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IN THIS SECTION



# Low-risk Prostate Cancer: Immediate Contemplation, Not Immediate Intervention

**Roxanne Nelson**

## VITALS

**Key clinical point:** Men with favorable-risk prostate cancer have a low risk for progression to a lethal phenotype and should consider active surveillance.

**Major finding:** Of 1,298 men with favorable-risk prostate cancer who were enrolled in an active surveillance program, overall, cancer-specific, and metastasis-free survival rates were 69%, 99.9%, and 99.4%, respectively, at 15 years.

**Data source:** A follow-up of a cohort of men with favorable-risk prostate cancer receiving active surveillance at a single institution that used a clearly defined protocol for enrollment, monitoring, and intervention.

**Disclosures:** There were no outside funding sources reported. Some coauthors reported consulting or advisory roles with Metamark Genetics, MDxHealth, Dianon Systems, DAKO, Trock, SonaCare Medical, Myriad Genetics, Rochon Genova, Rothwell Figg, and Roche.

Men with favorable-risk prostate cancer have a very low risk for disease progression to a lethal phenotype, and they should be encouraged to consider surveillance rather than curative intervention, investigators said online in the *Journal of Clinical Oncology*.

Cancer-specific survival rates were 99.9% at 10 years and again at 15 years, in a single-arm prospective study of 1,298 men with favorable-risk disease offered active surveillance beginning in 1995, Dr. Jeffrey J. Tosoian and his colleagues from Johns Hopkins University School of Medicine and Hospitals in Baltimore reported. The study enrolled 926 men (71%) who met all criteria for very-low-risk cancer and 372 (29%) who met criteria for low-risk disease, they said (*Journ Clin Onc.* 2015 Aug 31 [doi: 10.1200/JCO.2015.62.5764]).

Curative intervention was recommended for disease reclassification when patients no longer met the inclusion criteria following biopsy results.

A total of 38 men (3%) died from other causes before any reclassification or treatment, while nine succumbed to other causes after receiving prostate cancer treatment. The 47 men who died from causes other than prostate cancer had been receiving active surveillance for an average of seven years (range, 1 to 18 years).

There were two deaths (0.15%) from prostate cancer, both in patients with very-low-risk disease. In addition, there were two cases of lymph node metastases and one distant metastasis.

The overall, cancer-specific, and metastasis-free survival rates were 93%, 99.9%, and 99.4%, respectively, at 10 years, and 69%, 99.9%, and 99.4%, respectively, at 15 years.

Disease was reclassified during biopsy in 467 men at a median of two years (range, 0.3 to 16 years) after enrollment. Of this group, 233 involved reclassi-

fication of the tumor grade and 234 involved volume reclassification. At five, 10, and 15 years after active surveillance was initiated, the cumulative incidence of any biopsy reclassification was 35%, 49%, and 56%, respectively, while the cumulative incidence of grade reclassification was 17%, 26%, and 31%, respectively.

This study was begun at a time when there was substantial resistance to monitoring men with prostate cancer, the authors noted, and therefore, "our intents were to demonstrate the safety of this approach for carefully selected men and to identify markers of a lethal phenotype that might lead to wider inclusion in active surveillance."

"The expansion of active surveillance during the past decade and the sharing of institutional data sets will likely help delineate factors associated with varying outcomes and will allow patients to play a greater role in selecting the strategy that best suits their individual preferences," wrote Dr. Tosoian and coauthors.

"Our data suggest that, for men with favorable-risk prostate cancer, the paradigm of immediate intervention must be replaced by one of immediate contemplation—a thoughtful assessment of prognostic risk, life expectancy, and the relative risks and benefits of available management options considered in the context of personal preferences," the authors concluded.

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# Diabetes in Seniors Increases Dementia Risk

**Bianca Nogrady**

**VITALS**

**Key clinical point:** Even short-term hyperglycemia in late life can trigger or accelerate cognitive decline, and incident diabetes is a risk factor for dementia after adjustment for differences in cardiovascular disease and other common risk factors.

**Major finding:** Individuals diagnosed with diabetes later in life have a 16% higher risk for dementia than do those without diabetes.

**Data source:** A population-based matched cohort study in 225,045 seniors newly diagnosed with diabetes and 668,070 nondiabetic controls.

**Disclosures:** The Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario, the Canadian Institutes of Health Research, the University of Toronto, and the Ontario Ministry of Health and Long-Term Care supported the study. One author reported an unrestricted grant from Amgen, but there were no other conflicts of interest declared.

A diagnosis of diabetes in later life is associated with an increased risk for dementia, particularly in individuals with preexisting vascular disease. A population-based matched cohort study in 225,045 seniors newly diagnosed with diabetes and 668,070 without found a 16% higher risk for dementia among those with diabetes. The association remained after adjustment for hypertension, coronary artery disease, cardiovascular disease, peripheral vascular disease, and chronic kidney disease.

There is a growing body of evidence pointing to a link between diabetes and dementia, with their shared cardiometabolic risk factors suggesting dementia may be yet another vascular complication of diabetes, wrote Dr. Nisha Nigil Haroon of the University of Toronto.

"We hypothesized that exposure to even short-term hyperglycemia in late life can trigger or accelerate cognitive decline and therefore that incident diabetes is a risk factor for dementia after accounting for differences in cardiovascular disease and other common risk factors," wrote Dr. Haroon and her colleagues.

The risk for dementia was slightly higher in men with diabetes (hazard ratio [HR], 1.20; 95% confidence interval, 1.17-1.22) than in women (HR, 1.14; 95% CI, 1.12-1.16) compared with healthy controls, according to a paper published online in *Diabetes Care*.

Previous cardiovascular disease doubled the risk for dementia in patients with diabetes, while hospitalization or emergency department visits for hypoglycemia were associated with a 73% increase in dementia risk. Patients with chronic kidney disease or prior vascular disease were at increased dementia risk (*Diabetes Care.* 2015 July 27 [doi: 10.2337/dc15-0491]).

There was a 1% increase in the risk for dementia per year following the diagnosis of diabetes, such that patients who had had diabetes for 10 years had a nearly 30% higher incidence of dementia. The median age of the cohort was 73.

"This is of serious concern given the aging population, increasing prevalence of diabetes, and the limited effective treatment currently available for dementia," the authors wrote.

They also found that many commonly used vascular and antidiabetic medications did not impact the risk for dementia, except statins and calcium-channel blockers.

"Although such treatments have been postulated to be protective against dementia, numerous trials have failed to identify any beneficial role of glucose-, blood pressure–, or lipid-lowering agents on cognitive decline, as suggested by previous observational data," they noted.

Insulin use was associated with a 74% greater risk for dementia.

Recent immigrants or persons of South Asian or Chinese ethnicity had a reduced risk for dementia, and hypertension also seemed to lower the risk by 5%.

The authors found that individuals with diabetes living in the lowest income areas were 17% more likely to develop dementia than were those in the wealthiest area.

"Impaired health literacy, poorer self-management, and adverse health behaviors, such as smoking, have been linked to low income and could explain this association," reported Dr. Haroon and her coauthors.

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# Extremes of Sleep Linked With Early Signs of CVD

**Kari Oakes**

**VITALS**

**Key clinical point:** Individuals with very long or short sleep, or poor sleep quality, showed signs of early cardiovascular disease.

**Major finding:** Extremely short and extremely long sleep duration were associated with significantly increased levels of coronary artery calcification (CAC) and increased brachial-ankle pulse wave velocity (baPWV).

**Data source:** Cross-sectional study of more than 47,000 healthy adult men and women who reported sleep duration and quality and underwent either measurement of CAC.

**Disclosures:** The funding source was not reported. The authors reported no disclosures.

Extremely short or extremely long sleep was associated with increased incidence of preclinical signs of cardiovascular disease in a large cross-sectional study of healthy and relatively young adults. Poor subjective sleep quality was also associated with early signs of CVD.

Dr. Chan-Won Kim of the Sungkyunkwan University in Seoul, South Korea, and his coinvestigators gathered self-reports of sleep quality and sleep duration from 47,309 healthy adults who underwent regularly scheduled physical examinations. Of those, 29,203 adults (81% of whom were male) had measurement of coronary artery calcification (CAC); while 18,106 patients (69% of whom were male) underwent brachial-ankle pulse wave velocity (baPWV) measurement. The patients were relatively young, with a mean age of 42 for the CAC cohort and 46 for the baPWV cohort.

CAC and distal arterial stiffness are considered to be markers for preclinical CVD; by measuring these markers in a relatively young cohort, the investigators sought to avoid the many confounders that com-

plicate the association between CVD and sleep in older patients who have more comorbidities.

The study used multivariable analysis to control for factors such as smoking and alcohol use, marital status, and education attainment, and physiologic variables, including blood pressure, BMI, and cholesterol.

Overall, more than 80% of subjects reported good subjective sleep quality, regardless of duration. However, women who reported poor sleep had a higher incidence of CAC, and men with poor sleep had a higher mean baPWV.

For sleep duration, Dr. Kim and colleagues found a U-shaped association between sleep duration and CAC and baPWV. Compared with individuals who slept seven hours per night, individuals who reported sleeping less than five hours nightly had a CAC score ratio of 1.50 and an increase in baPWV of 6.7 cm/sec.

At the other extreme, those who slept nine or more hours per night had a CAC score ratio of 1.72 and an increase in baPWV of 9.6 cm/sec. All these differences were statistically significant (*Arterioscler Thromb Vasc Biol.* 2015 Sept 10 [doi: 10.1161/ATVBAHA.115.306110].).

The results help clarify that the previously known associations between sleep duration, quality, and CVD risk are not fully attributable to the comorbidities that can affect both sleep and heart health, said Dr. Kim and associates. Though they encourage further study to delineate sleep's contribution to CVD, their results "underscore the importance of adequate sleep quantity and quality, and support the need for considering subjects with extreme duration or poor subjective quality of sleep at high risk for CVD."

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# Sunscreens With DNA Repair Enzymes Might Lessen AK Progression

**Amy Karon**

**VITALS**
**Key clinical point:** Sunscreen containing DNA repair enzymes might prevent malignant progression of actinic keratosis better than sunscreen alone.
**Major finding:** Field cancerization and cyclobutane pyrimidine dimer levels improved significantly more with sunscreen plus enzymes than with sunscreen only ($P < .0001$ for each).
**Data source:** Six-month randomized trial of 28 patients with actinic keratosis.
**Disclosures:** Biodue S.p.A. provided the methyl aminolevulinate used in the study. Dr. Enzo Emanuele, the study's senior author, is a major shareholder of Living Research S.A.S., a privately held biomedical research organization that provided funding for the work. The other researchers reported no conflicts of interest.

Patients with actinic keratosis who used UPF 50 sunscreen containing DNA repair enzymes improved significantly more on two measures of malignant progression than did those who used sunscreen alone, according to research published in the *Journal of Drugs in Dermatology.*

At six months, improvements in field cancerization and levels of cyclobutane pyrimidine dimers were significantly greater ($P < .001$) for the sunscreen-plus-enzymes group compared with sunscreen-only patients, wrote Dr. Mauro Carducci of Centro Ortopedico di Quadrante in Omegna, Italy, and his associates.

The study is the first of its type to directly compare the clinical effects of two such topicals, the investigators wrote. The findings set the stage for longer, larger trials that are powered to assess the risk for progression to squamous cell carcinoma (SCC), they added.

For the study, 28 patients with AK were randomly assigned to use SPF 50 sunscreen alone or a formula that contained 1% photolyase from *Anacystis nidulans* and 1% endonuclease from *Micrococcus luteus.* Patients applied 2 mg/cm$^2$ of sunscreen to treatment areas that contained four to 10 AKs. They were not allowed to use other topicals during the trial or for two weeks beforehand.

All of the patients were white and older than 65; three-quarters were men. The investigators used

fluorescence diagnostics with methylaminolaevulinate to measure field cancerization and analyzed skin biopsies to quantify CPD levels (*J Drugs Dermatol.* 2015;14[9]:986-990).

Hyperkeratosis improved the same amount in both groups at month 6, according to the researchers. But field cancerizations dropped 29% from baseline in the sunscreen-plus-enzymes group, compared with a 10% decrease with sunscreen alone ($P < .0001$). Likewise, CPD levels fell 61% from baseline in the sunscreen-plus-enzymes group, compared with a 35% drop with sunscreen alone ($P < .0001$).

Despite those significant differences, the study was not powered to detect differences in the risk for transformation to SCC, the researchers cautioned.

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# Breastfeeding Protects Against Postpartum MS Relapse

**Alexander Otto**

**VITALS**

**Key clinical point:** Don't discourage new mothers with multiple sclerosis from breastfeeding.

**Major finding:** Among 81 women who did not breastfeed or who supplemented breastfeeding early on, 31 (38.3%) had an MS relapse within the first six postpartum months, compared with 29 women (24.2%) among the 120 who intended to breastfeed their children exclusively for at least two months (adjusted HR, 1.70).

**Data source:** A prospective study of 201 pregnant women with relapsing-remitting MS who were followed for one year post partum.

**Disclosures:** The work was funded by the German Research Foundation. The German MS and pregnancy registry was partly supported by Bayer HealthCare, Biogen Idec, Merck Serono, Novartis Pharma, and Genzyme Pharmaceuticals. Five of the researchers reported receiving speaker honoraria or other financial support from pharmaceutical companies.

New mothers with MS are less likely to have a relapse within six months of delivery if they breastfeed their babies exclusively for at least two months, according to the findings of a prospective study of 201 women published online in *JAMA Neurology*.

"Our findings indicate that women with MS should be supported if they choose to breastfeed exclusively, since it clearly does not increase the risk for postpartum relapse. Relapse in the first six months post partum may be diminished by exclusive breastfeeding, but once regular feedings are introduced, disease activity is likely to return," wrote Dr. Kerstin Hellwig of Ruhr-University Bochum (Germany) and her colleagues (*JAMA Neurol.* 2015 Aug 31 [doi: 10.1001/jamaneurol.2015.1806]).

The effect of breastfeeding on postpartum MS relapse has been controversial. Some studies have found that exclusive breastfeeding for at least the first two months might be beneficial, while others—studies that "defined breastfeeding crudely and/or measured breastfeeding retrospectively," the authors said—found no protective effect.

The 201 women in the study had relapsing-remitting MS for a median of 4.5 years and, while pregnant, had voluntarily enrolled in the German MS and pregnancy registry. They completed a series of questionnaires during pregnancy and the first postpartum year.

Overall, 120 women (59.7%) intended to breastfeed exclusively for at least two months, 42 (20.9%) combined breastfeeding with supplemental feedings within the first two months, and 39 (19.4%) did not breastfeed; 178 (88.6%) reported using disease-modifying therapies before pregnancy, most often glatiramer acetate or interferon beta.

Among the 81 women who did not breastfeed or who supplemented breastfeeding early on, 31 (38.3%) had an MS relapse within the first six postpartum months, compared with 29 women (24.2%)

among the 120 who breastfed their children exclusively (adjusted hazard ratio, 1.70; 95% confidence interval, 1.02-2.85; $P = .04$).

The researchers described exclusively breastfeeding as acting like a "modestly effective treatment with a natural end date."

"During exclusive breastfeeding, the pulsatile release of gonadotropin-releasing hormone and luteinizing hormone is suppressed with a corresponding suppression of the growth of ovarian follicles resulting in lactational amenorrhea and anovulation. Shortly after the breastfeeding frequency is reduced (one or two regularly replaced breastfeeding meals are sufficient to interrupt this cycle), the ovarian activity resumes with the return of menses," Dr. Hellwig and her associates wrote.

They also speculated that the "hormonal changes leading to anovulation might play a key role, since women with MS are less likely to receive the diagnosis during their anovulatory years (childhood or after menopause), and women with MS were found to be more likely to experience relapse shortly before menstruation."

The mean age in the study was about 31, but women who breastfed exclusively tended to be older than their peers and less likely to have received disease-modifying therapies before or at the time of conception. The first postpartum menses among exclusive breastfeeders came at a median of 185 days vs 64 days for other women.

"In the present study, we observed that an earlier return of menses was associated with a higher risk for relapse in the first six months post partum," the authors wrote.

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# *S aureus* Seen in 1% of Pediatric CAP Cases

**Jennie Smith**

**VITALS**

**Key clinical point:** About 1% of children presenting to a hospital with community-acquired pneumonia had *Staphylococcus aureus* infections, which do not respond to recommended firstline narrow-spectrum antibiotics for CAP.

**Major finding:** In a cohort of 554 children admitted with CAP, seven had *S aureus* infections, six classified as complicated. All received vancomycin within 24 hours of admission; anemia incidence was significantly higher in *S aureus* patients than for the rest of the cohort.

**Data source:** Retrospective cohort study of more than 3,400 children.

**Disclosures:** The study received no outside funding, and Dr. Hofto disclosed no conflicts of interest.

Current guidelines on community-acquired pneumonia (CAP) recommend penicillin, amoxicillin, or ampicillin as firstline treatment in children with CAP. However, a small minority will have *Staphylococcus aureus* infections not treatable with these antibiotics, raising some concern about how many of these cases might be missed.

At the Pediatric Hospital Medicine 2015 meeting, Dr. Meghan E. Hofto of Children's of Alabama at the University of Alabama, Birmingham, presented research from a study of 554 patients admitted to the hospital with CAP, including 78 patients with complicated pneumonia.

Seven patients in the cohort (1.3%) had *S aureus* infections, Dr. Hofto and her colleagues found. Of those, six were recorded as having complicated pneumonia, characterized by pleural effusion or cavitation.

Six patients with *S aureus* had been started on antibiotics in other health care settings prior to admission (amoxicillin, n = 4; multiple agents, n = 2). One patient positive for flu was first treated with oseltamavir only. However, all staph patients, once admitted, were started on vancomycin, which is effective against *S aureus*, within 24 hours. Five were diagnosed by pleural fluid culture; one case was identified by clinical presentation, and another by sputum culture, Dr. Hofto said at the meeting, sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, the AAP Section

on Hospital Medicine, and the Academic Pediatric Association.

The *S aureus* patients were younger than the cohort as a whole (median, 18 months vs. 40.5 months). Length of stay was significantly longer for these patients, compared with the rest of the cohort (median, 10 vs 2 d, $P < .01$), and *S aureus* patients had significantly higher incidence of anemia ($P < .01$), a finding that Dr. Hofto said was striking.

Within 24 hours of presentation, six of the seven staph cases had anemia, she said, while 12 of the 78 patients with complicated disease did. Community-acquired *S aureus* pneumonia has been linked in other studies to severe leukopenia, Dr. Hofto noted (*BMC Infect Dis.* 2013;13:359 and *Paediatric Resp Rev.* 2011 Sept;12:182-189). In an interview, Dr. Hofto said the findings supported current guidance in favor of firstline penicillin, amoxicillin, or ampicillin. "Part of what we're looking at with guideline adherence is the barriers to treating with empiric narrow-spectrum antibiotics—and obviously, one of the things people are concerned about is whether we are going to miss something," she said.

"I think we can pretty confidently say that if it's uncomplicated CAP—if there's no pleural effusion, no necrosis, no cavitation—you can treat with narrow spectrum, and the likelihood of it being staph is slim to none."

If within 48 hours, patients are not responding to the firstline treatment, "you should start thinking about other causes," Dr. Hofto said. Her review found that all *S aureus* patients were started on antibiotics effective against *S aureus*—mostly vancomycin and ceftriaxone—within 24 hours of presentation.

Dr. Hofto noted as a limitation of her study, which used retrospective chart reviews for more than 3,400 children hospitalized for suspected pneumonia over a three-year period, that additional *S aureus* cases could have been missed because of a lack of proper coding or microbial confirmation. Additional limitations were the single-site design and the relatively small number of *S aureus* cases.

Dr. Hofto said she is conducting a more in-depth chart review to ensure that no further cases of *S aureus* CAP were missed in her sample.

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# Higher Arrhythmia Risk for Psoriasis Patients

**Jennie Smith**

**VITALS**

**Key clinical point:** Patients with psoriasis are at increased risk for arrhythmia compared to those without psoriasis.

**Major finding:** After researchers adjusted for history and medication use, patients with psoriasis were at increased risk for overall arrhythmia (adjusted hazard ratio, 1.34; 95% confidence interval, 1.29-1.39).

**Data source:** A retrospective cohort study using data from almost 41,000 psoriasis patients identified from the Taiwan National Health Insurance Research Database, and almost 163,000 age- and sex-matched cohorts from the same database.

**Disclosures:** The study was institutionally funded. Dr. Chiu, Ms. Chang, and three other authors had no disclosures; one author disclosed having conducted clinical trials or received honoraria from several companies, including Pfizer and Novartis, and having received speaking fees from AbbVie.

Patients with psoriasis are at increased risk for arrhythmia, with the risk even greater for younger patients and those with psoriatic arthritis, according to a population-based cohort study conducted in Taiwan. Dr. Hsien-Yi Chiu of National Taiwan University and Wei-Lun Chang of National Yang-Ming University, both in Taipei, and their colleagues, looked at records from 40,637 patients diagnosed with psoriasis and 162,548 age- and sex-matched controls without psoriasis, over a mean follow-up of about six years, to determine the incidence of arrhythmia.

In an article published in the September issue of the *Journal of the American Academy of Dermatology*, the investigators reported that those patients with psoriasis were at significantly higher risk for arrhythmia, independent of traditional cardiovascular risk

factors (adjusted hazard ratio [aHR], 1.34; 95% confidence interval, 1.29-1.39). Increased risk for patients with mild disease (aHR, 1.35; 95% CI, 1.30-1.41) was comparable to that of patients with severe disease (aHR, 1.25; 95% CI, 1.12-1.39) and more pronounced in the subgroup of patients with psoriatic arthritis (aHR, 1.46; 95% CI, 1.22-1.74). Younger patients, between ages 20 and 39, were at higher risk (aHR, 1.39; 95% CI, 1.26-1.54) than older patients in the cohort (*J Am Acad Dermatol.* 2015 Sep;73:429-438).

Although previous studies have shown severe psoriasis to be associated with a nearly 60% increase in cardiovascular morbidity and mortality beyond traditional risk factors, less is known about arrhythmias specifically. "Inflammation may contribute to the alteration of cardiomyocyte electrophysiology, such as dysregulation of ion channel function, leading to increased risk for arrhythmia," the investigators wrote.

The authors noted that limitations of their study were the potential surveillance bias for psoriasis patients due to increased hospital visits, and the fact that alcohol and tobacco use was not captured in the patient data. Treatment with systemic therapies may lower cardiovascular risk in psoriasis patients, they added, which may explain why the arrhythmia risk among patients with severe disease was similar to that in persons with mild disease.

The findings indicate "that psoriasis can be added to future risk-stratification scores for arrhythmia," the investigators wrote, adding that patients with psoriasis, "especially young patients and those with PsA [psoriatic arthritis], should be more closely screened for various types of arrhythmia," with the hope of earlier intervention leading to reduction of cardiovascular morbidity and mortality.

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# Hepatitis C Drove Steep Rises in Cirrhosis, HCC, and Related Deaths

**Amy Karon**

**VITALS**

**Key clinical point:** Cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality rose substantially among Veterans Affairs (VA) patients over the past 12 years, mainly driven by hepatitis C virus infection.

**Major finding:** The prevalence of cirrhosis nearly doubled between 2001 and 2013, while cirrhosis-related deaths rose by about 50% and the incidence of HCC almost tripled.

**Data source:** A retrospective cohort study of 129,998 VA patients with cirrhosis and 21,326 VA patients with HCC between 2001 and 2013.

**Disclosures:** The Department of VA and the Veterans Health Administration funded the study. The investigators declared no competing interests.

Cirrhosis nearly doubled among Veterans Affairs (VA) patients between 2001 and 2013, while cirrhosis-related mortality rose by about 50% and deaths from hepatocellular carcinoma (HCC) almost tripled, investigators reported in the November issue of *Gastroenterology*.

Hepatitis C virus (HCV) infection was "the overwhelming driver of these trends, with smaller contributions from alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), and other liver diseases," said Dr. Lauren Beste of the University of Washington, Seattle, and her associates. Based on their data, the prevalence of cirrhosis in the United States will peak in 2021, they said. "In contrast, the incidence of HCC continues to increase, confirming worrisome predictions of rapid growth put forward by work (*Gastroenterology*. 2010;138[2]:513-521) conducted" in the early 2000s.

New HCV infections have dropped sharply in the US since about 1990, but cases of HCV-related cirrhosis and HCC continue to rise as chronically infected patients age and their liver disease progresses.

Although the burden of cirrhosis and HCC due to HCV infection is expected to peak in about the year 2020, the population-level effects of NAFLD, alcoholic liver disease, and hepatitis B virus infection remain unclear, the investigators said. Therefore, they retrospectively studied underlying etiologies among a national cohort of almost 130,000 VA patients with cirrhosis and more than 21,000 patients with HCC between 2001 and 2013 (*Gastroenterology*. 2015. doi: 10.1053/j.gastro.2015.07.056).

In 2013, the VA cared for more than 5.7 million patients, including about 1% with cirrhosis and 0.13% with HCC. Between 2001 and 2013, the prevalence of cirrhosis almost doubled, rising from 664 to 1,058 cases for every 100,000 patients. Deaths among cirrhotic patients also increased by about half, rising from 83 to 126 for every 100,000 patient-years. These liver-related deaths were mainly caused by HCC, whose incidence rose about 2.5 times from 17 to 45 per 100,000 patient-years, Dr. Beste and her associates reported.

Notably, deaths due to liver cancer rose threefold—from 13 to 37 per 100,000 patient-years between 2001 and 2013, "driven overwhelmingly by HCV with much smaller contributions from NAFLD and alcoholic liver disease," said the researchers. By 2013, almost half of cirrhosis cases and related deaths occurred among HCV-infected patients, as did 67% of HCC cases and related deaths, they noted.

About 60% of patients with cirrhosis and HCV infection also had a longstanding history of alcohol use, the researchers noted. Addressing both factors, as well as diabetes, obesity, and other drivers of NAFLD, could help ease the national burden of liver disease and liver-related mortality among US veterans and other groups, they added.

"The increasing burden of cirrhosis and HCC highlights the need for greater efforts to address their causes at a population level," Dr. Beste and her associates wrote. "Health care systems will need to accommodate rising numbers of patients with cirrhosis and HCC." **CR**

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## VIEW ON THE NEWS

### Improving treatment not enough to reduce liver disease burden

Despite recent advances in hepatitis C virus (HCV) treatment, many infected patients have preexisting liver fibrosis that puts them at risk for cirrhosis and hepatocellular carcinoma (HCC). Meanwhile, risk factors for nonalcoholic fatty liver disease (NAFLD) are increasingly prevalent. In this study, the investigators sought to understand the contribution of liver disease etiology to trends in adverse liver outcomes (prevalence, incidence, and mortality of cirrhosis and HCC). They identified all VA health care users from 2001 to 2013 with diagnoses of cirrhosis (n = 129,998) or HCC (n = 21,326) and compared outcomes by calendar year.

Over the study period, marked increases in cirrhosis prevalence (59%), cirrhosis mortality (52%), HCC incidence (164%), and HCC mortality (185%) were observed in this national VA cohort. The increasing prevalence of cirrhosis was mainly driven by increasing contributions from HCV or NAFLD, but increases in mortality from cirrhosis and in both incidence and mortality from HCC were almost entirely due to HCV. Based on these trends, the researchers forecasted that the prevalence of cirrhosis will plateau and begin to decline in 2021 (2020 in the HCV subgroup), but rates of HCC will continue to surge.

Although these results differ from two recent analyses of the national cancer surveillance registry (SEER) that found decelerations in HCC incidence and mortality in recent years, the current study included methodologic features (stratification by liver disease etiology and absence of age standardization) that likely facilitated more accurate estimates of HCC incidence and mortality. The generalizability of VA data to the general population is always debated (the former is nearly exclusively men, with a higher prevalence of HCV infection and other liver disease risk factors, all of whom have access to medical care), yet the researchers rightly note that the time trends in cirrhosis and HCC outcomes (rather than absolute numbers) are still applicable to the non-VA population, particularly men. This study highlights the dramatic rise in cirrhosis and HCC, and associated deaths from these conditions, over the past decade. In addition to aggressive treatment of the underlying cause of liver disease, meaningful reductions in the burden of advanced liver disease will require a renewed focus on measures to improve adherence with maintenance care for cirrhotic patients, especially liver cancer screening.

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