Henry Ford Hospital Medical Journal

Volume 32 | Number 1 Article 3

3-1984

Screening of Patients at High Risk for Cancer

Robert M. O'Bryan

Henry Ford Hosp Med J
Vol 32, No 1, 1984

Screening of Patients at High Risk for Cancer

Robert M. O'Bryan, MD*

A cancer other than non-melanoma skin cancer will occur in one of every seven persons. Individuals with higher risks for cancer are those with increasing age, hereditary disorders, and a family history of cancer. Lifestyle, especially the use of tobacco and alcohol, diet, and perhaps behavioral patterns influence the risk. Less well understood but clearly pertinent risk factors include environmental and occupational exposures. The risk factors specific for breast cancer include a positive family history of breast cancer, history of mastopathy, age at first pregnancy greater than 35 years, early menarche with late menopause, and history of carcinoma of the colon, endometrium, or ovary. The risk factors specific for colorectal cancer include history of polyps or prior colon cancer, family history of colon or rectal cancer, familial polyposis, Gardner's syndrome and ulcerative colitis. The asymptomatic patient should be screened according to the Henry Ford Hospital screening recommendations. The patients at risk should be screened according to the American Cancer Society recommendations. It is the responsibility of health professionals to identify patients at risk and to respond accordingly.

Recommendations for care of the asymptomatic patient were presented in a recent issue of the Henry Ford Hospital Medical Journal (1). The purpose was to provide reasonable health screening guidelines in an era when medicine is driven, on one hand, by the explosion of science and technology and, on the other, by the overwhelming mandate for cost containment. The health care profession recognizes the need to evaluate and adopt optimal screening standards that include cancer detection as a major goal.

If the asymptomatic patient is not properly identified, however, screening guidelines are of no value and, in fact, may be dangerous. Bridges, et al (1) defined as asymptomatic one who perceives his or her health to be good and has no known genetic, environmental, or historic risk factor, or adverse personal habits that place that person at high risk for a disease. In the general population the total incidence of cancer exceeds 300 cases per 100,000 each year (2,3). Therefore, in a "healthy" population followed for 72 years, a cancer will occur in one of four persons. If non-melanoma skin cancers are excluded, the incidence is one of seven. During 1984, 870,000 new cases of cancer will occur in the United States, and 32,500 will occur in Michigan (3). Within the general population, some persons are at greater risk for cancer than others and should not be classified as *asymptomatic*. Identification of these persons is essential, not only to attempt to reduce the risk factors but also to provide appropriate early detection and management. This paper reviews the overall risk factors for cancer and focuses on carcinoma of the breast and colon.

Overall Considerations

Age and hereditary disorders are two well-established risk factors for cancer. According to the Third National Cancer Survey (2), the age-specific incidence rates per 100,000 rose from 29.9 for those individuals 20-24 years of age, to 189.4 for those 40-44 years, to 912.1 for those 60-64 years, and to 2000.5 for those 80-84 years old. Colorectal cancer, lung cancer, and prostate cancer increased at a steady rate from the time of adulthood into the eighth decade of life. The incidence of breast cancer rose sharply from age 25 to 50 and then increased at a slower rate. Not all cancer increased in incidence with age. For example, the occurrence of uterine cancer declines after age 65, and the incidence of testicular cancer declines rapidly after it reaches a peak at age 30. Race and sex also influence the incidence of cancer; the annual rate per 100,000 was 397.1 for black men and 342.5 for white men, compared to 270.4 for white women and 256.5 for black women. Nonetheless, with all variables combined and excluding non-melanoma skin cancer, the incidence of cancer doubles every five years after the age of 25 (4).

Ever increasing evidence links hereditary disorders with increased cancer risk. Four disorders which are inherited as an autosomal recessive trait—Bloom's syndrome,

Submitted for publication: October 28, 1983

Accepted for publication: March 28, 1984

*Division of Oncology, Department of Medicine, Henry Ford Hospital

Address reprint requests to Dr. O'Bryan, Division of Oncology, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202.

Fanconi's pancytopenia, ataxia telangiectasia, and xeroderma pigmentosum—carry a predisposition to cancer. Retinoblastoma, a rare malignant eye tumor, occurs in some families as an autosomal dominant trait. About 40% of cases are hereditary, and, among these, the patients who survive initial treatment of the retinoblastoma develop a second malignancy more often than does the general population (5). Multiple endocrine adenomatosis (Werner's syndrome) is characterized by familial tumors of the anterior pituitary, parathyroid, and pancreatic islet cells. Pheochromocytoma and medullary thyroid cancer sometimes occur singly or together in families (6). Polyposis coli and Gardner's syndrome are familial disorders associated with precancerous colonic polyps. Neurofibromatosis, an autosomal dominant disorder that occurs in one of 3,000 live births, is characterized by cafe-au-lait spots and multiple neurofibromas (7). The neurofibromas undergo sarcomatous degeneration in about 10% of the patients.

The importance of hereditary cancer extends well beyond these disorders. Both retrospective and prospective epidemiologic studies of relatives of cancer patients have demonstrated an increased risk of cancer of the same type. Colonic and gastric carcinoma cases without preexisting polyps, as well as a sizable proportion of breast cancer cases, follow an autosomal dominant pattern and may be dominantly inherited (8). Hereditary cancer has its onset at a younger age than the same tumor in the general population. In paired organs, it is usually bilateral, and multiple primary tumors are common.

Higginson reviewed the importance of environmental and occupational factors in cancer (9). Cancers caused by well-defined exogenous factors usually occur in adults and arise from epithelial tissues of the skin, respiratory, and upper digestive tracts where sunbathing, smoking, and excess alcohol consumption are major etiologic factors. Geographically clustered tumors are associated with the environment but not proved to be caused by environmental factors.

The incidence of cancer differs dramatically in different parts of the world. For example, the annual incidence per 100,000 American men for colon cancer and stomach cancer are 31.5 and 13.5, respectively, compared with 5.6 and 84.6 for Japanese men. In limited circumstances, the incidence of cancer in immigrants assumes the level of the host country, suggesting that the influencing factors are related to environment. In Haenzel and Kurihara's study (10) of Japanese immigrants to the United States, Japanese born in Japan had gastric cancer mortality rates much closer to those of the country of origin than to the country of destination. Thus, the rates for Japanese born in the United States, although lower than those prevailing in Japan, still exceed those for whites in the United States. This observation suggests the gradual disappearance of some environmental factor from the lives of the immigrants and their descendants. In the same period, the mortality from colon cancer among both immigrants and their descendants rose to approach that for white men in the United States (10).

The role of industrial pollution is not clearly understood. Contamination of the environment by such carcinogens as polycyclic aromatic hydrocarbons lasts a long time. But, with the major exceptions of cancer of the lung and stomach, the overall cancer rates in the United States have been relatively stable for the past thirty years. The increasing incidence of malignancy observed in black men is largely due to cancers of the esophagus and prostate, cancers which are not readily attributable to industrial factors. Many attempts have been made to correlate cancer patterns with place of residence, population density, and urban versus rural environment. Data, however, are inconsistent. When population groups with homogeneous lifestyles are examined, urban versus rural differences largely disappear (9). An association between bladder cancer and exposure to chemical industries has been demonstrated in the United States but not in Japan. Prostatic cancer occurs twice as often among American black men as among whites living in the same county, but the incidence is much higher for both groups than for men in the industrialized United Kingdom and many times higher than for men in Japan (9).

Identification of high-risk occupational groups has proved an effective method of identifying exposures to specific chemical carcinogens. However, not all differences in cancer frequency necessarily reflect occupational chemical exposure. In the United Kingdom, although certain occupations are associated with a greater or lesser risk of cancer than the population average, nearly 90% of such variations can be eliminated if individuals of similar habits and social classes are compared (11). Such findings indicate that problems of occupational cancers are not limited to occupational exposure but include other factors of individual lifestyles. For example, inhalation of asbestos is associated with an increased incidence of bronchial, gastrointestinal, and mesothelial cancers (12). In cigarette smokers the combined effect of smoking and asbestos inhalation on the incidence of bronchial cancer is synergistic. An asbestos worker who smokes has eight times higher a risk than smokers of the same age who do not work with asbestos and 92 times the risk of those who neither smoke nor work with asbestos.

Diet as a risk factor in cancer has been implicated in the development of tumors of the gastrointestinal tract and breast, but the specific role of dietary factors is difficult to evaluate. Thus, while breast and colon cancer are thought to be related to meat, fiber, fat, and caloric

intake, such hypotheses have not been supported by studies in populations with homogeneous lifestyles (13). Evidence also differs about the effects of fecal flora and biliary steroids, as well as intestinal transit time, on the incidence of colon cancer of the large intestine. Even a seemingly consistent relationship like that of dietary fiber and colon cancer is apparent in only a few studies; and the nature of the protective effect of dietary fiber is not clearly understood.

Cigarette smoking is an important element of lifestyle that has become the single most important health hazard of our time (14). Cigarette smoking contributes to as much as 40% of the cancer burden in the United States. Its relation to many types of cancer, especially lung cancer, is indisputable (15). Approximately 85% of lung cancers (squamous cell and small cell anaplastic type) associated with cigarette smoking can be prevented (16). Tobacco and excessive alcohol use are two widely accepted factors that contribute to the development of squamous cell carcinoma of the esophagus as well as to epidermoid cancers of the oral cavity and pharynx.

Whether there is a cancer-prone personality is not certain (17). The relationship of behavior patterns to risk factors is implicit in the observation that cancer of the cervix is seen more frequently in persons who experience early coitus, multiple pregnancies, multiple sex partners, and venereal disease (18).

Therefore, age, sex, heredity, and specific carcinogens do influence the susceptibility to cancer. Environmental, occupational, and personality factors are less well understood. And since the origin of cancer is thought to be multifactorial, the relative importance of each individual cause is difficult to evaluate. It is therefore necessary to identify patients who are known to be at risk and to devise effective screening procedures that facilitate early diagnosis and better management. Since breast and colorectal cancers are commonly observed neoplasms for which early detection by screening procedures is feasible and for which early management results in better outcome, we will review the incidence, risk factors, and screening procedures for these neoplasms.

Specific Considerations

One woman in 14 will develop breast cancer in her lifetime, and this rate is expected to increase (19). Rates for blacks and whites in the United States differ little. One percent of breast cancer occurs in men. The principal risk factors include family history, history of benign disease, menstrual history, and reproductive history (see Table).

Daughters of patients with breast cancer have a two or three times greater risk of developing breast cancer than the average population. In succeeding generations, the cancer appears ten years earlier and may be bilateral.

TABLE
Risk Factors for Breast Carcinoma*

		Relative Risk
Family history of breast cancer		2-3
Family history of bilateral breast cancer		6-9
Family history of mastopathy		4.0
First-term pregnancy	age 20	0.4
First-term pregnancy	age 35	1.2
Menarche	age 16	1.8
Menopause	age 55	2.0
History of colon, endometrial, or ovarian cancer		1+

*Taken from MacMahon B, Cole P, Brown J. Etiology of human breast cancer: A review. J Natl Cancer Inst 1973;50:21-42.

Rarely, families have been reported in which breast cancer occurs in 50% of the female progeny. Relatives of patients with bilateral breast cancer are reported to have a six- to ninefold chance of developing breast cancer compared to the normal population (20).

The history of mastopathy is associated with a fourfold increased incidence of breast cancer, and the risk appears to last thirty years after the diagnosis of benign disease (21). Nonparous women are also at greater risk than parous women. A woman who bears her first full-term child before age 18 has a one-third risk compared with a woman who is 35 before she has her first baby. Nursing confers no protection against breast cancer. Women who have earlier menarche and more years of menstruation have a relatively greater risk. Breast cancer has been associated with ovarian, endometrial, and colon cancers, but the degree of risk is not clear.

Increased serum prolactin concentration in patients treated with reserpine for hypertension has not been established as a significant risk factor (22). Data are accumulating that long-term treatment with estrogens for symptoms of menopause increases the risk of breast cancer. Among women with intact ovaries treated with a total cumulative dose of estrogen in excess of 1500 mg, the risk is 2.5 greater than the risk for women not so treated (23). No increase in the risk of breast cancer has been observed in women taking estrogen-progesterone combinations commonly prescribed for contraception (24).

The question is debated as to whether the primary treatment of breast cancer reduces mortality. If initial therapy fails to alter the ultimate outcome of the disease, efforts at early detection have little significance. The negative position in the debate is based upon the crude historic observation that breast cancer patients may be self-selected into one of two groups: in the first, the disease has a rapid course resulting in death within limited years; in the second, the course is protracted, sometimes allowing the patient to live a normal lifetime. Phillips (25) compared two series of treated and untreated patients with cancer of the breast matched for age

at diagnosis and found that survival was greater for treated patients for each year up to eight years. When he compared two series matched for age at onset of symptoms, the differences in survival were not significant (25).

The positive position in the debate is based upon the theory that at least 60% of breast cancer is confined to the breast in its initial stages and can be cured by primary therapy if treated early. The risk of recurrence correlates well with the stage of the disease at the time of treatment, which is primarily a function of the size of the primary tumor and the number and distribution of involved regional lymph nodes (26).

The question of the value of primary treatment cannot be answered through a randomized trial since withholding such treatment is simply not acceptable. However, the following observations support the positive position.

The natural history of classic breast cancer is that it begins in the breast, spreads first to regional lymph nodes, and finally metastasizes hematogenously. The size of the primary tumor correlates directly with the number of involved axillary nodes, and survival is directly proportional to the number of lymph nodes involved at the time of primary treatment (27). The 10-year survival for patients with no involved axillary lymph nodes of 65-76% is compared to 38-67% for patients with one to three involved nodes and to 13-27% for patients with four or more involved nodes (28,29). Decreased mortality among patients who received treatment before the primary tumor was large enough to be palpable is even more convincing. The Health Insurance Plan of Greater New York randomly allocated patients into one of two groups to be screened for breast cancer. The study group had physical examination and mammography scheduled and conducted annually. The control group had the same studies but not on a regularly scheduled annual basis. There was a 30% decrease in mortality from breast cancer during 10 years of follow-up in the study group over the control group of women over age 50; and while there were fewer deaths in the study patients between age 40 and 49, the difference was not statistically significant (30). Patients with cancers which were too small to palpate and could be detected only by mammography had a 78% 10-year survival (31).

On the other hand, an important subset of breast cancer patients may not be cured by early detection and primary treatment of breast cancer. These are patients whose cancers are estrogen receptor negative (ER-). Approximately 40% of breast cancer is ER- and 60% ER+. In Osborne's series of 281 patients undergoing mastectomy for Stage I or II breast cancer (32), the rate of recurrence in patients with ER- tumors was higher than among patients with ER+ tumors, regardless of age, menopausal status, size of the tumor, or its location in the breast. After two years of follow-up, 35% of patients with ER- tumors had recurrence compared with 18% of ER+. The difference in Kaplan-Meirer survival curves was significant (P=0.004). Knight (33) has followed 171 post-operative Stage I cancer patients for 28 months. In 117 ER+ patients, 8% of the cancers recurred, compared with 54 ER- patients with 26% recurrence (P=0.0009). Although this advantage appears to disappear gradually as the interval after mastectomy increases, the frequency of early relapse in ER- is widely reported. Conceptually, the ER- tumor may not follow the orderly process of local to nodal to systemic disease, and its course may not be influenced by mastectomy.

Breast cancer can be detected in early stages through screening, as shown by the breast cancer detection demonstration project (BCDDP) (34). Women were screened with clinical examinations and mammography yearly for five years, and all patients were encouraged to practice breast self-examination on a monthly basis. Two hundred and eighty thousand women participated in the project. Of the 4,443 cancers recorded, one third were small, either non-infiltrating or infiltrating, and less than 1 cm in diameter. In over 80%, no evidence of nodal involvement was found. The diagnostic contribution of mammography alone in the absence of abnormal physical findings was 41.6%, compared to 8.7% for abnormal physical examination in the absence of positive mammogram findings. Of the 762 cancers detected in women aged 40 to 49, mammography alone was responsible for detecting 35.4%.

Therefore, it is important to detect breast cancer in its earliest possible stage and to provide primary management. It is reasonable to expect that mortality will be reduced in patients who present with Stage I or Stage II tumors and that better results will occur in patients whose cancer is ER+ rather than ER-.

Asymptomatic patients may be screened according to the Henry Ford Hospital screening recommendations. Patients with risk factors should be screened according to the following American Cancer Society recommendations (35,36):

1. Women aged 20 to 40 years should have a breast physical examination every three years, and women over 40 should have a breast physical examination every year. All women over 20 should perform breast self-examination monthly.
2. Initial mammograms should be obtained between ages 35 and 40. Women between 40 and 49 years should have a mammogram every one to two years, and women 50 and over should have a mammogram annually. Mammography should be low-dose, with the radiation kept preferably below 0.5 rads for two views.

Colorectal Cancer

Carcinoma of the colon and rectum will occur in 5% of men and 6% of women born in the U.S. There is approximately a twofold increase in incidence every 10 years between the ages of 40 and 75, and the incidence rate has not changed in the past 40 years. Although colon and rectal cancers are usually considered together, it has not been established that they are caused by the same agents. Within the past decade the incidence of colonic and rectal cancers is shifting from a predominance in the rectum to a predominance in the colon (37). Primary tumors of the colon are more frequent in women than in men, while primary tumors of the rectum are more frequent in men than in women. The principal risk factors include a history of polyps or prior colon cancer, family history of cancer of the colon or rectum, familial polyposis, Gardner's syndrome, and ulcerative colitis.

The concept of a polyp-to-cancer sequence is increasingly credible (38). Small foci of intramucosal cancer are common in polyps but are extremely rare in normal mucosa (39). The larger the polyp, the greater the likelihood of associated cancer. Adenomatous polyps under 1 cm in size have a 1% incidence of invasive cancer, polyps 1 to 2 cm have a 10.2% incidence, and polyps over 2 cm have a 37.7% incidence. As polyps increase in size and as the patient's age increases, so does the incidence of villous adenomas. The peak age incidence for villous adenomas is 65.2 years, and cancer is found in 40% of them. Perhaps the most significant clinical evidence of the polyp-to-cancer transition hypothesis is the observation that patients who remain polyp-free also remain cancer-free. In Gilbertson's study, 21,150 individuals underwent proctosigmoidoscopic examinations annually. Polyps found were removed, and 25 adenocarcinomas were detected on the initial examination. Over the subsequent 92,650 patient years of follow-up, 13 additional cancers were detected. Epidemiologic data predicted 1 cancer per 1,000 patient years or about 90 cancers. Therfore, only 15% (13/90) of the expected cancers appeared (40). Patients with previous colorectal cancers have an annual incidence of a second primary colorectal cancer of about 3.5 per 1,000 compared to the 1 per 1,000 expected in the general population (41).

Inheritance of colon cancer occurs without polyposis and is characterized by autosomal dominant inheritance, a low mean age (41 years) for occurrence, and a marked increase in the proportion of cancers located in the proximal colon (42). In addition to hereditary risk factors, having a single relative with colorectal cancer gives family members a three- to fourfold increased incidence of colorectal cancer compared to the general population (43). The causes are not clear but may be due to environmental factors. Familial polyposis is inherited as an autosomal dominant trait with 90% penetrance. It occurs in 1 of 8,000 live births. Polyps occur between the ages of 15 to 25 years. By age 37, over 50% of patients will develop colon cancer, and unless colectomy is performed in early adulthood, the death rate from colon cancer approaches 100% (44). About one in seven families with polyposis have one or more features of Gardner's syndrome, which is characterized by subcutaneous cysts, desmoid tumors, fibromas, facial bone osteomas, and abnormal dentition. In patients with ulcerative colitis, the incidence of colorectal cancer is 5 to 11 times higher than in the normal population. The risk is greater when the disease begins in childhood, has been present more than 10 years, involves the entire colon, has continuous rather than intermittent symptoms, and was severe in onset (45). Patients with granulomatous bowel disease (Crohn's disease) have an increased risk of colonic cancers, but it is not as great as that of patients with ulcerative colitis.

Survival depends on stage of the tumor at the time of treatment. The natural history of rectal cancer was first described by Dukes (46). The neoplasm classically begins on the mucosa, extends to the submucosa (Dukes A), into the muscularis propria (Dukes B), and finally to the perirectal tissues and local lymph nodes (Dukes C) (44). Although the Dukes classification has had many modifications, they all follow the natural history. Survival is proportional to the degree of bowel wall penetration and number of nodes involved at the time of surgical resection. Patients with Dukes A have a greater than 81% chance of survival compared to patients with five or more involved nodes, who have as low as a 10% survival rate (47,48).

Routine annual sigmoidoscopy for early detection in the asymptomatic patient is neither affordable nor acceptable. Because the doubling time of colorectal cancer is usually prolonged, it may take several years for a mass detectable by screening to progress to a symptomatic stage (49). The peak incidence of colorectal cancer occurs at age 59, while the peak age at which polyps are diagnosed precedes that of cancer by about five years (50). Therefore, sigmoidoscopy at age 50 is appropriate to identify the risk factors of polyps and to screen for early cancer. Hemoccult testing has a potential for a major impact in early detection. At the University of Minnesota Hospital, 525 of 23,500 patients had one or more positive tests; of 415 patients who returned for follow-up, 42 had primary cancers of the colon or rectum (51). Of these, 73% were Dukes A, 11% Dukes B, 9% Dukes C, and 7% Dukes D. Since about 50% of patients usually present with Dukes C tumors, a marked increase in survival is expected for those patients detected early and classified in the Dukes A category. Therefore, detection of colorectal cancer in the earliest possible stage is purposeful.

Asymptomatic patients may be screened according to the Henry Ford Hospital screening recommendations. Patients with risk factors should be screened according to the following American Cancer Society recommendations (52):

1. All persons age 40 and over should have digital rectal examination annually.
2. All persons age 50 and over should have annual stool guaiac tests.
3. All persons age 50 should have sigmoidoscopy performed every three to five years after two initial negative sigmoidoscopies one year apart.
4. Patients with risk factors of positive family history of colorectal cancer, familial polyposis, or ulcerative colitis should begin screening before age 40.

References

1. Bridges JD, Killip T, Krane NK, MacDougal DB, Petrozzi CF, Somand ME, Steigerwalt S. Recommendations for care of the asymptomatic patient. Henry Ford Hosp Med J 1983;31:95-100.
2. Cutler SJ, Young JL. Third National Cancer Survey. National Cancer Institute Monograph 1975;41:1-454.
3. Cancer Statistics 1983. CA 1983;33:8-25.
4. Miller DG. On the nature of susceptibility to cancer. Cancer 1980;46:1307-18.
5. Knudson AG. Retinoblastoma: A prototype hereditary neoplasm. Semin Oncol 1978;50:57-60.
6. Schimke RN, Hartmann WH, Prout TE, Rimoin DL. Syndrome of bilateral pheochromocytoma, medullary thyroid carcinoma and multiple neuromas. N Eng J Med 1968;279:1-7.
7. The genetics of neurofibromatosis in multiple neurofibromatoses. Springfield, IL: Charles C. Thomas, 1956.
8. Rapola J. Heredity of cancer. J Toxicol and Environ Health 1980;6:983-7.
9. Higginson J. Importance of environmental and occupational factors in cancer. J Toxicol and Environ Health 1980;6:941-51.
10. Haenzel W, Kurihara M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst 1968;40:43-51.
11. Fox AJ, Addstein AM. Occupational mortality: Work or a way of life. J Epidemiol Community Health 1978;32:73-8.
12. Selikoff IJ. Cancer risk of asbestos exposure. In: Hiatt HH, Watson JD, Winsten JA, eds. Origins of human cancer. New York: Spring Harbor Laboratory, 1977:1765-84.
13. Engroston JE. Cancer and total mortality among active Mormons. Cancer 1978;42:1943-51.
14. Surgeon General's Advisory Committee on Smoking and Health. Washington, DC: Govt Printing Office, 1979. (U.S. Dept. HEW, PHS 79-50066).
15. Hammond EC. Smoking in relation to death rates in one million men and women. IN: Haenzel W, ed. Epidemiology of cancer and other diseases. Bethesda, MD: Natl Cancer Inst, 1966:127-204.
16. Newell GR. Comments on epidemiology, etiology and prevention of lung cancer. Cancer Bull 1980;32:76-7.
17. Wellisch DK, Yager J. Is there a cancer-prone personality? CA 1983;33:145-53.
18. Rotkin ID. A comparison review of key epidemiological studies in cervical cancer related to current searches for transmissible agents. Cancer Res 1973;33:1353.
19. Kelsey JL. A review of the epidemiology of human breast cancer. Epidemiol Rev 1979;1:74-109.
20. MacMahon B, Cole P, Brown J. Etiology of human breast cancer: A review. J Natl Cancer Inst 1973;50:21-42.
21. Monson RR, Yen S, MacMahon B. Chronic mastitis and carcinoma of the breast. Lancet 1976;2:224-6.
22. Rauwolfia and breast cancer. Lancet 1975;2:312-3.
23. Ross RK, Paganini-Hill A, Gerkins VR. A case-control study of menopausal estrogen therapy and breast cancer. JAMA 1980;243:1635-9.
24. Brinton LA, Williams RR, Hoover RN. Breast cancer risk factors among screening program participants. J Natl Cancer Inst 1979;62:37-43.
25. Phillips AS. A comparison of treated and untreated cases of cancer of the breast. Br J Cancer 1959;13:20-5.
26. Brennan MJ. Breast cancer. In: Holland JF, Frei E, eds. Cancer medicine. Philadelphia: Lea & Febiger, 1973;1769-88.
27. Fisher B, Slack NH, Borss ID. Cancer of the breast: Size of neoplasm and prognosis. Cancer 1969;24:1071-80.
28. Hellman S, Harris JR, Carellos GP, Fisher B. Cancer of the breast. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer principles and practice of oncology. Philadelphia: JB Lippncott, 1982;920.
29. Fisher B, Slack NH, et al. Number of lymph nodes examined and the prognosis of breast cancer. Surg Gynecol Obstet 1970;131:79-88.
30. Mammography 1982: A statement of the American Cancer Society. CA 1982;32:226-30.
31. Shapiro S. Health insurance plan of Greater New York mammography study progress report, December 1, 1977 to November 25, 1978.
32. Osborne CK, Yochmowitz MG, Knight WA, McGuire WL. The value of estrogen and progesterone receptors in the treatment of breast cancer. Cancer 1980;46:2884-8.
33. Knight WA, Osborne CK. Steroid hormones in the management of human breast cancer. Ann Clin Res 1980;12:202-7.
34. ACS report on the cancer-related health checkup: Cancer of the breast. CA 1980;30:224-9.

35. Mammography guidelines 1983: Background statement and update of cancer-related checkup guidelines for breast cancer detection in asymptomatic women age 40 to 49. CA 1983;33:255.

36. Baker LH. Breast cancer detection demonstration project: Five-year summary report. CA 1982;32:194-225.

37. Rhodes JB, Holmes FF, Clark GM. Changing distribution of primary cancers in the large bowel. JAMA 1977;235:1641-3.

38. Hiromi S, Wolff WI. Morphology, anatomic distribution and cancer potential of colonic polyps. Ann Surg 1979;190:679-83.

39. Fenoglio CM, Lane N. The anatomical precursors of colo-rectal carcinoma. Cancer 1974;34:819-23.

40. Gilbertson VA, Knatterud GL, Lober PH. Invasive carcinoma of the large intestine: A preventable disease? Surgery 1965;57:363-5.

41. Schottenfeld D, Berg JW, Vitsky B. Incidence of multiple primary cancers. II. Index cancers arising in the stomach and lower digestive system. J Natl Cancer Inst 1969;43:77-86.

42. Lynch HT, Lynch PM. Heredity and gastrointestinal tract cancer. In: Lipkin M, Good RA, eds. Gastrointestinal tract cancer. New York: Plenum, 1978.

43. Lovett E. Familial factors in the etiology of carcinoma of the large bowel. Proc R Soc Lond [Biol] 1974;67:751-2.

44. Bussey HJR. Familial polyposis coli. Baltimore: Johns Hopkins University Press, 1975.

45. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Gut 1964;5:1-22.

46. Gordon-Watson C, Dukes C. The treatment of carcinoma of the rectum with an introduction on the spread of cancer of the rectum. Br J Surg 1930;17:643-69.

47. Bussey HJR, Dukes CE, Lockhart-Mummery HE. Results of the surgical treatment of rectal cancer. In: Dukes CF, ed. Cancer of the rectum. London: E&S Livingston, 1960;207-80.

48. Copeland EM, Miller LD, Jones RS. Prognostic factors in carcinoma of the colon and rectum. Am J Surg 1968;116:875-880.

49. Welin S, Yonker J, Spratt JS. The rates and patterns of growth of 375 tumors of the large intestine and rectum observed serially by double contrast enema study. Am J Roentgenol, Rad Therapy and Nuclear Med 1983;90:673-87.

50. Muto T, Bussey HJR, Morson BC. The evaluation of cancer of the colon and rectum. Cancer 1975;36:2251-70.

51. Gilbertson V. Colon cancer screening: The Minnesota experience. Gastrointest Endosc 1980;26:315-325.

52. Facts about colorectal cancer detection. CA 1983;33:366-7.