Is Fibrolamellar Carcinoma Different From Hepatocellular Carcinoma? A US Population-Based Study

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There have been no population-based studies of the epidemiology and prognosis of patients with fibrolamellar carcinoma (FLC). We conducted a retrospective cohort study using information collected by population-based registries of the Surveillance, Epidemiology, and End Results (SEER) program. The demographic features, stage at diagnosis, and type of therapy, as well as age-adjusted incidence rates and observed and relative survival rates were compared between persons with FLC and those with hepatocellular carcinoma (HCC) diagnosed between 1986 and 1999. A multivariate Cox proportional hazards model was constructed to examine the effect of histology (FLC vs. HCC) on the risk of mortality. There were 68 microscopically confirmed cases of FLC and 7,896 cases of HCC. FLC constituted 0.85% of all cases of primary liver cancer and 13.4% of all cases below the age of 40. Compared to HCC, patients with FLC were more likely to be younger (mean age 39 vs. 65), female (51.5% vs. 26.3%), and white (85.3% vs. 56.9%). A greater proportion of case with FLC had localized disease (41.2% vs. 30.9%), or received potentially curative therapy (resection, transplantation), compared to cases with HCC. The age-adjusted incidence rate for FLC was 0.02 per 100,000; No significant differences in age-adjusted incidence rates were observed by gender or race. The 1- and 5-year observed and relative survival rates were significantly longer in patients with FLC than HCC. The 5-year relative survival rate was 31.8% (95% CI, 20.5%-43.1%) for FLC, compared with 6.8% (95% CI, 6.3 %-7.4 %) for HCC. Adjusting for differences in age, gender, race, stage of disease, receipt of resection or transplantation, and time of diagnosis, FLC was independently associated with a 46% reduction in risk of mortality within 5years compared with HCC. In conclusion, in a population-based study, we observed remarkable differences in the epidemiology and prognosis of FLC compared to HCC. (HEPATOLOGY 2004;39:798–803.)

Fibrolamellar carcinoma (FLC) is a rare primary hepatic malignancy that is characterized histologically by well-differentiated malignant hepatic cells with deeply eosinophilic and granular cytoplasm due to the presence of numerous mitochondria, and by the presence of thick, fibrous lamellae throughout the tumor.[1]

Several aspects of the epidemiology and clinical course of FLC remain unclear. Since Edmondson first described FLC in 1956,[2] there have been conflicting reports on whether this malignancy is a histological variant of hepatocellular carcinoma (HCC) or a different biological entity. In previous studies, FLC was reported to constitute a widely variable proportion (between 4% and 40%) of primary liver cancer cases in children and young adults.[3–6] The case for distinguishing FLC from HCC is supported by reports of better prognosis with FLC compared to HCC.[7] However, most cases of FLC are diagnosed in young persons with no or minimal liver disease, while the majority of HCC cases are diagnosed after the age of 40 in patients with significant liver damage, usually cirrhosis. Studies that compared the outcomes of children and adolescents with primary liver cancer failed to detect significant differences in survival based on the histological type of primary liver cancer.[4]

Abbreviations: FLC, fibrolamellar carcinoma; HCC, hepatocellular carcinoma; SEER program, Surveillance, Epidemiology, and End Results program; SAS, Statistical Analysis System.

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The inconsistent findings in studies examining the epidemiology and clinical course of FLC is partly related to the small number of patients reported, with most studies being either individual case reports or small case series. In addition, selection bias was probably present in most reports in which only cases that survive long enough to be referred are included, and therefore patients with the worst prognosis are not routinely enrolled. Population-based large studies of FLC have been lacking.

Using data from the population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) program, we conducted a retrospective analysis to compare demographic features, stage at diagnosis, and type of therapy, as well as incidence and survival rates, between patients with FLC and those with classical HCC. To our knowledge, this is the largest report of FLC and the only population-based study of this malignancy.

Patients and Methods

Data Source. Beginning in 1973, the SEER registry program was established to identify all new cancer cases diagnosed within 7 geographic areas. By 1975, SEER included 9 geographic regions, 5 states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and 4 metropolitan areas (San Francisco-Oakland, Seattle-Puget Sound, Detroit, and Atlanta). In 1992, Los Angeles County and the San Jose-Monterey areas joined the SEER program, expanding the representation to approximately 14% of the US population. However, SEER regions are more urban and have a higher proportion of foreign-born persons compared to the general US population. Data for this study were obtained from SEER*Stat public-use data files, available on CD-ROM from the National Cancer Institute.[8]

Data Quality. Demographic and cancer-related information included in the SEER database is obtained by medical-record review. Studies are conducted annually at each SEER registry site to verify that data are being collected accurately and that case ascertainment is at least 98% or greater. Cancers are coded according to the International Classification of Disease-Oncology.[9] Race/ethnicity has several categories, including Hispanic white, non-Hispanic white, black, Chinese, Japanese, Filipino, Pacific Islander, and American Indian. However, accurate information on the underlying population in the areas covered by the SEER program is available only for race classified as white (includes Hispanic), black, or other (which includes all other ethnic groups listed above). As a result, valid incidence rates can be calculated only for these three broad racial groups (white, black, and other).

Study Population. We used the SEER site recode variable to identify all patients with primary liver cancer between 1986 and 2000. This variable, available from the SEER program, has defined all major cancer sites based on primary cancer site and morphology. Of those patients identified with primary liver cancer, we used histology codes (as defined by the International Classification of Diseases–Oncology to identify patients with FLC (8171) and HCC (8170). The histology code for FLC was first introduced in 1986. Only cases with a microscopically confirmed diagnosis of FLC or HCC were included in our study cohort. The histopathological diagnoses in SEER are based on local pathologists' reports and there is no second or central review of pathology reports.

Statistical Analysis. Age-adjusted incidence rates and their 95% CIs were calculated for FLC and HCC for all patients, for men and women separately, and for each of the 3 broad categories of race (whites, blacks, and other). For calculation of the age-adjusted incidence rates, we used the US general population for the year 1970 as a standard population. For each histologic type (FLC and HCC), we calculated the proportions of cases belonging to the following detailed race/ethnic groups: Hispanic white, non-Hispanic white, black, Asians (Chinese, Japanese, Filipino, Pacific Islander), and others.

We compared patients with FLC to those with HCC for demographic characteristics (age, gender, race), stage of disease at diagnosis, and receipt of potentially curative therapy. Chi-square tests were conducted for dichotomous variables and t tests for continuous variables. For patients diagnosed with HCC and FLC, the 1-year and 5-year observed and relative survival rates and their 95% CIs were calculated. The time to death within 1-year or 5-years following date of diagnosis was also modeled as the outcome variable in a Cox proportional hazards survival analysis that examined the effect of histological type of hepatic cancer (FLC vs. HCC), while adjusting for age, gender (female, male), race (white, nonwhite), stage of disease (local, regional, distant, unknown), receipt of potentially curative therapy (resection or transplantation), and time of diagnosis (1986–1990, 1991–1995, 1996–2000). Wald chi-square tests were used to determine the significance of each variable. Hazard-rate ratios and 95% CIs were calculated for each parameter estimate. The PROC PHREG procedure of the Statistical Analysis System (SAS) was used to conduct these analyses. The log-log survival plots were used to examine the proportional hazards assumption, which was met in all models. For this analysis, data from the SEER public-use CD-ROM were also converted into SAS datasets for further analyses (SAS version 8.2, SAS Institute, Cary, NC).

Table 1. The Demographic and Tumor-Related Features of Patients With Fibrolamellar Carcinoma Compared to Patients With Hepatocellular Carcinoma

	Fibrolamellar Carcinoma n = 68 (%)	Hepatocellular Carcinoma n = 7,896 (%)	*P* Value
Demographic features			
Age (y)			
Mean (SD)	39 (20)	65 (13)	<.0001
Age groups			
<40	43 (63.2)	284 (3.6)	
40–59	11 (16.2)	2209 (28.0)	
≥60	14 (20.6)	5403 (68.4)	
Gender			
Male	33 (48.5)	5818 (73.7)	<.0001
Female	35 (51.5)	2078 (26.3)	
Ethnicity			
Non-Hispanic white	58 (85.3)	4497 (56.9)	<.0001
White Hispanic	3 (4.4)	528 (6.7)	
Black	3 (4.4)	1030 (13.0)	
American Indian	0 (0.0)	68 (0.9)	
Chinese	4 (5.9)	594 (7.5)	
Japanese	0 (0.0)	304 (3.8)	
Filipino	0 (0.0)	300 (3.8)	
Hawaiian	0 (0.0)	96 (1.2)	
Other	0 (0.0)	497 (6.3)	
Stage at diagnosis			
Localized	28 (41.2)	2443 (30.9)	<.0001
Regional	16 (23.5)	2067 (26.2)	
Distant	16 (23.5)	1756 (22.2)	
Unstaged	8 (11.8)	1629 (20.6)	
Receipt of curative therapy*			
No	36 (52.9)	6245 (79.1)	<.0001
Yes	32 (47.1)	1030 (13.0)	
Unknown	0	621 (7.9)	

NOTE. Patients were diagnosed between 1986 and 2000.
*Resection or transplantation.

Results

We identified 71 patients diagnosed with FLC and 9,870 patients with HCC between 1986 and 2000. Of these, 68 (96%) microscopically confirmed cases of FLC and 7,896 (80%) cases of HCC were included in the analyses. Thus, FLC constituted 0.85% of all cases of primary liver cancer.

The mean age of diagnosis with FLC was 39 years; that of HCC was 65 years ($P < .0001$). The median ages of diagnosis for FLC and HCC were 33 and 66, respectively. Most cases with FLC (63.2%) were diagnosed before the age of 40, compared with only 4% of HCC cases. There were significant gender and ethnic differences between patients with FLC and HCC (Table 1). Approximately half of FLC cases occurred in men; 74% of HCC cases were in men ($P < .0001$). White patients comprised the majority (85.3%) of FLC cases; only 56.9% of HCC cases were white. The diagnosis of FLC was confirmed during an attempt at curative therapy (resection or transplantation) in 32 patients and during exploratory laparotomy in 23 additional patients.

The age-adjusted incidence rate for FLC was 0.02 per 100,000 (95% CI, 0.01-0.02) compared to 1.99 per 100,000 (95% CI, 1.95-2.04) for HCC. There were no statistically significant differences in the age-adjusted incidence rates between men and women; however, the age-adjusted incidence rates with HCC were more than 3-fold higher in men than women. The age-adjusted incidence rates of FLC were not significantly different among whites, blacks, or persons of other races. Conversely, age-adjusted incidence rates of HCC were 2-fold higher in persons of other race than those observed in blacks, and 2-fold higher in the latter group than whites. The age-adjusted incidence rates of FLC were 0.01 per 100,000, 0.02 per 100,000, 0.02 per 100,000 for 1986–1990, 1991–1995, and 1996–2000, respectively, with no significant increase over time (Fig. 1).

Stage of disease at the time of diagnosis was significantly different in patients with HCC compared to those with FLC. A greater proportion of patients with FLC were classified as having localized disease compared to patients with HCC (41.2% vs. 30.9%). The proportion of patients receiving potentially curative therapy (resection, transplantation) was greater in patients with FLC than HCC ($P < .0001$). Therapy could be ascertained for all 68 patients with FLC; of those, 32 (47.1%) received either resection or liver transplantation, whereas only 13% of HCC patients received such therapy.

There were remarkable differences in the observed and relative survival rates between HCC and FLC (Table 2). The overall 1-year observed and relative survival rates were significantly longer in patients with FLC than HCC. For example, the relative 1-year survival rate was 73.3% (95% CI, 62.6%–84.1%) in patients with FLC and 26.0% (95% CI, 25.0%–27.0%) in HCC. Five-year survival information was available for 65 patients with FLC and 7,638 cases of classical HCC. The observed and relative 5-year survival was also significantly longer for patients with FLC than HCC.

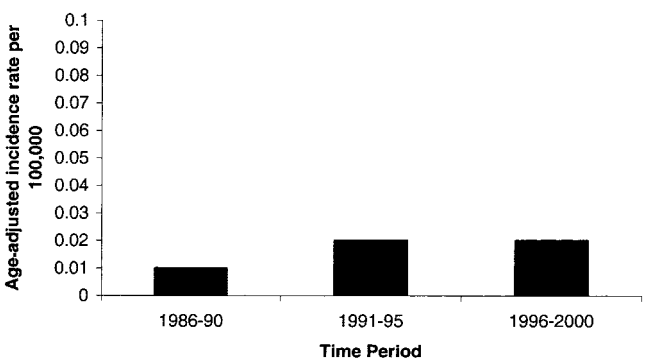

Fig. 1. The age-adjusted incidence rates of FLC in SEER registries.

Table 2. The Incidence and Survival Rates for Patients With Fibrolamellar Carcinoma Compared to Patients With Hepatocellular Carcinoma

	Fibrolamellar Carcinoma n = 68	Hepatocellular Carcinoma n = 7,896
Age-adjusted incidence rate (95% CI) per 100,000		
Overall	0.02 (0.01-0.02)	1.99 (1.95-2.04)
Men	0.02 (0.01-0.03)	3.29 (3.21-3.38)
Women	0.02 (0.01-0.02)	0.93 (0.88-0.97)
White	0.02 (0.02-0.03)	1.50 (1.46-1.54)
Black	0.01 (0.00-0.03)	3.23 (3.03-3.44)
Other	0.01 (0.00-0.03)	5.66 (5.40-5.93)
One-year survival rate % (SE)	n = 65	N = 7,638
Overall observed	72.80 (61.98-83.62)	25.20 (24.23-26.17)
Overall relative	73.34 (62.59-84.09)	26.01 (25.03-26.99)
	n = 43	N = 279
<40 observed	88.10 (78.42-97.78)	33.09 (27.57-38.61)
<40 relative	88.18 (78.53-97.83)	33.15 (27.52-38.65)
Five-year survival rate % (SE)	n = 65	N = 7,638
Overall observed	30.50 (19.31-41.69)	5.71 (5.19-6.23)
Overall relative	31.79 (20.47-43.11)	6.81 (6.25-7.38)
	n = 43	N = 279
<40 observed	36.32 (21.95-50.69)	10.49 (6.89-14.09)
<40 relative	36.52 (22.13-50.91)	10.59 (6.98-14.20)

NOTE. Patients were diagnosed between 1986 and 2000.

For example, the 5-year relative survival rate was 31.8% (95% CI, 20.5%–43.1%) for FLC, compared with 6.8% (95% CI, 6.3%–7.4%) for HCC.

Notably, the differences in survival rates between FLC and HCC were still significant in patients younger than 40 (Table 2). The 1-year relative survival rate was 88.2% (95% CI, 78.5%–97.8%) for FLC, and 33.2% (95% CI, 27.5%–38.7%) for HCC. Five-year survival information was available for 43 cases of FLC and 279 cases of HCC below the age of 40. The relative 5-year survival rate for patients with FLC was 36.5% (95% CI, 22.1%–50.9%) as compared with 10.6% (95% CI, 7.0%–14.2%) for HCC.

In a univariate Cox proportional hazards model, the risk of mortality was 77% higher in patients with HCC than in patients with FLC. Table 3 shows results of the multivariate Cox proportional hazards analysis examining the association between 1-year mortality and histologic type of hepatic carcinoma, while adjusting for age, gender, race, time of diagnosis, stage of disease, and receipt of potentially curative therapy. Patients diagnosed with FLC had approximately one-third the risk of mortality of patients with HCC. Significant predictors of reduced risk of death within 1 year of diagnosis were younger age, female gender, nonwhite race, more recent time of diagnosis, earlier stage of disease at diagnosis, and receipt of potentially curative therapy. Among these variables, the age at diagnosis was the strongest confounder of the association between histologic type of primary liver cancer and mortality, as indicated by the change in the parameter esti-

Table 3. Results From the Cox Proportional Hazards Model Examining the Association Between Risk of 1-Year and 5-Year Mortality and Histologic Type of Hepatic Carcinoma (Hepatocellular vs. Fibrolamellar)

	Risk of Mortality Within 1 Year			Risk of Mortality Within 5 Years		
Predictor Variable	Hazards Ratio	95% CI	*P* Value	Hazards Ratio	95% CI	*P* Value
Histologic type						
Hepatocellular	1.00		Reference			Reference
Fibrolamellar	0.36	0.22-0.58	<.0001	0.54	0.39-0.74	.0002
Time of cancer diagnosis						
1986-1990	1.00	–	Reference	1.00	–	Reference
1991-1995	0.88	0.82-0.94	.0002	0.92	0.86-0.97	.005
1996-2000	0.81	0.76-0.87	<.0001	0.83	0.78-0.88	<.0001
Age at time of diagnosis (per 10 years)	1.08	1.06-1.10	<.0001	1.08	1.06-1.10	<.0001
Gender						
Male	1.00	–	Reference	1.00	–	Reference
Female	0.88	0.83-0.94	<.0001	0.87	0.83-0.92	<.0001
Race						
Non-white	0.92	0.87-0.97	.004	0.93	0.88-0.98	.005
White	1.00	–	Reference	1.00	–	Reference
Stage at diagnosis						
Localized	0.50	0.46-0.54	<.0001	0.50	0.47-0.54	<.0001
Regional	0.66	0.62-0.71	<.0001	0.67	0.63-0.72	<.0001
Distant	1.00	–	Reference	1.00	–	Reference
Receipt of potentially curative therapy						
No	1.00	–	Reference	1.00	–	Reference
Yes	0.32	0.29-0.36	<.0001	0.36	0.33-0.40	<.0001

NOTE. The model adjusts for time period of diagnosis, age, gender, race, stage of disease, and receipt of potentially curative therapy among patients with primary liver cancer during 1986–2000 (7,703 cases with 5,604 deaths).

mate value of histological type variables between 2 models with and without age variable. Compared to patients diagnosed during 1986–1990, those diagnosed during 1991–1995 and 1996–2000 had 12% and 19% lower risk of 1-year mortality, respectively. Women had a 12% lower mortality risk than men. Nonwhites were also at an 8% lower risk of 1-year mortality compared to whites. Patients who received potentially curative therapy (resection or transplantation) had a 68% lower risk of 1-year mortality compared to those who did not receive therapy.

Table 3 also shows results of the Cox proportional hazards analysis examining the association between 5-year mortality and histologic type of hepatic carcinoma, while adjusting for time of diagnosis, age, gender, race, stage of disease, and receipt of potentially curative therapy. In general, the findings from the 5-year Cox proportional hazards model were similar to those from the 1-year model. Patients diagnosed with FLC had approximately half the risk of 5-year mortality compared to patients diagnosed with HCC. Consistent with results from the 1-year Cox proportional hazards model, more recent time of diagnosis, younger age, female gender, nonwhite race, earlier stage of disease at diagnosis, and receipt of potentially curative therapy were associated with a significant reduction in 5-year mortality. For example, there was an 8% increase in risk of 1-year mortality for each 10-year increment in the age of diagnosis. This "age effect" was independent of a 19% decrease in risk of mortality related to diagnosis during 1996–2000 as compared with 1986–1990.

Discussion

FLC constituted approximately 1% of all cases of primary liver cancer in SEER registries; this figure is likely to be generalizable to the United States. The age-incidence rates of FLC have remained low and relatively constant between 1986 and 2000. As compared to HCC, the majority of cases with FLC were young (<40 years) and of white race. Survival following FLC was significantly longer than HCC even after adjusting for age of cancer diagnosis and other demographic differences. This prolonged survival—although partly related to receipt of potentially curative therapy (resection or transplantation)—is also independent of such therapy.

The marked differences in epidemiology and clinical course indicate that FLC is likely to be a distinct entity from HCC. These differences were not consistent in the published literature. Some investigators reported a longer postresection survival in patients with FLC compared to patients with HCC in the absence of cirrhosis.[10–12] Similarly, a review of 17 cases with nonresectable metastatic FLC, referred to The Johns Hopkins Oncology Center between 1985 and 1990, reported a median survival of 57 months as compared with 14 months in patients with HCC.[13] Conversely, other studies found no differences in survival following surgical resection between patients with FLC and those with HCC. For example, a multicenter trial of postresection chemotherapy reported on 36 children with HCC and 10 with FLC found no statistically significant differences in survival according to histology. The 5-year survival for patients with FLC was 30% $\pm$ 15% compared with 16% $\pm$ 6% in other cases of HCC.[4] The study concluded that children with FLC do not have a favorable prognosis. However, caution should be exercised when interpreting these results because of a type II error resulting from small sample size. Previous studies were also affected by selection bias related to the referral setting. The complete ascertainment of all cases identified in the SEER regions included in our study, and the relatively large number of patients examined, increases the probability of valid and precise estimates of incidence and survival.

Limitations of our study include the absence of information on other factors that affect survival, such as disease comorbidity. Approximately 20% of HCC cases were microscopically confirmed. Furthermore, the diagnoses of HCC and FLC are made based on local pathologists' reports, and there is no central review to verify the diagnoses. While it is highly likely that patients identified with FLC had this diagnosis, some cases of FLC could have been misclassified as HCC. Therefore, it is possible that this study underestimated the true incidence of FLC. On the one hand, few cases of FLC could also have been confused with other rare sclerosing hepatic tumors, such as sclerosing hepatic carcinoma, a variant of cholangiocarcinoma). However, such a misclassification would make the already large differences in epidemiological and survival characteristics even greater. Lastly, SEER registries do not contain information on risk factors, comorbidity, or underlying conditions such as cirrhosis; adjustment for these conditions would have made the survival analyses more valid. However, adjustment for age differences as a surrogate for comorbidity was conducted.

In addition to being the first large population-based study of FLC, our study has several other strengths. Unlike most previous studies, in which FLC cases were restricted to either childhood or adulthood, all age groups were represented. Another advantage is the comparison of patients with FLC to a large number of patients with classical HCC diagnosed during the same time period and in the same geographic regions. All cases of FLC and HCC included in the analysis were microscopically confirmed. Lastly, there was complete follow-up in all cases

and accurate ascertainment of staging and surgical therapy.

Recent diagnostic trends in HCC emphasize the use of noninvasive methods such as imaging and laboratory testing.[14] However, given the relatively indolent course of FLC, and the significantly improved survival of patients with (and without therapy), we advocate vigorous pursuit of the diagnosis of FLC, including histology in patients with suspected FLC who are below age 40 and in patients with no obvious cirrhosis.

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