Cancer Family Syndrome
A Case Report and Literature Review

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It is well recognized that carcinoma of the colon may have a familial predisposition in such syndromes as familial multiple polyposis, Gardner's syndrome, and the glioma–polyposis syndrome—all associated with a high incidence of colonic carcinoma (1). In all of these familial diseases antecedent colonic polyposis is characteristic.

There are, however, at least two discrete familial syndromes in which the risk of colonic adenocarcinoma is high in the absence of antecedent colonic polyposis. First of all, there are a few families with simple autosomal dominant familial colonic carcinoma without antecedent polyposis (2). Second, there is "cancer family syndrome" (CFS) (3).

CASE REPORT

The proband is a 49-year-old white man who presented with three simultaneous colonic carcinomas in the transverse colon, sigmoid colon, and rectum. He had survived a right hemicolectomy for adenocarcinoma in the cecum 23 years earlier. He was a member of a sibship of 13, in five of whom colonic carcinoma had been documented at early ages. Endometrial or ovarian carcinoma had been documented in three sisters. One lung cancer and one brain tumor had also occurred among siblings. The proband and one sister, as well as the father, have exhibited multiple metachronous cancers.

The proband's father underwent removal of a carcinoma of the cecum at age 27, and died of carcinoma of the rectum at age 45. The proband's paternal uncle had a carcinoma of the colon at age 62, and a paternal aunt died of breast cancer at age 76.

The proband's grandfather died of colonic cancer at age 41, but in this case pathologic confirmation is not available.

Figure 1 is the pedigree of this family. No carcinoma has developed in the members of generations IV or V. In the genetic lines at risk, however, all members are so far under the age of 30.

Table 1 summarizes the locations of the colonic adenocarcinomas documented by pathologic specimens. Table 2 summarizes the nature of the female genital tract cancers documented by pathologic specimens. Table 3 summarizes the cancers at other sites.

Three members of the proband's generation had solitary adenomatous colonic polyps detected during annual radiographic examinations for the presence of cancer. These are summarized in Table 4.

Carcinoembryonic antigen (CEA) determinations were carried out on all living members of the family including one person with previously removed ovarian carcinoma who developed colonic carcinoma one year after the assay was performed. All determinations were less than 4.0 ng/ml by the Hansen method of radioimmunoassay (4).

DISCUSSION

CFS is a familial disease defined by the following criteria: (1) increased incidence of adenocarcinoma, (2) predominance in the colon and female genital tract, (3) absence of antecedent gastrointestinal polyposis, (4) increased occurrence of multiple primary neoplasms, (5) early age for development of cancers, risk beginning at age 25, and (6) autosomal dominant mode of inheritance.

CFS was first described in 1913 by Warthin (5). His original family has been reported several times through the years (6–8), most recently by Lynch (8) to include six generations and 650 family members. In this family the disease had continued to affect the offspring of affected members and has not affected the progeny of the unaffected.

Ten other families conform to the criteria for CFS (3, 9–13). In one family (9), endometrial carcinoma developed in a pair of identical twins at age 40. Ten years later in this family, colonic carcinoma developed in one twin and a brother of the twins. In another family (13), two sisters survived surgery for

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TABLE 1. COLONIC CANCERS

Member	*Location*	*Age*	*Result*
II-8	Cecum	27	Resection
	Rectum	45	Death
III-5	Transverse	33	Death
III-6	Rectum	64	Resection
III-7	Transverse	50	Resection
III-11	Sigmoid	27	Death
III-12	Cecum	26	Resection
	Transverse, sigmoid, and rectum	49	Death

endometrial carcinomas at ages 45 and 51, later to develop colonic carcinoma at ages 46 and 55, respectively.

None of the published reports mentions the absence or presence of occasional colonic polyps, although generalized polyposis is specifically denied in each of the reports. In the family here reported, three members of one generation had solitary benign adenomatous colonic polyps. One patient with a carcinoma in the transverse colon also had a polyp in the sigmoid colon. No cancers have developed in the other two patients after a follow-up of 12 and 6 years each.

It is estimated that anywhere from 5% to 69% of the adult population may have an adenomatous polyp of the colon. The discovery of single polyps when the colon is so carefully scrutinized may not represent a significant or distinctive feature of CFS. The absence of multiple polyps is considered characteristic of the syndrome.

Of particular importance is the early age at which affected persons are at risk. Colon carcinoma has been found as early as age 25 in CFS, far younger than the usual age for colon cancer and comparable to the risk in familial polyposis.

What are the features of interest in CFS? In case reports prior to 1930, gastric carcinoma was a common occurrence in CFS. In more recent family studies, colon carcinoma has become more common and gastric carcinoma much less common in these families. It is of particular significance that in the Warthin family (5–8) studied with pathologic confirmation over six generations from 1865 to 1970, this very transformation in site of carcinogenesis is observed. None of the other previously reported cases spans a period sufficient to support this observation in a single family. This phenomenon may simply parallel the well-recognized and dramatic drop in the incidence of gastric carcinoma and the near-mirror-image rise in colonic carcinoma in the general population (15). Changes in public health measures, diet, or environment exposures over this time period may be exaggerated in CFS families.

TABLE 2. GENITAL TRACT CANCERS

Member	*Location*	*Age*	*Result*
III-1	Endometrium	45	Death
III-3	Endometrium	33	Death
III-6	Ovary, premalignant endometrium	37	Resection

The women members of CFS families show a greater risk of carcinoma of the genital tract as well as of the colon. The specific site at risk in the reported patients is most commonly endometrium, but several cases of ovarian carcinoma have occurred, occasionally in association with simultaneous endometrial carcinoma. In the family under discussion there are two patients with endometrial carcinoma and one with ovarian carcinoma. The ovaries were not studied in the former two patients, but the endometrium in the patient with ovarian carcinoma showed hyperplastic and possibly premalignant changes. The simultaneous occurrence of ovarian and endometrial neoplasia has been noted in five other CFS patients in the literature (3, 12).

Finally, although assay for CEA revealed no persons with elevated titers, Lynch has reported one CFS family with elevations of CEA which are highest in persons who have had cancer, next highest in first-degree relatives, and normal in second-degree relatives. He also reports increased incidence of tissue culture SV40 viral transformation which correlates with cancer in a similar fashion in another of his CFS families (16).

TABLE 3. TUMORS AT OTHER SITES

Member	*Location*	*Age*	*Result*
II-9	Breast	76	Death
III-2	Lung	49	Death
III-6	Brain	62	Irradiated, in remission 5 years

TABLE 4. COLONIC POLYPS

Member	*Location*	*Age*	*Size (cm)*
III-7	Sigmoid	50	2 × 2
III-10	Descending	46	0.5 × 1.5
III-13	Rectum	45	2 × 2

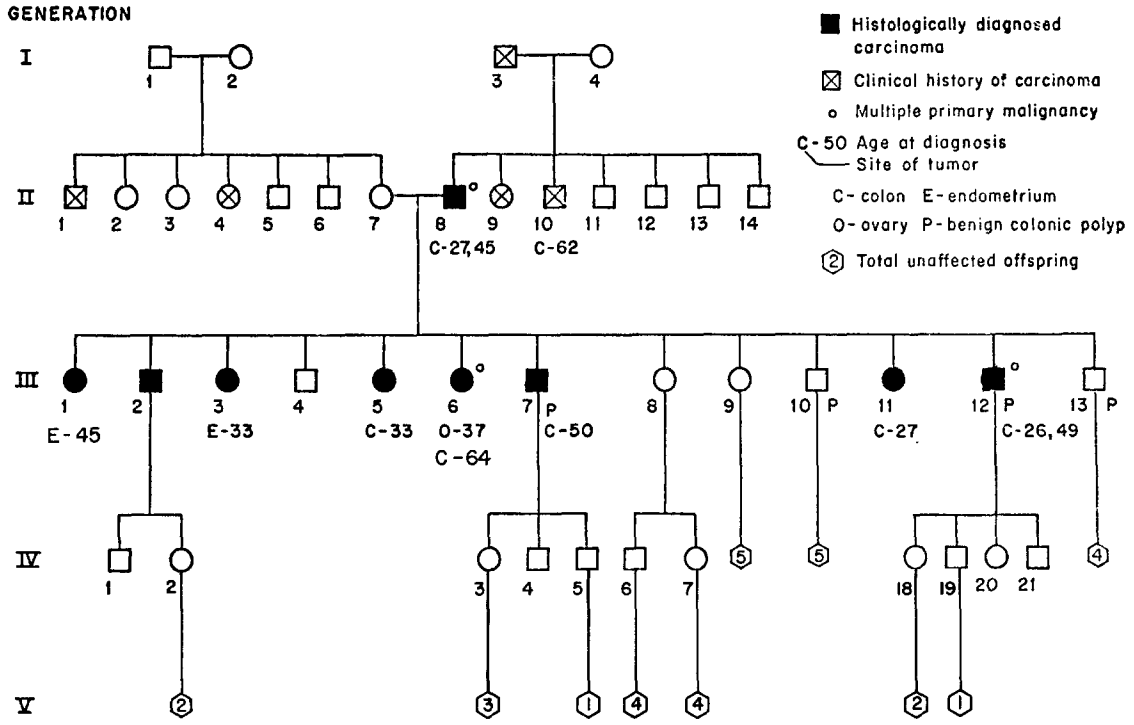

Fig 1. Pedigree of the proband's family.

CONCLUSION

A familial colonic carcinoma syndrome reported in at least 11 other families to date (in one family over six generations and 650 family members) is here reported. CFS is an autosomal dominant genetic disease in which the affected members are at risk at early age for carcinoma, especially in the colon and female genital tract. The carcinomas may be multiple and occur in the colon in the absence of preceding gastrointestinal polyposis.

SUMMARY

A familial cancer syndrome is reported in which a high incidence of colonic and female genital tract cancers occur at unusually early ages in the absence of polyps and other predisposing factors. A family is reported and the literature reviewed.

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