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Estrogen Replacement Reduces Risk and Increases Survival Times of Women With Hepatocellular Carcinoma

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BACKGROUND & AIMS: **Environmental factors have been identified that affect risk of hepatocellular carcinoma (HCC), but little is known about the effects of sex hormones on liver cancer development or outcome. The authors investigated whether menopause hormone therapy (MHT) affects risk, age at onset, or outcome of HCC.**

METHODS: **We performed a case–control study of 234 female patients treated for HCC at a tertiary medical center and with 282 healthy women (controls) from January 1, 2004 through May 31, 2015. We collected detailed information on environmental exposures, ages of menarche and menopause, hysterectomies, and uses of birth control and MHT. We performed multivariable logistic and Cox regression analyses to determine the independent effects of factors associated with women on risk and clinical outcome in HCC. The primary outcomes were effect of MHT on HCC risk, the relationship between MHT with hepatitis virus infection on HCC development, and effect of MHT on age at HCC onset or survival after diagnosis of HCC.**

RESULTS: **The estimated adjusted odds ratio (AOR) for HCC in women who ever used estrogen was 0.53 (95% confidence interval [CI], 0.32–0.88). This association was supported by the older age of HCC onset among estrogen users (mean, 64.5 ± 0.9 years) vs nonusers (mean 59.2 ± 1.1 years; $P = .001$) and the reduced risk of HCC among long-term users (more than 5 years) (AOR, 0.36; 95% CI, 0.20–0.63). Users of estrogen also had a reduced risk for hepatitis-associated HCC: AOR for users, 4.37 (95% CI, 1.67–11.44) vs AOR for nonusers, 17.60 (95% CI, 3.88–79.83). Estrogen use reduced risk of death from HCC (hazard ratio, 0.55; 95% CI, 0.40–0.77; $P = .01$). Median overall survival times were 33.5 months for estrogen users (95% CI, 25.7–41.3 months) and 24.1 months for nonusers (95% CI, 19.02–29.30 months; $P = .008$).**

Abbreviations used in this paper: AFP, alpha-fetoprotein; AOR, adjusted odds ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HR, hazard ratio; MHT, menopausal hormonal therapy; OS, overall survival.

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CONCLUSION: **In a case–control study of women with HCC vs female control subjects at a single center, we associated use of estrogen MHT with reduced risk of HCC and increased overall survival times of patients with HCC. Further studies are needed to determine the benefits of estrogen therapy for women and patients with HCC, and effects of tumor expression of estrogen receptor.**

Keywords: liver tumor; mortality; reduction; risk factor.

Irrespective of the worldwide variation in the incidence of hepatocellular carcinoma (HCC),[1] HCC is a male-dominant disease.[2] In the United States, gender disparity in HCC has been observed not only in disease incidence,[3,4] but also in etiological factors,[5,6] progression to cirrhosis,[7] and survival[8]; where male-to-female ratio is 3:1 with poorer prognosis and is commonly associated with chronic viral hepatitis, cigarette smoking, and alcohol consumption. The sex difference has also been observed in transgenic mice with hepatitis B– or hepatitis C–induced HCC.[9,10]

In view of the notable male predominance of HCC, several investigators raised the question about the importance of sex hormones in HCC risk and prognosis. The liver expresses estrogen and androgen receptors, both of which may act as transcription factors and may regulate expression of several regulatory genes involved in several pathways including those associated with cell proliferation and immune response.[11,12]

According to the National Health Statistics Report, in the United States, the percentage of women using contraception increases with age, with 75% of women aged 40–44 years now classified as users.[13] The association between contraception and HCC was not shown to be conclusive by a meta-analysis of 12 case-control studies. The null association was later confirmed by a U.S. liver cancer pooling project with an odds ratio (OR) of 1.12 (95% confidence interval [CI], 0.82–1.55).[14] Despite the available literature about the association between contraception and HCC, very little has been published about the association between menopausal hormonal therapy (MHT) and risk of HCC.[14,15]

This case-control study aimed at integrating clinical and epidemiological data to assess (1) the effect of MHT on HCC risk in women, (2) the relationship between MHT with hepatitis virus infection on HCC development, and (3) the effect of MHT on age at HCC onset or HCC survival.

Methods

The current investigation is part of an ongoing hospital-based case–control study, which was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center. Written informed consent for participation was obtained from each participant.

Cases were new patients with pathological or radiological evidence of HCC who were treated at MD Anderson. The control subjects were healthy and genetically unrelated family members (ie, spouses) of patients at MD Anderson who had cancers other than liver, gastrointestinal, lung, or head and neck cancer.

Between January 1, 2004, and May 31, 2015, 234 women (cases) with HCC and 282 female control subjects were eligible for the current investigation. HCC patients and control subjects were U.S. residents and were interviewed simultaneously in person for demographic features and HCC risk factors with the use of a structured and validated questionnaire.

All participants were asked about their age of menarche, age of menopause, history of hysterectomy, their age when they underwent a hysterectomy, and whether 1 or both ovaries were removed during their hysterectomy.

Each woman was interviewed for ever-use of various birth control types including pills, implant, or injection and the duration of use of various forms of contraception. Participants were also questioned about use of exogenous hormones including estrogen, progesterone, and combined estrogen-progesterone. Methods of use (oral pills, skin patch, injection, and vaginal) and duration of each method were documented. We missed to collect parity information from cases and control subjects. However, for case patients, we extracted the history of pregnancy, number of pregnancies, and number of children from the institutional epidemiological database of cancer patients. In addition, baseline clinical variables were retrieved from patients' medical records.

Statistical Methods

Stata software (StataCorp, College Station, TX) Version 14 was used for statistical analysis. We performed multivariate unconditional logistic regression analyses. We calculated the adjusted OR (AOR) and 95% CI values using maximum likelihood estimation after controlling for confounding effect of demographic and HCC risk factors.

Overall survival (OS) was defined as the time between HCC diagnosis and death or end of follow-up. Median survival was estimated by using the Kaplan-Meier product-limit method, and significant differences between the survival times were determined by using the log-rank test.[16] To identify independent prognostic factors for OS, hazard ratios (HRs) and 95% CIs were calculated by using Cox proportional hazard models with a backward stepwise selection.

Analysis of covariance was used to analyze patients' mean age at HCC onset by hormonal exposure. Linear regression models were used to estimate the mean differences in age at HCC onset associated with use of birth

control and exogenous hormones after adjusting for other factors associated with age at onset in this study population.

Results

Table 1 shows that cigarette smoking was not associated with HCC risk in women. Consistent with our previous reports race, hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol use, diabetes, hypothyroidism, early adulthood obesity, and positive family history of cancer were significant risk factors for HCC in U.S. women.[5,6,17]

Table 2 shows female characteristics in cases and control subjects. A significant impact was observed only among estrogen users yielding a 50% reduction in HCC risk compared with nonusers; the estimated AOR was 0.50 (0.29–0.86) (Table 3). Long-term use of estrogen alone (>5 years) was reported by 64.2% of control subjects and 55.5% of case patients, yielding a significant reduction in HCC risk (AOR, 0.36; 95% CI, 0.20–0.63) compared with never-users. Estrogen use was mainly postmenopausal in cases (87 of 94) and in control subjects (177 of 179). Restricted analysis among white cases and control subjects did not meaningfully change the observed reduced risk of HCC among estrogen users.

The mean age ± SE at HCC onset among case patients who recalled estrogen use was 64.5 ± 0.9 years, significantly higher than the mean age at onset of those with no estrogen use was, which was 59.2 ± 1.1 years

Table 1. Multivariate AOR and 95% CI for HCC Risk Factors

Demographic variable	HCC patients n = 234	Control subjects n = 282	AOR[a] (95% CI)	*P* value
Age				
<50 y	41 (17.5)	42 (14.9)	1 (Reference)	
≥50 y	193 (82.5)	240 (85.1)	0.76 (0.42–1.36)	.4
Race				
White	171 (73.1)	261 (92.6)	1 (Reference)	
Non-White	63 (26.9)	21 (7.4)	0.27 (0.14–0.55)	<.0001
Educational level				
< College Education	174 (74.4)	182 (64.5)	1 (Reference)	
≥ College Education	60 (25.6)	100 (35.5)	1.38 (0.86–2.21)	.2
HCV (anti-HCV+)[b]				
No infection	174 (74.4)	256 (90.8)	1 (Reference)	
HCV infection	60 (25.6)	1 (0.4)	71.6 (9.60–536.04)	<.0001
HBV[b]				
No infection	198 (84.6)	249 (88.3)	1 (Reference)	
HBsAg	10 (4.3)	1 (0.4)	13.95 (1.28–151.58)	.03
Anti-HBc	26 (11.1)	7 (2.5)	2.98 (1.10–8.07)	.03
Cigarette smoking[c]				
No smoking	128 (54.7)	191 (67.7)	1 (References)	
Smokers	106 (45.3)	91 (32.3)	1.43 (0.89–2.31)	.1
Alcohol drinking[d]				
No drinking	109 (46.6)	198 (70.2)	1 (Reference)	
Drinkers	125 (53.4)	84 (29.8)	2.9 (1.81–4.64)	<.0001
Prior history of diabetes				
No diabetes	179 (76.5)	256 (90.8)	1 (Reference)	
Diabetes	55 (23.5)	26 (9.2)	3.84 (1.96–7.5)	<.0001
Prior BMI (age 20–40 y)[e]				
Normal/slim	153 (65.4)	225 (79.8)	1 (Reference)	
Overweight	47 (20)	39 (13.8)	1.24 (0.67–2.30)	.5
Obese	32 (13.7)	17 (6.0)	2.35 (1.00–5.18)	.03
Hypothyroidism				
No	176 (75.2)	239 (84.8)	1 (Reference)	
Yes	58 (24.8)	43 (15.2)	2.43 (1.43–4.16)	.001
Family history of cancer				
No	52 (22.2)	91 (32.3)	1 (Reference)	
Yes	182 (77.8)	191 (67.7)	1.79 (1.07–2.98)	.03

NOTE. Values are n (%) unless otherwise indicated.
Anti-HBc, hepatitis B core antibody; AOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.
[a]Adjusted for age, race, education level, hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol drinking, cigarette smoking, history of diabetes, family history of cancer, obesity at age 20–40 years, and hypothyroidism.
[b]Serological evidence of HCV and HBV were not determined in 25 control females (8.9%).
[c]Smokers are as subjects who had smoked ≥100 cigarettes during their lifetime.
[d]Drinkers were subjects who had consumed at least 4 alcoholic drinks each month for 6 months in their lifetime.
[e]Prior BMI (age 20-40 years) was not known in 2 cases (.9%) and 1 control subject (.3%).

Table 2. Distribution of Female Characteristics by Disease Status (HCC Cases and Healthy Control subjects)

Demographic variable	HCC patients n = 234	Control subjects n = 282	*P* value
State of residency			
Texas	117 (50.0)	161 (57.1)	.06
Other states	117 (50.0)	121 (42.9)	
Marital Status			
Single	83 (35.5)	25 (8.9)	<.0001
Married	151 (64.5)	257 (91.1)	
Age of menarche, *y*	12.86 ± 1.70	12.91 ± 1.70	.7
Hysterectomy			
No	122 (52.1)	136 (48.2)	.2
Yes	112 (47.9)	146 (51.8)	
Oophorectomy			
No	25 (22.3)	46 (36.7)	.01
Yes	87 (77.7)	100 (63.3)	
1 ovary	14 (16.1)	15 (15.0)	.4
2 ovaries	73 (83.9)	85 (85.0)	
Age of hysterectomy, *y*	39.3 ± 1.1	41.4 ± 0.8	.1
Menopause			
No	35 (15.0)	39 (13.8)	.4
Yes	199 (85.0)	243 (86.2)	
Age of menopause, *y*[a]	48.78 ± 5.41	49.88 ± 4.48	.1
Prior history of cancer			
None	195 (83.3)	282 (100)	
Breast	20 (8.5)	0	
Endometrial	6 (2.6)	0	
Cervix	4 (1.7)	0	
Others	9 (3.8)	0	

NOTE. Values are n (%) or mean ± SD.
HCC, hepatocellular carcinoma.
[a]Exclude women who had an oophorectomy.

(P = .001). The mean difference in age at HCC onset between estrogen users and nonusers was statistically significant after adjusting for other factors associated with age at HCC onset including smoking, alcohol, obesity, hypothyroidism, diabetes, HCV, HBV, marriage, history of pregnancy, educational level, and family history of cancer. The estimated coefficient was 4.65 (95% CI, 1.59–7.70; P < .003). Considering the years of estrogen exposure in a continuous variable multiple linear regression analysis showed that predicted mean age at HCC onset increased with duration of estrogen use (Figure 1).

As compared with estrogen nonusers without hepatitis virus infection, the OR for estrogen use in the absence of hepatitis infection was 0.44 (0.27–0.74) and for hepatitis virus infection in the absence of estrogen use was 17.60 (3.88–79.83). However, estrogen use attenuated the magnitude effect of hepatitis virus infection on HCC risk, yielding an OR of 4.37 (95% CI, 1.67–11.44).

A total of 39 case patients recalled a prior history of cancer, especially breast cancer (n = 20) (Table 2), whereas additional 3 cases reported a prior history of nonalcoholic steatohepatitis, primary biliary cirrhosis, and autoimmune hepatitis. Restricted analysis among 192 cases and 282 control subjects without a prior history of cancers or chronic liver diseases did not change the observed reduced risk of HCC among estrogen users.

Figure 2*A* shows that OS of HCC patients was significantly longer among estrogen users than among nonusers (P = .008). Figure 2*B* shows the univariate HRs (95% CI) of estrogen use and the clinical features of HCC at the time of diagnosis. Multivariate Cox regression analysis of the significant factors related to HCC prognosis indicated that estrogen use was significantly associated with 45% reduced mortality (adjusted hazard ratio, 0.55; 95% CI, 0.40–0.77; P = .0001) after controlling for all confounding factors of HCC OS (Figure 2*C*).

Prior history of pregnancy and pregnancy numbers were not significantly associated with HCC prognosis. Among HCC cases, we found that 66 (28.2%) women never get pregnant, 142 (60.7%) women had ≤3 pregnancies, and 26 (11.1%) women had >3 pregnancies. As compared with no pregnancy the HRs were 0.91 (95% CI, 0.66–1.26), 0.86 (95% CI, 0.62–1.20), and 1.24 (95% CI, 0.74–2.10) for history of prior pregnancy, ≤3 pregnancies, and >3 pregnancies, respectively.

Discussion

This study demonstrates 50% reduction in HCC risk development among women who used MHT. The

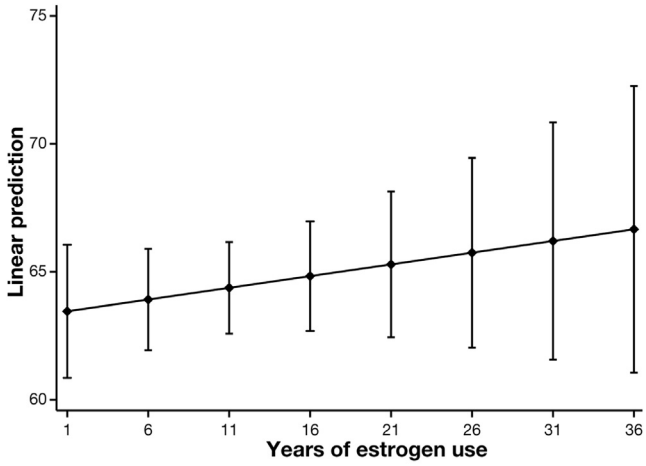
Table 3. Association Between Oral Contraceptives and Exogenous Hormonal Replacement With HCC

Demographic variables	HCC patients n = 234	Control subjects n = 282	AOR[a] (95% CI) All	*P* value
Contraception use				
No	88 (37.6)	74 (26.2)	1 (Reference)	
Yes	146 (62.4)	208 (73.8)	0.70 (0.42–1.18)	.18
Contraception duration[b]				
≤5 y	51 (35.7)	96 (46.2)	0.41 (0.22–0.79)	.01
6–10 y	26 (18.2)	47 (22.6)	0.54 (0.26–1.15)	.18
>10 y	66 (46.2)	65 (31.3)	1.38 (0.74–2.60)	.3
Estrogen use				
Never	140 (59.8)	103 (36.5)	1 (Reference)	
Ever	94 (40.2)	179 (63.5)	0.53 (0.32–0.88)	.01
Estrogen alone	63 (26.9)	130 (46.1)	0.50 (0.29–0.86)	.01
Estrogen and progesterone	31 (13.3)	49 (17.4)	0.62 (0.31–1.27)	.19
Ever estrogen duration[c]				
≤5, *y*	37 (44.6)	64 (35.8)	0.56 (0.34–1.02)	.06
6–10, *y*	13 (15.7)	36 (20.1)	0.32 (0.13–0.77)	.01
>10, *y*	33 (39.8)	79 (44.1)	0.45 (0.24–0.85)	.01
Progesterone use				
Never	196 (83.8)	219 (77.7)	1 (Reference)	
Ever	38 (16.2)	63 (22.3)	0.84 (0.47–1.52)	.57
Progesterone alone	7 (3.0)	14 (5.0)	1.22 (0.35–4.22)	.75
Progesterone and estrogen	31 (13.2)	49 (17.3)	1.38 (0.45–4.29)	.56
Ever progesterone duration[d]				
≤5, *y*	21 (60.0)	33 (52.4)	1.08 (0.51–2.31)	.84
6–10, *y*	4 (11.4)	11 (17.5)	0.57 (0.14–2.32)	.43
>10, *y*	10 (28.6)	19 (30.2)	0.57 (0.20–1.63)	.30

NOTE. Values are n (%).
AOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.
[a]Multivariate-adjusted odds for age, race, education level, marital status, hepatitis C virus, hepatitis B virus, alcohol drinking, cigarette smoking, history of diabetes, family history of cancer, obesity at age 20–40 years, hypothyroidism, oophorectomy, and marital status.
[b]Duration of OC use was unknown in 3 HCC cases.
[c]Duration of estrogen use was unknown in 11 HCC cases.
[d]Duration of progesterone use was unknown in 3 HCC cases.

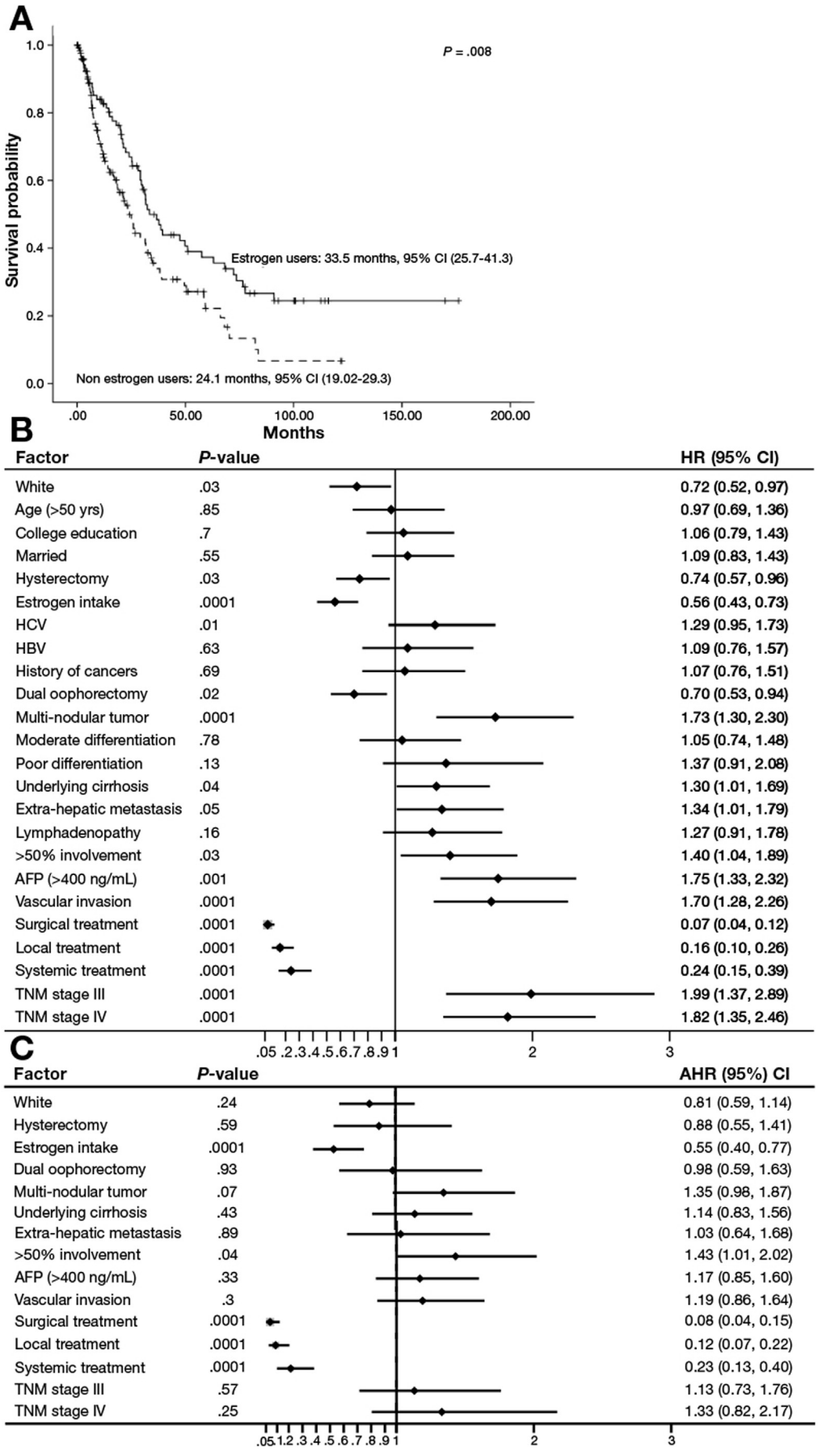
observed reduced risk of HCC among estrogen users in this study was supported by 3 additional findings: (1) The positive correlation between age at HCC onset and duration of estrogen use. The adjusted linear regression analysis revealed significant coefficients indicating that in women with long-term use of estrogen, HCC tended to be diagnosed at an older age. (2) Attenuation of the magnitude of association between hepatitis virus infection and HCC development among estrogen users compared with nonusers. (3) OS improvement in women with HCC who used estrogen compared with survival in nonusers. The favorable prognostic observation of estrogen use was independent of the significant baseline clinical features of HCC related to HCC outcome.

Very few studies have investigated the association between MHT and HCC. However, the protective effect that we observed with postmenopausal estrogen use in US women agreed with the results from different populations. The multivariate AOR reported by Yu et al[15] was .46 (95% CI, 0.27–0.79). In addition, large nested case-control study within the United Kingdom's Clinical Practice Research Datalink by McGlynn et al[18] showed that the use of estrogen therapy was associated with a



DxAge	6 yrs use	11 yrs use	16 yrs use	21 yrs use	26 yrs use	31 yrs use	36 yrs use
Mean	63.9	64.4	64.8	65.3	65.8	66.2	66.7
± SE	1.01	.9	1.1	1.5	1.9	2.4	2.9
P	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
95% CI	61.9-65.9	62.6-66.2	62.7-66.9	62.4-66.1	62.03-69.5	61.6-70.8	61.1-72.3

Figure 1. Predicted mean age at hepatocellular carcinoma onset and duration of estrogen use by linear regression; for example, the predicted mean ages (95% CI) at hepatocellular carcinoma onset at 6, 16, and 31 years of estrogen exposure were 63.9 (61.9-65.9), 64.8 (62.7-66.9), and 66.2 (61.6-70.8), respectively.



significantly lower risk of HCC (OR, 0.44; 95% CI, 0.22–0.88).

Findings from population studies with respect to the association between estrogen exposure and other cancers have been contradictory. Although some studies failed to show a significant impact of estrogen on pancreatic[19] or bladder cancers,[20] the preventive effect of estrogen against liver cancer in the current study and in others studies was observed for gastric cancer,[21] distal large bowel cancer,[22] and esophageal cancers,[23] with an average risk reduction of 28%, and the estimated ORs were 0.77 (95% CI, 0.64–0.92) and 0.68 (95% CI, 0.48–0.97), respectively. In contrast, estrogen use was significantly associated with increased risk of breast cancer.[24] Our statistical analysis after excluding HCC women with prior cancers continued to show the protective effect of estrogen use.

Whereas other epidemiological studies focused on the relationship between HCC and some reproductive factors that may modify endogenous levels of female hormones such as age at menarche, age at menopause, hysterectomy, oophorectomy, and parity,[14,15,25] we observed no significant independent effect of oophorectomy on HCC risk.

There are potential lines of evidence that estrogen may protect against HCC development: the anti-inflammatory effect of estrogen via inhibition of the NF- κB pathway[26] and possible suppression of the release of several proinflammatory cytokines that may deregulate the inflammatory and oxidative stress pathways involved in the carcinogenic process.[27,28] Given the key role of interleukin 6 in carcinogenesis and poor outcome in HCC patients, Naugler et al[29] showed that estrogen treatment inhibited interleukin 6 production from Kupffer cells in female mice, leading to a reduction in liver cancer induction. Others have suggested that estrogen may inhibit hepatic tumor growth and progression by acting as a suppressor for alternative activation of tumor-associated macrophages and inhibiting the Jak1-Stat6 signaling pathway.[30] A recent report provided new insight into the protection of estrogen in HCC via the regulation of NLRP3 inflammasome by estrogen through the ERβ/MARK pathway.[31]

Several systemic reviews have shown a negative impact of tamoxifen treatment in HCC.[32–36] A possible explanation for the tamoxifen failure is the lack of defined eligible patients for treatment according to hormonal receptor expression and the possibility that tamoxifen may not be a candidate therapy for patients with variant estrogen receptors.

Given the anti-inflammatory role of estrogen, our finding of the attenuated risk of hepatitis infection among estrogen users versus nonusers may not be surprising and is possibly explained by suppression of hepatitis-related hepatic inflammation and steatohepatitis[37] and observed antifibrotic effect of estrogen in animal studies.[38,39]

Similar to the natural history of HCC,[40,41] most of our HCC patients presented with advanced-stage disease. In addition, healthy control subjects were selected to represent the population from which case patients were ascertained. Only U.S. patients and control subjects were included, and the geographic distribution of their residential states was similar. Moreover, age of natural menopause in our control subjects were similar to the general U.S. population.[42] We chose not to use patients with cirrhosis as control subjects. We argue that this may lead to differential selection bias due to the significant association between estrogen and other environmental factors with fibrosis progression.

Given the U.S. Food and Drug Administration contraindication for MHT in patients with active liver diseases[43] we found that majority of women with MHT had preserved liver function at time of HCC diagnosis.

In conclusion, this study provides robust epidemiological evidence for the benefits of postmenopausal use of estrogen replacement against HCC development and has been corroborated by previous studies. However, this study is the first to highlight survival improvement among women with HCC who used estrogen replacement, after controlling for clinical prognostic factors, which raises the questions of whether similar effects can be observed in men who ever experienced hormonal exposure and whether estrogen can be used in targeted therapy for a selected population based on tumor expression and types of estrogen receptors.

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Figure 2. (*A*) Median overall survival and 95% confidence interval (CI) by estrogen use. (*B*) Univariate hazard ratios and 95% CI of hepatocellular carcinoma prognostic factors. (*C*) Multivariate-adjusted hazard ratio (AHR) of estrogen use (0.55; 95% CI, 0.40–0.77) after adjusting for significant confounding factors of survival including race, hysterectomy, oophorectomy, multinodular tumor, cirrhosis, extrahepatic metastasis, >50% liver involvement, alpha-fetoprotein (AFP), vascular invasion, TNM staging, and treatment type. HBV, hepatitis B virus; HCV, hepatitis C virus.

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