Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium

Ju Dong Yang, Essa A Mohamed, Ashraf O Abdel Aziz, Hend I Shousha, Mohamed B Hashem, Mohamed M Nabeel, Ahmed H Abdelmaksoud, Tamer M Elbaz, Mary Y Afihene, Babatunde M Duduyemi, Joshua P Ayawin, Adam Gyedu, Marie-Jeanne Lohouès-Kouacou, Antonin W Ndjitoyap Ndam, Ehab F Moustafa, Sahar M Hassany, Abdelmajeed M Moussa, Rose A Ugiagbe, Casimir E Omuemu, Richard Anthony, Dennis Palmer, Albert F Nyanga, Abraham O Malu, Solomon Obekpa, Abdelmounem E Abdo, Awatif I Siddig, Hatim M Y Mudawi, Uchenna Okonkwo, Mbang Kooffreh-Ada, Yaw A Awuku, Yvonne A Nartey, Elizabeth T Abbew, Nana A Awuku, Jesse A Otegbayo, Kolawole O Akande, Hailemichael M Desalegn, Abidemi E Omonisi, Akande O Ajayi, Edith N Okeke, Mary J Duguru, Pantong M Davwar, Michael C Okorie, Shettima Mustapha, Jose D Debes, Ponsiano Ocama, Olufunmilayo A Lesi, Emuobor Odeghe, Ruth Bello, Charles Onyekwere, Francis Ekere, Rufina Igetei, Mitchell A Mah`moud, Benyam Addissie, Hawa M Ali, Gregory J Gores, Mark D Topazian, Lewis R Roberts, and the Africa Network for Gastrointestinal and Liver Diseases

Summary

Background Hepatocellular carcinoma is a leading cause of cancer-related death in Africa, but there is still no comprehensive description of the current status of its epidemiology in Africa. We therefore initiated an African hepatocellular carcinoma consortium aiming to describe the clinical presentation, management, and outcomes of patients with hepatocellular carcinoma in Africa.

Methods We did a multicentre, multicountry, retrospective observational cohort study, inviting investigators from the African Network for Gastrointestinal and Liver Diseases to participate in the consortium to develop hepatocellular carcinoma research databases and biospecimen repositories. Participating institutions were from Cameroon, Egypt, Ethiopia, Ghana, Ivory Coast, Nigeria, Sudan, Tanzania, and Uganda. Clinical information—demographic characteristics, cause of disease, liver-related blood tests, tumour characteristics, treatments, last follow-up date, and survival status—for patients diagnosed with hepatocellular carcinoma between Aug 1, 2006, and April 1, 2016, were extracted from medical records by participating investigators. Because patients from Egypt showed differences in characteristics compared with patients from the other countries, we divided patients into two groups for analysis; Egypt versus other African countries. We undertook a multifactorial analysis using the Cox proportional hazards model to identify factors affecting survival (assessed from the time of diagnosis to last known follow-up or death).

Findings We obtained information for 2566 patients at 21 tertiary referral centres (two in Egypt, nine in Nigeria, four in Ghana, and one each in the Ivory Coast, Cameroon, Sudan, Ethiopia, Tanzania, and Uganda). 1251 patients were from Egypt and 1315 were from the other African countries (491 from Ghana, 363 from Nigeria, 277 from Ivory Coast, 59 from Cameroon, 51 from Sudan, 33 from Ethiopia, 21 from Tanzania, and 20 from Uganda). The median age at which hepatocellular carcinoma was diagnosed significantly later in Egypt than the other African countries (58 years [IQR 53–63] *vs* 46 years [36–58]; p<0·0001). Hepatitis C virus was the leading cause of hepatocellular carcinoma in Egypt (1054 [84%] of 1251 patients), and hepatitis B virus was the leading cause in the other African countries (597 [55%] of 1082 patients). Substantially fewer patients received treatment specifically for hepatocellular carcinoma in the other African countries than in Egypt (43 [3%] of 1315 *vs* 956 [76%] of 1251; p<0·0001). Among patients with survival information (605 [48%] of 1251 in Egypt and 583 [44%] of 1315 in other African countries), median survival was shorter in the other African countries than in Egypt (2·5 months [95% CI 2·0–3·1] *vs* 10·9 months [9·6–12·0]; p<0·0001). Factors independently associated with poor survival were: being from an African countries other than Egypt (hazard ratio [HR] 1·59 [95% CI 1·13–2·20]; p=0·01), hepatic encephalopathy (2·81 [1·72–4·42]; p=0·0004), diameter of the largest tumour (1·07 per cm increase [1·04–1·11]; p<0·0001), log α-fetoprotein (1·10 per unit increase [1·02–1·20]; p=0·0188), Eastern Cooperative Oncology Group performance status 3–4 (2·92 [2·13–3·93]; p<0·0001) and no treatment (1·79 [1·44–2·22]; p<0·0001).

Interpretation Characteristics of hepatocellular carcinoma differ between Egypt and other African countries. The proportion of patients receiving specific treatment in other African countries was low and their outcomes were extremely poor. Urgent efforts are needed to develop health policy strategies to decrease the burden of hepatocellular carcinoma in Africa.

Funding None.

Lancet Gastroenterol Hepatol 2017; 2: 103–11

Published Online December 2, 2016 http://dx.doi.org/10.1016/S2468-1253(16)30161-3

See Comment page 76

Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA (J D Yang MD, E A Mohamed BA, B Addissie MD, H M Ali BS, Prof G J Gores MD, Prof M D Topazian MD, Prof L R Roberts MBChB); **Endemic Medicine and Hepatogastroenterology Department** (Prof A O A Aziz MD, H I Shousha MD, M B Hashem MSc, Prof M M Nabeel MD, T M Elbaz MD) **and Department of Diagnostic and Interventional Radiology** (A H Abdelmaksoud MD), **University of Cairo, Cairo, Egypt; Department of Internal Medicine,** (M Y Afihene MBChB, J P Ayawin MBChB), **Department of Pathology** (B M Duduyemi MBChB), **and Department of Surgery** (A Gyedu MD), **Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; Department of Hepatology and Gastroenterology, Centre Hospitalier Universitaire de Cocody, Abidjan, Côte d'Ivoire** (Prof M-J Lohouès-Kouacou MD, A W N Ndam MD); **Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut Governorate, Egypt** (Prof E F Moustafa MD, S M Hassany MD, A M Moussa MSc); **Department**

of Medicine, University of Benin Teaching Hospital, Benin City, Nigeria (R A Ugiagbe MBBS, C E Omuemu MBBS); **Department of Internal Medicine, Effia Nkwanta Regional Hospital, Sekondi, Ghana** (R Anthony MBBS); **Department of Internal Medicine, Mbingo Baptist Hospital, Bamenda, Cameroon** (D Palmer DO, A F Nyanga MBBS); **Department of Medicine, Benue State University Teaching Hospital, Benue, Nigeria** (Prof A O Malu MBBS, S Obekpa MBBS); **Department of Gastroenterology, Ibnsina, Khartoum, Sudan** (A E Abdo MD, A I Siddig MD); **Department of Internal Medicine, University of Khartoum, Khartoum, Sudan** (Prof H M Y Mudawi MBBS); **Department of Internal Medicine, University of Calabar Teaching Hospital, Calabar, Nigeria** (U Okonkwo MBBS, M Kooffreh-Ada MBChB); **Department of Internal Medicine, School of Medical Sciences, Cape Coast, Ghana** (Y A Awuku MBChB, Y A Nartey MBChB, E T Abbew MBChB, N A Awuku MBChB); **Department of Medicine, University of Ibadan, Ibadan, Nigeria** (J A Otegbayo MBBS, K O Akande MBChB); **Department of Internal Medicine, St. Paul's Hospital Millenium Medical College, Addis Ababa, Ethiopia** (H M Desalegn MD); **Department of Medicine, Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria** (A E Omonisi MBBS, A O Ajayi MBBS); **Department of Medicine, University of Jos/Jos University Teaching Hospital, Jos, Nigeria** (Prof E N Okeke MBChB, M J Duguru MBBS, P M Davwar MBBS, M C Okorie MBBS); **Department of Medicine, University of Maiduguri Teaching Hospital, Maiduguri, Nigeria** (Prof S Mustapha MBBS); **Department of Medicine, University of Minnesota, MN, USA** (J D Debes MD); **Department of Medicine, Arusha Lutheran Medical Center, Arusha, Tanzania** (J D Debes); **Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda**

Research in context

Evidence before this study

Hepatocellular carcinoma is a leading cause of cancer-related death in Africa but there is still no comprehensive description of the current status of liver cancer epidemiology in Africa. We searched PubMed with the terms "Africa AND HCC" and "Africa AND liver cancer" for English-language reports on hepatocellular carcinoma published before Dec 31, 2015, and reviewed reference lists for additional publications. Most of the available epidemiology or clinical studies were single-centre or based in a single country, and retrospective in design with small sample sizes. A few previous studies reported on the survival of small numbers of patients with hepatocellular carcinoma in Africa, but a comprehensive description of the epidemiology, clinical features, management, and outcomes of patients with hepatocellular carcinoma in Africa is not available.

Added value of this study

Although the early age at onset of hepatocellular carcinoma in Africa has been reported previously in small cohort studies, we have also showed this in our large, multicountry African cohort study. Additionally, we showed that the early age at onset of hepatocellular carcinoma is common to most African countries, except for Egypt and Sudan. In this largest African hepatocellular carcinoma cohort reported up to now, we showed that the prognosis of African patients (except for patients in Egypt) is extremely poor and that most do not receive any treatment for hepatocellular carcinoma. We also used Cox regression to identify independent predictors of survival of African patients with hepatocellular carcinoma.

Implications of all the available evidence

This study provides substantial evidence that hepatocellular carcinoma develops at a younger age in Africa than in other regions of the world. Most patients with hepatocellular carcinoma in Africa do not receive any treatment that is specific for hepatocellular carcinoma and thus have a dismal prognosis, with most individuals affected dying within a few months of diagnosis at the most productive stages of their life. Our study highlights the need for urgent efforts to develop national and international health policy strategies to decrease the morbidity and mortality of hepatocellular carcinoma in Africa.

Introduction

The incidence of hepatocellular carcinoma (8·9 cases per 100 000 person-years)[1] is higher in Africa than in most of the rest of the world because of high prevalences of chronic infections with hepatitis B and C.[2–4] Hepatocellular carcinoma is a leading cause of cancer-related death in many African countries because of the combination of high incidence and high cancer-specific mortality.[1] The disease burden of hepatocellular carcinoma in Africa appears to be higher than has been reported in the scientific literature; this underestimation might be partly due to a shortage of resources and incomplete data collection.[5]

In addition to its high incidence, hepatocellular carcinoma is diagnosed at an earlier age and at more advanced stages in Africa than in the rest of the world. Findings from our previous study[6] showed that hepatocellular carcinoma occurs at a young age in Africa, at a median of 45 years (IQR 35–57). Findings from a previous cohort study[7] from The Gambia also showed an early onset of hepatocellular carcinoma, with the highest age-specific incidence occurring between ages 40 and 50 years. Results from another cohort study from The Gambia[8] showed that most patients in this country with hepatocellular carcinoma present at an advanced stage of disease.

By contrast with much of sub-Saharan Africa, Egypt has distinct features of hepatocellular carcinoma epidemiology. Hepatitis C virus (HCV) is the leading cause of hepatocellular carcinoma in Egypt, whereas hepatitis B virus (HBV) is the leading cause of the disease in sub-Saharan Africa.[9,10] In Egypt, compared with other African countries, patients present with hepatocellular carcinoma at an older age and most patients seen at tertiary referral centres receive treatments specific for hepatocellular carcinoma.[11,12]

Although a few single-centre-based small-case series of hepatocellular carcinoma have been reported from African countries, there is still no comprehensive description of the current status of liver cancer epidemiology in Africa. We initiated an Africa liver cancer consortium to establish a database of cases to describe the clinical features of patients with this disease in Africa, with the objective of providing a perspective from the entire African continent. Here, we describe the demographic characteristics, clinical features, management, and outcomes of patients with hepatocellular carcinoma in Africa.

Methods

Study design and patients

We did a multicentre, multicountry retrospective observational cohort study. We invited investigators of the African Network for Gastrointestinal and Liver Diseases to participate in the Africa liver cancer consortium. Participating institutions for this study were from Cameroon, Egypt, Ethiopia, Ghana, Ivory Coast, Nigeria, Sudan, Tanzania, and Uganda in west, central, east and north Africa. The institutional review boards of participating institutions approved the study.

Clinical information for patients diagnosed with hepatocellular carcinoma between Aug 1, 2006, and April 1, 2016, were extracted from medical records by participating investigators. The extracted clinical information consisted of: patient demographic

characteristics, the cause(s) of hepatocellular carcinoma (eg, HBV or HCV), liver-related blood tests, tumour characteristics, methods of treating hepatocellular carcinoma, last follow-up date, and survival status. HBV was confirmed on the basis of a positive HBsAg test. HCV was confirmed by HCV RNA or a positive anti-HCV test with chronic liver disease. The diagnosis of hepatocellular carcinoma was based on histology, aspiration cytology, radiology or serum α-fetoprotein concentrations (or both), including the presence of a growing mass lesion in the liver detected by ultrasound, typical imaging features on cross-sectional contrast CT or MRI, an increase in serum α-fetoprotein to more than 200 ng/mL, and the patients' progressive clinical course, according to local guidelines.[8] The diagnosis of hepatocellular carcinoma in patients with liver masses but without a serum α-fetoprotein concentration greater than 200 ng/mL, or in the absence of cross-sectional imaging with typical criteria consistent with hepatocellular carcinoma, was based on either biopsy and histology of the liver mass or on progressive tumour growth and clinical deterioration of the patient.

Tumour characteristics were assessed by abdominal ultrasound or cross-sectional imaging at the time of diagnosis of hepatocellular carcinoma. Patient survival was assessed from the time of hepatocellular carcinoma diagnosis to last known follow-up date or death. Patients were followed from the date of the first visit for hepatocellular carcinoma until death or the date of data cutoff (May 9, 2016). Follow-up and survival information were obtained from the medical records. Each investigator was encouraged to have telephone contact to obtain survival information for patients.

Statistical analysis

JMP (version 10) was used for statistical analyses. Because Egypt showed substantial differences in cause, tumour extent, and treatment methods compared with the other African countries, we divided patients into two groups for analysis (Egypt *vs* other African countries). We used student's *t* test or ANOVA to assess the differences between continuous variables and the χ^2 test or Fisher's exact test for comparisons of categorical variables. We estimated survival probabilities using the Kaplan-Meier method and compared them with the log-rank test. We undertook a multifactorial analysis using the Cox proportional hazards model to identify factors affecting survival (assessed from the time of diagnosis to last known follow-up or death). Variables with univariate significance were entered into a multifactorial Cox model. Variables with the highest p value were removed from the multifactorial model using backward stepwise elimination until all variables in the model remained statistically significant.

Role of the funding source

There was no funding source for this study. All authors had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We obtained information for 2566 patients with hepatocellular carcinoma at 21 tertiary referral centres in Africa: two in Egypt (n=1251), four in Ghana (n=491), nine in Nigeria (n=363), and one each in the Ivory Coast (n=277), Cameroon (n=59), Sudan (n=51), Ethiopia (n=33), Tanzania (n=21), and Uganda (n=20; figure 1).

The overall median age of patients was 54 years (IQR 44–61) and almost three-quarters were male (table 1). The median age at diagnosis of hepatocellular carcinoma was younger in other African countries than in Egypt (table 1). HCV was the leading cause of hepatocellular carcinoma in Egypt whereas HBV was the leading cause in other African countries. Overall, 64 (3%) of 2333 patients had evidence of HBV–HCV co-infection. The proportion of patients with unknown or other causes was higher in other African countries than in Egypt.

The age at onset of HCV-induced hepatocellular carcinoma was significantly different between African countries (p=0·02). The median ages of HCV-associated hepatocellular carcinoma were 62 years (IQR 52–75) in

(Prof P Ocama MBChB); **Division of Gastroenterology and Hepatology, Lagos University Teaching Hospital, Lagos, Nigeria** (Prof O A Lesi MBChB, Prof E Odeghe MBBS); **Department of Medicine, Lagos State University Teaching Hospital, Lagos, Nigeria** (C Onyekwere MBBS, F Ekere MD, R Igetei MBBS); **Department of Medicine, Dalhatu Araf Specialist Hospital, Lafia, Nigeria** (R Bello MBBS); **and Division of Gastroenterology, Duke University, Durham, NC, USA** (M A Mah`moud MD)

Correspondence to:
Prof Lewis R Roberts, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA
roberts.lewis@mayo.edu

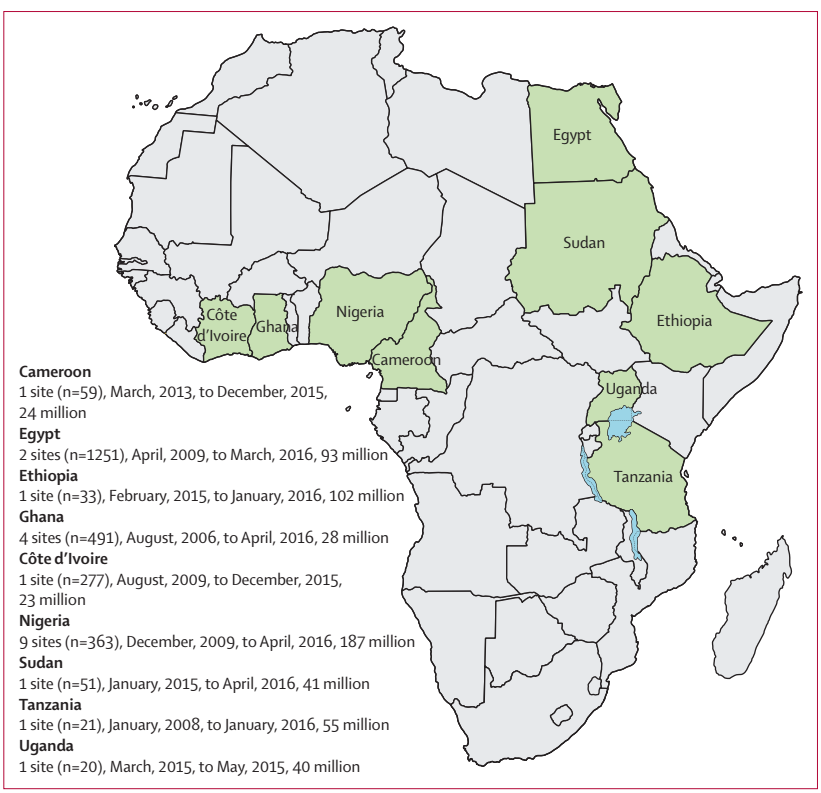

Figure 1: **Participating institutions and characteristics of patients with hepatocellular carcinoma in Africa**
Coloured regions represent the African countries in our study. Data are the number of participating institutions, the number of patients with hepatocellular carcinoma, the time window of diagnosis of hepatocellular carcinoma (first and last case), and the underlying general population size (per estimates for UN population divisions) for each country.

	Egypt (n=1251)	Other African countries (n=1315)	p value
Age at diagnosis (years)	58 (53–63)	46 (36–58)	<0·0001
Sex			
Male	972 (78%)	905 (69%)	<0·0001
Female	279 (22%)	410 (31%)	<0·0001
Liver cirrhosis present	1247 (100%)	601/915 (66%)	<0·0001
Cause of the hepatocellular carcinoma			
HCV	1054 (84%)	63/1082 (6%)	<0·0001
HBV	16 (1%)	597/1082 (55%)	<0·0001
HBV–HCV co-infection	29 (2%)	35/1082 (3%)	0·18
Alcohol	0	144/1082 (13%)	<0·0001
Other or unknown	152 (12%)	243/1082 (22%)	<0·0001
Laboratory data			
Platelet count (10^9/L)	133·00 (68)	244·00 (148)	<0·0001
INR	1·30 (0·30)	3·60 (2·90)	<0·0001
Albumin (g/L)	32·00 (6·00)	31·00 (9·00)	0·0013
Bilirubin (µmol/L)	29·07 (29·07)	82·08 (138·38)	<0·0001
α-fetoprotein (ng/mL)	47·00 (10·00–359·00)	139 (6·5–1011)	<0·0001
Tumour characteristics			
Multinodular	575/1247 (46%)	566/671 (84%)	<0·0001
Size of largest tumour (cm)	5 (3)	8 (4)	<0·0001
Macrovascular invasion	175 (14%)	72/553 (13%)	0·57
Extrahepatic metastasis	94/1212 (8%)	114/649 (18%)	<0·0001
ECOG performance status			
0	496/1240 (40%)	279/1028 (27%)	<0·0001
1	542/1240 (43%)	157/1028 (15%)	<0·0001
2	147/1240 (12%)	245/1028 (24%)	<0·0001
3	55/1240 (4%)	177/1028 (17%)	<0·0001
4	0	170/1028 (17%)	<0·0001
Ascites			
None	925/1247 (74%)	290/878 (33%)	<0·0001
Mild–moderate	313/1247 (25%)	493/878 (56%)	<0·0001
Severe	9/1247 (1%)	92/878 (11%)	<0·0001
Hepatic encephalopathy			
None	1201 (96%)	642/848 (76%)	<0·0001
Mild–moderate	39 (3%)	171/848 (20%)	<0·0001
Severe	11 (1%)	35/848 (3%)	<0·0001
Child-Pugh score			
A	400/1103 (36%)	19/288 (7%)	<0·0001
B	681/1103 (62%)	191/288 (66%)	0·15
C	22/1103 (2%)	78/288 (27%)	<0·0001
BCLC stage			
A–B	342/1103 (31%)	27/288 (5%)	<0·0001
C	672/1103 (62%)	125/288 (23%)	<0·0001
D	73/1103 (7%)	393/288 (72%)	<0·0001

Data are median (IQR), n (%), or mean (SD). Missing data: age (none in Egypt and 15 [1%] in other African countries); cirrhosis (none in Egypt and 400 [30%] in other African countries); causes (viral serology, none in Egypt and 233 [18%] in other African countries); platelet counts (seven [0.6%] in Egypt and 567 [43%] in other African countries); INR (141 [11%] in Egypt and 775 [59%] in other African countries); albumin (five [<1%] in Egypt and 778 [59%] in other African countries); bilirubin (five [<1%] in Egypt and 621 [47%] in other African countries); α-fetoprotein (119 [10%] in Egypt and 839 [64%] in other African countries); multinodular tumours (four [<1%] in Egypt and 638 [49%] in other African countries); tumour size (four [<1%] in Egypt and 809 [62%] in other African countries); vascular invasion (none in Egypt and 762 [58%] in other African countries); metastasis (39 [3%] in Egypt and 666 [51%] in other African countries); ECOG performance status (11 [<1%] in Egypt and 286 [22%] in other African countries); ascites (four [<1%] in Egypt and 437 [33%] in other African countries); hepatic encephalopathy (none in Egypt and 467 [36%] in other African countries); Child-Pugh score (148 [12%] in Egypt and 1027 [78%] in other African countries); and BCLC stage (164 [13%] in Egypt and 770 [59%] in other African countries). HCV=hepatitis C virus. HBV=hepatitis B virus. INR=international normalised ratio. ECOG=Eastern Cooperative Oncology Group. BCLC=Barcelona-Clinic Liver Cancer.

Table 1: **Clinical characteristics of African patients with hepatocellular carcinoma**

Cameroon, 67 years (55–72) in Ivory Coast, 59 years (44–69) in Ethiopia, 65 years (54–75) in Ghana, 55 years (47–67) in Nigeria, 58 years (53–63) in Egypt, and 80 years in Sudan (only one patient; appendix). The median age of HBV-associated hepatocellular carcinoma also varied by country (appendix; p<0·0001). Although the median age of HBV-associated hepatocellular carcinoma was younger than 45 years in most other African countries (Cameroon 41 years [IQR 29–48]; Ivory Coast 44 years [36–54]; Ethiopia 39 years [31–50]; Ghana 41 years [34–50]; Nigeria 38 years [31–49]; Tanzania 43 years [34–48]; and Uganda 32 years [27–43]), the median age was older in Sudan (57 years [IQR 45–65]) and Egypt (52 years [50–62]). Thus the median age at onset of HBV-associated hepatocellular carcinoma was younger than the median age at onset of HCV-associated hepatocellular carcinoma in all African countries (42 years [IQR 34–51] *vs* 58 years [53–63]; p<0·0001). The median ages of patients with hepatocellular carcinoma associated with HBV–HCV co-infection were older in Egypt (59 years [IQR 54–62]), Cameroon (52 years [52–52]), and Ivory Coast (60 years [50–63]) than in Uganda (45 years [33–56]), Ghana (43 years [37–51]), and Nigeria (47 years [38–58]; p=0·003; appendix).

See Online for appendix

For HCV-associated hepatocellular carcinoma, the peak age ranges were 57·5–62·5 years in Egypt and 47·5–52·5 years in other African countries (figure 2). The most frequent age range at diagnosis for HBV-associated hepatocellular carcinoma was 47·5–52·5 years in Egypt and 37·5–42·5 years in other African countries (figure 2); for hepatocellular carcinoma associated with HBV–HCV co-infection, the peak age ranges were 57·5–62·5 years in both Egypt and other African countries (figure 2).

Cumulatively, of 592 patients with HBV-associated hepatocellular carcinoma in other African countries, 11 (2%) developed hepatocellular carcinoma before age 20 years, 89 (15%) before age 30 years, and 262 (44%) before age 40 years, compared with none of 16 in Egypt before age 20 years or 30 years, and one (6%) before age 40 years ($p<0·002$ for hepatocellular carcinoma before age 40 years; appendix). In comparison, of 63 patients with HCV-induced hepatocellular carcinomas in other African countries, only one (2%) developed hepatocellular carcinoma before age 20 years, two (3%) before age 30 years, and five (8%) before age 40 years, compared with none of 1054 in Egypt before age 20 years, one (<1%) before age 30 years, and seven (1%) before age 40 years in Egypt ($p=0·0003$ for hepatocellular carcinoma before age 40 years; appendix). Although the most frequent age range at diagnosis for hepatocellular carcinoma associated with HBV–HCV co-infection was the same for other African countries and Egypt, a higher proportion of these patients developed early-onset hepatocellular carcinoma in other African countries: no patients with this subtype were younger than 40 years old in Egypt, and of 35 patients with this subtype in other African countries, none developed hepatocellular carcinoma before age 20 years, four (11%) before age 30 years, and seven (20%) before the age 40 years ($p=0·01$ for hepatocellular carcinoma before age 40 years; appendix).

Consistent with the high prevalence of HBV in other African countries and the known tendency of HBV-associated hepatocellular carcinoma to develop in the absence of cirrhosis, the proportion of patients with non-cirrhotic hepatocellular carcinoma and mean platelet counts were higher in other African countries than in Egypt (table 1). The severity of underlying liver dysfunction, tumour extent, serum α-fetoprotein concentrations, patient performance status, and the Barcelona-Clinic Liver Cancer (BCLC) stage were all worse in other African countries than in Egypt (table 1), most probably reflecting the absence of surveillance and the consequent diagnosis of hepatocellular carcinoma at advanced symptomatic stages in other African countries.

More Egyptian patients received treatments specific for hepatocellular carcinoma and received potentially curative treatments than in other African countries ($p<0·0001$ for both; table 2). As expected, a higher proportion of patients with earlier-stage disease received any specific treatment in both other African countries and Egypt. At any given BCLC stage, patients in Egypt were more likely to receive specific treatment than patients in other African countries. Among patients for whom BCLC stage could be calculated, 14 (52%) of 27, six (5%) of 125, and 18 (5%) of 393 patients at BCLC stages A–B, C, and D, respectively, in other African countries received specific treatment ($p<0·0001$), whereas in Egypt 315 (92%) of 342 patients at stage A–B, 505 (75%) of 672 at stage C, and 33 (45%) of 73 at stage D received treatment specific for hepatocellular carcinoma ($p<0·0001$).

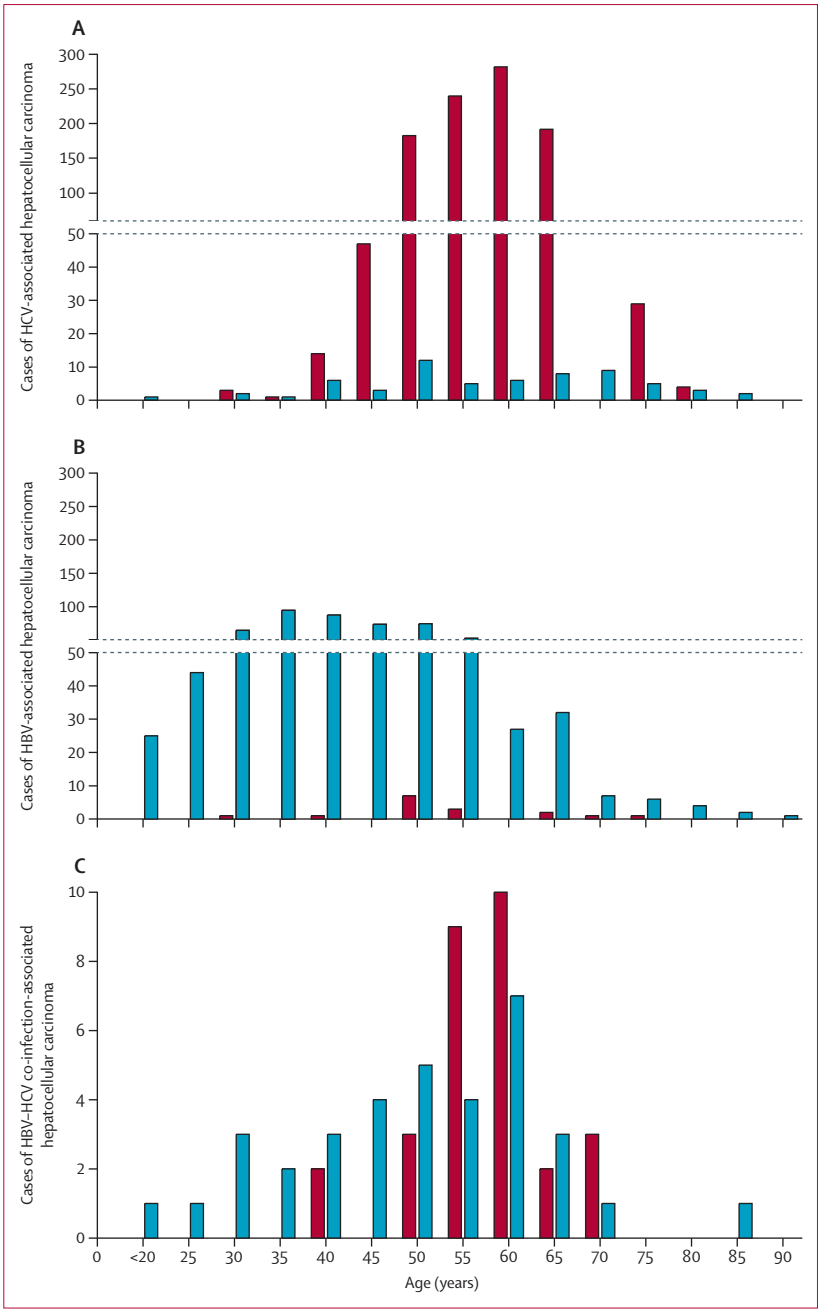

Figure 2: **Distribution of age at diagnosis of hepatocellular carcinoma**
Red bars represent data for Egypt, blue bars represent data for other African countries. Data are the number of hepatitis C virus (HCV)-associated cases of hepatocellular carcinoma per 5-year age range (A), the number of hepatitis B virus (HBV)-associated cases of hepatocellular carcinoma per 5-year age range (B), and the number of cases of hepatocellular carcinoma associated with HBV–HCV coinfection per 5-year age range (C; note the scale is different from A and B).

Follow-up and survival information were available for 605 (48%) of 1251 patients in Egypt and 583 (44%) of 1315 in other African countries. Among those, median overall survival was significantly longer in Egypt than in other African countries (10·9 months [95% CI 9·6–12·0] *vs* 2·5 months [2·0–3·1]; $p<0·0001$; hazard ratio [HR]

	Egypt (n=1251)	Other African countries (n=1315)	p value
Any specific treatment	956 (76%)	43 (3%)	<0·0001
Curative treatment (transplantation or resection or local ablation)	442 (35%)	8 (<1%)	<0·0001
Transplantation	10 (<1%)	0	0·001
Resection	26 (2%)	8 (<1%)	0·002
Local radiofrequency ablation	406 (32%)	0	<0·0001
TACE	451 (36%)	5 (<1%)	<0·0001
Sorafenib	63 (5%)	12 (1%)	<0·0001
Other systemic treatment	0	18 (1%)	<0·0001

Data are n (%). Primary treatment was reported per each patient in the following order of treatment option: transplantation>resection>local radiofrequency ablation>transcatheter arterial chemoembolisation (TACE)>sorafenib>other systemic treatment.

Table 2: **Primary treatment of African patients with hepatocellular carcinoma**

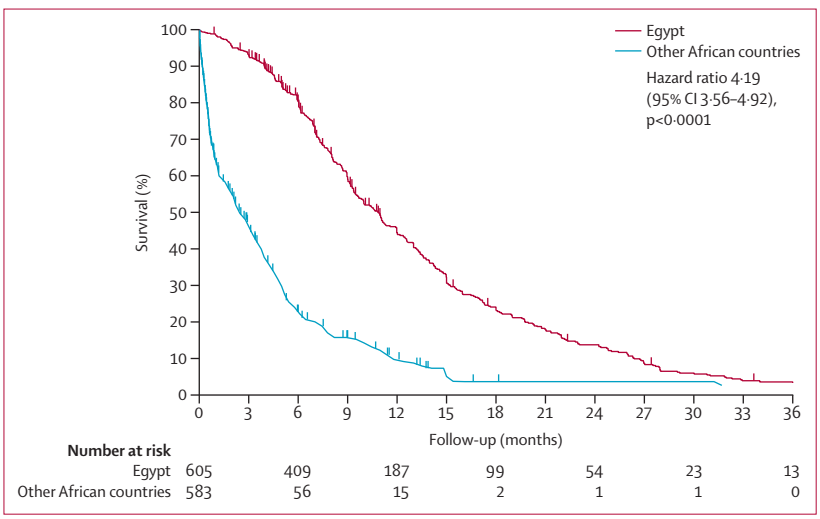

Figure 3: **Overall survival of patients with hepatocellular carcinoma in Africa**

4·19 [95% CI 3·56–4·92]; p<0·0001; figure 3). 44% of patients (95% CI 39–49) in Egypt survived for 1 year, compared with 10% (6–14) from other African countries.

In the subgroup of patients with hepatocellular carcinoma presenting with BCLC stage A–B disease, overall survival did not differ between Egypt and other African countries (HR 0·63 [95% CI 0·22–1·40]; p=0·28), but overall survival was worse in other African countries compared with Egypt for patients with BCLC stage C disease (2·07 [1·42–2·92]; p=0·0002), BCLC stage D disease (3·37 [2·31–5·07]; p<0·0001) and those for whom BCLC information was missing (5·96 [4·16–8·67]; p<0·0001; appendix).

By multifactorial analysis, factors independently associated with poor survival were: being from an African country other than Egypt, hepatic encephalopathy, diameter of the largest tumour, log α-fetoprotein, Eastern Cooperative Oncology Group (ECOG) performance status 3–4, and receiving no specific treatment (table 3). Age, cirrhosis, multinodular tumour, vascular invasion, having ascites, and extrahepatic metastasis were not significant factors in the multifactorial analysis. Cause of hepatocellular carcinoma was not tested as a factor in the Cox model because of strong co-linearity between cause and country and there were only a few HBV-only cases in Egypt and HCV-only cases in other African countries.

Because the interaction between Egypt and no treatment was significant (p=0·02 in the univariate Cox model, p=0·004 in the multifactorial Cox model), survival models were built separately for Egypt and other African countries (appendix). In these separate models, diameter of the largest tumour (HR 1·07 per cm increase [95% CI 1·04–1·11]; p=0·0001), log α-fetoprotein (1·12 per unit increase [1·03–1·22]; p=0·01), ECOG performance status 3–4 (2·38 [1·61–3·39]; p<0·0001) and no specific treatment (1·70 [1·35–2·14]; p<0·0001) were independently associated with poor overall survival in Egypt (appendix), and diameter of the largest tumour (HR 1·07 per cm increase [95% CI 1·01–1·12]; p=0·02), ECOG performance status 3–4 (2·01 [1·43–2·82]; p<0·0001) and no specific treatment (6·97 [2·61–28·40]; p<0·0001) were independently associated with poor overall survival in the other African countries (appendix).

Reflecting the shortage of health care and financial resources in the local environments, a large proportion of patients with hepatocellular carcinoma in other African countries had incomplete information at the time of initial presentation (table 1). For example, 809 (62%) patients in other African countries had no information on the size of the largest tumour. To explore the potential effect of missing data on the treatment and survival analysis, we compared the treatment and overall survival of patients with tumour size information versus patients without tumour size information in the other African countries cohort. As expected, the presence of tumour size information was associated with a higher likelihood of receiving treatment for hepatocellular carcinoma than the absence of this information (odds ratio 2·3 [95% CI 1·2–4·3]; p=0·0086), reflecting better access to diagnostic and therapeutic modalities. Concomitantly, there was a suggestion of better overall survival of patients with tumour size information than those without this information (HR 0·83 [95% CI 0·66–1·04]; p=0·11), although this finding was not statistically significant.

Discussion

In this large multicentre, multicountry, retrospective cohort study we showed distinct differences in epidemiology, clinical features, treatment methods, and overall survival in patients with hepatocellular carcinoma in Egypt compared with other African

countries. The proportion of patients receiving specific treatment in other African countries was low and their outcomes were poor.

HCV was the leading cause of hepatocellular carcinoma in Egypt, while HBV was the leading cause in other African countries.[13] The mean age at diagnosis of hepatocellular carcinoma was substantially younger in patients with HBV-associated disease than in those with HCV-related disease, regardless of the country. The mean age at diagnosis of HBV-induced hepatocellular carcinoma was also younger in sub-Saharan African countries than in Egypt and Sudan. For both HBV-associated and HCV-associated hepatocellular carcinoma, earlier onset of hepatocellular carcinoma was more common, and the peak age range of hepatocellular carcinoma diagnosis was younger, in other African countries compared with Egypt, suggesting that specific environmental, biological, or genetic factors might determine the likelihood of development of hepatocellular carcinoma at a younger age in these countries.[12,14]

Patients from other African countries were more likely to present with advanced stage hepatocellular carcinoma with severe liver dysfunction and compromised performance status. Virtually no patients in other African countries received any treatments specific for hepatocellular carcinoma, and they had a poor overall survival (median 2·5 months). By contrast, the disease extent of hepatocellular carcinoma at diagnosis was significantly less in Egypt and three-quarters of patients received treatment specific for hepatocellular carcinoma, resulting in substantially better overall survival (median 10·9 months).

The dismal prognosis of patients with hepatocellular carcinoma in other African countries is consistent with anecdotal reports but still striking, with a median survival of patients with hepatocellular carcinoma of only 10 weeks. Our survival model showed that living in African countries outside Egypt, extent of tumour, tumour biology (serum α-fetoprotein concentrations), severity of liver dysfunction (as determined by hepatic encephalopathy), ECOG performance status, and treatment were independent predictors of overall survival in African patients with hepatocellular carcinoma. Thus, the poor outcomes of these patients in Africa seem to be mainly due to the advanced stage at diagnosis of hepatocellular carcinoma, with patients already showing severe underlying liver dysfunction and poor performance status at the time of initial presentation. This reflects at-risk individuals not being identified, the absence of comprehensive surveillance programmes for hepatocellular carcinoma, a shortage of access to expert medical care, an absence of trust in health-care systems in Africa, and poor health-seeking behaviour.[15,16]

Primary prevention of chronic hepatitis, including universal HBV vaccination, identification of the at-risk population (patients with HCV or HBV) by mass screening of the general population, prevention of liver disease progression and hepatic dysfunction by providing antiviral treatment, minimisation of aflatoxin exposure through post-harvest interventions, implementation of hepatocellular carcinoma surveillance among the population at risk for the disease, and establishment of centres of excellence for hepatocellular carcinoma treatment are essential components of attempts (both ongoing and future) to curb the morbidity and mortality from hepatocellular carcinoma in Africa.[2,17–21] Concerted, multilevel efforts by governments; primary, secondary, and tertiary health-care institutions; and advocacy groups will be required to achieve and sustain the long-term commitment needed to build, establish, and maintain a robust and effective infrastructure focused on these goals.[22–26] Although obtaining information on HBV immunisation statuses was beyond the scope of our report, HBV immunisation programmes have been in place for fewer than 10 years in most of the countries of sub-Saharan Africa. Therefore, HBV immunisation might have had little influence on the occurrence of hepatocellular carcinoma in adults in our study, but we anticipate that should successful universal HBV vaccination be implemented broadly in Africa, the increase in HBV immunisation will lead to a decrease in incidence of hepatocellular carcinoma in the next several decades, as has been shown in Taiwan and other Asian countries.[27,28]

Although our study included many patients with hepatocellular carcinoma from a wide distribution of 21 tertiary referral centres in nine African countries, it also had several major limitations. It was designed as a retrospective study to acquire data from centres in Africa within contexts with a severe shortage of

	Univariate model		Multifactorial model	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	0·98 (0·97–0·98)	<0·0001	..	..
Male sex (ref: female)	1·03 (0·87–1·22)	0·73	..	..
Being from an African country other than Egypt	4·19 (3·56–4·92)	<0·0001	1·59 (1·13–2·20)	0·01
Cirrhosis	0·39 (0·29–0·53)	<0·0001	..	..
Ascites	1·83 (1·58–2·12)	<0·0001	..	..
Hepatic encephalopathy	4·12 (3·32–5·07)	<0·0001	2·81 (1·72–4·42)	0·0004
Log α-fetoprotein (per unit increase)	1·19 (1·10–1·27)	<0·0001	1·10 (1·02–1·20)	0·02
Multinodular tumour	1·47 (1·25–1·71)	<0·0001	..	..
Largest tumour diameter (per cm increase)	1·11 (1·08–1·14)	<0·0001	1·07 (1·04–1·11)	<0·0001
Vascular invasion	1·39 (1·11–1·72)	0·005	..	..
Metastasis	1·82 (1·42–2·30)	<0·0001	..	..
ECOG PS 3–4 (ref: ECOG PS 0–2)	3·91 (3·26–4·67)	<0·0001	2·92 (2·13–3·93)	<0·0001
No treatment	3·25 (2·79–3·80)	<0·0001	1·79 (1·44–2·22)	<0·0001

Cox proportional hazards analysis was done for patients with follow-up and survival status information and if any relevant clinical data were available (n=1188). ECOG=Eastern Cooperative Oncology Group. ..=not significant.

Table 3: **Predictors of survival in African patients with hepatocellular carcinoma**

resources. Therefore, a large proportion of patients had missing information including survival statuses, particularly outside Egypt, which could have biased the analysis, especially the survival analysis results. To explore the potential effect of a large proportion of missing data on the treatment and survival analysis, we did further exploratory analyses and showed that the presence of tumour size information was associated with a higher likelihood of receiving treatment specific for hepatocellular carcinoma (*vs* missing tumour size information), suggesting that better access to diagnostic and therapeutic methods led to superior outcomes.

Also because of a shortage of medical resources, we were unable to obtain clinically relevant information on other items such as HBV DNA, HIV co-infection, and aflatoxin exposure status. However, these limitations reflect the current exigencies of the care of patients with hepatocellular carcinoma in Africa. We believe that prospective enrolment of patients in a multi-institutional hepatocellular carcinoma registry will help maximise the chances of identifying consecutive patients with hepatocellular carcinoma and facilitate systematic collection of survival status information. We are in the process of designing a feasible clinical research protocol and securing funding to launch a prospective hepatocellular carcinoma epidemiology and biorepository study in Africa; this future investigation will hopefully address some of the aforementioned limitations of our current study.

Patients included in this study were seen at tertiary referral centres, where only selected groups of patients can afford to visit. Hence, the data from these institutions might not fully reflect the general affected population of the countries of participating institutions. This limitation might have introduced a referral bias and the true prognosis of patients with hepatocellular carcinoma in the general population in Africa might be even worse than shown in our analysis, since people of low socioeconomic status and with poor access to medical resources might not have been able to travel to tertiary referral centres and thus might not have been well represented in our study. Additionally, potential referral biases might exist in relation to sex and age (eg, a higher referral rate among male or young patients) and the inference about younger age of onset in many African countries could be influenced by referral bias, because younger patients might be more likely than older patients to be referred to hospital when they become ill.

Because we aimed to provide the most comprehensive data possible on patients with hepatocellular carcinoma in this retrospective study, we did not limit the number of institutions from each country to adjust for the populations of individual countries. For this reason, the time window from which patients were enrolled varied between participating institutions and countries. Additionally, our cohort did not represent the whole of Africa, and in particular, we did not have any representation from southern Africa. Hence, the observations from the other African countries in our study might not be applicable to southern African countries such as South Africa. The diagnosis of hepatocellular carcinoma was based on local institutional guidelines at the discretion of the participating investigators and was mainly based on the presence of raised serum α-fetoprotein concentrations or progressively increasing liver mass or masses by ultrasound (or both) in patients at risk for the disease.[12,29]

In conclusion, HCV was the leading cause of hepatocellular carcinoma in Egypt, and HBV was the leading cause of hepatocellular carcinoma in the other African countries in our study. Hepatocellular carcinoma tends to develop at a younger age in Africa than in other regions of the world, with a generally dismal prognosis and leading to deaths of most individuals affected at their most productive stages of life. By contrast with the other African countries, mostly sub-Saharan, outcomes for hepatocellular carcinoma in Egypt are substantially better, perhaps because of earlier detection of the disease and the availability of effective treatment options in this country. Urgent efforts are needed to develop national and international health policy strategies to decrease the burden of disease and death from hepatocellular carcinoma in Africa.

Contributors

JDY contributed to study concept and design, data analysis, interpretation of data, and drafting of the manuscript. AOAA, HIS, MBH, MMN, AHA, TME, MYA, BMD, JPA, AG, M-JL-K, AWNN, EFM, SMH, AMM, RAU, CEO, RA, DP, AFN, AOM, SO, AEA, AIS, HMYM, UO, MK-A, YAA, YAN, ETA, NAA, JAO, KOA, HMD, AEO, AOA, ENO, MJD, PMD, MCO, SM, JDD, PO, OAL, EO, BR, CO, FE, and RI contributed to study concept and design, acquisition of data, interpretation of data, and critical revision of the manuscript. EAM, MAM, BA, HMA, GJG, and MDT contributed to study concept and design, and interpretation of data, and critical revision of the manuscript. LRR contributed to study concept and design, and interpretation of data, and critical revision and final approval of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

JY was supported by grant T32 DK07198 from the National Institute of Diabetes and Digestive and Kidney Diseases, and a 2016 Hans Popper Memorial Postdoctoral Research Fellowship award received from the American Liver Foundation. EM was supported by grant UL1TR000135 from the US National Institute of Health (NIH). The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

References

1 International Agency for Research on Cancer. Globocan 2012. www.globocan.iarc.fr (accessed July 1, 2016).
2 Yang JD, Roberts LR. Hepatocellular carcinoma: a global view. *Nat Rev Gastroenterol Hepatol* 2010; **7:** 448–58.
3 de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012; **13:** 607–15.
4 Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet* 2016; **388:** 1081–88.
5 Sartorius K, Sartorius B, Aldous C, Govender PS, Madiba TE. Global and country underestimation of hepatocellular carcinoma (HCC) in 2012 and its implications. *Cancer Epidemiol* 2015; **39:** 284–90.

6 Yang JD, Gyedu A, Afihene MY, et al. Hepatocellular carcinoma occurs at an earlier age in Africans, particularly in association with chronic hepatitis B. *Am J Gastroenterol* 2015; **110:** 1629–31.

7 Kirk GD, Lesi OA, Mendy M, et al. The Gambia Liver Cancer Study: infection with hepatitis B and C and the risk of hepatocellular carcinoma in West Africa. *Hepatology* 2004; **39:** 211–19.

8 Umoh NJ, Lesi OA, Mendy M, et al. Aetiological differences in demographical, clinical and pathological characteristics of hepatocellular carcinoma in The Gambia. *Liver Int* 2011; **31:** 215–21.

9 Abdelaziz AO, Elbaz TM, Shousha HI, et al. Survival and prognostic factors for hepatocellular carcinoma: an Egyptian multidisciplinary clinic experience. *Asian Pac J Cancer Prev* 2014; **15:** 3915–20.

10 de Martel C, Maucort-Boulch D, Plummer M, Franceschi S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. *Hepatology* 2015; **62:** 1190–200.

11 Aziz AO, Omran D, Nabeel MM, et al. Aggressive treatment of performance status 1 and 2 HCC patients significantly improves survival–an Egyptian retrospective cohort study of 524 cases. *Asian Pac J Cancer Prev* 2016; **17:** 2539–43.

12 Ladep NG, Lesi OA, Mark P, et al. Problem of hepatocellular carcinoma in West Africa. *World J Hepatol* 2014; **6:** 783–92.

13 Mekonnen HD, Sharma S, Shewaye A, Feld J, Lulu E. Major risk factors, clinical and laboratory characteristics of patients with hepatocellular carcinoma; a retrospective study at Tikur Anbassa hospital, Addis Ababa university, Addis Ababa, Ethiopia. *Ethiop Med J* 2015; **53:** 127–32.

14 Gong YY, Egal S, Hounsa A, et al. Determinants of aflatoxin exposure in young children from Benin and Togo, West Africa: the critical role of weaning. *Int J Epidemiol* 2003; **32:** 556–62.

15 Tognarelli J, Ladep NG, Crossey MM, et al. Reasons why West Africa continues to be a hotbed for hepatocellular carcinoma. *Niger Med J* 2015; **56:** 231–35.

16 Olivier J, Tsimpo C, Gemignani R, et al. Understanding the roles of faith-based health-care providers in Africa: review of the evidence with a focus on magnitude, reach, cost, and satisfaction. *Lancet* 2015; **386:** 1765–75.

17 Turner PC, Sylla A, Gong YY, et al. Reduction in exposure to carcinogenic aflatoxins by postharvest intervention measures in west Africa: a community-based intervention study. *Lancet* 2005; **365:** 1950–56.

18 Hainaut P, Boyle P. Curbing the liver cancer epidemic in Africa. *Lancet* 2008; **371:** 367–68.

19 Stulac S, Binagwaho A, Tapela NM, et al. Capacity building for oncology programmes in sub-Saharan Africa: the Rwanda experience. *Lancet Oncol* 2015; **16:** e405–13.

20 Harford JB. Barriers to overcome for effective cancer control in Africa. *Lancet Oncol* 2015; **16:** e385–93.

21 Eltabbakh M, Zaghla H, Abdel-Razek W, et al. Utility and cost-effectiveness of screening for hepatocellular carcinoma in a resource-limited setting. *Med Oncol* 2015; **32:** 432.

22 Gelband H, Sankaranarayanan R, Gauvreau CL, et al. Costs, affordability, and feasibility of an essential package of cancer control interventions in low-income and middle-income countries: key messages from Disease Control Priorities, 3rd edition. *Lancet* 2016; **387:** 2133–44.

23 Busolo DS, Woodgate RL. Cancer prevention in Africa: a review of the literature. *Glob Health Promot* 2015; **22:** 31–39.

24 PROLIFICA. West African treatment cohort for Hepatitis B (WATCH), 2011. https://clinicaltrials.gov/ct2/show/NCT02129829 (accessed July 1, 2016).

25 Howell J, Ladep NG, Lemoine M, et al. Prevention of liver fibrosis and cancer in Africa: the PROLIFICA project–a collaborative study of hepatitis B-related liver disease in west Africa. *S Afr Med J* 2015; **105:** 185–86.

26 Shimakawa Y, Lemoine M, Mendy M, et al. Population-based interventions to reduce the public health burden related with hepatitis B virus infection in The Gambia, west Africa. *Trop Med Health* 2014; **42** (suppl 2)**:** 59–64.

27 Chang MH, You SL, Chen CJ, et al. Long-term effects of hepatitis B immunization of infants in preventing liver cancer. *Gastroenterology* 2016; **151:** 472–80.

28 Wichajarn K1, Kosalaraksa P, Wiangnon S. Incidence of hepatocellular carcinoma in children in Khon Kaen before and after national hepatitis B vaccine program. *Asian Pac J Cancer Prev* 2008; **9:** 507–09.

29 Kew MC. Hepatocellular carcinoma in developing countries: prevention, diagnosis, and treatment. *World J Hepatol* 2012; **4:** 99–104.