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**In Reply** We thank Heathcote et al<sup>1</sup> for their reply to the recent Viewpoint calling for action in cancer survivorship.<sup>2</sup> We were heartened at the response to the call to action from practitioners and cancer survivors who responded to us directly, including faculty within our own medical center. These responses support the comments from Heathcote et al advocating that “better survivorship care must think outside the confines of the biomedical model alone.” Survivorship care indeed extends beyond the walls of the oncologist’s office. Heathcote et al state that “mindsets matter,” a statement with which we concur.

However, we caution equating treatment with anthracycline chemotherapy with unhelpful mindsets, which increase the severity of anxiety and worsen quality of life. Treating the mind and body in tandem, and not at the expense of the other, is necessary to improve survivorship care. Within our sarcoma survivorship program, longitudinal collection of patient-reported outcomes confirms that patients experience anxiety and depression—often directly related to their cancer experience driven by the fear of recurrence. Educating survivors of their risks, including recurrence, yielded a reduction in anxiety, depression, and fear over time. Consequently, we began using the term *cure* when appropriate, demonstrably influencing the patient’s mindset. The mounting evidence of the relationship between anthracycline exposure and coronary artery disease necessitates patient education coupled with support of health behaviors to decrease their risk (eg, diet modification, physical activity).<sup>3</sup> We advocate that for patients with multiple complex care needs, this team be led by the treating medical oncologist, who is also trained in internal medicine and able to treat chronic illnesses, such as hypertension, dyslipidemia, and kidney disorders, which increase the risk of

coronary artery disease. Treating a 13-year-old patient with osteosarcoma with a year of anthracycline chemotherapy and limb salvage surgery and pronouncing cure is a hollow victory if the same patient develops a myocardial infarction at 38 years old, especially if preventive measures could have avoided an early death.

Central to improving survivorship care is integration across disciplines. Mindsets—core associations about the nature and working of things and processes in the world—matter both within the patient and within the health care system. The experience of matching practice to the ideals under which we initiated the program has proved to be challenging in a medical landscape where prevention is not a lucrative endeavor. The call to extend survivorship beyond the biomedical model heightens our commitment to this call to action. Mindsets matter, for survivors of cancers and for those who have the power to support a holistic, integrated model of care.

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**Additional Information:** The authors are affiliated with the Sarcoma Survivorship Program at the University of Michigan. The authorship was extended beyond that of the original Viewpoint to researchers outside of oncology to indicate that survivorship care necessitates a multidisciplinary approach inclusive of behavioral health and to reflect the program’s extension beyond oncology as well.

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## Risk of COVID-19 in Patients With Cancer

**To the Editor** We read the article by Yu and colleagues<sup>1</sup> published in *JAMA Oncology* with great interest. In this article, Yu et al reported that patients with cancer have a notably higher risk of coronavirus disease 2019 (COVID-19) compared with that of overall population in Wuhan, China, which shares a similar conclusion with a recent report by Liang et al.<sup>2</sup> Also, the authors found that age older than 60 years is an independent risk factor of COVID-19 in individuals with lung cancer.

COVID-19 has been officially declared a global pandemic, and the needs of patients with particular vulnerabilities require particular attention. To date, a number of comorbidities have evidently contributed to the incidence of COVID-19.<sup>3</sup> However, it has been well documented that diseases such as chronic obstructive pulmonary disease, hypertension, and cancer are closely related to age. In China Statistical Yearbook

2019,<sup>4</sup> people older than 50 years accounted for 32% of the total population. In a report by Guan et al<sup>5</sup> among 1011 patients with COVID-19, 44% were older than 50 years, suggesting that the risk of COVID-19 in older adult patients may be higher. Thus, before probing the underlying diseases associated with higher susceptibility to COVID-19, we must stratify the patients in terms of age. Hence, to determine the role of cancer in COVID-19, a comparison of incidence of COVID-19 between patients in the same age group with and without cancer will be of great importance.

Second, the incidence of COVID-19 in patients who periodically visit hospitals for cancer care is higher than that in the community does not necessarily lead to the conclusion that cancer is a risk factor of COVID-19. Medical visit-related exposure should not be neglected, especially in an epidemic region. Of note, this could be the general potential explanation for higher incidence of COVID-19 in patients having underlying diseases.

Third, by reviewing the data derived from the study by Yu et al,<sup>1</sup> we found that cancer-related interventions seemed to be correlated with neither severe events nor death caused by COVID-19. These observations further raise the concern that whether the disease of cancer indeed contributes to the susceptibility and/or prognosis of COVID-19.

Fourth, a *P* value of .486 was shown for the incidences of COVID-19 in patients with lung cancer older than 60 years compared with patients younger than 60 years. This was a numeric but not statistically significant difference.

Collectively, the question regarding the specific susceptibility of patients with cancer to COVID-19 remains to be resolved. Further investigations with larger sample sizes and rigorous study designs are warranted.

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1. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. Published online March 25, 2020. doi:10.1001/jamaoncol.2020.0980

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**To the Editor** In their article in *JAMA Oncology*, Yu et al<sup>1</sup> reported an increased incidence of coronavirus disease 2019 (COVID-19) in patients with cancer compared with the general population of Wuhan, China. The authors hypothesized this relation to be secondary to an immunocompromised state in patients with cancer. Contrary to hematologic cancers, the link between solid cancers and risk of infection is unclear. It is this author's opinion that this report provides no support for this connection.

The authors compared the total number of cases with the number of patients with cancer diagnosed with COVID-19. This approach is hampered by an insufficient understanding of the true number of cases. One study estimated that up to 50% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Wuhan might be asymptomatic.<sup>2</sup> Considering this degree of uncertainty and the low number of affected patients with cancer in this study, there is insufficient certainty to reliably conclude an increased incidence in patients with cancer.

The results might also have been influenced by confounding factors. Most patients were treated for non-small cell lung cancer (7 of 12 patients). Patient history of cigarette smoking was not provided. Smoking leads to structural and immunologic changes to the airway, leading to more frequent and more severe viral infections.<sup>3</sup> It also leads to upregulation of ACE2,<sup>4</sup> the hypothesized protein used by SARS-CoV-2 for cellular entry. In one COVID-19 study,<sup>5</sup> 14.5% of patients were current or former smokers. In the group of patients that reached a study end point (intensive care unit admission, mechanical ventilation, or death), this percentage rose to 33.4%.<sup>5</sup> Only 0.9% of 1099 patients had cancer, with just 1 patient reaching the study's end point. These results suggest that smoking increases the risk of severe disease more than the presence of cancer and could have been a confounding factor.

Most patients were in a phase of their disease where frequent hospital visits are expected. Receiving cancer treatment (6 patients) or supportive care (4 patients) and having a recent diagnosis of malignant neoplasm (1 patient) are reasons for frequent contacts with health care providers. As the authors state, considering the reports of hospital-acquired infections in this COVID-19 pandemic, frequent hospital visits are another potential confounder.

Although this study provides no support for increased susceptibility for SARS-CoV-2 infection in patients with cancer based on cancer-related immunosuppression, it is important to consider the fragility of patients with cancer during the COVID-19 pandemic. Considering the risk of nosocomial infections, delay of necessary treatments, and uncertainty regarding health care availability, SARS-CoV-2 undoubtedly poses a great risk for patients with cancer.

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1. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. Published online March 25, 2020. doi:10.1001/jamaoncol.2020.0980
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5. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032

**To the Editor** We are grateful to Yu et al<sup>1</sup> for their efforts to control the coronavirus disease 2019 (COVID-19) pandemic and for taking time to collect and report their findings to advance care for patients elsewhere in the world.<sup>1</sup> We greatly appreciated their proposal “that aggressive measures be undertaken to reduce frequency of hospital visits of patients with cancer during a viral epidemic going forward.”

However, basic statistical analysis of the data in Table 2 contradicts their interpretation (and now widespread reporting). In their review of medical records of 1524 patients with cancer admitted from December 30, 2019, to February 17, 2020, to Zhongnan Hospital, they reported 7 COVID-19 cases among the 228 who had non-small cell lung cancer (NSCLC). The authors stated that “patients with NSCLC older than 60 years had a higher incidence of COVID-19 than those aged 60 years or younger (4.3% vs 1.8%).”<sup>1</sup> These percentages correspond to 5 of 117 patients older than 60 years and 2 of 111 patients aged 60 years or younger. However, a standard  $\chi^2$  analysis of this difference between patients in these age groups of 2.5% has 95% CIs of -2.6% to 8.0% with  $P = .28$ . So, their data are also consistent with their acknowledgment that “a population study of 1099 patients with COVID-19 did not indicate that age was associated with susceptibility to infection.”<sup>2</sup>

We share their concern for urgency in managing the pandemic effectively and saving patients' lives through sharing data and recognize that later in their report they qualified that “a larger sample size in patients with cancer will resolve these potential associations.”<sup>1</sup> There is urgency to first-line reports, but the reports are most informative, especially as they are transmitted through the lay press and social media, if usual statistical analyses are applied to the interpretations. This rigor is essential as we move from the study of the epidemiology to the treatment of COVID-19 and its complications. Clearly, patients with cancer are at elevated risk for complications from COVID-19 infection. Health systems and cancer care centers like ours should still continue to establish a series of processes intended to minimize visits and reduce the risk for

patients of contracting COVID-19 infection in our region. Especially in the context of this pandemic and “infodemic,” we all should strive for rigorous scientific assessment and reporting of results.

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1. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. Published online March 25, 2020. doi:10.1001/jamaoncol.2020.0980
2. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032

**To the Editor** We read with interest the Research Letter by Yu et al on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission in patients with cancer at a tertiary care hospital in Wuhan, China, recently published in *JAMA Oncology*.<sup>1</sup> Among 1524 admitted patients with cancer, 12 (0.79%) had coronavirus disease 2019 (COVID-19). Seven of these 12 patients had lung cancer, suggesting a predilection for patients with lung cancer. Notably, only 1 of the 7 patients (14%) with lung cancer who were diagnosed with COVID-19 had a positive result on real-time reverse transcriptase polymerase chain reaction (PCR) testing. In contrast, 3 of the 5 patients (60%) with a cancer other than lung cancer had a positive PCR result. This does not reach statistical significance given the small sample size ( $P = .09$  using the  $\chi^2$  test).

Other than chance, there are 2 possibilities for this apparent difference. The first is that patients with lung cancer are indeed at a higher risk of SARS-CoV-2 infection but are more likely to have negative results when tested by PCR, which has implications for universal screening strategies that are being discussed for patients with cancer and may suggest a need to augment screening in these patients.

The second consideration would be bias—either ascertainment bias or misclassification bias. Computed tomography scans form an important part of the diagnostic criteria used, and ascertainment bias would occur if patients with lung cancer were more likely to receive a computed tomography scan of the chest with modest symptoms (eg, fever, cough). Misclassification bias occurs if a patient who does not have a true SARS-CoV-2 infection is classified as SARS-CoV-2 positive. When there is a clear criterion standard (eg, biopsy, culture), misclassification is unlikely, but when diagnosis is based on a



constellation of symptoms and signs or radiologic findings—many of which are similar to those seen in lung cancer—the possibility of a misclassification exists.

We congratulate the authors on getting this important information out quickly and urge critical interpretation prior to adopting this information into guidelines.<sup>2</sup> Other larger series that report SARS-CoV-2 infection outcomes by cancer site should also report the diagnostic criteria so that we can better understand if we need to approach universal testing differently across cancers and whether we should consider potential methodologic biases before we begin changing effective curative or palliative therapies.

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1. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. Published online March 25, 2020. doi:10.1001/jamaoncol.2020.0980

2. Passaro A, Peters S, Mok TSK, Attali I, Mitsudomi T, de Marinis F. Testing for COVID-19 in lung cancer patients. *Ann Oncol*. Published online April 9, 2020. doi:10.1016/j.annonc.2020.04.002

**In Reply** We thank Dekker, Peng et al, Maitland et al, and Robinson et al for their interest and insightful comments on our article.<sup>1</sup> These authors raised salient points on confounders, such as older age and cigarette smoking, on the higher incidence of coronavirus disease 2019 (COVID-19) in our cohort of patients with cancer. Additionally, Maitland et al and Robinson et al queried our secondary observation that older patients with lung cancer represented a particularly susceptible subgroup. We will attempt to respond to these points.

In our article, we had acknowledged that age is a confounder of our findings because most solid cancers tend to occur in older patients. Compounding this conundrum, a study of 32 583 COVID-19 cases in Wuhan, China, from December 8, 2019, to March 8, 2020, revealed a positive association between the daily rate of cases and age (relative risk of 2.33 for patients aged 60-79 years compared with those aged 20-39 years).<sup>2</sup> To resolve this, one would need to perform an age-standardized comparison of incidence of COVID-19 cases between patients with cancer and patients without cancer.

Nonetheless, in an age-matched case-control study, Dai and colleagues<sup>3</sup> observed that patients with cancer were more susceptible to in-hospital infection compared with patients without cancer (19.04% vs 1.49%). The increased risk of infection is likely multifactorial. As raised by Dekker and Peng et al, cigarette smoking and repeat visitation to the hospital are potential risk factors for severe acute respiratory syndrome coronavirus 2 in-

fection. The association of cigarette smoking would be difficult to ascertain without information on the number of pack-years and current cigarette smoking status; moreover, the dose dependency of ACE2 upregulation by cigarette smoking is unclear. Regarding the latter, it is widely recognized that repeated hospital visits for chemotherapy and radiotherapy pose a heightened risk of virus transmission to patients with cancer. Guidelines on contingency planning to adapt cancer treatment and infection control protocols have thus been proposed.<sup>4</sup>

We also wholly agree with Maitland et al that the association of older patients with lung cancer and COVID-19 is at best suggestive and requires validation in larger cohorts. While we found that patients with non-small cell lung cancer older than 60 years had a higher incidence of COVID-19 than those younger than 60 years, this difference was not statistically significant (4.3% vs 1.8%;  $P = .45$  using Fisher exact test).<sup>1</sup>

Finally, Robinson et al raised valid comments on ascertainment and misclassification bias. The former is unlikely, because computed tomography (CT) of the chest was part of the diagnostic workup for COVID-19 in Wuhan during the outbreak, and the patients in our study only underwent a CT because of COVID-19-like symptoms. Nonetheless, we acknowledged that other types of viral pneumonia could manifest similar CT changes. However, such misclassification errors would have systematically affected both the study cohort and community cases, and thus it may be reasonable to still expect a higher relative risk of COVID-19 in patients with cancer than patients without cancer.

Regardless, there is now conclusive evidence highlighting that patients with cancer with COVID-19 fare significantly worse than patients without cancer.<sup>3,5</sup> The main message of our study is therefore consistent with the widespread advocacy among the oncology community that cancer centers must enforce robust infection control and avoid immunosuppressive anticancer therapies in this vulnerable group of patients during this pandemic.

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**Additional Information:** Drs Chua, Yu, and Xie contributed equally to this work.

1. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. Published online March 25, 2020. doi:10.1001/jamaoncol.2020.0980
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5. Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York hospital system. *Cancer Discov*. Published online May 1, 2020. doi:10.1158/2159-8290.CD-20-0516

## CORRECTION

**Change to Licensing Type:** In the Original Investigation titled "Efficacy of Savolitinib vs Sunitinib in Patients With *MET*-Driven Papillary Renal Cell Carcinoma: The SAVOIR Phase 3 Randomized Clinical Trial,"<sup>1</sup> published online May 29, 2020, there was a change made to the license type from standard to open access. This article was corrected online.

1. Choueiri TK, Heng DY, Lee JL, et al. Efficacy of savolitinib vs sunitinib in patients with *MET*-driven papillary renal cell carcinoma: the SAVOIR phase 3 randomized clinical trial. *JAMA Oncol*. Published online May 29, 2020. doi:10.1001/jamaoncol.2020.2218

**Error in Units of Measure Reported In Methods Section of the Text:** The Original Investigation titled "Vaginal Testosterone Cream vs Estradiol Vaginal Ring for Vaginal Dryness or Decreased Libido in Women Receiving Aromatase Inhibitors for Early-Stage Breast Cancer: A Randomized Clinical Trial,"<sup>1</sup> published in March 2017, contained an error in units of measure reported in the Treatment subsection of the Methods section of the text. The correct units are grams, and the corrected sentence reads "Patients were instructed to insert 0.5 g of cream vaginally using a calibrated applicator daily for 2 weeks, then 0.5 g 3 times a week for the remaining 10 weeks." This article has been corrected online.

1. Melisko ME, Goldman ME, Hwang J, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol*. 2017;3(3):313-319. doi:10.1001/jamaoncol.2016.3904

**Middle Initial Omitted From Author Name:** In the Original Investigation titled, "Evaluation of First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases: The FIRE-SCLC Cohort Study," which published online June 4, 2020, in *JAMA Oncology*,<sup>1</sup> the middle initial was omitted from an author's name. Her name should appear in the byline as Stephanie E. Combs, MD, PhD. This article was corrected online.

1. Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: the FIRE-SCLC cohort study. *JAMA Oncol*. Published online June 4, 2020. doi:10.1001/jamaoncol.2020.1271

**Misspelled Word in Title:** The Special Communication titled "Applying Lessons Learned From Low-Resource Settings to Prioritize Cancer Care in a Pandemic," which was published online August 6, 2020, in *JAMA Oncology*,<sup>1</sup> was corrected for a misspelled word in the title. This article was corrected online.

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