Inherited Predisposition to Cancer: A Historical Overview

HENRY T. LYNCH,* TRUDY G. SHAW, AND JANE F. LYNCH

The hereditary predisposition to cancer dates historically to interest piqued by physicians as well as family members wherein striking phenotypic features were shown to cluster in families, inclusive of the rather grotesque cutaneous findings in von Recklinghausen’s neurofibromatosis, which date back to the sixteenth century. The search for the role of primary genetic factors was heralded by studies at the infrahuman level, particularly on laboratory mouse strains with strong susceptibility to carcinogen-induced cancer, and conversely, with resistance to the same carcinogens. These studies, developed in the 19th and 20th centuries, continue today. This article traces the historical aspects of hereditary cancer dealing with identification and ultimate molecular genetic confirmation of commonly occurring cancers, particularly of the colon in the case of familial adenomatous polyposis and its attenuated form, both due to the APC germline mutation; the Lynch syndrome due to mutations in mismatch repair genes, the most common of which were found to be MSH2, MLH1, and MSH6 germline mutations; the hereditary breast-ovarian cancer syndrome with BRCA1 and BRCA2 germline mutations; the Li-Fraumeni (SBLA) syndrome due to the p53 mutation; and the familial atypical multiple mole melanoma in association with pancreatic cancer due to the CDKN2A (p16) germline mutation. These and other hereditary cancer syndromes have been discussed in some detail relevant to their characterization, which, for many conditions, took place in the late 18th century and, in the more modern molecular genetic era, during the past two decades. Emphasis has been placed upon the manner in which improved cancer control will emanate from these discoveries. © 2004 Wiley-Liss, Inc.

KEY WORDS: hereditary cancer syndromes; Lynch syndrome; hereditary breast-ovarian cancer syndrome; neurofibromatosis; molecular genetics; germline mutations; Amsterdam criteria; Amsterdam II criteria; Bethesda Guidelines; genetic counseling; history

INTRODUCTION

The early history of hereditary cancer is steeped in observations of familial clusters of patients who often manifested exotic and, indeed, striking phenotypes, such as the type that may occur in neurofibromatosis [Paré, 1585; Aldrovandi, 1642; Leclerc de Busson, 1749; Tilesius von Tilernau, 1793; Zanca and Zanca, 1977; Happle, 1997; McKusick, 1998; Morse, 1999; Ruggieri and Huson, 2001; Ruggieri and Polizzi, 2003]. The bizarre appearance of certain family members not infrequently led their physicians, and even affected family members, to consider their fate as a curse from God. However, more recently, physicians and geneticists began considering causal factors as due to a biologic or genetic event [Macklin, 1960]. This reasoning has been epitomized in the new era of modern medicine, with attribution of the phenotype to primary genetic factors. Indeed, this new mole-
cular discipline has depicted all varieties of disorders, including such death-dealing conditions as cancer, to be of genetic origin. Even extremely subtle hereditary phenotypes caused by low-penetrant genes are being recognized through molecular genetic advances. This molecular research has provided a veritably explosive increase in the elucidation of genetic disorders in man, particularly for oncology [Vogelstein and Kinzler, 1998; Balmain et al., 2003]. In turn, they have contributed heavily to societal interest in its public health implications.

This fascination with molecular genetics has impacted heavily upon physicians as well as the laity. Indeed, it has progressed at such a remarkably rapid pace and, not surprisingly, has led to a potpourri of questions about how this "new" knowledge might benefit society. For example, certain pressing questions relate to concerns about how environmental factors as well as modifier genes might perturb the cancer phenotype, leading to a lesser or greater virulence of the cancer phenotype [Mulvihill, 1978, 1982; Mulvihill et al., 2000]. Will this knowledge enable us to develop molecular-based designer drugs to prevent cancer? Will patients with germline mutations predisposing to cancer manifest severe anxiety, once they learn that their lifetime cancer destiny might be determined through gene testing? Importantly, will they become so distressed by their fear of insurance or employment discrimination that they might withdraw from genetic counseling and germline testing, perhaps even showing reduced compliance to highly-targeted cancer surveillance and management recommendations due to their concern about being identified as a "hazardous risk" by their insurer or employer? Will genetic counseling help them to accept the plight of their increased cancer risk?

Our purpose is to provide a brief review of the historical contributions to several selected areas of cancer genetics. However, this subject is so extensive that we have elected to focus briefly on only a few examples, namely, medullary thyroid carcinoma (MEN2), neurofibromatosis, colorectal cancer (through discussion of its two most common hereditary forms, familial adenomatous polyposis and Lynch syndrome), breast and ovarian cancer, and malignant melanoma (including its recent link to pancreatic cancer).

**INBRED ANIMAL STRAINS AND CARCINOGEN-INDUCED CANCER: SUSCEPTIBILITY AND RESISTANCE**

What have we gleaned about cancer genetics from infrahuman studies? When did this research begin? How was the road paved to our present comprehension of cancer genetics, particularly its entry into the current molecular genetic era? In answer to all of these questions, the scientific evolution of knowledge regarding hereditary cancer in man must duly credit the astute observations of many of our predecessors who, at the turn of the nineteenth century, began initiating formal genetic studies of cancer susceptibility and resistance in inbred animal strains [Lathrop and Loeb, 1913; Heston and Dunn, 1951; Heston, 1956; Heston, 1965]. Much of this work took place on the common laboratory mouse at the Jackson Laboratory at Bar Harbor, Maine [Green, 1966]. These studies of cancer genetics at the infrahuman level, particularly in these murine models, provided enormous advantages for controlled genetic experimentation of the type which, on ethical grounds, could not take place in humans. This enabled geneticists to delineate inbred animal strains that were strongly susceptible to specific carcinogens, in contrast to inbred strains that were highly resistant to the same carcinogenic exposures. This should lead the reader to immediately ask, "Does the same biological phenomenon of cancer susceptibility versus cancer resistance to carcinogenic exposures apply to humans?" Consider asking this question in regard to the horrific environmental assault to mankind, namely the cigarette-smoking induced pandemic of lung cancer: Are all cigarette smokers equal with respect to their risk for smoking-associated cancers (lung, oral cavity, larynx, esophagus [particularly in association with alcohol consumption], pancreas, and urinary bladder)? [Lynch et al., 1986] A similar question can be asked with respect to the more rarely occurring mesothelioma and its asbestos association [Mulvihill, 1978; Lynch et al., 1985c; Lynch and Hirayama, 1989; Ascoli et al., 2001]. Clearly, this same logic of genetic-environmental interaction phenomenon in man can be extended to cancer susceptibility and resistance encompassing all forms of cancer, which is referred to as ecogenetics [Mulvihill, 1978, 1982; Mulvihill et al., 2000].

**NEUROFIBROMATOSIS**

Neurofibromatosis (NF) is one of the most common neurocutaneous hereditary diseases. Its multifaceted manifestations include a wide variety of phenotypic components which include optic gliomas, glioblastomas, neurofibrosarcomas, multiple café-au-lait spots, neurofibromas, Lisch nodules of the eye, bony changes, and a tendency to occasional intellectual impairment.

The history of neurofibromatosis type 1, also known as von Recklinghausen’s disease, is traced to ancient times, with descriptions of rather grotesque phenotypes. For example, Morse [1999] comments on a 13th-century drawing of a male with skin nodules that was thought to be a patient with NF. Furthermore, Morse notes that, “…both Quasimoto of Victor Hugo’s *The Hunchback of Notre Dame* and John Merrick, known as the Elephant Man (who subsequently has been more properly classified as having Proteus syndrome, a quite different disorder) are two infamous examples that have shaped many popular misconceptions about this disease.”

Ruggieri and Polizzi [2003] discuss neurofibromatosis type 1 (NF1) and type 2 (NF2), which occur in mosaic (segmental) forms [Ruggieri and Huson, 2001]. These authors define NF1 as its occurrence in a linear, patchy quadrant, or an otherwise localized form, wherein two different types of mosaicism could be distinguished [Happle, 1997]. Specifically, “Type 1 segmental involvement...
reflects heterozygosity for a post-zygotic mutation occurring in an otherwise healthy embryo. The segmental lesions are limited to the affected area and show the same degree of severity as that found in the corresponding non-mosaic trait. . . . Type 2 segmental involvement occurs in a heterozygous embryo and reflects loss of heterozygosity that occurred at any early developmental stage. Clinically, the lesions of type 2 segmental involvement are markedly more pronounced and superimposed on a milder, nonsegmental, heterozygous manifestation of the same trait [Happle, 1997].

These modern concepts become particularly important when evaluating detailed descriptions of clinical findings by our predecessors in medicine, some of which go back to antiquity, 600 or 700 or more years ago (for more detail, see Ruggieri and Polizzi [2003]). Using these concepts of mosaicism, Ruggieri and Polizzi [2003] diagnosed as having mosaic/segmental NF1 “ . . . the Indian man (‘Homunculus’) in the ‘Monstorum Historia’ [Aldrovandi, 1642] of the Italian naturalist and philosopher Ulisse Aldrovandi (1522–1605), the horned monster in ‘Des Monstres et Prodiges’ [Paré, 1585] of the French surgeon Ambroise Paré (1510–1590), and the goitered woman in the ‘Buch der Natur’ [Zanca and Zanca, 1977] of the German naturalist Conrad von Megengen (1303–1374). Type 2 segmental manifestations of NF1 were recognizable in Buffon’s girl (1707–1788) [Leclerc de Busson, 1749] and the ‘Wart Man’ of Tlesius (1793) [Tlesius von Tilenau, 1793].”

McKusick [1998] briefly discusses neurofibromatosis type I, type II, type III, and type IV forms of this disease. He cites the work of Riccardi and Eichner [1986], who designated classical von Recklinghausen’s disease as NF-I and familial acoustic neuromas as NF-II. Furthermore, he notes that they “ . . . suggested the existence of an entity labeled NF-III that combines features of both with some additional distinctive features.” Café-au-lait spots (CLS), freckling, and cutaneous neurofibromas occur as in NF-I, although typically the CLS are few in number, pale, and may be relatively large, and cutaneous neurofibromas are few in number. The palms of the hands may provide a characteristic site for cutaneous neurofibromas in NF-III. Iris Lisch nodules do not occur. Bilateral acoustic neuromas, posterior fossa, and upper cervical meningiomas, and spinal/paraspinal neurofibromas are the predominant features of NF-III, but optic gliomas have not been seen. The central nervous system (CNS) tumors make their presence known usually by the second decade or early in the third decade, and develop rapidly thereafter. Their natural history and, therefore, their prognosis, is different from that of classical von Recklinghausen disease. A relatively rapid and fatal course for multiple CNS tumors is usual [McKusick, 1998].

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN-2)

Advances in the understanding of endocrinology and cancer were heralded by the discovery of MEN-2. For example, Cote and Gagel [2003] discuss the MEN-2 syndrome and the manner in which the association between thyroid cancer and pheochromocytoma in this disorder was discovered by Sipple [1961]. Subsequently, a specific type of transformed cell in the thyroid, the parafollicular C cell, was found to produce the newly discovered hormone calcitonin [Williams, 1966]. Serum calcitonin was then used to identify at-risk family members who manifested medullary thyroid carcinoma [Wells et al., 1994].

Subsequently, more identifiable thyroid abnormalities were found, in which C-cell hyperplasia was identified as a precursor of medullary thyroid carcinoma [Wolfe et al., 1973]. Calcitonin measurements were, nevertheless, of value for identifying early C-cell abnormalities inclusive of hyperplasia or microscopic medullary thyroid carcinoma, and thereby demonstrated the value of early prophylactic thyroidectomy [Gagel et al., 1988].

Cote and Gagel [2003] note dramatic changes in MEN-2’s management, however, with discovery of mutations of the RET proto-oncogene [Donis-Keller et al., 1993; Mulligan et al., 1993], a tyrosine kinase receptor that plays an important role “ . . . for the differentiation of neural-crest tissues, including the thyroidal C cells, adrenal medulla, and components of the nervous system [which] were identified and mapped in kindreds with MEN-2. Initial reports described the use of [DNA] testing to manage hereditary medullary thyroid carcinoma in patients with this syndrome” [Lips et al., 1994; Wells et al., 1994] (cited by Cote and Gagel [2003]).

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Cote and Gagel [2003] conclude that progress in the management of this form of hereditary cancer over the past three decades has been truly remarkable. Implications abound for other hereditary cancer disorders, such as hereditary breast-ovarian cancer (HBOC) syndrome caused by BRCA1 and BRCA2 mutations, and Lynch syndrome caused by mismatch repair mutations, particularly in MLH1 and MSH2, as discussed below.

COLORECTAL CANCER

Our discussion of hereditary colorectal cancer (CRC) will focus on the two most common CRC-prone hereditary syndromes: familial adenomatous polyposis (FAP) and Lynch syndrome (also
called hereditary nonpolyposis colorectal cancer or HNPCC). Figure 1 shows the relative numbers of cases involving sporadic CRC, familial CRC, and CRC in various hereditary syndromes.

**History of FAP**

Our historical review of FAP has been aided significantly by the detailed description provided by Bussey [1990]. Specifically, this history begins with observations by Menzelio [1721] who may have reported the first example of a patient with a large number of polyps in the GI tract. Many decades later, more definition of histology, number, and location of polyps and associated lesions, and possible familial incidence, began to be identified. The science of histopathology, initiated in the early 1860s, recognized the importance of intestinal polyps. Woodward [1881] divided polyposis into “primary” (no apparent antecedent disease), and “secondary” (when polyps followed previous inflammation and ulcers of the colon).

Cripps [1882] reported polyposis coli in two members of the same family (brother and sister). This was likely the first indication that it was familial and possibly of genetic origin. Bussey [1990] believes that this important observation dates the point at which the history of FAP began. Bickersteth [1890] reported a family with affected members in two generations (mother and son), which strengthened the issue of FAP’s inheritance. Smith [1887] mentioned the presence of “adenocarcinoma” of the colon when describing three members of a family with multiple polyps.

At the end of the 19th century, three of the four most prominent features of FAP had been recognized: 1) there was a large number of polyps; 2) histologically, they were adenomatous; and 3) they were inherited. The fourth feature, the association with CRC, is mentioned by Smith [1887].
It was reasoned that the risk of rectal cancer following colectomy and ileorectal anastomosis would be minimal when rectal examinations were carried out every six months. It then became a policy at St. Mark’s Hospital to retain the rectum. Therein, the first ileorectal anastomosis was conducted in 1948. Many surgical innovations have been adopted since, including abdominal perineal resection, mucosectomy, and ileal pouch reservoir to protect against rectal carcinoma.

Associated Extracolonic Lesions

Gardner and Richards [1953] published a report on a polyposis family in which affected members also exhibited: 1) multiple osteomas of the cranium and mandibles; 2) multiple epidermoid cysts; and 3) fibromas of the skin. This was subsequently called Gardner’s syndrome. Further study of this large Utah family added dental abnormalities (supernumerary teeth), desmoid tumors of the abdominal wall, and extension of osteomas to any part of the skeletal system [Bussey, 1990].

Utsunomiya and Nakamura [1975] found that X-rays of the mandibles among more than 90% of all Japanese polyposis patients they examined had occult osteomas in this area, a finding which was subsequently confirmed at other centers. Lewis et al. [1984] added congenital hypertrophy of the retinal pigment epithelium (CHRPE). Bulow et al. [1985] showed that about one-third of FAP patients also had gastric polyps, mainly of two types: adenomas and fundic gland polyps.

Carcinomas, in addition to CRC, include stomach, duodenum, jejunum, pancreas, bile ducts, papillary thyroid carcinoma, and hepatoblastoma.

Desmoids, while not strictly cancerous, cause a high rate of morbidity and mortality through their propensity to extend and obstruct vital anatomic structures. The very surgery for control of CRC may provoke desmoid formation [Lynch and Fitzgibbons, 1996].

Chromosome 5 and the APC Mutation

Herrera et al. [1986] examined a patient with multiple developmental abnormalities as well as multiple colonic polyps. Interstitial deletion of chromosome 5 was observed. Bodner et al. [1987] provided evidence that the FAP gene, now known as APC, was on chromosome 5. Since then, there have been numerous advances in the understanding of the genotypic and phenotypic heterogeneity of this APC mutation.

Attenuated FAP

One particular FAP phenotype deserves special discussion. Lynch et al. [1988a] described a colon cancer-prone family with few adenomas (one to 50, with up to 100 in rare patients). Because this early report showed the adenoma morphology to be similar to the “flat adenoma” of Muto et al. [1985], the term hereditary flat adenoma syndrome was proposed [Lynch et al., 1992b]. Spirio et al. [1992, 1993] linked this family, and others with similar phenotypes, to chromosome 5q and characterized the proximal mutations at the APC locus [Leppert et al., 1990; Spirio et al., 1992, 1993]. The term attenuated familial adenomatous polyposis (AFAP) was then considered as a more appropriate name for the condition. This FAP may be exceedingly difficult to diagnose, given its limited polyposis phenotype. Therefore, a well-described family history is essential.
I1307K, Ashkenazi Mutation

A variant of the adenomatous polyposis coli (APC) gene was described by Laken et al. [1997]. The variant features a missense mutation (T to A transversion) that causes a substitution of lysine for isoleucine at codon 1307 (I1307K). This change is believed to be silent, i.e., it does not alter the function of the APC protein; hence it may be called both a mutation and a polymorphism. Although protein function is not affected, the transversion changes the base sequence from (A)3T(A)4 to (A)8, resulting in an unstable tract at risk for somatic mutations [Laken et al., 1997].

Approximately 6% of Ashkenazi Jews and a lower proportion of other Jews are carriers of the I1307K mutation/polymorphism. A total of 10% of Ashkenazi Jews with CRC and 28% with familial clustering of CRC were found to have the I1307K alteration [Laken et al., 1997]. It has not been seen in non-Jews [Laken et al., 1997; Prior et al., 1999; Rozen et al., 1999]. Carriers have an approximately two-fold risk of CRC compared with noncarriers [Laken et al., 1997]. The mechanism of predisposition is that the T to A change results in a stretch of eight adenosines (As), which is believed to predispose to somatic mutations due to slippage at replication [Kinzler and Vogelstein, 1996; Laken et al., 1997]. The investigation of the phenotype in this disorder is still in its early stages.

History of Lynch Syndrome

The history of what is now known as Lynch syndrome dates to an observation of a familial cancer cluster by Aldred Warthin, then a pathologist at the University of Michigan School of Medicine [Thorson et al., 1999]. Specifically, he became deeply moved when his seamstress, in 1895, told him that she would likely die of cancer of the colon, stomach, or her female organs, because of the enormous proclivity for these cancers in her family (unfortunately, just as she had told Warthin, she died at a young age of metastatic endometrial carcinoma). Warthin listened intently, developed her pedigree, along with the pedigrees of other similar cancer-prone families, and published this work [Warthin, 1913]. Warthin updated the family pedigree in 1925 [Warthin, 1925]. The seamstress’s family has since been known as Family G.

Lynch et al. [1966] described the natural history and genetics of two large Midwestern kindreds (Families N and M). The clinical genetic features in these families were similar to those of Family G. Dr. A. James French, Warthin’s successor as chairman of pathology at the University of Michigan, heard about Lynch’s research on Families N and M [Lynch et al., 1966], and recalled that Warthin, his predecessor, had discovered a similar family (Family G) in 1895. Lynch was then invited by French to take custody of all the detailed documents and pathology specimens that the meticulous Warthin had investigated, catalogued, and published over a span of more than 30 years [Warthin, 1913, 1925].

Family G was then updated and published in 1971 [Lynch and Krush, 1971a], and is discussed in a more detailed review of the history of HNPCC [Lynch et al., 1998]. Through the use of conversion technology [Yan et al., 2000], an MSH2 mutation was identified in Family G in the year 2000. Table I shows important points in the history of HNPCC.

Muir–Torre Syndrome (MTS)

Lynch et al. [1981] reported the first observation of MTS, as characterized by multiple cutaneous sebaceous adenomas, sebaceous carcinomas, multiple keratoacanthomas, and multiple visceral cancers, in Lynch syndrome families. Several reports [Lynch et al., 1982, 1985b, 1999; Lynch and Fusaro, 1993] have elucidated the clinical and molecular genetic features of MTS. Data suggest that the identification of these MTS cutaneous features in a patient merit a detailed family history in the search for evidence of the Lynch syndrome. Indeed, the researchers suggest that patients with these stigmata merit germline testing, particularly for evidence of the MSH2 germline mutation.

Mismatch Repair Mutations and the Lynch Syndrome

The molecular genetic era for HNPCC began when Peltomäki et al. [1993] identified a locus on chromosome 2p through linkage analysis as a site for a gene predisposing to HNPCC. Shortly thereafter, a second locus on chromosome 3p, believed to be etiologic for HNPCC, was identified by Lindblom et al. [1993] in Sweden. At the 2p and 3p loci, HNPCC genes were identified: MSH2 and MLH1, which encode proteins involved in the identification and repair of DNA mismatch errors [Fishel et al., 1993; Leach et al., 1993; Bronner et al., 1994; Papadopoulos et al., 1994].

Wagner et al. [2003] discuss the difficulty of identifying germline mutations in families with HNPCC, which is attributed to the extensive genotypic and phenotypic heterogeneity that characterizes many of these families. Wagner et al. [2003] note that a large proportion of HNPCC may not be accounted for by the major mismatch repair (MMR) genes; they inferred that some of the problems in gene identification resulted from a lack of sensitivity of mutation detection techniques, while they tentatively reasoned that additional genes may be contributing to the remaining cases. They studied a cohort of 59 clinically well-defined United States families with HNPCC to search for MSH2, MLH1, and MSH6 germline mutations. A variety of techniques were utilized, which included denaturing gradient gel electrophoresis, Southern analysis, MSI, immunohistochemistry, and monoallelic expression analysis. Their findings disclosed that “…In 45 (92%) of the 49 Amsterdam-criteria-positive families and in 7 (70%) of the 10 Amsterdam-criteria-negative families, a mutation was detected in one of the three analyzed MMR genes. Forty-nine mutations were in MSH2 or MLH1, and only 3 were in MSH6. A considerable proportion (27%) of the mutations were genomic rearrangements (12 in MSH2 and 2 in MLH1). Notably, a deletion encompassing 1–6 of MSH2 was detected in 7 apparently unrelated families (12%) of
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the total cohort, and was subsequently proven to be a founder...” [Wagner et al., 2003]. These authors concluded that they had identified a common North American deletion in MSH2, which could account for approximately 10% of the cohort and, therefore, that this represents a North American founder mutation that was traced back to the 19th century. This subject has been advanced significantly, with the addition of two more Lynch syndrome families that are likely linked to the MSH2 del 1–6 mutation [Lynch et al., 2004].

Cancer Control in Lynch Syndrome

Jarvinen et al. [2000] demonstrated the benefit of colonoscopic screening in HNPCC through a controlled clinical trial extending over 15 years. The incidence of CRC was compared in two cohorts of at-risk members of 22 HNPCC families. CRC developed in eight screened subjects (6%), compared with 19 controls (16%; \( P = 0.014 \)). The CRC rate was reduced by 62% in those who were screened. All CRCs in the screened group were local, causing no deaths, compared with nine deaths caused by CRC in the controls. It was concluded that CRC screening at three-year intervals more than cuts in half the risk of CRC, prevents CRC deaths, and decreases overall mortality by about 65% in HNPCC families. The relatively high incidence of CRC even in the screened subjects (albeit without deaths), in our opinion, argues for shorter screening intervals, e.g., one year. For example, Vasan et al. [1995] discovered five interval cancers in HNPCC patients within 3.5 years following a normal colonoscopy.

We advocate annual colonoscopy, based upon the pathology phenomenon of accelerated carcinogenesis in Lynch syndrome [Jass, 1995a]. We initiate colonoscopy at age 25 years because the average age of CRC onset is earlier in Lynch syndrome than in the general population [Lynch and de la Chapelle, 1999, 2003].

Hereditary Breast and Ovarian Cancer

Tumor Variations in Breast Cancer-Prone Families

The first significant description of a pedigree (Fig. 2) outlining familial breast cancer was published in 1866 by the French surgeon Paul Broca. He traced the causes of death of 38 members of his wife’s family through five generations between 1788 and 1856 [Broca, 1866]. Of the 24 women in the family, 10 died of breast cancer. Broca documented all other types of malignant neoplasms that included an excess of cancer of the gastrointestinal tract and, importantly, was concerned about the possibility of the inheritance of a general diathesis for cancer in the family.

Jacobsen [1946] was one of the first investigators to question the inheritance of cancer of the breast as being solely site-specific. His findings in a series of 200 propositi with breast cancer documented an increased frequency of cancer of all sites in the first-degree relatives of probands. Stephens et al. [1958] described a family (Kindred 107) with breast cancer, showing a variety of histologic types of malignant neoplasms.

Lynch et al. [1972] documented the occurrence of breast cancer and other malignancies in first-degree and second-degree relatives of breast cancer patients in a group of 34 families selected for breast cancer. This report called attention to pedigree data that suggested that selected breast cancer-prone kindreds may be affected with familial factors that are etiologically relevant to malignancies at extrabreast cancer sites, including the “...colon, endometrium, stomach, ovary, and the conglomerate category of sarcoma, leukemia, and brain tumors.” [Lynch et al., 1972]
colorectal cancer was by Lynch et al. [1972], followed by the report of multiple such families in Lynch et al. [1973].

Recently, Meijers-Heijboer et al. [2003] defined what they considered to be a new set of families characterized by carcinoma of the breast and CRC. Therein, the 1100delC variant of the cell cycle checkpoint kinase CHEK2 gene was present in 18% of 55 families with hereditary breast and colorectal cancer (HBCC) as compared with 4% of 380 families with non-HBCC (P < .001), thus providing genetic evidence for the HBCC phenotype.” These authors believe that the HBCC phenotype was predisposed through synergy with an as-yet-to-be-defined susceptibility gene(s). Studies of this type are exceedingly important, given the extant genotypic and phenotypic heterogeneity that characterizes breast cancer-prone families.

There have been numerous reports since the publication by Broca [1866] that there were familial concentrations of breast cancer in which there was a two-fold to three-fold risk for this disease in individuals who had one or more of their first-degree relatives affected with breast cancer [Macklin, 1959; Lynch, 1967]. However, with minor exceptions, up to that time, the predilection for breast cancer was considered by many to be hereditary, but transmitted on a site-specific basis, and therein it was often presumed that first-degree relatives of probands with breast cancer had as much as a two-fold to four-fold increased empirical risk of developing a similar lesion [Lynch, 1967].

**Li-Fraumeni Syndrome**

Li and Fraumeni [1969] described breast cancer in association with soft-tissue sarcomas, leukemia, and lymphoma in four families. Subsequently, the Li-Fraumeni syndrome was characterized by early age of onset of breast cancer in concert with sarcoma, brain, lung, leukemia, lymphoma, and adrenal cortical carcinoma and, therefore, is also known as the SBLA syndrome [Lynch et al., 1978c].

With respect to the sarcoma connection, one of the most remarkable sarcoma-prone families in the world’s literature is one which dates to the 1960s, when it was described by Bottomley et al. [1967, 1971] and Bottomley and Condit [1968]. This family was updated by Lynch et al. [1990b]. In 1993, Jean Feunteun, Ph.D., of Paris, France, identified the p53 germline mutation in this family. In our most recent publication dealing with familial sarcoma and challenging pedigrees [Lynch et al., 2003], our update of the family pedigree (Fig. 3) has shown sixteen patients with sarcoma of variable types (Table II). Two of the patients had metachronous sarcomas. Thus, historically, we see what is likely to have been the first family which now bears the eponym Li-Fraumeni syndrome.

**Carcinoma of the Breast and Ovary**

Lynch and Krush [1971b] described three families characterized by carcinoma of the breast and ovary. Lynch [1981] had reported that breast cancer may be under control of several different genotypes, giving rise to the association of other histologically verified varieties of cancer, inclusive of carcinoma of the
ovary [Lynch and Krush, 1971b]. These authors concluded that, “... for possibly the first time, they document a possible genetic etiologic association between both carcinoma of the breast and ovary. The findings in each family are consistent with an autosomal dominant mode of inheritance, although additional studies of a large number of families with carcinoma of the breast and carcinoma of the ovary will be required to delineate the mode of inheritance” [Lynch and Krush, 1971b].

Understanding of the genetic etiology of breast cancer advanced dramatically when Hall et al. [1990] identified linkage for early onset site-specific breast cancer on chromosome 17q. Shortly thereafter, Narod et al. [1991] showed linkage to this same locus (17q12-q23), in concert with ovarian cancer in the hereditary breast-ovarian cancer (HBOC) syndrome. The gene, now known as BRCA1, has been cloned [Miki et al., 1994]. Subsequently, a second breast cancer gene, BRCA2, was shown to be linked to chromosome 13q [Wooster et al., 1994], and has been identified [Wooster et al., 1995]. These important events contributed greatly to our understanding of hereditary breast cancer.

**Prophylactic Bilateral Mastectomy and Oophorectomy in HBOC**

Prophylactic mastectomy (PM) and bilateral prophylactic oophorectomy (BPO) on patients at inordinately high risk for HBOC were initially recommended by Lynch and colleagues in the early 1970s [Lynch, 1967, 1969; Lynch and Krush, 1971b,c; Lynch et al., 1972, 1976, 1979]. Prophylactic contralateral mastectomy in high-risk women with ipsilateral breast cancer was considered a logical option, given the enormous risk of bilaterality in hereditary cases [Harris et al., 1978]. This was predicated by the concern that women at inordinately high familial breast and ovarian cancer risk required special cancer control measures. PM, for example, was suggested as an option for members of breast cancer-prone families wherein the risk to first-degree relatives of the proband “... approach 50%, consistent with an autosomal dominant factor...” [Lynch and Krush, 1971c].

Patients who were candidates for the option of PM included those who failed to comply with screening recommendations, often because of their fear of “finding” breast cancer [Lynch, 1969]. A relative who develops a crippling cancer phobia resulting from her
awareness of this disease in her family may express a strong desire to have what she correctly considers her highly cancer-prone breast tissue excised. Also included as candidates for PM, were women at high hereditary breast cancer risk who manifested severe fibrocystic breast disease (or the more ominous pathology finding of atypical hyperplasia) that made it difficult for them and their physicians to determine which palpable masses were significant [Lynch and Krush, 1971c]. Even in those “early days,” counseling and consultation with a medical geneticist was recommended when weighing genetic risk factors relevant to considerations of prophylactic surgery [Lynch, 1969; Lynch et al., 1979].

PM has long been a controversial issue, raising such questions as: Will it work? Will patients accept it? Will insurance companies cover the cost? Will it effectively reduce breast cancer’s and ovarian cancer’s morbidity and mortality? Is this considered to be a particularly radical medical and surgical concern, so that patients who harbor BRCA1/2 germline mutations, and who therefore may have an enormous lifetime risk for breast cancer (in the range of 70–85%), or some of their physicians, may remain reluctant to advocate PM?

**Recent Surgical Prophylaxis Studies**

Hartmann et al. [1999] used “high-risk” criteria such as the number of breast cancer-affected first- and second-degree relatives for consideration of PM. They found that PM was effective in these high-risk women, in that there was a 90% reduction in the risk of breast cancer, with a significant reduction in mortality. Seven breast cancers occurred in their study after subcutaneous bilateral mastectomy; there were none after total mastectomy [Hartmann et al., 1999]. Subsequently [Hartmann et al., 2001], they employed genetic testing to distinguish the BRCA1/2 mutation carriers in this cohort and proved that PM works in these BRCA1/2 mutation carriers [Hartmann et al., 2001]. For example, breast cancer did not develop in any of the women with a confirmed BRCA1 or BRCA2 mutation after a median follow-up of 16 years [Hartmann et al., 2001]. Therefore, PM appears to reduce the long-term risk of breast cancer in those women with a BRCA1 or BRCA2 mutation.

A prospective study by Meijers-Heijboer et al. [2001] also showed significant benefit of PM among BRCA1/2 mutation carriers.

**Bilateral Prophylactic Oophorectomy (BPO) in BRCA1 Mutation Carriers**

Recent studies [Kauff et al., 2002; Rebbeck et al., 2002] have provided prospective findings about the risk-reducing effects, on both breast and ovarian cancer, in patients who were harbingers of BRCA1 and BRCA2 mutations, and who underwent prophylactic salpingo-oophorectomy. Rebbeck et al. [1999] studied a cohort of women with BRCA1 mutations who underwent BPO, to test the hypothesis that decreases in ovarian hormone exposure following BPO may alter breast cancer risk in BRCA1 mutation carriers. This study showed a statistically significant reduction in breast cancer risk following BPO, which was greater in women who were followed for five to 10 years, or for at least 10 years, after surgery. BPO also provided a potential for reduction of risk for ovarian cancer. Hormone replacement therapy did not negate this reduction in breast cancer risk following BPO. Rebbeck et al. [1999] concluded that BPO “…is associated with a reduced breast cancer risk in women who carry a BRCA1 mutation. The likely mechanism is reduction of ovarian hormone exposure…”

The significant benefit of BPO was crystallized more recently by Rebbeck et al. [2002], in a prospective study that evaluated a total of 551 women with BRCA1 or BRCA2 germline mutations identified from registries; 259 of these women had undergone BPO, and 292 were matched controls who had not undergone the procedure. They concluded that BPO reduced the risk of ovarian cancer and breast cancer in those women who were harbingers of BRCA1 or BRCA2 germline mutations.
We believe these findings indicate that third-party carriers should defray the expenses of not only surveillance but, moreover, prophylactic mastectomy and prophylactic salpingo-oophorectomy, among women at inordinately high risk for carcinoma of the breast, including those who harbor BRCA1/BRCA2 germline mutations.

Public Health Impact of Surgical Prophylaxis

What will be the public health impact of the findings by Hartmann et al. [1999, 2001], Meijers-Heijboer et al. [2001], and Rebbeck et al. [1999, 2002], given the enormous magnitude of breast cancer in the general population, particularly in women in highly-industrialized Western nations? How will women determine if they are at high risk [Lynch et al., 2001; Rebbeck et al., 1999, 2002] and, moreover, prophylactic mastectomy and prophylactic salpingo-oophorectomy, in women at inordinately high risk for carcinoma of the breast, including those who harbor BRCA1/BRCA2 germline mutations.

HEREDITARY MALIGNANT MELANOMA

The first report of the likely involvement of a hereditary component for malignant melanoma was by Norris [1820], when he described a remarkable family with multiple cases of malignant melanoma. Of particular interest is that the patient and his children had numerous cutaneous moles. This led Norris to conclude that, “These facts, together with a case that has come under my notice, rather similar, would incline me to believe that this disease is hereditary.”

Subsequent clinical observations showed melanoma clustering in families [Cawley, 1952; Lynch and Krush, 1968; Clark et al., 1978; Reimer et al., 1978; Lynch et al., 1978a]. Malignant melanoma shows a strong correlation with pancreatic carcinoma in association with the CDKN2A (p16) germline mutation in the familial atypical multiple mole melanoma (FAMMM) syndrome [Goldstein et al., 1995, 2000; Goldstein and Tucker, 1997; Vasen et al., 2000; Lynch et al., 2002; de Vos tot Nederveen Cappel et al., 2003].

HEREDITARY PANCREATIC CANCER

Bartsch [2003] reviewed familial pancreatic cancer (PC), and noted that the first systematic study of a cohort of familial PC families was published in 1989 [Lynch et al., 1989]. Lynch et al. [1990a] and Lynch et al. [1996b] provided additional updated reviews of the subject in search of host factors that may influence susceptibility to PC; attention was focused upon the manner in which genetic factors might interact with environmental exposures in PC’s etiology. The advent of molecular genetics and the discovery of germline PC-causing mutations have contributed immensely to knowledge of the genotypic and phenotypic heterogeneity of several hereditary PC syndromes (Table III) [Lynch et al., 2002].

SUMMARY AND CONCLUSIONS

We have attempted to depict the historical aspects that have contributed to an understanding of the clinical and, more recently, molecular genetic basis for hereditary forms of cancer. Space limitations have necessitated that we give attention to only a few of these, including the most common cancer types, namely breast and colorectal carcinoma. However, the surface relevant to hereditary cancer has barely been grazed and, undoubtedly, through the help of our molecular genetic colleagues in concert with astute clinical observations of cancer clusters in families, this knowledge will continue to mount.

Indeed, some of the rare cancer clusters with strong potential for cancer control benefit will include the recent success that was found in the case of the gastrointestinal stromal tumor (GIST). The gene crucial for GIST development is KIT [Nishida et al., 1998; Isozaki et al., 2000; Hirota et al., 2002]. The KIT receptor is a tyrosine kinase that is crucial in the pathogenesis of GIST tumors. Imatinib mesylate is a selective tyrosine kinase inhibitor, which has been shown in preclinical models, as well as in several preliminary clinical investigations, to have activity against these tumors [Demetri et al., 2002]. The GIST tumor has therefore become an excellent therapeutic model, in that its otherwise grave prognosis has changed due to its sometimes dramatic response to imatinib mesylate (Glivec; Novartis, Basel,
Switzerland) chemotherapy [Joensuu et al., 2001; Demetri et al., 2002; Rossi et al., 2003]. GIST also occurs in certain families in accord with an autosomal dominant mode of inheritance, caused by germline KIT mutations [Beghini et al., 2001]. This same drug has also shown promise in treatment of some hematological cancers in particular, chronic myelogenous leukemia [Druker et al., 2001a,b]. We expect that in the near future, comparable therapeutic success through molecular-based designer drugs for other disorders discussed in this review will be achieved.

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REFERENCES


TABLE III. Genetic Syndromes With Inherited Predisposition to Pancreatic Cancer

<table>
<thead>
<tr>
<th>Familial syndromea</th>
<th>Gene (locus)</th>
<th>Relative risk</th>
<th>Frequencyb</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial pancreatitis</td>
<td>Cationic trypsinogen (7q35)</td>
<td>50–60</td>
<td>Unknown</td>
<td>Lowenfels et al. [1993, 2000]; Whitcomb et al. [1996]</td>
</tr>
<tr>
<td>Familial pancreatic cancer syndrome</td>
<td>Unknown (4q32–34)</td>
<td>18–57</td>
<td>Unknown</td>
<td>Tersmette et al., 2001; Eberle et al., 2002</td>
</tr>
<tr>
<td>FAMMM syndrome</td>
<td>p16INK4a / MTS1 (9p21)</td>
<td>13–22</td>
<td>98%</td>
<td>Lynch and Fusaro [1991]; Goldstein et al. [1995]; Caldas et al. [1994]; Schutte et al. [1997]</td>
</tr>
<tr>
<td>Hereditary breast-ovarian cancer syndrome</td>
<td>BRCA2 (13q12)</td>
<td>10</td>
<td>7%</td>
<td>Wooster et al. [1994]; Tulinius et al. [1994]; Goggins et al. [1996]</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC (5q21)</td>
<td>5</td>
<td>40%</td>
<td>Lynch et al. [1996b]; Kinzler et al. [1991]; Horii et al. [1992]; Yashima et al. [1994]</td>
</tr>
<tr>
<td>HNPCCc</td>
<td>hMSH2 (2p22–21)</td>
<td>Unknown</td>
<td>4–11%</td>
<td>Lynch et al. [1985d]; Jacob and Praz [2002]; Goggins et al. [1998]</td>
</tr>
<tr>
<td></td>
<td>hMLH1 (3p21.3)</td>
<td>Unknown</td>
<td>4–11%</td>
<td>Lynch et al. [1985d]; Jacob and Praz [2002]; Goggins et al. [1998]</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM (11q22–23)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Lynch et al. [2001a]; Swift et al. [1976]</td>
</tr>
</tbody>
</table>

aAll of the above syndromes are inherited in an autosomal dominant fashion, except ataxia telangiectasia, which is an autosomal recessive disorder.

bFrequency refers to the frequency of genetic mutation found in sporadically occurring pancreatic carcinomas.

cHNPCC: hereditary nonpolyposis colorectal cancer, also known as cancer family syndrome or Lynch syndrome II. HNPCC is typically caused by germline mutations in DNA mismatch repair genes including hMSH2, hMLH1, hPMS2, and hMSH6. hMSH2 and hMLH1 mutations account for half to two-thirds of HNPCC. The frequency refers to a defect in any one of the five DNA mismatch repair genes causing HNPCC. (Table reproduced by permission from Yee et al. Cancer Biol Ther 2003; 2:1:38–47.)


