

Is primary biliary cirrhosis a risk factor for hepatic and extrahepatic malignancies?

Melanie Deutsch

SUMMARY

Primary biliary cirrhosis (PBC) represents a classical cause of liver cirrhosis but clear data about the true risk of the development of hepatocellular carcinoma (HCC) are still lacking. Data are based especially on epidemiologic studies from different geographical areas and, since PBC is a relatively rare disease with a very slow natural course, the true incidence of HCC is not well known. However, most of the studies agree that patients with cirrhotic stage PBC are at increased risk and they should be included in a surveillance program. On the other hand, some authors suggested during the 1970s and early 1980s that PBC patients are at increased risk for development of extrahepatic cancer, especially breast cancer. These findings could not be confirmed in more recent larger studies and finally no higher risk of developing extrahepatic cancer has been documented in these patients.

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic progressive, cholestatic, liver disease of probable autoimmune etiology usually affecting middle aged women. It is characterized by non-suppurative destructive cholangitis with progressive loss of intralobular bile ducts, fibrosis and finally cirrhosis. Its clinical course is prolonged, characterized by progressive cholestasis manifested with pruritus and jaundice resulting ultimately in clinical features of liver failure and end stage liver disease.^{1,2}

The natural history of PBC is extremely variable, while treatment with ursodeoxycholic acid (UDCA), especially when started in early stages of the disease, seems to im-

prove liver function tests, but there are conflicting data on whether it can delay histological progression and prolong survival time without liver transplantation.³⁻⁷

Although PBC represents a classical cause of liver cirrhosis, the risk of the development of hepatocellular carcinoma (HCC) was considered relatively low even in populations with high incidence of PBC.⁸⁻¹¹ In contrast, there are several other reports which have found a minimal difference in the risk of HCC development in patients with PBC compared with other causes of liver disease especially in late stages of PBC.⁹⁻¹⁵ However the true incidence of HCC in PBC is still unknown.

On the other hand, several authors reported that PBC may be associated with extrahepatic malignancies⁹⁻¹¹ especially breast cancer⁹⁻¹¹ but the data are quite controversial.

The aim of this review is to point out the current knowledge regarding the association of PBC with HCC and possible extrahepatic malignancies.

PBC AND HCC

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world; it represents the third leading cause of cancer death with an estimate of more than 500000 new cases each year. There is a striking difference in the incidence of HCC worldwide, with the majority of the cases occurring in developing countries but with a trend of rising rates in developed countries, where the incidence has doubled in the past two decades.^{9,10}

Unlike other malignancies, where pathogenesis has been established based on molecular events; in the case of HCC the mechanisms of carcinogenesis still remain practically unknown. However, clearly identified risk factors have been associated with hepatocarcinogenesis and in-

2nd Department of Internal Medicine,

Author for correspondence:

Melanie Deutsch, Hippokraton General Hospital, Athens, Greece

clude hepatitis B (HBV)¹¹ and C (HCV)¹² viral infection, alcohol, the presence of cirrhosis, older age, male gender and aflatoxin exposure.¹³ Other risk factors include hereditary metabolic diseases such as haemochromatosis, α -1-antitrypsin deficiency and hereditary tyrosinemia. Metabolic syndrome can lead to non-alcoholic steatohepatitis which is also a risk factor for HCC mostly through progression to cirrhosis.^{14,15}

It is obvious that cirrhosis, regardless of its etiology, can be considered the major risk factor for the development of HCC as indicated by the fact that the majority of virus-associated HCC are accompanied by cirrhosis.¹⁶ However, studies have shown that the risk of HCC development differs according to the underlying cause of cirrhosis.¹⁷ The cancer risk of hepatitis virus associated cirrhosis is much greater than in alcohol related cirrhosis. On the other hand, especially in HBV associated HCC, cancer may also develop in non-cirrhotic liver tissue, demonstrating that, in addition to cirrhosis per se, other factors play an important role in liver carcinogenesis. PBC, as an unknown chronic inflammatory disorder which leads to cirrhosis, may hypothetically be a reasonable cause of HCC.

The association of PBC and HCC is especially based on epidemiological studies with relative conflicting re-

sults.^{8-18,18,19} Some authors suggest that PBC is a rare precursor of HCC with a prevalence similar to that of the normal population,⁸⁻¹⁰ while other studies revealed higher incidence of HCC cases in PBC patients compared to those with other etiologies of chronic liver disease.¹² There are several reasons which may explain the discrepancy among the above studies. First, it is noteworthy that PBC is a rare disease. Moreover, the true frequency of the disease worldwide is unknown as many countries have no reported incidence and prevalence of PBC. On the other hand, differences in the health care systems result in inhomogeneous surveillance programs for HCC and in difficulties to follow up patients and to collect their data on an evidence basis for a prolonged follow up period. The sample size of the majority of the studies is relative small. Moreover, a gender-matched case control study is very difficult to conduct in this context because PBC occurs especially in females, while male gender seems to be associated with a higher risk of HCC as demonstrated in studies including patients with viral or alcoholic cirrhosis with a well known male predominance. On the other hand, HCC seems to have a different preponderance in different countries and most of the studies are not well controlled. In addition, the different studies used different methodologies; therefore a clear comparison of the data is very difficult to perform.

Table 1. Studies on the prevalence of HCC among patients with PBC

Reference (year)	Country	Patients (N)	Follow up	Prevalence of HCC	PBC/HCC association
Krasner, 1979	UK	98	autopsy study	4.1%	+
Nakanuma, 1990	Japan		autopsy study	5.4%	+
Floreani (14), 1992	Italy	175	6.8 years	2.3% (10,8% in stage IV) HCV superinfection in 50%	+/-
Farinati (15), 1994	Italy	89	57 months	0.4% (1.4% in stage IV)	-
Loof (10), 1994	Sweden	559	9 years	1.6	-
Turissini (11), 1997	USA	614	registry	0.65%	-
Jones (16), 1997	UK	667	79 months	2.4% (5.9% in stage IV)	+/-
Van Dam, 1997	Netherland	417	Death registry	SMR 25.5	+
Nijhawan (13), 1999	USA	1692	4,4 years	RR:46(females), 55 (males)	+
Howel (9), 1999	UK	769	Cancer registry	SIR 74, SMR 39	+
Caballeria(12), 2001	Spain	140	74.4 months	3.6% (11.1% in stage IV)	+
Findor (34), 2002	Argentina	292	36.5 months	1.3% (3.4% in stage IV)	-
Shibuya (18), 2002	Japan	396	43 months	3.5%	+
Deutsch (17), 2008	Greece	212	6 years	3.8% (15% in stage IV)	+

SIR = Standard Incidence Ratio, SMR = Standard Mortality Ratio, RR=relative risk

Except of some anecdotal case reports, library search revealed very few prospective studies of systematical follow up of a cohort of patients, some studies of retrospective chart review, two autopsy studies and one study performed on the base of a death register. (Table 1)

One of the most important and best organized registry of PBC with long term follow up of the patients has been conducted in the United Kingdom in Newcastle upon Tyne.²⁰ The authors performed a study in 667 patients with PBC followed up for over a 20 year period (minimum 1 year).¹⁶ 273 patients (243 female and 30 males) were in histological stage III or IV with 130 patients diagnosed as having cirrhosis and were followed up for 87.7±55.3 months. Sixteen patients developed HCC during follow up, all were in advanced stages of the disease at the time of HCC diagnosis. The overall incidence of HCC was 2.4% but was much higher if the cases with advanced disease were considered (5.9%). Moreover, the incidence of HCC was significantly higher in males (20%) than in females (4.1%). HCC played a causal role of death in PBC patients in 11.8% of the cases. (45.4% in males). This study clearly demonstrated the association of PBC with HCC especially in advanced stages of the disease and in males.

In contrast, a report from Sweden,¹⁰ in a cohort of 559 patients followed for 9 years, found a much lower incidence of HCC (1.6%) suggesting that an association is less probable than in other liver diseases.

The same data are reported from the large Mayo Clinic PBC cohort study (the Mayo experience). During a follow up of 9 years HCC developed in less than 1% of their PBC patients (12/1689)¹³. However this study has been performed retrospectively reviewing the charts of 1692 patients with PBC. Although HCC patients seem to represent a relatively small number of cases, when the expected number of malignancies was computed based on the general population data, a significant discrepancy between observed and expected cases of cancer was documented. So the authors finally concluded that hepatobiliary cancers had a relative risk of 46 ($P < 0.0001$) for women and 55 ($P < 0.0001$) for men which was considered an important risk. There are no data about the PBC stage at the time of cancer diagnosis in this study.

The same methodology has been used by investigators in Italy who included 175 patients in a prospective follow up study for a mean 6.8 years.¹⁴ They compared the incidence of malignancies in this cohort with the expected number of malignancies in the general population determining the proportional incidence ratio (PIR). Four cases of HCC have been documented (2.3%) with an incidence

/100000 people/year of 337. The PIR for HCC was 26.27 indicating a strong association between PBC and HCC. All HCC cases developed in females with stage IV disease (incidence in stage IV disease of 10.8%). However, in two of the 4 HCC cases, the HCV-RNA was found positive. The presence of HCV was considered a possible important factor contributing to the development of HCC.

Two further comparative studies have been performed using a matched control group of patients with cirrhosis of another etiology. The results of these studies are more relevant regarding the risk of HCC in PBC.

The first is a relatively small study from Italy which compared 89 female patients with PBC with 73 female patients with cirrhosis of another etiology.¹⁵ The relative risk of HCC development was found low (0.7) in PBC. However, when considering the cirrhotic patients with PBC the relative risk was 1.5 with respect to controls. These data confirmed the PBC/HCC association in advanced stages of the disease as suggested by the other studies, concluding that the risk of HCC is similar in PBC to other causes of cirrhosis.

The same message came from a study in Spain which compared a group of 140 PBC patients with a matched group of HCV cirrhotic patients.¹² In the cohort of PBC patients 5 (3.6%) developed HCC (all in stage IV disease). The probability of developing HCC was overall significantly higher in patients with HCV cirrhosis than in PBC patients but became quite similar when compared with advanced stage PBC (15% versus 11.1%) These data reinforce the concept that cirrhosis per se represents an important risk factor for HCC development.

In our experience, following up 212 Greek patients with PBC for a mean period of 6 years (range 1-23 years) we found an overall HCC incidence of 4% (eight patients).¹⁷ All patients had stage IV disease at the time of HCC diagnosis. The overall cumulative HCC incidence rates were 0,14% respectively at 1,5 and 10 years of follow up. Moreover, the HCC cumulative incidence rate was found significantly higher in the 55 patients with stage IV PBC included in the study (0,2, and 16% at 1,5, 2 and 10 years). In our cohort, HCC was diagnosed incidentally in two cases during the histological evaluation of the whole liver (explant and autopsy). These findings suggested that the true incidence of HCC may be underestimated. Similar findings have been reported in two autopsy studies where HCC was found in the liver at autopsy in 4.1-5.4% of patients with PBC who died without a known HCC^{11,21}.

In conclusion, despite the paucity of the data found in the literature and despite the different study methodologies

used, PBC seems to represent a real risk factor for HCC development. There are 4 studies which reveal a negative PBC / HCC association while 7 studies suggest a positive association. However, in all studies the crude frequency was found to be 0.7-3.6% in PBC patients for a mean follow up period of 5.6-7.3 years.²² Although this global incidence may be relatively low, all studies confirm that in stage IV PBC (cirrhotic PBC) HCC occurs with an increased frequency.

These findings further support the concept of cirrhosis as a very significant risk factor for development of HCC in any chronic liver disease. Therefore, surveillance for HCC in PBC patients with advanced disease is needed. The AASLD practice guidelines for the management of HCC recognize stage IV PBC as a high risk patient population and recommend inclusion of those patients in a surveillance program.²³⁻²⁵ However, they do not include specific surveillance recommendations.

A very recent study from the Mayo clinic, where a surveillance program for patients with PBC is in place since 2000 with monitoring of serum a-FP levels and abdominal ultrasound, retrospectively analyzed the data of 36 patients with HCC diagnosed between 1976 and 2007.²³ Five patients were diagnosed incidentally, 17 during surveillance and 14 outside a surveillance program. Patients on the surveillance program had improved survival as compared with those who were not on surveillance. The authors developed a model in order to identify high risk PBC patients who should be included in such a program. This model include evidence of portal hypertension, age > 70 years, male sex, and history of blood transfusion. The performance of this model has not yet been evaluated and further studies are needed to determine the optimal HCC surveillance recommendations in PBC patients.

There are some other open questions on this topic which are difficult to answer due to the rarity of the dis-

ease. None of the above studies made any comment on the role of the treatment with ursodeoxycholic acid (UDCA) in the risk of HCC development. There are some data regarding the chemopreventive role of UDCA used in patients with primary sclerosing cholangitis^{24,25} and in chronic hepatitis C.²⁶ In the case of PBC, UDCA treatment especially if started in the early stage may improve disease progression but it is not known if it may possibly delay the development of HCC.²⁷

PBC AND EXTRAHEPATIC MALIGNANCIES

Whether cirrhosis regardless of etiology can be associated with other types of cancer except for HCC has not been entirely established. There is some evidence that cancer risk in cirrhotic patients may be customized by changes in hormonal levels, metabolism of carcinogens, or alteration of the immunological status²⁸. In a follow up study of patients with cirrhosis compared with patients without liver disease based on the Danish Cancer Registry, the overall cancer incidence was found higher than expected in the cirrhotic patients compared with the expected number of cancers.²⁹ However, HCC cases have been included, while for the other types of cancer a substantial excess was documented in cancers associated with smoking and alcohol use habits (lung, pharynx, pancreas, urinary bladder). A relative increase in the risk of breast cancer was observed especially in patients with alcoholic cirrhosis at it was assumed that this increase is caused especially by the direct effect of alcohol rather than the elevated estrogen levels observed in cirrhosis.³⁰

The association with extrahepatic malignancies has been especially investigated in the case of PBC, leading finally to very conflicting results (Table 2).

The debate started in the 1980 when a significant increase in breast cancer was reported in patients with

Table 2. PIR of extrahepatic cancer in PBC patients

Reference-year of study	No of patients	Type of extrahepatic cancer (PIR)			
		Breast	Genito-urinar	Gastro-intestinal	Hematologic
Wolke(23) 1984	208	4.3			
Goudie(24) 1985	195	3.77	-	-	-
Loof(10) 1994	559	0.9	1.4	1.8	3.3
Nijhawan(13) 1999	1692	0.9	1.6	1.2	-
Floreani(21) 1999	175	0.43	0.9	1.4	2.8
Howel(9) 1999	769	1	1.6	1	2.6
Deutsch(17) 2007	212	0.6	2.3	1	1.2

(PIR = Proportional incidence ratio: ratio between reported cases and those expected in the specific population)

PBC.¹⁹ 208 patients with PBC were included in a retrospective study by a group of researchers from the USA. They were followed up from 1 month to 15.9 years and their medical records were studied. Eleven patients presented extrahepatic malignancies 6 of whom had breast cancer.²³ The incidence of breast cancer in PBC patients was found to be 4.4 times greater than the incidence expected in a comparable healthy population of the same age irrespective of the PBC disease stage. On the other hand, two patients experienced lymphoproliferative diseases. No statistical significant association could be demonstrated, but a link with PBC, either through the high incidence of Sjogren syndrome in these patients, or due to the use of immunosuppressive agents was speculated. Therapeutic agents, like azathioprine, methotrexate and colchicine, were used in early 1970 without any benefit while PBC patients thereafter were only treated with ursodeoxycholic acid. There are some opinions that some of these agents may have a possible carcinogenic effect³¹ but data based on their wide use in other diseases do not confirm the above concerns.

In another study from Scotland 195 patients with PBC were studied retrospectively.²⁴ The incidence of breast cancer in women with PBC (6 patients) was found to be significantly higher than expected in an age matched control population from the same geographical region (1.59 cases $p < 0.0015$). The authors suggested that patients with PBC should be closely surveilled for early detection of breast cancer.

However more recent studies in the 90's did not confirm the increased incidence of extrahepatic cancer, especially of breast cancer, in PBC patients.

In a study from Italy in 175 PBC patients¹⁴ only two patients had breast cancer, two skin melanomas, one endometrial cancer, one colorectal cancer, one kidney cancer and one non-Hodgkin lymphoma. The incidence of each was found to be even lower than in the general population in the same region.

The fact that PBC patients have no increased risk of breast cancer is also confirmed by a study in Sweden.¹⁰ Among the 559 PBC patients 5 women presented breast cancer while the number of expected cases in that population was 5.5. No cases of lymphoma were reported.

The same data are reported by the Mayo experience.¹³ The ratio between observed/expected cancer cases was 0.9 for breast cancer, 1.7 for gynecologic cancer and 1.3-1.8 for other cancers with no significant differences.

In a cohort of 769 PBC patients from Northern Eng-

land the standardized cancer incidence (SIR) and mortality ratios (SMR) were raised for extrahepatic cancers, especially respiratory cancer (SMR=2.4) and haematological cancers (SMR=3.9) while the SIR and SMR for breast cancer was low (0.4 and 0.3 respectively).⁹ The association of PBC with breast cancer could not be confirmed in this study, but an increased risk for cancers at sites not previously reported in PBC patients was found. However, these results are based on few cancer events and the evidence is not conclusive, a longer follow up period may be useful for better conclusions.

In our experience from Greece, various malignancies have been found in 15 (7%) patients out of a cohort of 212 patients with PBC.¹⁷ Breast cancer developed in 2/193 female patients (1%). Two patients had endometrial cancer, one patient vulvar cancer, one ovarian cancer, one cancer of the prostate and two patients developed colon cancer. The cumulative incidence of extrahepatic malignancy was not found to be significantly associated with the stage of the disease, patients' sex, age, Mayo risk score at baseline or the treatment of ursodeoxycholic acid. Two out of the 212 patients (0.9%) had lymphoproliferative diseases but this association was found to be significant either. In comparison to the cancer registries of other mediterranean country, like Italy, the incidence of extrahepatic malignancy, breast included, was not found to be increased in PBC patients.⁵⁰

In conclusion, the higher incidence of extrahepatic cancer in PBC patients reported during the 1970s and early 1980s, has not been confirmed in more recent larger studies. Therefore, surveillance programs for extrahepatic cancer are not necessary for PBC patients, as no higher risk of developing cancer was documented in these patients.

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