Annals of Internal Medicine | Review

Eradication of Hepatitis C Virus Infection and the Development of Hepatocellular Carcinoma

A Meta-analysis of Observational Studies

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Background: Hepatitis C virus (HCV) is a leading cause of hepatocellular carcinoma (HCC). In the United States, this form of cancer occurs in approximately 15 000 persons annually. A systematic review of the evidence is needed to assess the benefits of treatment of HCV-infected persons on development of HCC.

Purpose: To systematically review observational studies to determine the association between response to HCV therapy and development of HCC among persons at any stage of fibrosis and those with advanced liver disease.

Data Sources: MEDLINE, EMBASE, CINAHL, the Cochrane Library, Web of Science, and the Database of Abstracts of Reviews and Effectiveness from inception through February 2012.

Study Selection: English-language observational studies that compared therapy-derived sustained virologic response (SVR) with no response to therapy among HCV-infected persons, targeted an adult population, and had an average follow-up of at least 2 years.

Data Extraction: Two investigators independently extracted data into uniform relative risk measures. The Grading of Recommendations Assessment, Development and Evaluation framework was used to determine the quality of the evidence.

Data Synthesis: Thirty studies fulfilled the inclusion criteria, and 18 provided adjusted effect estimates that were used to calculate pooled relative risks. Among HCV-infected persons, SVR was associated with reduced risk for HCC (relative risk for all persons, 0.24 [95% CI, 0.18 to 0.31], moderate-quality evidence; advanced liver disease hazard ratio, 0.23 [CI, 0.16 to 0.35], moderate-quality evidence).

Limitation: In the meta-analyses, some variables could not be controlled for because of the observational design of the included studies.

Conclusion: Sustained virologic response after treatment among HCV-infected persons at any stage of fibrosis is associated with reduced HCC. The evidence was determined to be of moderate quality.

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Hepatitis C virus (HCV) infection is one of the most common blood-borne viral infections worldwide, with approximately 3% of persons infected globally (1). In the United States, it is estimated that 1.3% of the population, or 3.2 million persons, is chronically infected (2). Incidence of HCV infection in the United States increased throughout the 1960s and 1970s and peaked at an average of 230 000 new infections per year in the 1980s (3). Since the late 1980s, incidence has decreased dramatically (to 16 000 infections in 2009 [4]); however, HCV-related morbidity and mortality are increasing due to the aging of persons who were infected decades ago. Because liver disease progresses slowly with few or no symptoms, infected persons are often unaware of it and therefore do not seek prevention, care, or treatment. As this population ages, studies project that the incidence of cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma (HCC) will markedly increase over the next 10 to 20 years (5, 6). Hepatitis C virus–related deaths increased by 50% from 1999 to 2007 and, without intervention, are predicted to reach 35 000 per year in the next 10 to 20 years (5, 7).

Similarly, rates of HCC in the United States have more than tripled, from 1.6 per 100 000 persons to 4.9 per 100 000 persons, over the past quarter century, and an estimated 15 000 cases of HCC occur annually (8). Chronic HCV infection is the most commonly reported risk factor for HCC, and approximately half of all patients with HCC have serologic evidence of HCV infection (9). Observational data suggest that among patients with cirrhosis, HCC occurs at an annual rate of 1% to 7% (10). Models indicate that if HCV is left untreated, 60% of infected persons will develop cirrhosis, 14.4% will develop HCC, and 37% will die of HCV-associated causes (11).

Care and treatment of HCV are available and can reduce HCV-related morbidity and mortality. Care may include provision of interventions designed to reduce or cease alcohol use (which accelerates the progression of liver disease [12]); vaccinations against hepatitis A and B infection, as appropriate; and prevention messages specific to reducing the risk for transmission to others. Unlike treatment of some other viral infections (for example, HIV), antiviral therapy for HCV can eradicate the virus (that is, absence of detectable HCV RNA) after treatment, known as sustained virologic response (SVR) (13). Sustained virologic response has been associated with a 54% reduction in all-cause mortality (14), and persons who achieve it typically show histologic improvement (15) and are at lower

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risk for progression of liver disease (16, 17), HCC, and liver-related death (18). Recent advances in the effectiveness of HCV antiviral treatments have made achievement of SVR possible for most patients receiving therapy (19). Two new direct-acting antiviral protease inhibitors, telaprevir and boceprevir, were approved by the U.S. Food and Drug Administration in May 2011. The addition of 1 of these 2 drugs to the standard treatment regimen of pegylated interferon with ribavirin in clinical trials increased SVR rates from 44% to 75% for telaprevir and from 38% to 63% for boceprevir in persons with HCV genotype 1 (the most common genotype in the United States) (20, 21). However, although it is well-documented that treatment can effectively eliminate HCV, the relationship between SVR and HCC requires further study.

Several meta-analyses have examined the relationship between achievement of SVR and subsequent development of HCC (18, 22–26). Although these studies universally agree that SVR is strongly associated with a reduction in HCC, especially among persons who have progressed to advanced liver disease, the degree to which this association is true remains uncertain. Long-term outcomes of HCV treatment are difficult to assess because the diagnosis of HCV infection typically occurs after symptom onset at a later stage of disease. Extended natural history studies examining persons treated for HCV are lacking because the disease progresses over several decades. As a result, most available evidence examining the relationship between SVR and HCC is observational and often retrospective in nature. Previous meta-analyses have used raw numerator and denominator data to analyze these effects. However, without controlling for other known risk factors of HCC, including age, genotype, co-infections with hepatitis B virus (HBV) or HIV, and fibrosis stage, these studies are likely to produce incorrect effect estimates due to misspecification. Furthermore, these reviews do not include some of the more recent cohort studies with larger patient populations and longer follow-up (27).

This study presents the available evidence examining the association between achieving an SVR and development of HCC in HCV-infected adults.

Methods

Data Sources and Searches

We conducted a comprehensive literature search in MEDLINE, EMBASE, the Cochrane Library, CINAHL, Web of Science, and the Database of Abstracts of Reviews and Effectiveness from database inception through February 2012 (**Appendix Figure 1**, available at www.annals.org). Searches were limited to English-language studies and those with human participants. The search terms we used were database-specific variations of *HCV*, *SVR*, and *HCC* (**Appendix Table 1**, available at www.annals.org).

Study Selection

Two investigators independently screened all citations by title and abstract. Full articles were examined, and data were extracted and entered into an abstraction form. Disagreement between investigators was reconciled through discussions or by a third investigator.

Most inclusion and exclusion criteria were determined a priori; however, 2 criteria were modified during the analysis process to strengthen the results. We included studies if they compared HCC diagnoses by SVR and nonresponse. Sustained virologic response was initially defined as the absence of detectable serum HCV RNA at least 24 weeks after treatment; however, because of recent findings that 12-week follow-up provides a similarly accurate positive predictive value, we modified this criterion to include a 12-week SVR (13). In addition, studies had to report that participants were screened and confirmed to be negative for HCC and HBV co-infection at study initiation, although this criterion was expanded during the review process to include studies that reported adjusted analyses accounting for HBV presence at baseline. We excluded studies if they had fewer than 20 participants, patients received ongoing therapy, the mean follow-up after SVR was less than 2 years, the average age of the study population was less than 18 years, the population included patients who had previously received a liver transplant, or the primary population was co-infected with HIV. We contacted study authors if articles were unclear or had incomplete information. After 2 unanswered attempts at contact, studies were considered to have incomplete information and were excluded from the analysis.

Data Extraction and Risk of Bias Assessment

Two investigators independently used a standardized abstraction form to extract data on study design; study population characteristics (demographic characteristics, co-infections, and comorbid conditions); study location (country, facility, or database); treatment regimens; methods for HCC follow-up screening; risks of bias, including study design and attrition; and outcomes. Inconsistencies among collected study information were discussed until resolved. Many articles contained information on the same or overlapping study populations; we reviewed those articles and included the manuscript with the most complete information in the analysis. Risk of bias relevant to observational studies was assessed using the Newcastle-Ottawa Scale (28), which determines study quality on the basis of selection, comparability, and outcome.

We evaluated the confidence in the estimate of effect of the included studies by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (29, 30). Two investigators with experience using GRADE independently produced the evidence tables. The factors considered when determining the quality of the evidence were risk of bias, imprecision, indirectness (addressing a different population from the one

under consideration), inconsistency of results, publication bias, dose–effect response, magnitude of the effect, and plausible confounders. The final quality of evidence for the outcome of development of HCC could be categorized as: very low, low, moderate, or high.

Data Synthesis and Analysis

The primary summary outcome measure was the relative effect of developing HCC after achieving an SVR versus nonresponse in patients treated with any antiviral regimen capable of viral eradication. We applied a random-effects model to pool hazard ratios from adjusted studies by using the inverse variance method (Review Manager, version 5.1; The Nordic Cochrane Center and the Cochrane Collaboration, Copenhagen, Denmark). Pooled hazard ratios and 95% CIs were obtained separately for HCV-infected persons at any stage of fibrosis and those with advanced fibrosis. Several studies had more than 2 comparison groups (for example, SVR, nonresponse, and no interferon treatment) and did not make a direct comparison between SVR and nonresponse. In such instances, before pooling estimates we calculated the log hazard ratio for the comparison between SVR and nonresponse and estimated its associated SE (31).

We used the Q statistic to examine the presence of heterogeneity in hazard ratio estimates and the I^2 statistic to measure the proportion of total variability explained by heterogeneity (32). As determined a priori, any considerable heterogeneity ($I^2 > 60\%$) was explored further through sensitivity or stratified analyses. Publication bias was assessed by constructing funnel plots and performing visual inspection for asymmetry. Because of changes made to the study inclusion criteria during the review process, we conducted sensitivity analyses to examine the effect on the summary relative effect estimates of including studies that used a 12-week SVR or adjusted for HBV co-infection. In addition, to examine the effect of varying HCC rates by country, summary estimates were further stratified by geographic region (Asia vs. Europe and North America). We explored the extent to which pooled estimates changed when the number and types of confounders adjusted for in the studies (for example, age, demographic characteristics, and indicators of cirrhosis) were varied. Finally, we conducted a sensitivity analysis to determine whether including adjusted versus unadjusted study results affected the final estimate of effect.

In a separate meta-analysis, we obtained pooled incidence rates through a random-effects model using the inverse variance method (33, 34). A correction factor of 0.5 was added to case counts and person-years of follow-up for studies with zero events. For studies that did not report incidence rates or associated measures of uncertainty, we estimated incidence rates and approximated the log SE as the inverse of the square root of case counts (35). As a result of the geographic, demographic, and clinical variability in the composition of the study populations, we expected inconsistency in study-specific incidence rates and sought to confirm this using the standard statistics mentioned previously.

The evidence summary for this review was prepared in GRADEpro, version 3.6 (McMaster University, Hamilton, Ontario, Canada).

Role of the Funding Source

This research was funded by the Centers for Disease Control and Prevention's Division of Viral Hepatitis, which employed 2 authors who participated in conceptualization, review, and revisions.

Results

Literature Flow

An electronic database search retrieved 10 580 citations. An additional 14 citations were identified through a review of reference lists of relevant studies, gray literature, and data requests submitted to study authors. After duplicates were removed, abstracts of 6407 citations were reviewed and 309 citations were identified, for which full-text articles were obtained. Thirty studies met the inclusion criteria and are considered in this review (17, 27, 36–63).

Comparative Effectiveness of Viral Eradication Versus Failed Response to Treatment on Development of HCC

The 30 included studies comprised 31 528 participants from 17 countries. The average age of participants ranged from 37 to 61 years, and the average length of follow-up after treatment ranged from 2.5 to 14.4 years. Eighteen studies reported on patients at all stages of disease progression (17, 27, 36, 43, 45, 46, 49–51, 53–59, 61, 62), 4 provided information for a subset of patients with advanced liver disease (METAVIR score of F3 or F4 or Ishak score of 4 to 6) (53, 61, 64, 65), and 12 reported on patients with advanced liver disease only (37–42, 44, 47, 48, 52, 60, 63). In total, 10 853 patients (34.4%) achieved an SVR to treatment. Approximately 5.5% of all patients developed HCC ($n = 1742$).

Table 1 displays the characteristics of the 18 observational studies that provide adjusted analyses examining development of HCC among HCV-infected persons at all stages of fibrosis and with advanced liver disease who achieved an SVR or did not respond to treatment (17, 27, 36–38, 40, 46, 50–54, 56–58, 60, 61, 63–65). Studies that adjusted for confounders, such as age, other demographic characteristics, HBV co-infection, chronologic markers of SVR, or markers of cirrhosis, were interpreted as providing more confidence in the estimate of association.

Risk of bias of each primary study was judged on the basis of the findings from the Newcastle-Ottawa Scale (**Appendix Table 2**, available at www.annals.org), and an assessment of the quality of the body of evidence for each outcome was reflected in the GRADE evidence profile (**Table 2**). Because of the retrospective nature of most included studies, loss to follow-up was rarely reported. Other limi-

Table 1. **Characteristics of Included Studies**

Study, Year (Reference)	Country	Cohort Design	Patients, *n*		HCC, %		Follow-up, *y*	Participant Age, *y*	Advanced Fibrosis, %*		Funding Source
			SVR	NR	SVR	NR			F3	F4	
Studies including persons at all fibrosis stages											
Asahina et al, 2010 (36)	Japan	Retrospective	686	1356	3.2	11.0	Mean, 7.5 (SD, 4.4)	Mean, 55.4 (SD, 12.1)	20.5	4.7	Government
Hung et al, 2011 (46)	Taiwan	Retrospective	1027	443	3.2	12.2	Median, 4.4	Median, 53	–	27.8	Chang Gung Hospital
Kawamura et al, 2010 (50)	Japan	Retrospective	1081	977	1.1	6.2	Median, 6.7	Median, 50	6.9	0.0	Okinawa Memorial Institute/ government
Kramer et al, 2011 (27)	United States	Retrospective	4292	10 276	1.2	4.2	Mean, 8.7	Mean, 50.0 (SD, 8.0)	–	13.2	Government/ Schering-Plough
Kurokawa et al, 2009 (51)	Japan	Retrospective	139	264	2.9	8.0	Mean, 3.0 (SD, 1.2)	Mean, 55.8 (SD, 10.9)	22.8	2.0	Unknown
Okanoue et al, 2002 (53)	Japan	Retrospective/ prospective	375	995	1.1	11.1	Mean, 5.6 (SD, 2.1)	Mean, 50.4 (SD, 11.5)	19.2/31.3†	1.1/4.4†	Government
Osaki et al, 2012 (54)	Japan	Retrospective	185	197	0.5	11.2	Median, 4.1	Median, 59.0	–	–	Government
Pradat et al, 2007 (17)‡	Europe	Prospective	91	266	0.0	6.4	5–7	Median, 47	–	–	Schering-Plough
Sinn et al, 2008 (56)	South Korea	Retrospective	296	194	1.4	5.2	Median, 4.6	Mean, 48.4 (SD, 10.8)	49.0§		Unknown
Takahashi et al, 2011 (57)	Japan	Retrospective	89	114	1.1	10.5	Mean, 4.3 (SD, 1.6)	Mean, 55.4 (SD, 10.6)	18.2	4.9	Unknown
Tateyama et al, 2011 (58)	Japan	Retrospective	139	234	2.2	18.8	Mean, 8.2 (SD, 4.4)	Median, 57.0	17.2/10.8†	20.9/13.2†	Government
Yoshida et al, 1999 (61)	Japan	Retrospective	789	1611	1.3	4.9	Median, 4.4	Mean, 49.5 (SD, 11.3)	20.7/24.8†	6.7/10.7†	Government
Studies including persons with advanced fibrosis/cirrhosis											
Braks et al, 2007 (37)	France	Retrospective	37	76	2.7	31.6	Mean, 7.7 (SD, 3.0)	Mean, 54.1 (SD, 11.2)	0.0	100.0	Unknown
Bruno et al, 2007 (38)	Italy	Retrospective	124	759	5.6	16.1	Mean, 8.0 (SD, 3.2)	Mean, 54.7 (SD, 8.6)	0.0	100.0	ARME
Cardoso et al, 2010 (40)	France	Retrospective	103	204	5.8	19.6	Median, 3.5	Mean, 55 (SD, 10)	47/39†	53/61†	Schering-Plough
Hasegawa et al, 2007 (64)‖	Japan	Retrospective	48	57	6.3	28.1	Median, 4.6	Median, 56	0.0	100.0	Unknown
Hung et al, 2006 (65)¶	Taiwan	Retrospective	73	59	6.9	18.6	Median, 3.1	Mean, 56.1 (SD, 9.1)	0.0	100.0	Chang Gung Hospital
Morgan et al, 2010 (52)	United States	Prospective	140	386	1.4	8.5	6.6–7.2	Mean, 49.2	79.3/59.6†	20.7/40.0†	Government/ Hoffmann-La Roche
van der Meer et al, 2012 (63)	Europe/ Canada	Retrospective	192	338	3.6	22.5	Median, 8.4	Median, 48	27.0	73.0	Foundation for Liver and Gastrointestinal Research
Velosa et al, 2011 (60)	Portugal	Retrospective	39	91	2.6	22.0	Mean, 6.4 (SD, 4.0)	Mean, 51.7 (SD, 10.2)	0.0	100.0	Unknown

ARME = Associazione per la Ricerca sulle Malattie Epatiche (Association for Research on Liver Diseases); HCC = hepatocellular carcinoma; NR = nonresponse; SVR = sustained virologic response.
* Based on the METAVIR scale.
† SVR/NR.
‡ Study included 49 participants who were not treated.
§ This study did not specify the number of participants at each stage. The number shown is the percentage of those at stage F3 or F4.
‖ Published subanalysis of reference 50.
¶ Published subanalysis of reference 46.

tations inherent to observational study designs, such as risk of selection bias, are recognized by the starting point of low confidence in the estimate (low-quality evidence) within the GRADE system for observational evidence. Additional limitations (such as failure of adjustment for fibrosis stage seen in some, but not all, studies) were judged to be insufficient for further rating down of the overall quality for each outcome for the entire body of evidence. The final overall quality of evidence was rated up to moderate confidence in the estimate of effect based on the magnitude of the association, as demonstrated by the consistent reduction seen across studies.

HCC Development After Treatment of Hepatitis C in Persons at All Stages of Fibrosis

Pooled analysis of 12 studies (17, 27, 36, 46, 50, 51, 53, 54, 56–58, 61) with a total of 25 497 patients showed that achieving an SVR is associated with a reduction in the

Table 2. **GRADE Evidence Profile for Association of SVR Versus Nonresponse to Treatment With the Development of HCC Among HCV-Infected Persons**

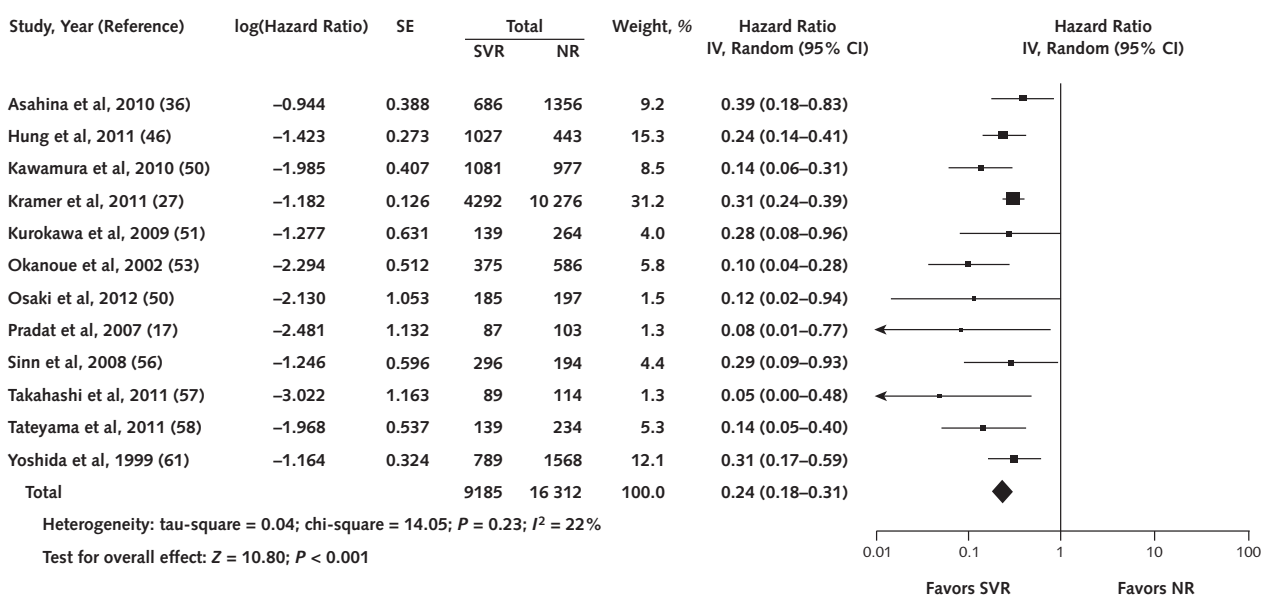
Outcome	Quality Assessment		Summary of Findings						
	Participants (Studies), *n*	Overall Quality of Evidence	Study Event Rates, *n/N (%)*		Relative Effect (95% CI)	Anticipated Absolute Effects			
			Failed or No Treatment	Viral Eradication		Risk With Failed or No Treatment		Absolute Effect With Viral Eradication (95% CI)	
						All Stages of Fibrosis, per Year	Advanced Fibrosis, per Year*	All Stages of Fibrosis, per Year	Advanced Fibrosis, per Year*
HCC among HCV-infected persons at all fibrosis stages; follow-up, 3.0–8.2 y	25 906 (12)	Moderate†	990/16 312 (6.1)	145/9185 (1.6)	Adjusted HR, 0.24 (0.18–0.31)	17 HCCs per 1000 persons	33 HCCs per 1000 persons	14 fewer HCCs per 1000 persons (12 to 15 fewer)	23 fewer HCCs per 1000 persons (18 to 26 fewer)

GRADE = Grading of Recommendations Assessment, Development and Evaluation; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = hazard ratio; SVR = sustained virologic response.
* Separate analysis of studies that reported event rates in patients with cirrhosis (HR, 0.23 [95% CI, 0.16 to 0.35]).
† Rated up because of large relative risk effect. Most studies controlled for baseline liver disease severity (for example, presence of cirrhosis) and other important confounders, such as hepatitis B virus infection.

relative risk for HCC for persons at all stages of liver disease (hazard ratio, 0.24 [95% CI, 0.18 to 0.31]; $P < 0.001$) (**Figure 1**). Approximately 1.5% ($n = 145$) of the 9185 patients responding to treatment developed HCC, compared with 6.2% ($n = 990$) of the 16 312 patients who did not respond. As a result, the absolute reduction in risk was 4.6% (CI, 4.2% to 5.0%) for patients achieving an SVR.

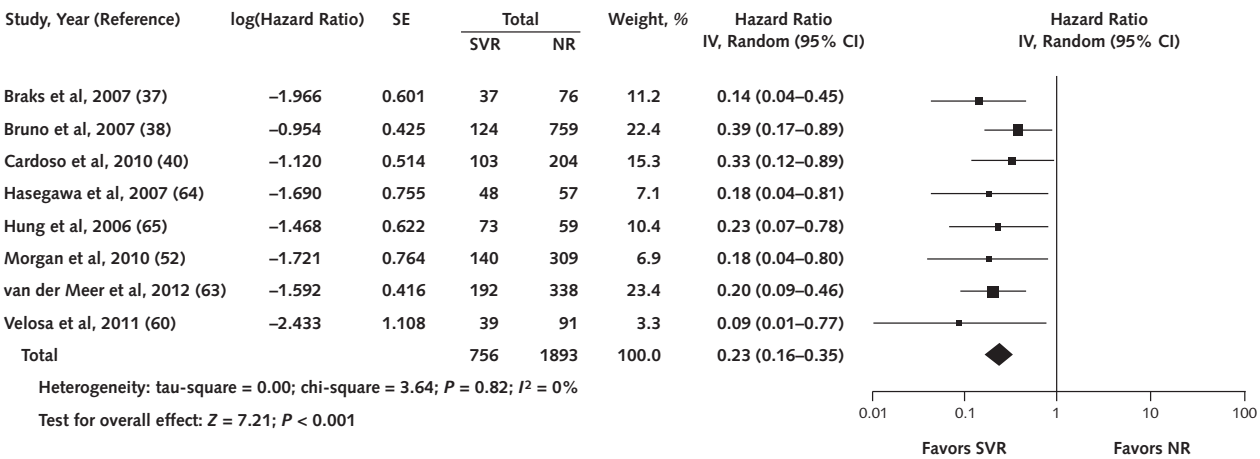
All of the studies included in the meta-analysis adjusted for age, 9 studies controlled for fibrosis stage (17, 27, 36, 50, 51, 53, 57, 58, 61), and some studies (46, 54) controlled for fibrosis stage with typical markers for advanced fibrosis. One study did not exclude patients with positive hepatitis B serologic test results, but its model was adjusted for the presence of hepatitis B (27). This same study defined SVR as having an undetectable viral load at 12 weeks. Subgroup and sensitivity analyses examined the effect of geographic location, adjustment for varying confounders, and inclusion of unadjusted studies, but these had no noticeable impact on the overall effect estimate.

Figure 1. **Forest plot of adjusted hazard effects in persons at all stages of fibrosis.**



IV = inverse variance; NR = nonresponse; SVR = sustained virologic response.

Figure 2. **Forest plot of adjusted hazard effects in persons with advanced liver disease.**



IV = inverse variance; NR = nonresponse; SVR = sustained virologic response.

Heterogeneity tests identified little inconsistency among the included studies (chi-square = 14.05; I^2 = 22%).

Among patients who achieved an SVR, 158 developed HCC in an estimated 65 817 person-years of follow-up compared with 1098 cases of HCC in 129 377 person-years of follow-up among nonresponders. In the pooled analysis, HCC developed at a rate of 0.33% per person-year (CI, 0.22% to 0.50%) among persons who achieved SVR compared with 1.67% per person-year (CI, 1.15% to 2.42%) among nonresponders.

HCC Development After Treatment of Hepatitis C in Persons With Advanced Liver Disease

Meta-analysis of 6 studies (37, 38, 40, 52, 60, 63) and 2 subanalyses (64, 65) of 2649 patients with advanced liver disease found that SVR was associated with a similar reduction in the risk for HCC (hazard ratio, 0.23 [CI, 0.16 to 0.35]; $P < 0.001$) (**Figure 2**). Overall, 756 patients with advanced liver disease (28.5%) had achieved an SVR; among those, 4.2% developed HCC (n = 32). In contrast, 337 of 1893 nonresponders (17.8%) developed HCC.

All studies adjusted for age and factors known to be predictive of HCC. Four studies adjusted for HCV genotype (37, 38, 60, 65). Further subgroup and sensitivity analyses examining the effect of geographic region, adjustment for varying confounders, and inclusion of unadjusted studies found no noticeable effect on the overall estimate of effect. Little or no heterogeneity was identified among the included studies (chi-square = 3.64; I^2 = 0%) (**Figure 2**).

In total, 62 patients who responded to treatment developed HCC during 6934 person-years of follow-up, with an estimated pooled incidence of 1.05% per person-year (CI, 0.73% to 1.50%). In comparison, HCC developed at a rate of 3.30% per person-year (CI, 2.61% to 4.16%) among nonresponders, with 552 developing HCC over 19 841 person-years of follow-up.

Funnel plot asymmetry was seen for the studies presenting adjusted results, suggesting that publication bias could not be entirely excluded (**Appendix Figure 2**, available at www.annals.org).

DISCUSSION

Attaining treatment-related SVR among persons with HCV is associated with a reduction in the relative risk for HCC. This systematic review summarizes the evidence from 30 observational studies examining the risk for HCC among HCV-infected persons who have been treated and either achieved an SVR or did not respond to therapy. Separate analyses were done to examine the association between an SVR and risk for HCC among persons at all stages of fibrosis and among those with advanced liver fibrosis.

Examining the 2 groups of interest in this study (persons at all stages of fibrosis and persons with advanced liver disease) contributes to understanding the following questions: What is the association between SVR and development of HCC? What is the annual rate of HCC development in persons at all stages of fibrosis compared with persons with advanced liver disease? In which group does treatment-related SVR have an effect at a population level?

Persons in the earlier stages of liver disease progression are more likely to respond to treatment than those in the later stages, specifically persons with bridging fibrosis and cirrhosis (67). This suggests that targeting persons at lower fibrosis stages for treatment is more effective in achieving an SVR than initiating treatment after liver disease has progressed to advanced fibrosis or cirrhosis. Still, regardless of this difference in SVR attainment, the relative risk reduction for HCC is similar between the groups. On the one hand, this would suggest that treating persons in the

earlier stages of disease would be more efficient because of the better chance of achieving an SVR after treatment. On the other hand, when the 3-fold baseline risk for HCC among persons with advanced liver disease versus those in all stages of disease progression is taken into account at the population level, more cases of HCC are prevented when persons with advanced liver disease achieve an SVR, providing a higher absolute benefit.

This study controls for relevant variables by analyzing adjusted effect measures and conducting sensitivity analyses on possible confounders, and it reduces overreporting of certain study findings by including only studies with mutually exclusive study populations, thereby increasing confidence in the effect estimates of the intervention. However, some limitations remain for which we could not account. First, although we conducted a comprehensive systematic review of findings across 6 databases, including conference abstracts and gray literature, articles not written in English were excluded and some studies may have been missed. Second, almost all included studies were done in Asia, and evidence suggests that rates of HCC are higher in Asian populations than in European or U.S. populations (1). Although this should not impact the relative effect estimate, the absolute benefit of viral suppression may be overstated. However, because we identified a higher proportion of persons in studies from Western countries, this should not impact the effect estimate. No significant difference was identified in a subgroup analysis comparing studies done in the 2 geographic areas. Third, we could not completely exclude publication bias because the funnel plot of studies reporting adjusted results showed some asymmetry. Because most of the studies had retrospective designs and were more likely to be written and published if they provided significant results, publication bias could account for some—but probably not all—of the observed effect.

These limitations notwithstanding, our findings show a protective effect of treatment-related SVR on the development of HCC among HCV-infected persons at all stages of fibrosis and among those with advanced liver disease. With the availability of newer and more effective therapies, SVR rates can be increased and HCC incidence rates can be reduced in HCV-infected persons. The association between SVR and HCC should be considered when weighing the benefits and harms of identifying and treating HCV-infected persons.

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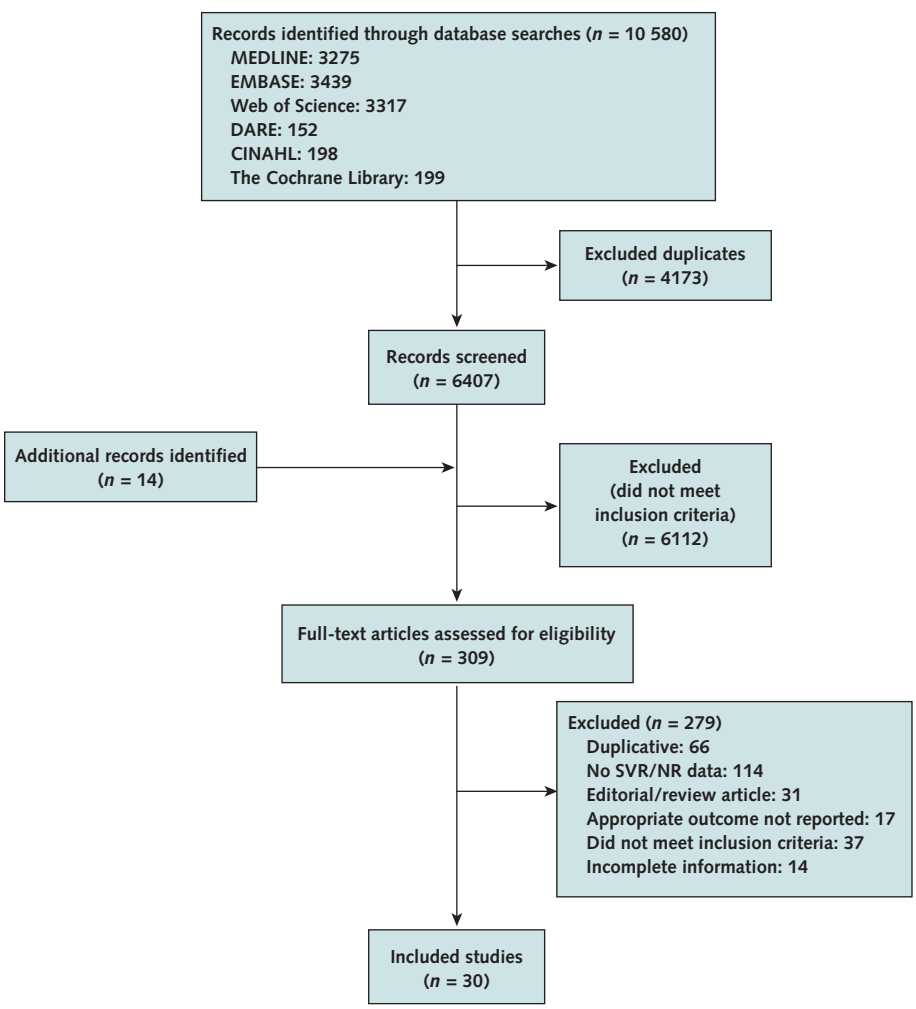
Appendix Figure 1. **Summary of evidence search and selection.**



DARE = Database of Abstracts of Reviews and Effectiveness; NR = nonresponse; SVR = sustained virologic response.

Appendix Table 1. Search Strategy

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE (1946 to February 2012)
Hepatitis C[MeSH] OR "hepatitis c" OR "hep c" OR HCV
HCC OR hepatocellular
#1 AND #2
Treatment OR therapy OR treat* OR therap*
#3 AND #4
#5 Limits: English

EMBASE (1988 to February 2012)
(hcc or hepatocellular carcinoma).mp
Limit 1 to English Language
(hepatitis c or hep c or hcv).mp
2 and 3
(treatment or therapy).mp
4 and 5

Web of Science (1950 to February 2012)
Topic=(hcc OR hepatocellular) AND topic=("hepatitis c" OR hep-c OR hcv)
#1 Refined by Languages=English
Topic=(treatment OR therapy)
#3 AND #2

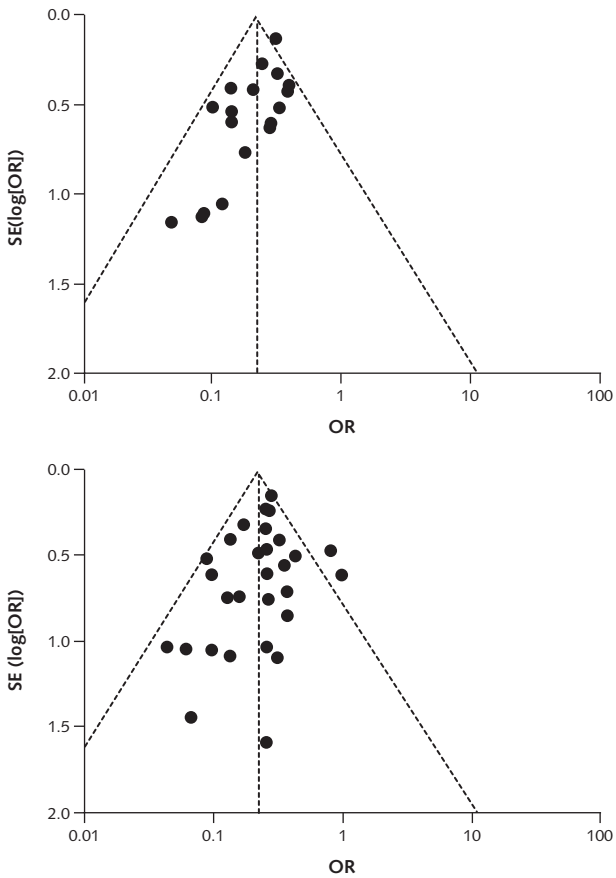
CINAHL (1937 to 2012)
(Hep c OR hep-c OR hepatitis-c OR hepatitis C) AND (HCC or hepatocellular) AND (treatment OR therapy)

Cochrane Library (inception to February 2012)
Hepatitis c OR hcv OR hepc OR hepatitis-c OR hep-c
HCC OR hepatocellular

DARE (inception to 2012)
(hcc OR hepatocellular) AND (hepatitis-c OR hepc OR hep-c OR hepatitis c OR hcv)

*DARE = Database of Abstracts of Reviews and Effectiveness.

Appendix Figure 2. Funnel plots of studies reporting adjusted (*top*) and unadjusted (*bottom*) analyses (all stages of fibrosis and advanced fibrosis).



OR = odds ratio.

Appendix Table 2. Risk of Bias of Included Studies

Study, Year (Reference)	Study Quality*								
	Selection				Comparability		Outcome		
	Representativeness of Exposed Cohort	Selection of Nonexposed Cohort	Ascertainment of Exposure	Outcome of Interest Not Present at Study Start	Comparability of Control Groups on Design or Analysis (Study Controls for Most Important Factor)	Comparability of Control Groups on Design or Analysis (Study Controls for Any Additional Factor)	Assessment of Outcome	Appropriate Follow-up	Adequacy of Follow-up of Cohorts
Studies including persons at all fibrosis stages									
Asahina et al, 2010 (36)	●	●	●	●	●	●	●	●	○†
Hung et al, 2011 (46)	●	●	●	●	●	●	●	●	○†
Kawamura et al, 2010 (50)	○‡	●	●	●	●	●	●	●	●
Kramer et al, 2011 (27)	●	●	●	●	●	●	●	●	○†
Kurokawa et al, 2009 (51)	○‡	●	●	●	●	●	●	●	○†
Okanoue et al, 2002 (53)	○‡	●	●	●	●	●	●	●	○†
Osaki et al, 2012 (54)	○‡	●	●	●	●	●	●	●	○†
Pradat et al, 2007 (17)§	○‡	●	●	●	●	●	●	●	○†
Sinn et al, 2008 (56)	○‡	●	●	●	●	●	●	●	○†
Takahashi et al, 2011 (57)	○‡	●	●	●	●	●	●	●	○†
Tateyama et al, 2011 (58)	○‡	●	●	●	●	●	●	●	○†
Yoshida et al, 1999 (61)	●	●	●	●	●	●	●	●	○†
Studies including persons with advanced fibrosis/cirrhosis									
Braks et al, 2007 (37)	●	●	●	●	●	○	●	●	○†
Bruno et al, 2007 (38)	●	●	●	●	●	●	●	●	○†
Cardoso et al, 2010 (40)	○‡	●	●	●	●	●	●	●	●
Hasegawa et al, 2007 (64)‖	○‡	●	●	●	●	●	●	●	●
Hung et al, 2006 (65)¶	●	●	●	●	●	●	●	●	○†
Morgan et al, 2010 (52)	●	●	●	●	●	●	○	●	○†
van der Meer et al, 2012 (63)	●	●	●	●	●	●	●	●	○†
Velosa et al, 2011 (60)	●	●	●	●	●	●	●	●	○†

* Study quality is based on the Newcastle-Ottawa Scale. Black circle = the study met the criterion; white circle = the study did not meet the criterion or the criterion was unreported.
† Exact number of persons lost to follow-up was not reported.
‡ Sampling method for included persons was not explicitly reported.
§ Study characteristics include 49 participants who were not treated.
‖ Published subanalysis of reference 50.
¶ Published subanalysis of reference 46.