Special Section: COVID-19 and Cancer

What Is COVID-19?

Coronavirus disease 2019 (COVID-19) is the illness caused by a virus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 is a novel coronavirus (newly identified type) responsible for the global pandemic that began in early 2020. Coronavirus is the name of a family of viruses that cause illness ranging from mild upper respiratory tract infections, like the common cold, to more serious lower respiratory infections, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). The first known case of COVID-19 was reported in China in December 2019.

Although the true number of infected individuals is unknown because some people are asymptomatic and testing prevalence remains low, as of mid-November 2020, there were 53 million people diagnosed with COVID-19 and 1.3 million deaths worldwide, including more than 10 million cases and 240,000 deaths in the US.[1] The US has one of the highest COVID-19 death rates in the world, 60.3 per 100,000 compared to 3.3 in Australia and 0.7 in South Korea from February through September 2020.[2] As a result, the US accounts for about 20% of COVID-19 deaths worldwide, despite reflecting less than 5% of the total population.

However, the death toll of the pandemic extends well beyond COVID-19 deaths, which account for just two-thirds of the excess deaths in the US from March through July 2020 (Figure S1). Increased deaths from other causes are partly due to misclassification of deaths from COVID-19, but also because of disruptions in care.[3] Additional excess mortality from other illnesses will likely be protracted. For example, cancer deaths dipped during the early months of the pandemic (Figure S1), but will likely rebound in higher numbers than expected in the months and years to come because of delays in diagnosis and treatment.

What Are the Symptoms of COVID-19?

People with COVID-19 report a wide range of symptoms from none to severe illness. The most common symptoms are cough, fever, shortness of breath, loss or change in sense of taste and smell, muscle aches, chills, fatigue, congestion or runny nose, sore throat, headache, nausea or vomiting, and diarrhea. Many individuals also experience gastrointestinal symptoms. The average time from exposure to symptom onset is 3-7 days but can be as long as 14 days. The Centers for Disease Control and Prevention currently estimates that as many as 40% of persons infected with SARS-CoV-2 are asymptomatic, although the exact percentage remains uncertain and likely varies by age.[4]

How Does COVID-19 Spread?

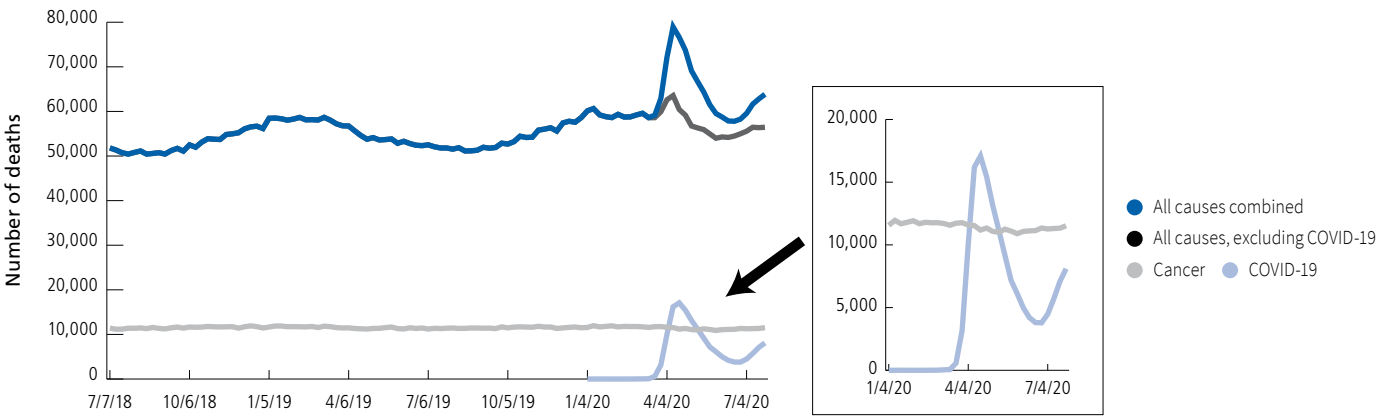
Current knowledge indicates that risk of infection is highest with prolonged close exposure to an infected person (i.e., being within 6 feet for at least 15 minutes) in indoor areas, and even brief exposure to people who are

Recommendations for protecting yourself and others from COVID-19:

1. Wash your hands often.
2. Stay at least 6 feet apart from people who do not live in your household and from sick household members.
3. Cover your mouth and nose with a mask when around others.
4. Cover coughs and sneezes with a tissue or the inside of your elbow, then immediately wash your hands with soap and water or, if unavailable, use hand sanitizer that contains at least 60% alcohol.
5. Clean and disinfect frequently touched surfaces daily.
6. Monitor your health daily.

Source: Centers for Disease Control and Prevention (cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html)

Figure S1. Weekly Number of Deaths in the US, January 2018 - July 2020*



*Counts during 2019 and 2020 are provisional (i.e., ≥75% complete within 8 weeks of death) and exclude Connecticut and North Carolina. COVID-19 deaths include deaths for which COVID-19 was identified on the death certificate as the underlying cause of death or a contributing cause (among multiple causes).

Source: NCHS, 2020. Available from: https://data.cdc.gov/NCHS/Weekly-Counts-of-Deaths-by-State-and-Select-Causes/muzy-jte6. Accessed November 2, 2020.

symptomatic (e.g., coughing).[5] Infected individuals appear to be most contagious during the 2-3 days before the onset of symptoms and remain infectious for up to 10 days following symptom onset for those with mild to moderate illness.[5] Up to 50% of transmission from one person to another may occur prior to the onset of symptoms.[4] Those with more severe illness or who are severely immunocompromised may be contagious for up to 20 days after symptom onset. Current evidence suggests that contact with contaminated surfaces or small droplets that remain suspended in air (aerosols) are not primary modes of transmission, although there is increased attention focused on the role of aerosol transmission, especially in closed spaces.[5,6] There has been widespread documentation of instances around the world where a single infected person who was in close contact with others at a large gathering (church, funeral, bar, family event, assembly line, etc.) has infected large numbers of people who then spread the virus to others. These occasions are referred to as "superspreader events" and underscore the importance of contact tracing, social distancing, and wearing a mask in combating the spread of COVID-19.

Who Is at Risk for COVID-19?

Anyone can become infected with SARS-CoV-2 and develop COVID-19, but the likelihood of severe illness increases with age and the presence of certain other health conditions, such as cancer; chronic kidney disease; chronic obstructive pulmonary disease (COPD); obesity (body mass index of 30 kg/m^2 or higher); hypertension; type II diabetes; and serious heart conditions. Other factors associated with severe illness include male sex and race or ethnicity other than non-Hispanic White, partly due to occupational exposures that do not allow for social distancing. Higher amounts of viral particle exposure may also result in more serious illness.[7] Children may be at increased risk for poor outcomes if they have complex medical conditions; neurologic, genetic, or metabolic conditions; or congenital heart disease.

COVID-19 in People With Cancer

People with active cancer are generally more susceptible to infectious agents because of an impaired immune system due to the cancer itself and/or its treatment (e.g., surgery and chemotherapy). This has led to concerns that cancer patients may be at greater risk of COVID-19 complications and death. However, factors that have been most consistently linked with increased risk of severe disease and/or death in patients with cancer mirror those in the general population, and include male sex, older age (≥60 years), a history of smoking, obesity, hypertension, cardiovascular disease, and diabetes.[8-13] For cancer-associated factors specifically, findings related to prognosis have been inconsistent. Early studies

suggested that COVID-19 patients with cancer were at higher risk for severe complications or death than those without cancer, especially individuals with lung and hematological cancers (e.g., leukemia, lymphoma) or who had undergone treatment in the past month.[14-16]

However, larger, more recent studies dispute these findings. A study of 928 patients from the US, Canada, and Spain enrolled in the COVID-19 and Cancer Consortium found no increased risk of death associated with cancer type or timing of cancer treatment.[10] Another analysis of 423 patients with symptomatic COVID-19 at a New York cancer center found that neither recent receipt of chemotherapy or surgery nor having metastatic cancer were associated with a higher risk of complications.[12] A study of COVID-19 patients with cancer who were matched 1:4 to individuals without cancer in terms of age, sex, and other health conditions again found similar outcomes for both groups, including those with recent anticancer therapy.[17] An evaluation of 22,900 Veterans Affairs patients with a history of cancer found that individuals who had received recent cancer therapy had a lower prevalence of COVID-19 and similar mortality compared to those who had not, but did find a higher prevalence of SARS-CoV-2 infection among those with hematologic versus solid cancers.[18] Finally, preliminary results from an international study of thoracic cancer patients with COVID-19 found that smoking history was the only predictor of death.[11]

The influence of cancer on COVID-19 outcomes is difficult to identify because these diseases share many risk factors, such as older age, a history of smoking, and obesity. In addition, patients with more severe COVID-19 disease may be overrepresented in studies to date due to the lack of comprehensive testing early in the pandemic. Thus, prospective studies with long-term follow up are needed to better understand the effects of COVID-19 in patients with cancer. The National Cancer Institute (NCI) is currently conducting a study of 2,000 people who are undergoing cancer treatment and have also been infected with COVID-19 (NCI COVID-19 in Cancer Patients Study) and will be followed for up to 2 years. Several longer-term prospective cohort studies, including the American Cancer Society's Cancer Prevention-3 (CPS-3), have also collected information about COVID-19 to examine the effects on cancer outcomes.

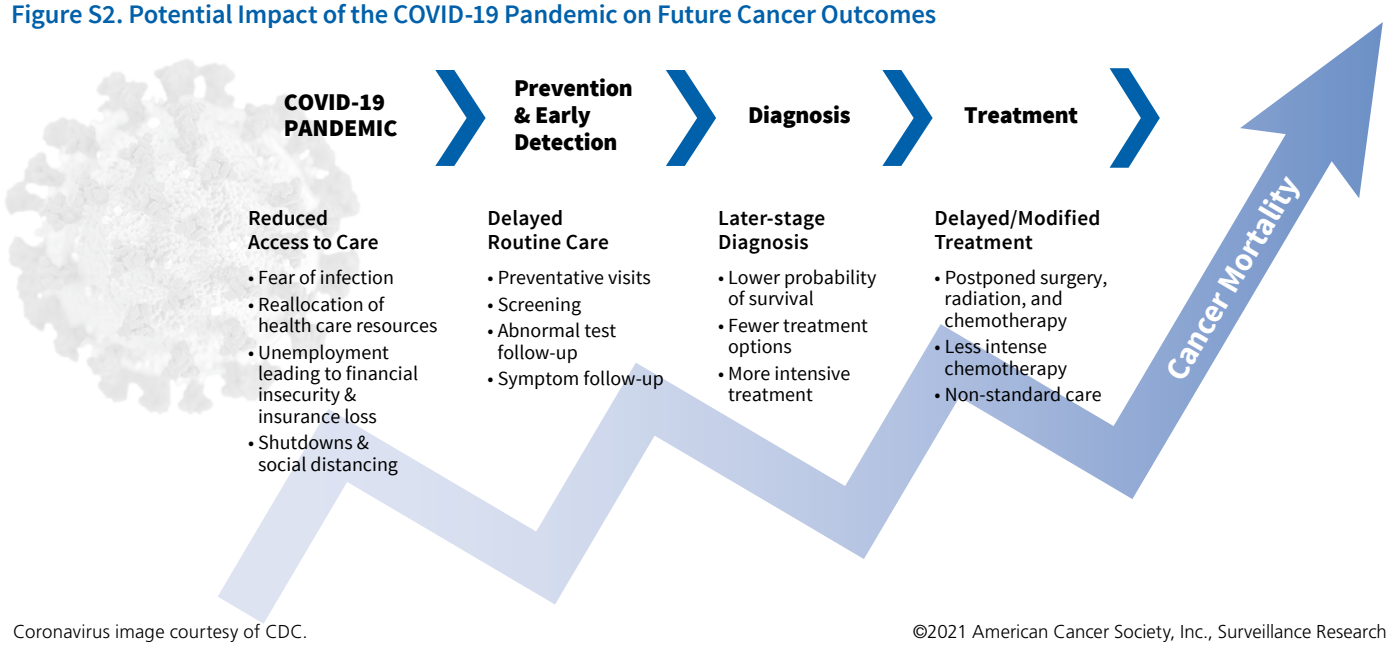
Public Health Impact of COVID-19 Across the Cancer Continuum

The COVID-19 pandemic has had numerous consequences secondary to the disease itself, including reduced access to care for other illnesses. Early in the pandemic there was a need to divert health care resources to address a rapidly growing number of individuals ill with COVID-19 and also protect healthy people from exposure to SARS-CoV-2 by suspending non-urgent health care. While these measures were necessary, delays in cancer screening, diagnosis, and treatment due to reduced health care access will likely result in a short-term drop in cancer diagnoses followed by increases in late-stage diagnoses and preventable cancer deaths (Figure S2). Some individuals may continue to delay preventive care and symptom follow-up due to fear of exposure or loss of employment and/or employer-based health care. These ramifications will particularly affect historically disadvantaged communities that already have challenges accessing quality medical care and face a disproportionate burden of COVID-19 illness, hospitalization, and death. Additionally, behavioral changes adopted during the pandemic, such as weight gain, physical inactivity, and alcohol consumption, may carry over into long-term health consequences.

Cancer prevention and early detection

At the onset of the COVID-19 pandemic, the American Cancer Society and other organizations recommended that routine cancer screenings and other elective medical procedures be postponed in order to prioritize urgent medical needs and reduce the spread of COVID-19. This guidance, along with fear of contracting the virus in health care settings, resulted in a steep drop in screening. One electronic medical record company reported an estimated 80% to 90% decline in screening for breast, colorectal, and cervical cancers among their patient population during March and April of 2020 compared to the same time period in 2019.[19-21] Screening for these cancers had risen by June of 2020, but was still down 29% to 36% from pre-pandemic levels.[22] In addition, according to data from the Centers for Disease Control and Prevention, HPV vaccinations dropped 73% between February and April 2020.[23] The full impact of the COVID-

Figure S2. Potential Impact of the COVID-19 Pandemic on Future Cancer Outcomes



Coronavirus image courtesy of CDC.

19 pandemic on cancer prevention and early detection will not be known until population-based nationwide data become available in the years to come.

Preventive visits have continued to increase as medical facilities have taken extensive infection-control precautions. As non-COVID-related health care has resumed, individuals who are at high risk of cancer due to genetic factors, personal or family medical history, or other reasons should be prioritized in capacity-limited situations. In addition, targeted efforts to promote screening are especially needed among historically underserved populations to counteract the disproportionate impact of COVID-19 and the pandemic's secondary consequences. For colorectal cancer (CRC) screening, in-home stool-based tests are a safe and effective alternative to colonoscopy for individuals at average risk and are being increasingly deployed.[24] However, a positive result must be followed up with a colonoscopy within 10 months for maximum benefit.[25] Colonoscopy is also required for individuals with CRC symptoms and others at elevated risk of developing CRC. Efforts to ensure safe delivery of colonoscopy for screening purposes through the COVID-19 era and beyond are ongoing.[26] For more information, see Cancer Screening During the COVID-19 Pandemic on the American Cancer Society's website at cancer.org.

Individuals with new or concerning symptoms associated with cancer, including lumps in the breast or elsewhere, abnormal vaginal bleeding, blood from the rectum or in stool, unexplained weight loss, fever, fatigue, or skin changes, should promptly seek medical attention and undergo diagnostic evaluation. In health care facilities throughout the country, aggressive infection control measures are being taken to ensure that diagnostic procedures are conducted safely.

Cancer Incidence

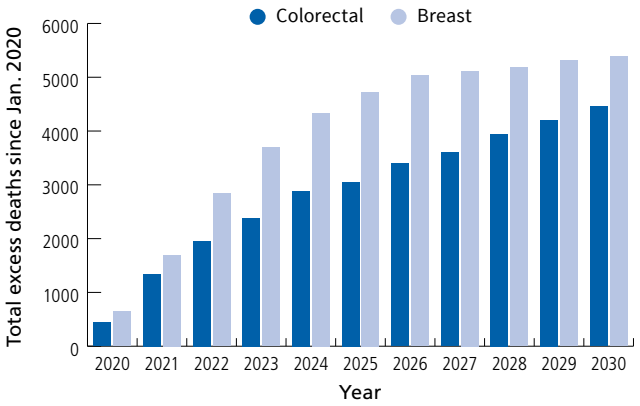
New cancer diagnoses in 2020 will likely be lower than expected due to aforementioned declines in cancer screening and other preventive care visits during the COVID-19 pandemic. One study of diagnostics data reported that among people who received medical testing for any reason, there was a 46% decline in diagnoses of six common cancers (breast, colorectal, lung, pancreas, stomach, and esophagus) during March 1 to April 18, 2020, compared with January 6, 2019, to February 29, 2020, ranging from a 25% drop for pancreatic cancer to 52% for breast cancer.[27] Another analysis reported that new CRC diagnoses were down by 30% from January to mid-April 2020 compared to that time period in 2019.[28] Likewise, an analysis of 20 US health care institutions that included more than 28 million people reported that patient

encounters related to new cancer diagnoses were 40% to 50% lower in April 2020 compared to April 2019.[21] Similar declines have been observed around the world, including in the Netherlands[29] and the United Kingdom.[21] Although these preliminary snapshots may provide a glimpse into the impact of the pandemic on cancer diagnoses, population-based cancer registry data and the extent to which these delays will translate to more advanced stage disease will not be known for some time.

Cancer treatment and survivorship

The COVID-19 pandemic has resulted in unprecedented challenges to the care and treatment of patients with cancer. Many patient visits and procedures were abruptly cancelled at the onset of the pandemic to preserve health care resources and reduce the risk of exposure to SARS-CoV-2. The American Cancer Society Cancer Action Network℠ (ACS CAN) began surveying cancer patients and survivors in late March to examine the influence of the pandemic on health care delivery. In May 2020, 79% of respondents in active treatment reported delays in their care, up from 27% in April.[30] The most commonly reported delays were for in-person provider visits (57%), imaging services (25%), surgical procedures (15%), and access to supportive services (20%), including physical therapy or mental health care. The surveys also found that nearly half (46%) of respondents were facing significant financial stress, including 23% who were concerned about losing health insurance. Importantly, these results likely underestimate the impact on people of color, especially those who are Black, who have experienced a disproportionate burden of both COVID-19 and the pandemic's economic impact.

Figure S3. Estimated Cumulative Excess Deaths From Colorectal and Breast Cancers in the US Due to the COVID-19 Pandemic, 2020 to 2030



Source: Sharpless NE. COVID-19 and cancer. *Science.* 2020;368(6497): 1290. Reprinted with permission from AAAAS.

Cancer clinical trials have also been affected by the COVID-19 pandemic, with 60% of research programs halting screening and/or enrollment for clinical trials.[31] In addition, a large portion of research resources have been reallocated to COVID-19, for which there were more than 3,370 registered clinical trials at clinicaltrials.gov as of September 2020. It is hoped that recently enacted regulatory changes by US Federal agencies to support decentralized clinical trials will increase patient access and enrollment. Currently, these new regulations and rules are applicable only during the COVID-19 Public Health Emergency (PHE) and will expire after the PHE declaration is rescinded.

Guidelines for cancer care during the pandemic carefully balance concerns about limiting potential exposure to SARS-CoV-2 while preserving delivery of necessary care. The American Society of Clinical Oncology issued a special report on cancer care during the pandemic based on COVID-19 status that contains numerous links to additional resources.[32] Many organizations collaborated early in the pandemic to offer guidance around adjusting cancer treatment. Among them, the European Society of Medical Oncology issued recommendations that patients with potentially curable cancers be treated according to existing guidelines, including use of systemic therapies.[33] They also urged considerations for particularly vulnerable patients, including the use of supportive measures (e.g., growth factors) in individuals receiving treatments associated with a high risk of immunosuppression and adjusting chemotherapy regimens when appropriate to reduce the number of clinic visits. The Cancer and Aging Research Group published recommendations to guide delivery of care for older patients with cancer, which include a careful weighing of risks and benefits for those who are frail, especially elderly, and/or have significant underlying medical conditions.[34] More recently, the University of California Cancer Consortium published a summary of broad interventions implemented as a result

of the pandemic, but with the additional intent to permanently enhance cancer care delivery.[35]

Cancer mortality

The COVID-19 pandemic is expected to result in increased cancer mortality over the long term due to delayed diagnoses; interruptions or alterations in potentially curative treatment; the possibility that some adults will abandon prior patterns of preventive care; and the expectation that millions of adults will remain unemployed and without health insurance. The National Cancer Institute estimated a 1% increase in deaths from breast and colorectal cancer over the next 10 years, the equivalent of approximately 10,000 excess deaths due to the pandemic's impact on screening and treatment (Figure S3).[36] However, this may be an underestimate because models assumed a 6-month disruption in care followed by the return to routine care, which has since proven too optimistic. A similar study estimated that cancer diagnosis delays in England would result in additional deaths ranging from 5% for lung cancer to about 15% for colorectal cancer.[37]

Consequences of the COVID-19 Pandemic

Telehealth (Telemedicine)

In response to the pandemic, health care providers transitioned many patient visits to virtual care, consisting of telephone or video consultations. Telehealth allows receipt of many aspects of necessary care remotely while minimizing transmission of coronavirus or other infectious agents to clinicians and patients. Telehealth was not widely used prior to the pandemic, despite evidence of substantial patient interest, in large part due to restricted reimbursement. However, the landscape had begun to change in recent years because of increased passage by many states of parity laws that require private insurers to reimburse for telemedicine services.[38] Although Medicare reimbursement had remained limited to patients in rural areas prior to COVID-19, major changes in federal and state policy in March 2020 facilitated the rapid expansion of telehealth by granting equal reimbursement; relaxing Health Insurance Portability and Accountability Act (HIPAA) requirements to allow for the use of video,

Figure S4. Disproportionate Burden of COVID-19 Cases, Hospitalizations, and Deaths Among People of Color Compared to Non-Hispanic White Persons

	American Indian or Alaska Native	Asian	Black or African American	Hispanic/ Latinx
Cases	2.8x higher	1.1x higher	2.6x higher	2.8x higher
Hospitalizations	5.3x higher	1.3x higher	4.7x higher	4.6x higher
Deaths	1.4x higher	No increase	2.1x higher	1.1x higher

Comparisons are rate ratios, with non-Hispanic White persons as the reference group. Categories for persons of American Indian, Alaska Native, Asian, Black or African American race exclude individuals of Hispanic ethnicity.

Source: Centers for Disease Control and Prevention, 2020. Available from: cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Accessed October 30, 2020.

telephone, and text-based applications; and reducing the burden of multi-state licensing requirements for out-of-state providers.[39] Although some of these changes may be temporary, the facilitation of necessary health care delivery that ensured the protection of both staff and patients was a critical need during the pandemic.[40] Additional information on current state laws and policies regarding telehealth can be found at the Center for Connected Health Policy website (cchpca.org/).

A report using data from 22 health systems across the US that included information on 7 million patients found that telehealth visits increased 300-fold from March/April 2019 to March/April 2020.[41] Usage peaked in mid-April 2020, with telehealth visits comprising 69% of total health care visits, but declined to 21% as the country began to reopen in late April and May.[42]

Telehealth offers many benefits to patients and providers.[38] For example, it eliminates some of the ancillary costs associated with traditional health care visits including transportation, childcare, and some of the time lost from work. In addition, telemedicine can allow more frequent check-ins with providers, which is particularly helpful for patients with chronic conditions. It can also allow patients to consult with specialists who would otherwise be inaccessible to them. For clinicians, telemedicine allows increased flexibility and may help alleviate burnout. However, some patients may not be comfortable with telehealth or have access to the

technology or bandwidth necessary to use it, especially those in rural areas.[43] It remains unclear whether the increased levels of telemedicine use will persist post-pandemic and how it may affect future health care prioritization and utilization.

Health equity

The COVID-19 pandemic has highlighted and exacerbated existing health inequities in the United States. Black and Hispanic/Latinx individuals and people with lower incomes have a disproportionate burden of COVID-19, as they do for cancer and other chronic diseases, as well as the adverse economic consequences of the pandemic. A nationwide study of cancer patients within the Veterans Affairs health care system found that the prevalence of COVID-19 was 3 times higher among individuals who were African American and 2 times higher among those who were Hispanic, compared to those who were White.[18] A comparison of COVID-19 outcomes across New York City boroughs found the highest rates of hospitalization and death in the Bronx, which has the highest proportion of people of color, the most persons living in poverty, and the lowest levels of educational attainment.[44] According to the Centers for Disease Control and Prevention, as of September 1, 2020, 19% of cases and 22% of deaths had occurred among Black individuals, who make up only 12% of the US population, compared to 41% of cases and 51% of deaths among non-Hispanic White individuals, who comprise 60% of the population.[45] People with COVID-19 who are Black, Hispanic, or American Indian/Alaska Native are about five times more likely to be hospitalized than those who are non-Hispanic White (Figure S4).

This disproportionate burden likely reflects long-standing inequities in social and structural determinants of health, including housing, transportation, and employment.[46, 47] Black and Hispanic individuals are more likely than others to live in densely populated housing; depend on public transportation; and be employed in public-facing essential services, such as food service or health care, in which risk of infection with SARS-CoV-2 is greatest.[48] In addition, compared to White persons, Black persons have a higher prevalence of chronic health conditions, including severe obesity and diabetes, which are associated with increased risk for hospitalization and death due to COVID-19; however, one study suggested the contribution of these factors to poorer outcomes in Black persons may be minimal.[48] The American Indian and Alaska Native communities have also been disproportionately affected by the pandemic,[49] with the Navajo Nation surpassing New York City for the highest rates of COVID-19 infection in May 2020.[50] Although the rate of COVID-19 among Asian Americans is similar to that in the White population, Asian Americans have faced another crisis. Anti-Asian racism in the form of assaults, harassment, and hate crimes has become prevalent because of inflammatory racist rhetoric at the national level and in the popular press that refers to SARS-CoV-2 as the "China virus" in reference to the origin of the outbreak.[51]

Moreover, the COVID-19 pandemic threatens to worsen existing disparities that occur across the cancer continuum. (See Cancer Disparities on page 49 for details.) For example, the rapid dissemination of telehealth services could increase disparities in access to care without proactive efforts by health systems and providers to ensure equity.[52] Alternatively, telehealth could potentially reduce disparities by providing easier access to medical services for patients who live in rural areas; reducing missed time from work; and eliminating costs associated with in-person visits (e.g., childcare and transportation).[38] The backlog of screening and other preventive health care visits will likely further exacerbate delayed diagnosis and substandard treatment among Black and low-income individuals. The economic ramifications of the pandemic will only further widen this gap among individuals who were already financially insecure.[53]

Unemployment and insurance loss

The COVID-19 pandemic has resulted in unprecedented job loss, eliminating employer-based health insurance as an option for millions of Americans. According to the US Bureau of Labor and Statistics, the unemployment rate rose from a 50-year low of 3.5% in February 2020 to 14.7% in April overall, 16.7% among Black individuals, and 18.9% among Hispanic individuals. Between March and May 2020, more than 40 million people lost their jobs and filed for unemployment insurance. Actual job and income loss were likely even higher because some people were only

marginally employed or did not file for unemployment benefits. As of June 2020, an estimated 14.6 million people had become uninsured due to the loss of employer-sponsored insurance as a result of COVID-19.[54] Others may be eligible for Medicaid coverage. Research has shown that disruptions in insurance coverage are associated with less frequent cancer screening, advanced stage at diagnosis, treatment delays, and poorer survival.[55-57] Although people are returning to work, the economy is not expected to fully rebound in the near future, leaving many individuals uninsured, especially people of color. The Affordable Care Act played a large role in reducing inequalities in health insurance coverage pre-COVID-19 and is even more important now for mitigating the effects of the pandemic on America's health.[58]

Resources

Knowledge about COVID-19 and its long-term effects is constantly evolving as new information and data accumulate. The information contained in this section was current as of September 1, 2020. Sources for up-to-date information about COVID-19 and cancer include:

- American Cancer Society (cancer.org/coronavirus)
- National Cancer Institute (cancer.gov/about-cancer/coronavirus)
- Centers for Disease Control and Prevention (cdc.gov/coronavirus).
- Johns Hopkins University Coronavirus Resource Center (coronavirus.jhu.edu/map.html)

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