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Medical Intelligence Report

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Topic: Update on COVID-19 Research

COVID-19 Treatments

Metformin

Metformin is a medication used for the treatment of type-2 diabetes and obesity, and it is thought to function by reducing the inflammatory response produced by these diseases (Bramante et al., 2020). Specifically, researchers have observed reductions in the amount of cytokines in individuals taking metformin, and the response is larger in women when compared to men.

In this study, researchers investigated the outcomes of individuals who were hospitalized for COVID-19 who had been taking metformin for the last 90 days as a treatment for diabetes or obesity. Based on current hospitalization protocols, treatment with metformin is stopped upon admission to the hospital. Therefore any benefits observed would be due to effects on the body from metformin before treatment for COVID-19 in the hospital.

> **Previous use of metformin was found to lead to a statistically significant reduction in mortality of 21.5% for women with obesity or type 2 diabetes who were admitted to hospital for COVID-19.**

Based on these results, use of metformin may have a beneficial effect on COVID-19 symptoms and prevent COVID-19 mortality in a group that is at higher risk for poor outcomes. This study only investigated the use of metformin before hospitalization for COVID-19, and it is not known if use of the medication during SARS-CoV-2 infection is beneficial. The effect observed here suggests that the increased risk from COVID-19 in those who are obese or have diabetes may, in part, result from higher levels of inflammation and particularly the response mediated by cytokines. The authors also stress that this is a preliminary study that examined the medical records of hospital patients and not a randomized and controlled study. Therefore further evidence is needed for confirmation of the effect.

> **However, because metformin is available as a generic drug, it is inexpensive (less than $4.00 per month), widely available, and safe for most people who do not have severe kidney disease, the medication could be widely distributed to adults at high risk of COVID-19 for the prevention of death from the disease.**

The medication is also safe for use in women who are pregnant, which is a group that has an increased risk, but few treatment options at the moment.

COVID-19 Vaccine

The peer-reviewed results from two Phase 3 vaccine trials have been published. Information about the vaccine developed by Pfizer and BioNTech was published in *The New England Journal of Medicine*, and information about the vaccine developed by Oxford University and AstraZeneca was published in *The Lancet* (Polack et al., 2020 and Voysey et al., 2020).

This final review of the data from the study funded by Pfizer included 43,548 participants with 21,720 receiving the vaccine and 21,728 receiving the placebo. There were eight cases of COVID-19 after the second dose of the vaccine and 162 cases among those who received the placebo. This corresponds to a vaccine that is 95% effective at preventing COVID-19. Similar results were observed across sub-groups of participants, including those of different age, sex, race, ethnicity, baseline body-mass index, and the presence of chronic medical conditions. There were ten severe cases of COVID-19, with nine occurring in the group receiving the placebo and one in the vaccine group. Overall, the results were consistent with other earlier reports.

The analysis of the clinical trial from AstraZeneca included the combination of results from four studies in the United Kingdom, Brazil, and South Africa. During the trial, there were two groups that received different doses due to a procedural error, and the efficacy of the vaccine for the group that received two, full doses was 62.1%. A smaller subset of participants received a half dose and then a full dose, and the efficacy in this group was 90.0%. Overall, when combining the two groups, the efficacy was found to be 70.4%. Due to the large variation between the two groups of participants, questions remain about the vaccine, but the safety of the vaccine was good, and none of the people with severe symptoms from COVID-19 were in the group that received the vaccine. Again, the reported results were consistent with previous reports of the trial.

Transmission of SARS-CoV-2

The CDC has released a summary of public health strategies that can help to protect communities from transmission until there is high coverage with effective vaccines (Honein et al., 2020).

> **The CDC estimates that with more time spent indoors with the change of seasons and a transmission rate from asymptomatic carriers of around 50%, there will be a period of high-level transmission of SARS-CoV-2.**

While efforts to distribute the newly authorized vaccines in the United States are underway, vaccination of enough people to provide a reduction in transmission will be a long process. Additionally, it may take up to two months after the first dose of the vaccine (two are required in most cases) for full immunity to emerge.

The CDC has identified sustainable strategies that have been shown by clinical research to reduce transmission of COVID-19.

The key components that have been identified include

- Universal face mask use
- Maintaining physical distance from other persons and limiting in-person contacts
- Avoiding nonessential indoor spaces and crowded outdoor spaces
- Increasing testing in order to rapidly identify infected persons so they can be isolated from susceptible individuals
- Prompt quarantine of people exposed to individuals with a known COVID-19 diagnosis
- Safeguarding those at increased risk for severe illness or death
- Protecting essential workers with provision of adequate personal protective equipment and safe work practices
- Postponing travel
- Enhancing ventilation and hand hygiene

Based on the available research, the combination of these strategies can reduce SARS-CoV-2 transmission, long-term symptoms or disability, and death while also mitigating the pandemic's economic impact. Additionally, consistent implementation of these strategies "improves health equity, preserves health care capacity, maintains the function of essential businesses, and supports the availability of in-person instruction for kindergarten through grade 12 schools and preschool."

The authors of the report also stress that "No single strategy can control the pandemic; rather, a multipronged approach using all available evidence-based strategies at the individual and community levels can break transmission chains and address high levels of community transmission."

Transmission in Indoor Eating Environments

An investigation of transmission of SARS-CoV-2 in a South Korean restaurant indicates that long-distance droplet transmission is possible when eating in indoor environments (Kwon et al., 2020). The incident began with a single infected individual who was found to transmit SARS-CoV-2 to two other patrons, one of whom was seated 1.2 meters away (3.9 feet) and the other who was 6.5 meters away (21.3 feet) and only in the restaurant for five minutes with the infected individual.

Based on their analysis of air flow, security video, and cell phone data, the researchers found that droplet transmission was possible at a longer distance than previously reported (approximately two meters or six feet) if there is direct air flow from the infected person.

The index case in the investigation (Case A) had symptoms that began on June 16. Location data showed that Case A had only one overlap with another of the 538 confirmed, domestic cases at that time in South Korea on June 12. There were eleven other customers and two employees present in the restaurant, and the contact (Case B) identified by cell phone data was found to be the primary case leading to the infection of a total of two people at the restaurant. There was one other person who sat at the same table and ate with Case B (who is identified as Case D). Case D was exposed to someone with COVID-19 on June 11. The incubation period of the virus dictates that this person could not yet have been able to infect others, and he was not included in the other parts of this investigation. Genetic sequencing of the virus from the infected individuals showed that the two people infected at the restaurant and the primary case had identical viruses.

With the primary case infecting two individuals out of 13, the attack rate for the encounter was found to be 15.4%.

The restaurant was on the first floor of a six-story building and did not have windows or ventilation that incorporated outside air. A diagram of the restaurant is shown below in Figure 1. There were two doors to the restaurant and two air conditioners on the ceiling that recycled the air in the room.

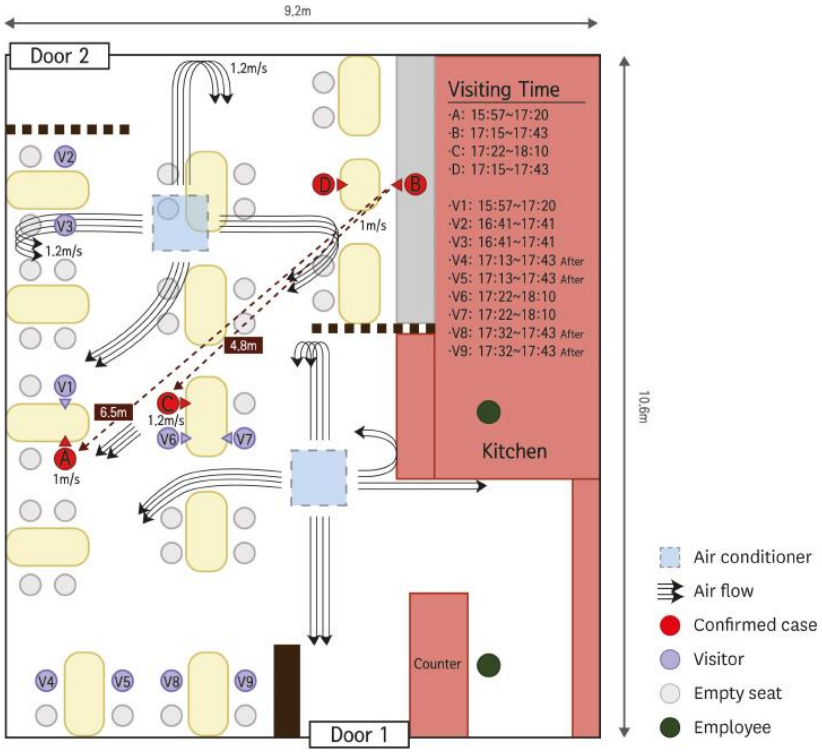

Figure 1. The individuals with COVID-19 are shown in red. Case B is the primary case that infected two other people. Case A is the index case and was in the restaurant with Case B for five minutes while both remained seated 6.5 meters from each other. Case C was also infected while at the restaurant. The arrows indicate the measured speed and direction of the air from the two air conditioners. Adapted from Kwon et al., 2020.

The index case had already finished his meal when Case B entered, and Case A sat and talked to one person at his table before leaving. All of the customers at the tables, including the index case and primary case, and the two employees were not wearing masks while in the restaurant. The other person who was infected (Case C) at the restaurant entered about two minutes after Case A left and remained for 21 minutes. Other people who were sitting at the same tables as Case A and Case C did not test positive or show symptoms during the quarantine period.

Based on the evidence that infectious SARS-CoV-2 can travel farther than six feet in indoor settings, the authors suggest updated guidelines on what constitutes close contact for purposes of prevention, contact tracing, and quarantine for COVID-19.

Restrictions of High-Risk Activities

Researchers used mobility information from cell phone data to map the hourly movements of 98 million people from their neighborhoods to points of interest, such as restaurants and religious establishments, to simulate the spread of SARS-CoV-2 in ten of the largest metropolitan areas in the United States (Chang et al., 2020). Based on the mobility data, the researchers were able to determine the number of visitors per hour at a location and the length of time people stayed there. The model resulting from this information accurately predicted the actual cases and transmission dynamics of COVID-19 observed between March 8 and May 9 in each city. By adjusting different parameters, the researchers were also able to estimate how curtailing different activities would change transmission.

Using their model, the researchers found that the amount of reduction in mobility and the timing of restriction were both important in reducing the transmission. Using the Chicago metro area as an example, they found that visits to points of interest in the area fell by 54% between the first week of March and the first week of April. By adjusting the model, it was determined that if the reduction in mobility had been 25% lower, the number of infection would have been 3.3 times higher. If the reduction in mobility had been implemented one week later, the number of infections would have been 1.5 times higher. If there had been no reduction in mobility, the number of infections in the area would have been 6.2 times higher.

Additionally, the researchers report that activity at a small number of specific points of interest account for a large majority of the infections.

Again using the Chicago metro area as an example, it was found that 10% of points of interest accounted for 85% of the infections. At first, points of interest such as restaurants and hotels contributed more to the number of infections, but their contribution waned as they were closed due to lockdowns. As mobility declined from closure of many other businesses, the contribution of the number of infections from grocery stores remained steady or increased.

The researchers also completed simulations of reopening starting on May 1 in Chicago. These calculations indicated that a full reopening with no regulation of the maximum occupancy of each space would cause a 32% increase in the number of infections by the end of May. However, if the occupancy of each venue was capped at 20% of the maximum occupancy the

predicted number of new infections was reduced by more than 80%, and the number of overall visits to the establishments was only reduced by 42%. Similar results were observed for the other metropolitan areas included in the study.

Thus, reducing the maximum occupancy substantially reduced the risk of transmission without fundamentally reducing overall mobility and allowing businesses to remain open.

The researchers also found that the type of establishment affected the number of transmissions resulting from reopening, as might be expected.

Full-service restaurants, gyms, hotels, cafes, religious organizations, and limited-service restaurants produced the largest increase in infections when reopened.

The establishments found to have the highest risk of transmission were those that normally have a high density of individuals at one time and where visitors stayed longer. **The highest increase in the number of infections was observed for reopening of full-service restaurants.** In Chicago, it was estimated that completely reopening full-service restaurants would lead to an additional 595,805 new infections by the end of May, which was three times the number of infections seen at the type of establishment with the next highest number of infections.

Along with identifying points of interest that contribute more to transmission than others, the model indicates that restricting the maximum occupancy at the 'super-spreader' points of interest is more effective than uniformly reducing mobility within the community in a lockdown like scenario.

When the model was used to investigate infection rates in disadvantaged racial and socioeconomic groups, the researchers found that the increased rates observed were solely the result of differences in mobility, and disadvantaged groups were not able to reduce their mobility as much because they are less likely to be able to work from home. In Chicago, individuals from lower-income areas had 27% more visits to points of interest than people who lived in higher-income areas. It was observed that individuals from lower-income areas made substantially more visits per capita to grocery stores than people who live in higher-income areas. Additionally, the points of interest that these groups visit are more crowded, which is also associated with a higher risk. In one simulation, it was found that a single visit to the grocery store had twice as much risk in a lower-income area compared to higher-income areas.

Suggestions for more equitable reopening plans included creating food and supply distribution centers in lower-income areas to reduce the density of people in stores with the longer-term goals of free and widely available testing in neighborhoods predicted to be high risk; improved paid leave policy or income support that enables essential workers to curtail mobility when sick; and improved workplace infection prevention for essential workers, such as high-quality personal protective equipment, good ventilation, and physical distancing.

Evaluation of the Efficacy of Masks

Researchers evaluated the filtration efficiency of a number of consumer-grade and improvised face masks, as well as several popular modifications of medical procedure masks to determine the degree to which they protect the wearer from infectious particles (Clapp et al., 2020).

The masks evaluated were

- A 2-layer woven nylon mask with ear loops that was tested with and without an optional aluminum nose bridge and nonwoven filter insert in place
- A cotton bandana folded diagonally once to make a triangle
- A cotton bandana folded in a multilayer rectangle according to the instructions presented by the United States Surgeon General
- A single-layer woven polyester/nylon mask with ties
- A nonwoven polypropylene mask with fixed ear loops
- A single-layer woven polyester gaiter/neck cover balaclava bandana
- A 3-layer woven cotton mask with ear loops.

Also tested were medical procedure masks with modifications for improved comfort and fit, including tying the mask's ear loops and tucking in the side pleats, fastening the ear loops behind the head using ear guards, fastening ear loops behind the head with a claw-type hair clip, enhancing the mask/face seal with rubber bands over the mask, and enhancing the mask/face seal with a band of nylon hosiery over the fitted mask.

The masks were tested on an adult man who did not have a beard as described in the OSHA mask fit testing protocol. The filtration efficiency corresponds to the percentage difference in the amount of particles behind the mask compared to the amount of particles in the air, and a 100% filtration efficiency would mean that no particles from the room's air were found behind the mask. The results of the testing are listed in Table 1.

Changes in the procedural masks that led to a better seal against the face improved the filtration efficiency.

The consumer-grade, 2-layer woven nylon mask with ear loops was similar to or exceeded the procedural masks in filtration efficiency.

When the nylon mask was fitted to the face using a metal nose bridge, use of nylon mask with a non-woven insert kept 74.4% of the particles in the room outside of the mask. Washing of the mask in a typical washing machine did not reduce the filtration ability, and in fact, seemed to improve it.

While the exact filtration efficiency required to prevent respiratory virus transmission is not precisely known, evidence from previous studies suggests that face masks with a filtration efficiency less than 95% are still effective at

preventing transmission of SARS-CoV-2, and there are consumer-grade mask options available that are nearly equivalent to some medical-grade masks.

Table 1. Filtration efficiency of the masks tested in the study.

Type of Face Mask	Filtration Efficiency
3M approved N95 respirator	**98.4%**
2-Layer woven nylon mask with ear loops without aluminum nose bridge	44.7%
2-Layer woven nylon mask with ear loops with aluminum nose bridge	56.3%
2-Layer woven nylon mask with ear loops with aluminum nose bridge and a nonwoven insert	74.4%
2-Layer woven nylon mask with ear loops with aluminum nose bridge, washed (no insert)	79.0%
Cotton bandana folded using Surgeon General's instructions	49.9%
Cotton bandana folded into triangle	49.0%
Single-layer woven polyester gaiter/neck cover (balaclava bandana)	37.8%
Single-layer woven polyester/nylon mask with ties	39.3%
Nonwoven polypropylene mask with fixed ear loops	28.6%
3-Layer woven cotton mask with ear loops	26.5%
Surgical mask with ties	71.5%
Procedure mask with ear loops	38.5%
Procedure mask with ear loops with the loops tied and corners tucked in	60.3%
Procedure mask with ear loops Ear guard	61.7%
Procedure mask with ear loops 23-mm Claw hair clip	64.8%
Procedure mask with ear loops fitted to the face with rubber bands	78.2%
Procedure mask with ear loops Nylon hosiery sleeve	80.2%

Factors Leading to High Transmission Rates of SARS-CoV-2

Researchers determined the time of peak infectivity of SARS-CoV-2 and the number of secondary infections that occurred during the infectious period in 1,158 participants with available information in a patient database in China up to February 11 (Lu et al., 2020).

Based on the evaluation,

- The median incubation period was 7.2 days with a range between 6.9 and 7.5 days.
- The median serial interval (the time between successive cases in a chain of transmission) was 4.7 days with a range between 4.2 and 5.3 days.
- Children under the age of 18 years had a longer incubation period than adults.

Peak infectivity occurred one day before symptom onset, and transmission during the incubation period accounted for 70% of cases.

Based on the parameters determined by the researchers, they concluded that the high infectivity during the incubation period leads to a short time period between cases of COVID-19, and aggressive control measures such as early case finding and quarantine of close contacts is required to control the spread of the virus.

Mother to Infant Infection in Maternity Ward

A study that included 61 mothers who were infected with COVID-19 and breastfed and roomed with their newborns while in the hospital indicates that transmission to the infant is rare (Ronchi et al., 2020). Of the 62 newborns, only one was diagnosed with COVID-19. The study followed the mothers for 20 days after the birth of their children. The recommendations of the study personnel to the women were to wash their hands and don a surgical mask before breastfeeding or providing other care and to otherwise stay 2 meters (6.6 feet) away from their infants. Of the mothers, 72% were diagnosed before the delivery, and 55% had symptoms at the time of diagnosis. No deaths were reported, and all infants remained in good condition throughout the study.

The new study is in agreement with a previous report from the American Academy of Pediatrics including the outcome of 4,000 newborns who were tested for COVID-19. Of the group, 60% roomed together, and less than 2% of the infants tested positive for COVID-19 (van Beusekom, 2020).

Risks of Transmission from Children

The role of children in community transmission of SARS-CoV-2 is still being investigated. While the symptoms of COVID-19 in infected children are typically mild, the possibility of infecting vulnerable adults in childcare programs is a concern for reopening daycares and schools.

Association with Working in Childcare Facilities and COVID-19

Researchers investigated the COVID-19 outcomes in childcare providers that continued to work during the pandemic and those who did not (Gilliam et al., 2020). The study included information on 57,335 individuals, and within this group, there were 427 cases of COVID-19.

The researchers found that working in a childcare role was not associated with an elevated risk for COVID-19 transmission to providers during the early months of the pandemic in the United States.

The authors stress, however, that there were considerable mitigation efforts in place at most childcare facilities, and many areas of the country were still experiencing low community transmission rates at the time. During periods of more widespread community transmission, the outcome may be different.

Transmission of SARS-CoV-2 among Children

Researchers investigated the level of transmission between index patients and their household contacts in 58 households between March and May in Wisconsin and Utah (Laws et al., 2020 and van Beusekom, 2020). There were a total of 188 contacts, 120 adults and 68 children, who were followed by daily symptom screens, PCR-based testing, and antibody testing. The secondary infection rates, or the percentage of people infected by the index case, was similar for adults and children at 30% and 28%, respectively. Also the transmission rate to adult contacts was similar in households with children (28%) and households without children (33%), suggesting that children are not the only intermediary for household transmission. Child-to-adult transmission was observed in two of ten cases (20%), and child-to-child transmission was observed in one of six cases (17%). It was found that children whose parents were infected were more likely to get sick compared to households where the index patient was not a parent. However, the odds of becoming infected did not differ substantially by age, sex, race, underlying illnesses, size of the household, number of household members, or ratio of children to bedrooms and bathrooms.

When the symptoms of the infected children and adults were compared, children had less frequent and less severe symptoms in agreement with previous reports. The most common symptoms in children were headache (79%), sore throat (68%), and runny nose (68%). The presence of symptoms was not well correlated with testing positive for COVID-19, however, except in cases where individuals had a fever. Children were less likely than adults to report cough, loss of taste, and loss of smell. The authors stressed that using symptoms for screening for children with COVID-19 is difficult because of the large amount of overlap of symptoms with other infections and the fact that children are less likely to display symptoms.

However, based on this study, they recommend that children be tested regardless of symptoms if they have an infected person in their household because they are as likely to have contracted COVID-19 as adults in the household.

Association between Cancer and COVID-19

Because many people with cancer have weakened immune systems either from the cancer itself or treatment, it is likely that they may be at an increased risk of being infected with SARS-CoV-2 and also having poor outcomes from the illness. Additionally, individuals with cancer are found to have a higher occurrence of other chronic medical conditions such as type-2 diabetes, obesity, and cardiovascular diseases, which also puts them at higher risk for COVID-19. There is some information that has been reported on the association between cancer and COVID-19 risk, but large scale studies are not yet available.

In this study, the researchers used medical records of 73.4 million patients from 360 hospitals and 317,000 clinicians throughout the United States to investigate the possible association between cancer and COVID-19 up to August 14 (Wang et al., 2020). During the record review, 2,523,920 individuals were identified across the United States who had been diagnosed with at least one of the 13 most common types of cancer a year or more ago, and 273,140 individuals were identified who had been diagnosed with cancer this year. There were 16,570 people out of the total 73.4 million who were diagnosed with COVID-19, and 1,200 of the individuals with COVID-19 also had a cancer diagnosis more than one year ago while 690 had a recent cancer diagnosis in the last year.

The 13 most common types of cancer in the United States are

- Thyroid cancer
- Prostate cancer
- Non-Hodgkin lymphoma
- Pancreatic cancer
- Melanoma
- Lung cancer
- Liver cancer
- Leukemia
- Kidney cancer
- Endometrial cancer
- Colorectal cancer
- Breast cancer
- Bladder cancer

Based on their finding, the researchers report that individuals with cancer had a statistically significant increase in risk for COVID-19 infection compared with individuals without cancer. The difference in risk was larger in those with a recent cancer diagnosis who were most likely to have active cancer growth occurring.

Individuals with active cancer were found to be the most vulnerable to infection with SARS-CoV-2 among the population with cancer.

The type of cancers with the highest risk, in order, are leukemia, non-Hodgkin lymphoma, lung cancer, liver cancer, and pancreatic cancer. The two with the lowest risk were thyroid cancer and endometrial cancer, but even with the lowest risk among individuals with cancer, people with thyroid or endometrial cancer still had a higher risk of infection with SARS-CoV-2 than the general population.

Removing the contribution of other chronic medical conditions such as diabetes and others from the assessment reduced the risk for infection somewhat, suggesting that there is an additional contribution from chronic conditions. However, the presence of active cancer was a larger contribution to the increased COVID-19 risk. Other factors that were associated with a higher risk for COVID-19 in people with cancer were those who were African American with breast cancer, colorectal cancer, lung cancer, or leukemia and women with colorectal cancer or non-Hodgkin lymphoma. Age did not further contribute to the risk of COVID-19 in people with cancer.

The hospitalization rate for the treatment of COVID-19 in adults with cancer was found to be 25.7%. The rate of hospitalization for COVID-19 in adults recently diagnosed with cancer was higher at 47.7%. African American individuals with cancer had a higher rate of hospitalization for COVID-19 than those who were white (55.56% versus 43.24%). For comparison, the hospitalization rate for adults with cancer who did not have COVID-19 was 12.39%. The overall death rate for all adults in the study with COVID-19 was 5.61%, and the death rate for adults with both cancer and COVID-19 was 14.93%. The death rate for adults with cancer who did not have COVID-19 was 4.03%.

The researchers conclude that cancer was a contributing factor to the increase in both hospitalization rates and death rates in people with COVID-19.

There was a difference in the risk of hospitalization and death based on the type of cancer, and individuals with blood cancers had the highest risk from COVID-19. However, the types of cancer that normally have the highest risk of death or poor outcome from the effects of the cancer, e.g. pancreatic cancer and liver cancer, were not associated with the highest risk from COVID-19. People with pancreatic and liver cancer have a high rate of interaction with medical staff due to the intensive cancer treatment required but did not have the largest risk from COVID-19.

Based on this information, the researchers suggest that the increased risk from COVID-19 in people with cancer is not due to exposure during medical treatments but instead due to changes in the body and immune system from the cancer.

Association between COVID-19 Outcome and an Individual's Sex

There were early reports of increased mortality in men with COVID-19 compared to women, and the increased number of cases reported has allowed for a better investigation of the potential differences (Peckham et al., 2020). In this study, researchers evaluated 3,111,714 records of COVID-19 cases from around the world that occurred between January 1 and June 1.

The researchers found that there was no difference in the number of men compared to the number of women who were diagnosed with COVID-19 during the time period, suggesting that infection rates are similar between the sexes.

However, men had an increased odds of admission to intensive care units and an increased odds of dying.

This difference is in agreement with previous research showing that men have an overall higher risk of bacterial, viral, fungal and parasitic infections compared to women. The increased risk for poor outcomes in men was also observed during the SARS outbreak and the MERS outbreak. During the MERS outbreak in Saudi Arabia from 2013 to 2014, the case fatality rate was 52% in men and 23% in women. The variations in risk are thought to arise from differences in the immune response to infection, such as a more robust innate interferon response and increased adaptive immunity towards viruses in females.

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