# The Epidemiology of Sepsis in Patients With Malignancy*

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***Study objectives:*** **To evaluate the longitudinal epidemiology of sepsis in patients with a history of cancer and to specifically examine sepsis-related disparities in risk or outcome.**

***Design:*** **Sepsis cases from 1979 through 2001 using a nationally representative sample of nonfederal acute-care hospitalizations in the United States (the National Hospital Discharge Survey) integrated with cancer prevalence from the Surveillance, Epidemiology, and End Results database.**

***Setting:*** **Eight hundred fifty-four million acute-care hospitalizations and 8.9 million patients with cancer.**

***Patients or participants:*** **Patients with a history of cancer hospitalized with a diagnosis of sepsis.**

***Measurements and results:*** **From 1979 to 2001, there were a total of 1,781,445 cases of sepsis in patients with cancer, yielding a mean annual incidence rate of 1,465 cases per 100,000 cancer patients and a relative risk [RR] of 9.77 compared to noncancer patients (95% confidence interval [95% CI], 9.67 to 9.88). In contrast to the absolute number of cases, the incidence rate of sepsis decreased over time, from a peak of 1,959 cases per 100,000 cancer patients in 1987 to 995 cases per 100,000 in 2001. The distribution of infectious sources causing sepsis was associated with the type of malignancy. White cancer patients had a lower risk for sepsis compared to nonwhites (African-American RR, 1.28; 95% CI, 1.16 to 1.40) and other races (RR, 1.47; 95% CI, 1.22 to 1.72); and male cancer patients had a higher risk for sepsis compared to female cancer patients (male RR, 1.17; 95% CI, 1.10 to 1.23). Cancer was an independent predictor of death among sepsis patients by multivariable analysis (adjusted odds ratio for death, 1.98; 95% CI, 1.97 to 1.99).**

***Conclusions:*** **Patients with a history of cancer are at increased risk for acquiring and subsequently dying from sepsis, compared to the general population, although incidence and fatality rates are decreasing over time. There are significant racial and gender disparities in the incidence and outcome of sepsis among cancer patients that require explanation.**

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**Key words:** cancer; disparity; epidemiology; malignancy; outcomes; sepsis

**Abbreviations:** CI = confidence interval; ICD-9-CM = International Classification of Diseases, Ninth Revision-Clinical Modification; NHDS = National Hospital Discharge Survey; RR = relative risk; RSE = relative SE; SEER = Surveillance, Epidemiology, and End Results database

Sepsis is the host immune response to infection, defined clinically as the intersection between physiologic derangements known as the systemic inflammatory response syndrome and infection.[1] Sepsis is a relatively common reason for acute-care hospitalization, occurring in > 700,000 people each year in the United States and occurring in 2% of all hospitalizations.[2,3] Sepsis is known to be increasing in frequency, and certain patient populations are at higher risk than

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others.[2] The risk for sepsis among male patients is approximate 30% higher compared to female patients, while African Americans and other races have nearly twice the risk for sepsis compared to whites. Certain subsets of sepsis, such as sepsis with acute organ dysfunction (severe sepsis) and sepsis with refractory hypotension (septic shock), have case-fatality rates $> 40\%$.[2,4] At present, sepsis is the tenth-leading cause of death overall in this country.[5]

Cancer is one of the most common diseases in the US population. It occurs with an approximate 3% prevalence in this country, yielding 9.8 million people living with the diagnosis of cancer in the year 2001.[6] Cancer incidence rates and death rates are highest in African Americans, although women generally have lower rates than men irrespective of race.[7] Prostate cancer incidence rates are 1.5 times higher in African Americans than whites, while breast cancer is 1.2 times more common in whites than African Americans. Invasive cancer was diagnosed in an estimated 1.4 million Americans in 2004, and this number is expected to double in the next 50 years.[7] It is estimated that cancer costs society $>$ \$60 billion annually.[8] Cancer is the second-leading cause of death in this country behind heart disease and accounts for one in four deaths overall.[9]

Chronic comorbid medical conditions are common among sepsis patients. Epidemiologic studies[2,4,10] show that chronic comorbidities are present in 54 to 65% of all sepsis patients. Cancer is the most common comorbid medical condition in patients with sepsis, reported to occur in 16.8% of US sepsis patients and in 16.7% of European and Canadian sepsis patients.[2,11] Cancer has been found in 11.6% of patients with severe sepsis.[4] Thus, the prevalence of cancer among sepsis patients is disproportionate compared to the prevalence in the US population.

Epidemiologic estimates of sepsis among cancer patients are limited. A study[12] of severe sepsis reported a rate of 1,640 cases per 100,000 cancer patients in 1999. Previous studies have not provided a longitudinal examination of sepsis in cancer patients, nor have they examined differences in risk based on race or gender that may be expected based on known disparities in both sepsis and cancer. We sought to define these relationships while additionally examining clinically relevant information regarding the source and type of infection according to tumor types and providing comparisons of sepsis incidence in other common chronic comorbid medical conditions.

## Materials and Methods

### *Data Source*

The National Center for Health Statistics has conducted the National Hospital Discharge Survey (NHDS) continuously since 1965.[13] Since 1979, the NHDS has conformed to the guidelines of the Uniform Hospital Discharge Data Set for consistency of reporting in records. The NHDS is composed of a sample of all nonfederal acute-care hospitals in the United States, including approximately 500 hospitals, with equal representation of all geographic regions. The database is constructed through the surveying of discharge records for inpatients from each participating hospital, representing approximately 1% of all hospitalizations, or 350,000 discharges annually in the United States. Discharge records are abstracted for demographic information (age, sex, ethnic background, geographic location, and marital status), seven diagnostic codes and four procedural codes (International Classification of Diseases, Ninth Revision-Clinical Modification [ICD-9-CM]), dates of hospital admission and discharge, sources of payment, and disposition at discharge.[2]

The National Cancer Institute maintains the Surveillance, Epidemiology, and End Results (SEER) database, which can be accessed through the SEER Web site.[14] The SEER Program collects and publishes cancer incidence, prevalence, and survival data from 14 population-based cancer registries and 3 supplemental registries covering approximately 26% of the US population. The SEER Registries collect data on patient demographics, primary tumor site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status. The prevalence of cancer for the United States is estimated from SEER for individual years through 2001, as determined by population incidence data and a survival model that has been previously validated.[15] For our purposes, this prevalence method was applied by a software package (SEER*Stat; National Cancer Institute, Statistical Research and Application Branch; Bethesda, MD).[16] Annual cancer prevalence data were subclassified by race, gender, and/or according to 13 of the most common cancer subtypes: GI, lung, breast, female reproductive, prostate, urinary tract, multiple myeloma, CNS, lymphoma, leukemia, pancreas, head and neck, and skin.

For comparison purposes, prevalence data for the most common chronic comorbid medical conditions were obtained from published sources: diabetes mellitus,[17] COPD,[18] HIV/AIDS,[19] coronary artery disease,[20] and hypertension[20] were obtained from several peer-reviewed sources. All data were publicly available in the biomedical literature or through the American Heart Association, the Centers for Disease Control and Prevention, the HIV InSite Knowledge database, or the National Center for Health Statistics. Statistical testing was not performed on these data for lack of access to the primary data sources. This project was considered exempt from the requirement for informed consent according to Federal Regulations of Human Subjects Protection 45 CFR § 46.101(b).

### *Definitions*

Cases of sepsis in patients with malignancy were identified from discharge records in the NHDS during the years 1979 through 2001 that included ICD-9-CM codes for both sepsis and for cancer. Sepsis was defined as previously validated[2,21]: 038.x (septicemia), 20.0 (septicemic), 790.7 (bacteremia), 117.9 (disseminated fungal infection), 112.5 (disseminated candida infection), and 112.81 (disseminated fungal endocarditis). Cancer was defined by the range of ICD-9-CM codes 140.x–239.x. Other comorbid conditions were identified by standard ICD-9-CM codes as modified from Charlon et al and Deyo et al[22–24]: diabetes mellitus (250.x), COPD (490.x–496.x), HIV/AIDS (042.x), coronary artery disease (410.x–414.x, 429.2), and hypertension (401.x). Cancer prevalence was determined from SEER (as above) from 1979 to 2001, and reporting categories were matched to tumor-specific sets of ICD-9-CM codes to carry out tumor type-specific analyses.