. However, they are definitely at increased risk for carcinoma of breast, ovary, and endometrium.
3. Women during their childbearing period will be followed closely by physicians for their pregnancies, but they may not recognize the need, or due to cost, they may not go for routine checkups after their fertility period.
4. Women who have had hysterectomies may believe that they are no longer at risk for genitourinary cancer. The fact of the matter is that many of them may not know whether or not their ovaries were removed. Hence, they may not seek routine evaluation by their family physician or a gynecologist. In short, their erroneous assumption may be "I have had a hysterectomy, and that's that!"
5. Myths of the past (evil connotations) relevant to menstrual bleeding may have a carryover in postmenopausal women who have and ignore bleeding which could be due to carcinoma. Women need to be educated about the significance of postcoital bleeding as well as postmenopausal bleeding.
6. Masturbation connotations about self-breast examination (women don't play with their own breasts) have to be addressed.
7. There are generations of women in certain cultures, particularly in Third World countries, who have not had the advantage of our new era of highly sophisticated medicine; hence, the problem of bridging the educational "gap". There is now developing a more heightened awareness about concepts of wellness but we must consider individuals in the later decades of life who, heretofore, were not exposed to this knowledge. Heightened awareness would apply particularly to breast and cervical carcinoma, but to a lesser extent, for ovarian carcinoma.
8. Popular magazines for the laity provide information about medical problems in women but fail to address in an integrated manner how these may impact upon specific preventive measures. Such lay literature almost totally ignores genetics as an etiologic factor in cancer. There has been recent, albeit limited focus, in the lay literature on genetics in breast cancer but very little, if any, material has been devoted to genetics in other cancers, such as ovarian and endometrial carcinomas.
9. Insurance carriers more often stress coverage of males as opposed to females. Women heretofore were not considered to be the economic strength of the family. This pattern has been changing in the U.S. as well as in other areas of the world. For example, in the U.S., it is the rare household where there are not two breadwinners. Most executives, however, are male (pattern is changing slightly) and they are more likely to receive "executive type", comprehensive, physical examinations. Women do not share in this particular endeavor to the same extent as men.
10. Women are a minority in the Armed Forces. Men are more likely to have been in the military service and have medical care available through Veteran's Administration Hospitals.

## IV. IMPACT

These issues are addressed in order to provide perspective for the reader relevant to the myriad facets of cancer genetics pertaining to women discussed throughout this book. Since some pose serious problems in surveillance and management, it is hoped that their recognition as obstacles to health education and wellness will lead to their resolution.

In conclusion, the importance of cancer genetics in preventive oncology has been astutely crystallised in a recent editorial[11] by John Mulvihill, M.D., Chief of the Clinical Genetics Section at the National Cancer Institute, who states " . . . Clinicians can contribute to the national goal of reducing mortality from cancer by 50 percent by the year 2000 by asking each patient with or without cancer about his/her family history of cancer." Given advances in knowledge of cancer epidemiology and genetics, it would seem logical that the plea of our colleague Mulvihill will be realized ever so much more swiftly.

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Chapter 2

# LEGAL ASPECTS OF CANCER GENETICS — SCREENING, COUNSELING, AND REGISTERS

**Charlotte L. Tsoucalas**

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