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Family History as a Marker for Increased Risk of Breast Cancer and Colon Cancer†

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Cancer of the breast and colon are well known to occur with high frequency in families with certain inherited cancer syndromes. These cancers also occur with increased frequency in families which do not have a recognizable genetic cancer syndrome. The fact of familial occurrence can be used to identify people with increased risk of cancer. In high-risk people methods for early detection can be developed which may reduce morbidity and mortality from these cancers, as has been done for certain inherited cancer syndromes.

Common breast and colon cancer occur in families more frequently than would be expected by chance. A very high frequency of occurrence within a family is well known for certain inherited cancer syndromes such as Gardner syndrome (1), familial polyposis (2), medullary thyroid cancer (multiple endocrine neoplasia type II) (3), and hereditary breast cancer (4). When the clinician elicits a family history consistent with one of these syndromes, methods of early cancer detection can be applied to relatives at risk, and many cancers can be found at a curable stage.

Colon Cancer

The basic method of identifying familial aggregation of cancers is to identify a group of patients (the probands) with the cancer of interest. The frequency of cancer in the relatives of these probands is then compared with the frequency of cancer in the relatives of a control group who do not have this cancer. Lynch, et al (5), applying this approach to colon cancer, found a colon cancer frequency of 3.6% in 1,058 first-degree relatives of affected patients, but with only a 0.6% incidence in 460 relatives of control subjects.

In studies of this kind, inadvertent inclusion of a few kindreds with inherited cancer syndromes will exaggerate the familial incidence. This possibility was minimized by Lovett (6), who reviewed all cases of colon cancer admitted to one hospital in a three-year period. She excluded patients referred for evaluation because of a strong family history of colon cancer. For the rest, she obtained histories of cancer in the relatives of the patients and documented these reports by review of hospital records and death certificates. Of 352 deceased first-degree relatives, 41 had died from colon cancer, whereas only 11 such deaths were expected from the frequency of colon cancer in the general population (p > 0.01). The familial aggregation did not include families with multiple polyposis or a few families with very high frequency of cancer. Thus, the results are considered to represent the familial incidence of common colon cancer.

Further data on the frequency of positive family history were collected by Duncan and Kyle (7), who based their study on 50 consecutive cases of cancer of the colon or rectum from northeast Scotland, an area of high frequency of these tumors. They compared medical histories of the parents, children, and siblings of these index patients with those of the relatives of control patients matched for age and sex, who were hospitalized for nonmalignant disorders. Eight of the 50 cancer index cases had one relative each with colon cancer among 349 first-degree relatives. Among the 386 relatives of control subjects, only one case of colon cancer was found. The incidence of only one affected relative in each family suggests that none of these families had a cancer syndrome gene; however, only first-degree relatives were studied. A more extensive study might have disclosed more cases. Macklin (8) reported an increased death rate from colon cancer in both first- and second-degree relatives of index colon cancer cases.

In their study, Duncan and Kyle (7) found that the incidence of adenomatous polyps was the same (25%) in index cancer cases whether or not there was an affected...
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relative. This finding further distinguishes their series from syndromes of colon cancer associated with multiple polyposis. In addition, index cases with an affected relative were the same age as those without an affected relative, in contrast to the early age of onset which characterizes many cancer syndromes (4).

If colon cancer is unusually common in relatives of colon cancer patients, a systematic search in families might find many cases. Anderson and Romsdahl (9) reported results of examinations for presymptomatic colon cancer in relatives of colon cancer patients. These examinations of people who had at least two relatives with colon cancer included history, physical examination, proctosigmoidoscopy, and air contrast barium enema. In 188 relatives from families without polyposis, they found five cases of colon cancer. All were among the 135 subjects over 35 years of age, yielding a detection rate in this group of 3.7%. Reported rates for detection programs in the general population are about 0.1% (10).

The opportunity for the early detection of colon cancer resides with these high-risk persons, who are the relatives of colon cancer patients. The basis for applying methods of early detection to asymptomatic individuals should include evidence that early detection and treatment actually do reduce morbidity and mortality.

Furthermore, the reliability, indicated frequency, and cost-effectiveness of particular means of cancer detection, such as fecal occult blood testing, barium contrast radiograph, proctosigmoidoscopy, and colonoscopy, require continued evaluation. Early detection testing must have significantly low risks to patients to be appropriate for the risk of the disease. Relatives of colon cancer patients are especially good candidates for the colon cancer screening methods recommended by the American Cancer Society (11). In light of existing data, clinical trials to examine these questions are clearly appropriate.

Breast Cancer

Several studies indicate that female relatives of breast cancer patients have an increased incidence of breast cancer with an overall risk two to three times greater than that of the general population (12).

The risk of occurrence in a family is influenced by the number of women already affected, their age when the cancer was found, whether the cancer is uni- or bilateral, and the degree of relationship between the woman at risk and her affected relatives. Anderson (13) compared a group of breast cancer patients with a family history of breast cancer to a control group of patients with a family history of other neoplasms. Breast cancer pedigrees were sorted as to whether the affected individuals were the patient and a second degree relative, the patient and her sister, or the patient and her mother.

The frequency of breast cancer in the patients' remaining sisters was then determined. In the control group, 2.3% of the sisters developed breast cancer. In the group in which the patient and her second-degree relative were affected, 1% of the remaining sisters developed breast cancer. In the second group, with patient and sister affected, 6% of the remaining sisters developed breast cancer. In the last group, with the patient and mother affected, 11% of the remaining sisters developed breast cancer. In this last group, the increase in frequency was concentrated in younger age groups of the remaining sisters. Of 17 sisters aged 30-39, five had developed breast cancer, yielding a relative risk of 47-fold when compared to controls. In all cases, the proband of these 17 sisters was young (between 20 and 49 years) when breast cancer was diagnosed, or she had bilateral breast cancer. Evidence of a hereditary cancer syndrome was apparent in a few instances among all pedigrees in the study, but none contributed to the increased frequency of cases found. The results suggest that the risk of breast cancer is increased among the other sisters of two sisters with breast cancer and, to a greater degree, among sisters of a woman whose mother was also affected.

Ottman, et al (14) assessed the frequency of breast cancer in the sisters and mothers of breast cancer patients sampled from the general population. White women with breast cancer diagnosed before age 65 were classified according to whether the cancer was diagnosed before or after age 51 (arbitrarily called pre- and postmenopausal) and whether cancer was present in one or both breasts if diagnosed before age 51. Breast cancer cases were recorded among the mothers and sisters of women in each category. The frequency of breast cancer among mothers of patients with unilateral breast cancer was no higher than that of the general population, but the frequency of breast cancer in both mothers and sisters in all other categories was increased, especially among the relatives of bilateral premenopausal cases. Eleven of 82 mothers (13%) of bilateral premenopausal cases had developed breast cancer. Among the sisters of bilateral premenopausal cases, 17 of 96 had breast cancer. The cumulative incidence of breast cancer in these sisters by age 70 was 55% (± standard error of 14%). In Fig. 1, cumulative incidences reported by Ottman, et al (14) have been plotted. It is notable that for sisters of bilateral premenopausal breast cancer cases, the highest risk of breast cancer occurs after menopause.

Among the sisters of unilateral premenopausal cases, the cumulative incidence by age 70 was 7.7% (± 3.5%). Among the sisters of unilateral postmenopausal cases the cumulative frequency of breast cancer by age 70 was 18.4% (± 9.2%). Thus, the sisters of even isolated bilateral premenopausal breast cancer patients are an identifiable high-risk group.

Ottman, et al (14) used life table analysis to compute the risk of breast cancer for 10-year intervals from age 30 to 70 for mothers and sisters of breast cancer patients. Anderson and Badzioch (15) added further data showing a lower but still dramatic risk of breast cancer in sisters of affected women. Despite large standard errors, these estimates are helpful in advising women of their risk. Additional important considerations in the estimate of risk are the presence of two cases of breast cancer in the kindred, as reported by Anderson (13), and any evidence in the kindred of an inherited cancer syndrome or recognizable pattern of inherited cancer, both of which increase the risk of breast cancer.

Thus, some women with a high risk for breast cancer can be identified by their family history. They can then be advised of their risks as well as the available means of managing these risks. The experience of the Health Insurance Plan trial indicates the value of mammography and physician examination of the breasts for early detection (16). Additional trials of the early detection of breast cancer are in progress.

**Hereditary Cancer Syndromes**

Early detection has been refined in some examples of hereditary cancer syndromes where the risk of cancer approaches 50% in many individuals. In polyposis coli, the occurrence of numerous polyps, and in the Gardner syndrome, other clinical manifestations such as exostoses help to identify carriers of the gene who are very likely to develop colon cancer (1,2). In multiple endocrine neoplasia type two (MEN2), the medullary thyroid cancer can be detected before metastasis by measuring blood calcitonin secreted by the tumor in response to stimulation with pentagastrin (3). Early detection has been advanced by the recent report of Babu, Van Dyke, and Jackson (17). These investigators have found a small deletion in one of the number 20 pair of chromosomes in subjects carrying the gene for MEN2 (both A and B syndromes). Thus, a person destined to develop inherited medullary thyroid cancer can be identified at birth and perhaps even before birth if amniotic fluid cell karyotyping for this deletion can be developed.

In the inherited cancer syndromes, examination of pedigrees indicate that a gene-causing cancer is present. Perhaps these genes are similar to the recently discovered oncogenes, small pieces of DNA that induce cultured cells to behave like malignant tumors (18). Needleman, et al (19) recently reported the results of a series of experiments in which DNA extracts from hereditary cancer syndromes apparently did not contain transforming activity in vitro. Possibly the transformation assay system used lacks a component necessary for the expression of transforming activity. The existence of genes that cause cancer in the hereditary cancer syndromes is well established by the inheritance patterns. These genes may be localized by genetic linkage studies such as those of Gusella, et al (20), which demonstrate linkage of a DNA restriction variant to the gene for Huntington chorea.

Help in identifying persons with a gene for an inherited cancer syndrome can be obtained from other biologic markers. Studying patients with Gardner syndrome or hereditary colon cancer, Danes (21) demonstrated tetraploidy of skin cells cultured in vitro. Kopelovich also reported on cultured skin cells from patients with hereditary colon cancer (22). Although the results of such tests are encouraging, a negative result in a patient at risk for inherited cancer is not sufficiently reliable to preclude the use of other early detection measures.

Genetically linked markers or in vitro abnormalities of cultured cells would be useful to identify the risk for members of a family with inherited cancer. Efforts for early detection could then be concentrated on those for whom it is appropriate. At present, the occurrence of breast cancer or colon cancer in a relative is one of the most powerful indications of increased risk of these common cancers.
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References


