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Extrahepatic Bile Duct Cancer

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This review was undertaken after one of the authors (S.M.B.) noted an increased incidence of extrahepatic bile duct cancer at Montefiore Hospital and Medical Center. Although the etiology of this uncommon tumor is not known, one hypothesis is that extrahepatic bile duct cancer may be caused by a carcinogen in the bile, either ingested or inhaled, or a transformation product of an ingested or inhaled substance.

At Montefiore Hospital and Medical Center the number of cases of extrahepatic bile duct cancer reported was:

Before 1960	7
1960–65	10
1965–70	12
1970–75	20
Jan. 1, 1976, to Dec. 31, 1979	19

Possible explanations for this increase are: (1) increased diagnostic skills resulting in more diagnoses; (2) referral of cases to a large center; and (3) a true increase in incidence. It is unlikely that the second hypothesis is true because almost all patients were self referred to Montefiore Hospital and Medical Center or to its affiliated physicians.

Incidence

All authors agree that tumors of the biliary tract are comparatively rare, although there is a possibility of significant underreporting because of difficulties in both macroscopic and microscopic diagnosis. There is a 2:3 female-to-male ratio, with the age-adjusted incidence rate generally higher in whites. The age range is wide, with peak incidence in the sixth decade in several series.[1] Incidence is significantly higher in American Indians,[2,3] in the Mexican population in the southwestern part of the United States,[4] and in Japanese migrants to the United States.[5]

The incidence of cancer of the extrahepatic bile ducts may be expressed in several ways. In a review of 12 autopsy series published in 1957,[6] there was a variation in incidence from 0.012 percent to 0.458 percent, while carcinomas were found in 0.3 percent and 1.8 percent of all biliary tract operations performed in 2 series. As a percentage of all hospital admissions, cancer of the extrahepatic biliary tract accounted for 0.007 to 0.041 percent of the total figure.

The National Cancer Institute's Third National Cancer Survey[7] estimated 11,800 new cases of carcinoma of the liver and biliary passages in 1976, while the U.S. government vital statistics report for 1975 listed 4,276 deaths due to malignant lesions of the biliary passages. If 40 percent of the anticipated new cases of liver and bile passage malignant neoplasms during 1976 are bile duct carcinomas, approximately 4,500 new cases can be expected in this country in 1980.

The average annual crude incidence rate from 1969 through 1971 for biliary tract cancer in the United States is 1.2 per 100,000, while the average annual age-adjusted incidence rate (1970 standard) is 1.3 per 100,000.[7] It is difficult to ascertain a trend because, while the Third National Cancer Survey[7] classifies gallbladder cancer separately from other biliary tract neoplasms, which are primarily extrahepatic bile duct carcinomas, in previous cancer surveys data for gallbladder cancer and other biliary tract neoplasms were lumped together. Another handicap is the failure of the International Classification of Diseases to distinguish between cancers of the liver and the biliary system until the seventh revision in 1958.[8]

Many authorities believe that gallstones are etiologically related to bile duct cancer. Data published by Stewart, Lieber, and Morgan,[9] Neibling, Dockerty, and Waugh,[10] Sako, Seitzinger, and Garside,[6] and Ross, Braasch, and Warren[11] have shown that gallstones are associated with 20 to 57 percent of such cancers. Although, on the average, gallstones are found in about one third of patients with bile duct cancer, this fact is of unknown significance.

Biliary tract carcinoma is possibly 10 times more frequent in patients with ulcerative colitis than in the general population.[12] A series of 13 patients with bile duct cancer (excluding gallbladder cancer) and associated chronic ulcerative colitis seen at the Mayo Clinic from 1935 to 1973[13] and a review of the literature suggest that the relationship between chronic ulcerative colitis and bile duct cancer is not just a chance occurrence. The carcinoma has an onset approximately three decades earlier than cancer of the bile ducts without chronic ulcerative colitis, and

neither surgical removal of the diseased colon, mode of medical management of the unresected colon, nor extent or severity of the colonic disease have any relationship to the subsequent development of cancer of the bile ducts.[13] However, no mechanism of causation is apparent, and "it would appear that biliary tract cancer is another member of the spectrum of hepatic disorders that may occur in patients with ulcerative colitis, but which progress independently of the colonic disease."[13]

There is a strong association of bile duct carcinoma with congenital biliary tract cysts (choledochal cysts). This may result from interaction between chronic inflammation and carcinogenic substances excreted in the bile. The presence of a cyst could lead to bile duct stasis with resultant prolonged exposure of the mucosa to bile.[14]

Studies of vinyl chloride workers have shown a much higher rate of liver and biliary tract cancer than that expected, but, unfortunately, the significance of these data could not be ascertained because extrahepatic biliary tract cancer was not classified separately.[15,16]

In 1970, an epidemiologic survey of rubber workers suggested an excess of cancer of the gallbladder and bile ducts.[17] There was also a shift in age distribution to younger groups, which would support association with employment. Occupational mortality statistics from California demonstrate that gallbladder and bile duct cancers are prominent among automotive and rubber plant workers, while bile duct cancers show increased incidence in workers in the aircraft, chemical, and wood finishing industries.[18]

Chemical factors

Laboratory animals have been used to demonstrate the excretion in the bile of experimental carcinogens or their metabolites, with associated concentration in the bile and gallbladder. A number of chemicals tested by animal bioassay have produced biliary tract changes, proliferation of bile ducts, bile duct hypertrophy, cholangiomas, cholangiocarcinomas, and carcinomas in the bile ducts.

A number of complex chemicals used in the rubber industry, including nitrosamine compounds, benzidine, Flectol H, and M-toluylene diamine were shown by investigators to be injurious to the hepatobiliary system. Rats fed Flectol H, a polymer of 1-2 dihydro-2,2,4-trimethyl quindine, developed biliary tract hyperplasia, atypical proliferation of the biliary ducts and of fibrous tissue, and cholangiofibrosis, considered a precursor to biliary duct carcinoma. Oral administration of M-toluylene diamine induced proliferation of the bile ducts, followed by carcinoma. Cyclohexylamine, a carcinogenic metabolic product of cyclamates, is also used in the rubber industry. Therefore, many investigators conclude that certain chemicals are an etiologic factor in the development of carcinoma of the bile ducts among rubber workers.[17]

An increased number of self-referred patients with extrahepatic bile duct cancer have been seen at Montefiore Hospital and Medical Center in the last ten years. Although improved diagnostic methods may partially explain this phenomenon, actual increased incidence is suggested. The literature is reviewed for known causative factors in extrahepatic bile duct cancer. Transhepatic cholangiography, routinely carried out in extrahepatic bile duct cancer patients, would be a good source of bile for study of carcinogenic and mutagenic activity.

Daily oral doses of the pesticide aramite led to the production of gallbladder and bile duct carcinoma in dogs in at least one experiment.[18] Two dogs who were fed 8-aminoazotoluene, one for 30 months and the second for 62 months, developed adenocarcinomas involving the entire biliary tract which resembled the diffuse involvement of the biliary tract by cancer in human beings.[19] Mice fed cholesterin, cholic acid, and the carcinogen 2-acetamidofluorene or its N-hydroxy derivative developed proliferation of mucosa in the extrahepatic bile duct, atypical cells in the mucosal epithelium of the bile duct, and, occasionally, adenocarcinoma of the common bile duct. Metabolites of the carcinogen and its derivative were found in the bile of these mice.[20]

Some investigators believe that the typical American diet of 45 percent fat results in the excretion of large quantities of bile acids which may act as cocarcinogens.[21] People who eat large quantities of smoked food or work in meat-smoking factories have a particularly high incidence of digestive cancers, possibly caused by polycyclic aromatic hydrocarbons and/or N-nitrosamines. Nitrites and secondary amines present in food and nitrates and nitrites added as preservatives react to form N-nitrosamines under mild conditions of temperature and pH. N-nitrosamines have been implicated in cancer causation in a wide variety of animals and in virtually every organ in the rat, and it is therefore postulated that man is also sensitive to these compounds.[22]

The carcinogenic action of aflatoxins, metabolites of some strains of *Aspergillus flavus*, has been studied in fish, birds, and mammals. Although the liver was the organ most affected in all species, marked intrahepatic bile duct proliferation, possibly representing a premalignant lesion, was noted in the rat, duckling, chicken, cattle, monkey, guinea pig, dog, and trout. Cholangiocarcinoma in the intrahepatic bile duct was seen in one rat, while bile duct hyperplasia occurred in the rabbit and in the cat. It is assumed that aflatoxin in the bile may be a factor in the production of bile duct proliferation and occasional areas of fibrosis. Although there is now no direct evidence that man is susceptible to aflatoxins, their demonstrated carcinogenicity in a broad spectrum of animals make them suspect as a hazard to

man. Furthermore, there is a high incidence of hepatocellular carcinoma but not extrahepatic bile duct cancer in many areas where climatic conditions favor the growth of such molds.[23]

Liver-fluke infections of the orient, *Clonorchis sinensis* and *Opisthorchis felineus* in the most populous countries of Asia, and *Opisthorchis viverrini* in parts of Thailand and Malaysia, are highly associated with bile duct carcinoma. The simplest explanation is that these flukes are responsible for an inflammatory reaction in the bile ducts, potentiating the action of carcinogenic agents excreted in the bile.

Cancer did not develop in any Syrian golden hamsters given the carcinogen dimethylnitrosamine in their drinking water in an experiment, but cholangiocarcinomas and cholangiofibrosis appeared in all when intragastric metacercariae of *O. viverrini* were administered first. The diet of northeastern Thais is rich in a fermented fish product containing substances transformable to nitrosamines.[14]

The etiology of extrahepatic biliary tract cancer is unknown, but there is certainly evidence from the literature to suggest that environmental factors cause biliary tract cancer, and that further epidemiologic investigation is warranted. Case-control studies are unlikely to provide clues as to the cause of bile duct cancer. Study of carcinogenic and mutagenic activity in bile of cancer patients compared to controls without malignant illness might be more productive. At present the best way to diagnose bile duct cancer is to perform a transhepatic cholangiogram. This technique allows the physician to collect bile for study without added risk to the patient. Bile could also safely be collected from patients who have abdominal surgery for benign conditions. Comparative studies could then be carried out for carcinogenic and mutagenic activity.

Specific carcinogens could be isolated, and bile could be studied for distribution patterns of bile acids and their conjugates.

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