The Cancer-family Syndrome:
A Pragmatic Basis for Syndrome Identification*

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In 1913, ALDRED WARTHIN18 described a cancer-prone family (Family G), which was the first reported kindred that clearly fulfilled the criteria for what is now known as the cancer-family syndrome. These criteria include: a familial tendency to develop adenocarcinomas of numerous histologic types (but predominantly involving the proximal colon and endometrium); significantly early age of onset of cancer (compared with the same histologic varieties in the general population); an extraordinary frequency of multiple primary malignant neoplasms; and vertical transmission with segregation patterns consistent with an autosomal dominant mode of genetic transmission.10,11,14 The history of Family G has been updated on several occasions,7,13,19 and a number of similar kindreds have been reported, lending support to classification of the cancer-family syndrome as a bona fide hereditary cancer syndrome.1–5,8,17,20

Identification of this syndrome in the practical clinical setting provides an opportunity to identify those unaffected patients who are at extraordinary risk for the early onset of cancer at specific anatomic sites. We still do not know the chromosomal, histopathologic, and biochemical markers of the pre-neoplastic trait that would enable unequivocal identification of the predisposed individual. Consequently, estimation of cancer risk has heretofore been possible only through characterization of extended pedigrees showing segregation of cancer (in this case, of the colon or endometrium) over two or more generations. Nevertheless, recent experience indicates that it may no longer be necessary to perform extensive genetic segregation analysis of extremely large kindreds, such as Family G, in order to arrive at risk figures that will enable genetic counseling and initiation of specific surveillance and management programs for family members at high risk for the development of cancer.6,11,15

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In presenting the pedigree of an extended kindred showing classic features of the cancer-family syndrome, our primary purpose is to stress the role of the nuclear family that enabled its full ascertainment and description. The practical implications of this experience are discussed.

Ascertainment, Materials, and Methods

Family C-113 was originally referred to us in 1968 by a pathologist who reported that the proband had recently been the subject of autopsy examination, having died of disseminated adenocarcinoma of the descending colon at the age of 34 years. This physician also mentioned that colonic cancer had developed in the patient’s sister when she was 27 years old, and that both parents might have had colorectal or gastric carcinoma. Possessing only this information, the pathologist had already concluded that the family might fit the criteria for the cancer-family syndrome (we had recently reported two kindreds).16

Initial follow up of the family yielded a paucity of information from living relatives. For several years after initial analysis of the family’s status (Fig. 1), in 1968, the records were maintained in our registry of colonic cancer-prone families. However, when we became aware of the high frequency of proximal colonic cancer involvement in the cancer-family syndrome,6 all inactive pedigrees in our registry were reviewed for evidence of the proximal colonic cancer excess. The case of the proband’s 27-year-old sister with carcinoma of the cecum thus provided the basis for a renewed study of the kindred.

Standardized medical and genealogic history questionnaires completed by informative relatives, with telephone follow up and personal interviews when possible, enabled extension of the pedigree. Reported tumors were verified through attending physicians, hospitals, and pathology laboratories. When primary
records could not be obtained (because of their destruction or the unavailability of next-of-kin to sign authorizations), death certificates provided the necessary information.

Results

Pedigree Data: The status of the family as it is now known is shown in the main body of the pedigree (Fig. 1). Minor discrepancies between the data as reported initially and as subsequently verified are evident. Eleven members of the proband's maternal line have been reported to have had carcinoma of the colon; five cases were verified by medical records and two were verified by death certificates. The mean age at initial onset of colonic cancer was 35 years. In four of the five cases of colonic cancer with specified primary subsites, the malignancy occurred at the proximal colon. Medical records contained no evidence of colonic polyposis. Flexible-sigmoidoscopic examinations of two former cancer patients (IV-1 and IV-2) and their children revealed no evidence of polyposis. Three women in the direct family line have had endometrial or endocervical cancers; the average age at onset was 53 years.

Crude estimates of genetic segregation reveal that of the eight sibships constituting the class of offspring...