Adverse Events Reported by Patients With Cancer After Administration of a 2-Dose mRNA COVID-19 Vaccine

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ABSTRACT

Background: Most safety and efficacy trials of the SARS-CoV-2 vaccines excluded patients with cancer, yet these patients are more likely than healthy individuals to contract SARS-CoV-2 and more likely to become seriously ill after infection. Our objective was to record short-term adverse reactions to the COVID-19 vaccine in patients with cancer, to compare the magnitude and duration of these reactions with those of patients without cancer, and to determine whether adverse reactions are related to active cancer therapy. **Patients and Methods:** A prospective, single-institution observational study was performed at an NCI-designated Comprehensive Cancer Center. All study participants received 2 doses of the Pfizer BNT162b2 vaccine separated by approximately 3 weeks. A report of adverse reactions to dose 1 of the vaccine was completed upon return to the clinic for dose 2. Participants completed an identical survey either online or by telephone 2 weeks after the second vaccine dose. **Results:** The cohort of 1,753 patients included 67.5% who had a history of cancer and 12.0% who were receiving active cancer treatment. Local pain at the injection site was the most frequently reported symptom for all respondents and did not distinguish patients with cancer from those without cancer after either dose 1 (39.3% vs 43.9%; $P=.07$) or dose 2 (42.5% vs 40.3%; $P=.45$). Among patients with cancer, those receiving active treatment were less likely to report pain at the injection site after dose 1 compared with those not receiving active treatment (30.0% vs 41.4%; $P=.002$). The onset and duration of adverse events was otherwise unrelated to active cancer treatment. **Conclusions:** When patients with cancer were compared with those without cancer, few differences in reported adverse events were noted. Active cancer treatment had little impact on adverse event profiles.

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Background

More than 338 million doses of the COVID-19 vaccine were administered in the United States from December 2020 to July 2021. This far-reaching public health initiative generated 5,325 reports of vaccine-related deaths.[1,2] Although deaths have been exceedingly rare, mild to moderate complications, even in healthy adults, have been common. Adverse events that include body aches, chills, and headaches are especially frequent after the second dose of the COVID-19 vaccine, affecting one-half to two-thirds of those vaccinated. For patients with cancer, it is especially important to clarify the risk of vaccination because these patients are more likely than healthy individuals to contract SARS-CoV-2 and more likely to become seriously ill if infected.[3,4] Those with hematologic malignancies and lung cancer are particularly vulnerable. As a group, patients with cancer infected with COVID-19 are reported to have a mortality rate 3 times that of people without cancer.[5]

Despite their vulnerability to infection, patients with cancer were not included in most pilot investigations of the SARS-CoV-2 vaccines and were rarely analyzed as a group in follow-up studies.[6,7] However, several lines of evidence indicate that these patients may present unique challenges when a strategy for broad vaccination coverage is initiated. Some of those challenges, including the imposition of stricter isolation, are logistical. Other challenges remain theoretical. Both the Moderna mRNA-1273 and the Pfizer BNT162b2 vaccines are delivered as lipid nanoparticles containing mRNA that encodes the coronavirus spike protein.[8] Lysosomal particles tend to accumulate in solid tumors, a phenomenon exploited in the delivery of some anticancer drugs. It is not known whether vaccines of this kind may also be diverted to malignant cells, thus altering tumor biology and perhaps interfering with the immune response to the vaccine in unforeseen ways.

A further concern has been vaccine hesitancy by those who are priority candidates for vaccination. Within this group, patients with cancer figure prominently. A European study reported that 11.2% of patients with cancer who were offered vaccination refused it, usually out of fear of adverse events.[9] Circulation of false or misleading reports may have fueled much of the alarm, underscoring the need for accurate reporting of scientific progress. With these considerations in mind, we undertook a study of adverse reactions to vaccination reported by the attendees of an outpatient clinic serving a large population of patients with cancer. The aims of the study were (1) to record short-term adverse reactions to the COVID-19 vaccine in patients with cancer and compare these reactions to those of patients without cancer and (2) to determine whether adverse reactions are associated with active cancer therapy.

Patients and Methods

This Institutional Review Board–approved study was conducted at Fox Chase Cancer Center, an NCI-designated Comprehensive Cancer Center serving patients with and without cancer. Participants were enrolled from February 16, 2021, to May 15, 2021. All respondents received 2 doses of the Pfizer BNT162b2 vaccine given approximately 3 weeks apart. A detailed survey eliciting a report of adverse reactions to dose 1 of the vaccine, including their time of onset and duration, was completed by patients upon their return to the clinic for dose 2. An identical survey was completed either by telephone or online approximately 2 weeks after the second vaccine dose. Vaccine recipients were asked to report whether they had experienced any of the following symptoms: tiredness, local pain or swelling at the injection site, joint pain, muscle pain, fever, chills, headache, nausea, or an allergic reaction (eg, hives, facial swelling, shortness of breath, or wheezing). They were also given an opportunity to report symptoms not specified in the survey. Additional participant data obtained from the institution's data warehouse included age, race, ethnicity, history of cancer (if any), and recent or ongoing cancer treatment, including surgery, radiation, chemotherapy, immunotherapy, targeted therapy, and hormone therapy. Patients with a cancer diagnosis who received cancer treatment (other than immunotherapy) at any point during a time interval beginning 30 days before the first vaccine dose and ending with the second dose were considered to be undergoing active treatment. For patients receiving immunotherapy, the time period for active treatment was extended to 90 days before the first vaccine dose. Early symptom onset was defined as an adverse event within 24 hours of vaccination.

Baseline characteristics of the study population were tabulated separately for patients without cancer, unselected patients with cancer, and patients undergoing active cancer treatment. The incidence of all reported adverse reactions was tallied for dose 1 and dose 2 of the vaccine. Fisher exact and chi-square tests were used to determine whether the incidence of each type of adverse reaction was related to demographic characteristics, history of malignancy, active cancer treatment, or type of therapy. Mean duration and mean time to onset of symptoms were recorded for recipients without cancer, patients with cancer, and patients undergoing active cancer treatment with 95% confidence intervals and compared using the Wilcoxon rank sum test. McNemar's test was used to compare symptom rates for participants who responded to both postvaccination surveys. All hypothesis tests were 2-sided with a 5% type I error. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc.).

Results

A total of 2,033 patients were enrolled in the study. The first survey was completed by 1,752 patients after vaccine dose 1; both surveys were completed by 1,260 patients (Figure 1). Patient dropouts before the first survey (233/1,986) were more likely to be male (48.5% vs 38.8%; $P=.005$) and less likely to have a cancer diagnosis (60.5% vs 67.5%; $P=.034$). Of the respondents that completed at least one postvaccination survey, 67.5% (1,183/1,753) had a history of cancer, of which 17.8% (n=211) were receiving active cancer treatment. Of the 1,183 patients with a history of cancer, 92.5% (n=1,094) had a solid malignancy and 7.5% (n=89) had a hematologic malignancy. Forms of active treatment included surgery for 24.2% (51/211) of patients, radiation therapy for 18.0% (38/211), chemotherapy for 39.8% (84/211), and other systemic therapy (immunotherapy [16.6%; 35/211], targeted therapy [24.2%; 51/211], or hormone therapy [59.2%; 125/211]) for 26.1% (55/211) (Table 1). Patients with a cancer diagnosis were older than those in the noncancer cohort (median age, 68 vs 66 years; $P<.001$) and were more likely to be African American/Black (20.0% vs 9.8%; $P<.001$) and male (42.2% vs 31.9%; $P<.001$). A history of COVID-19 infection before vaccination was reported by 3.4% of all respondents.

Postvaccination symptoms were common and reported with similar frequencies by patients with and without cancer (73.3% vs 72.5%; $P=.71$). No significant differences between patients with and without cancer, respectively, in the frequency of adverse events were found when responses to the first and second vaccine dose were tabulated separately (dose 1: 61.3% vs 60.2%; $P=.67$ vs dose 2: 64.2% vs 62.8%; $P=.63$). Among respondents to both surveys, at least one adverse event was reported more often for dose 2 than for dose 1 (63.7% vs 60.2%; $P=.024$). For patients with cancer, adverse events that were reported more frequently after dose 2 included fatigue, joint pain, fever, chills, headache, and nausea. Allergic reactions were rare after both dose 1 (6/1,752) and dose 2 (9/1,261). Postvaccination symptoms for all patients

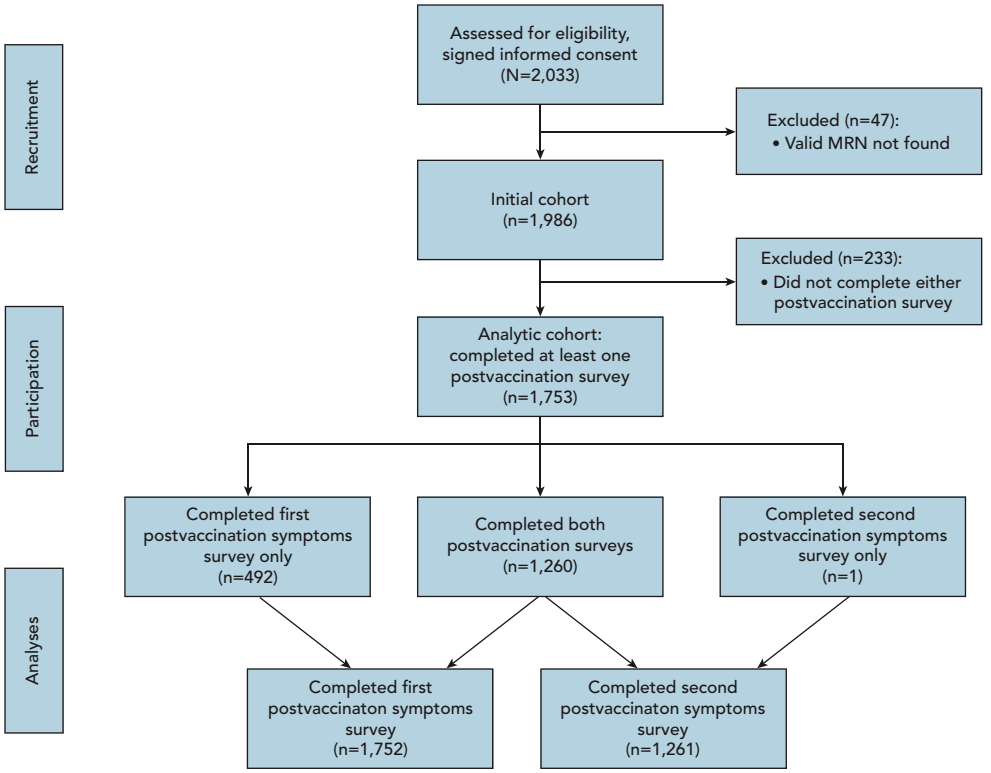

Figure 1. STROBE flow diagram.
Abbreviation: MRN, medical record number.

were more likely to be reported by women than by men (77.8% vs 65.5%; $P<.001$) and were more common in younger patients (age 18–59 years: 84.4%; 60–79 years: 72.2%; ≥80 years: 50.0%; $P<.001$).

Local pain at the injection site was the most frequently reported symptom for all respondents and did not distinguish patients with cancer from those without cancer after either dose 1 (39.3% vs 43.9%; $P=.07$) or dose 2 (42.5% vs 40.3%; $P=.45$). Muscle pain after the first vaccination was more frequent in patients with cancer than in those without (16.5% vs 11.9%; $P=.012$), but was of shorter duration (mean, 2.2 vs 3.0 days; $P=.04$). Joint pain, fever, chills, headache, and nausea were unrelated to cancer status (Figure 2).

Data regarding the onset and duration of symptoms were obtained for 84.2% of the patients with cancer. Most patients reported their first symptom on the day of vaccination or the day after. The frequency of early symptom onset was the same for patients with cancer not undergoing active treatment and those receiving active treatment (83.2% vs 81.4%; $P=.63$). Reports of any symptom lasting longer than 5 days were uncommon for both groups (10.2% vs 9.8%; $P=.90$). Among patients with cancer, those receiving active treatment were less likely to report pain at the injection site after dose 1 compared with those not on active treatment (30.0% vs 41.4%; $P=.002$). The adverse event profile for patients with cancer receiving active treatment did not differ by treatment type for either dose 1 or dose 2.

Discussion

This is the largest published study to date examining the short-term adverse events of COVID-19 vaccination in patients with cancer and the potential impact of active cancer treatment on such effects. As in previous reports, the most frequently reported adverse event of vaccination was pain at the site of injection. Systemic adverse events were generally more frequent after the second dose of the vaccine, a pattern particularly noted for fatigue, joint pain, and chills. Of these systemic symptoms, the most commonly reported by patients with cancer after the second vaccine dose were fatigue (33.9%), muscle pain (12.0%), and headache (16.0%). The comparable results in a recent study of vaccinated patients with cancer receiving immunotherapy were fatigue (34%), muscle pain (34%), and headache (16%)[10]—remarkably similar figures given the nature of patient self-reports. Other systemic adverse events in our study occurred with a frequency of <10%. When patients with cancer were compared with those without cancer, few differences were noted. Active cancer treatment similarly had little influence on adverse event profiles. The results can be

Table 1. Characteristics of Respondents Who Completed at Least One Postvaccination Symptom Survey

	All n (%)	No Cancer Diagnosis n (%)	Cancer Diagnosis n (%)	On Active Treatment n (%)
Patients, n	1,753	570	1,183	211
Sex				
Female	1,072 (61)	388 (68)	684 (58)	116 (55)
Male	681 (39)	182 (32)	499 (42)	95 (45)
Median age (IQR), y	67 (59–74)	66 (54–72)	68 (61–74)	66 (57–73)
Race				
African American/Black	293 (17)	56 (10)	237 (20)	33 (16)
Asian/Indian/Pacific Islander	61 (3)	32 (6)	29 (2)	6 (3)
Caucasian/White	1,213 (69)	369 (65)	844 (71)	137 (65)
Other	138 (8)	70 (12)	68 (6)	34 (16)
Unknown	48 (3)	43 (8)	5 (0.4)	1 (0.5)
Ethnicity				
Hispanic	47 (3)	21 (4)	26 (2)	2 (1)
Non-Hispanic	1,625 (93)	491 (86)	1,134 (96)	201 (95)
Unknown/Missing	81 (5)	58 (10)	23 (2)	8 (4)
Cancer type				
Hematologic malignancy			89 (7.5)	19 (9)
Solid malignancy			1,094 (92.5)	192 (91)
Type of treatment[a]				
Surgery				51 (24)
Radiation				38 (18)
Chemotherapy				84 (40)
Immunotherapy				35 (17)
Hormone therapy				125 (59)
Targeted therapy				51 (24)

Abbreviation: IQR, interquartile range.
[a]Patients could receive >1 type of treatment.

summarized by observing that any group differences in symptoms reported in this study were not of a frequency or magnitude that would impose special precautions on clinics dispensing COVID-19 vaccine to patients with cancer.

The current study addresses only the short-term adverse events of COVID-19 vaccine in patients with cancer. Reassuringly, early reports suggest that the 2-dose protocol of mRNA vaccine induces immunity in most patients with cancer, including those receiving active immunotherapy.[10–12] Future studies of vaccination for COVID-19 involving patients with cancer will need to address possible rare and long-term adverse events in this population, assess the durability of the vaccine-mediated immune response, and determine the impact, if any, of the vaccine on cancer treatments. Furthermore, this study of unselected patients with cancer seeking vaccination in an outpatient clinic did not produce a study population representative of patients with cancer at large. Hematologic malignancies were underrepresented and relatively few patients were receiving active treatment. No conclusions could be drawn regarding cancer subgroups of particular interest, including those receiving immune checkpoint inhibitors. The contribution of cell-mediated immunity to the anti–SARS-CoV-2 response is another subject about which little is known. This limitation assumes greater importance because immunity after vaccination is currently judged exclusively by serologic testing for antibody production.[11] It is also important to note that our study population received only the mRNA Pfizer BNT162b2 vaccine. The alarm raised by the COVID-19 pandemic has prompted the development of numerous vaccine candidates, requiring a variety of delivery strategies—including >180 vaccines still under clinical investigation.[13] A future vaccine that utilizes an inactivated virus, for example, will require a fresh evaluation of its safety and efficacy in patients with cancer.

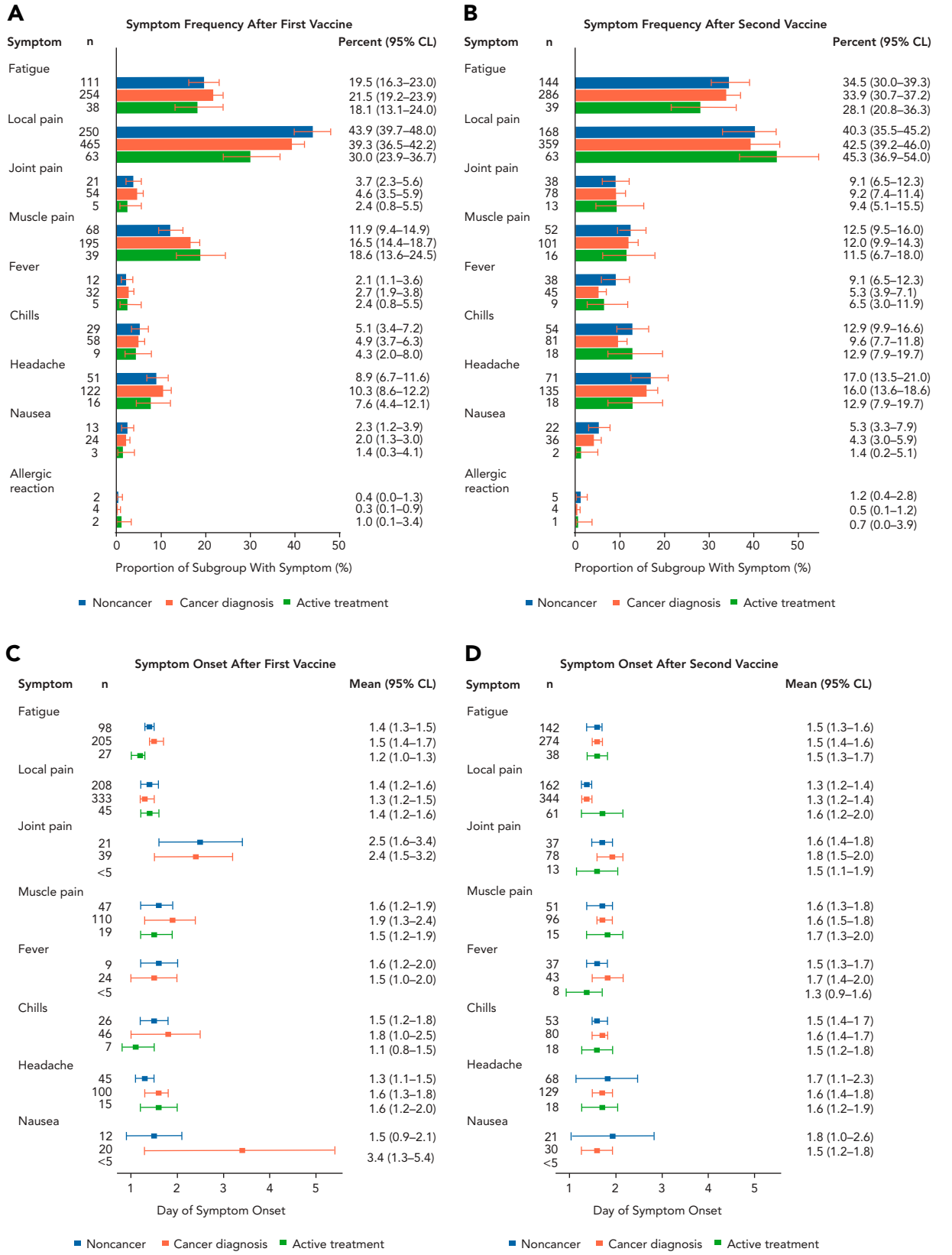

Figure 2. (A, B) Frequency, **(C, D)** onset of adverse events after the first and second dose of the COVID-19 vaccine for patients without cancer, patients with cancer, and patients undergoing active treatment.

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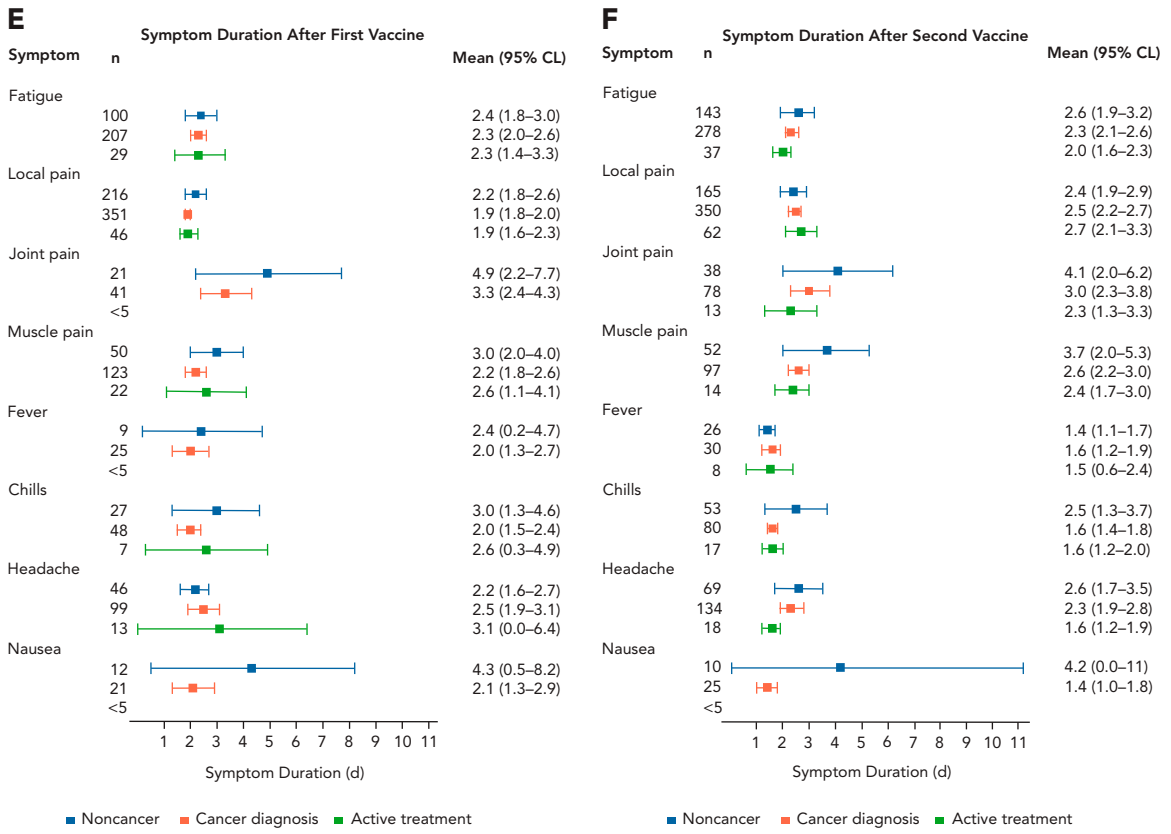

Figure 2 (cont.). (E, F) Duration of adverse events after the first and second dose of the COVID-19 vaccine for patients without cancer, patients with cancer, and patients undergoing active treatment.

Much of the harm wrought in patients with cancer by COVID-19 has not been the direct result of infection, but rather has been inflicted indirectly by delayed diagnoses and suspended or aborted treatments.[14] This harm is compounded for patients with cancer who have refused vaccination. Our data, in combination with those from other sources, show that the mRNA COVID-19 vaccine is well tolerated by patients with a history of cancer, including those receiving active treatment. Adverse events occurring shortly after vaccination closely resemble those seen in patients without cancer. As noted, our vaccination program, which targeted a sizable population of patients in fragile health, encountered no obstacles of either an administrative or clinical nature to the timely delivery of the vaccine.

Conclusions

What explains vaccine hesitancy among patients with cancer described in earlier studies? As already noted, media reports are an undoubted influence, especially when misleading or misinformed. The rate of vaccine refusal after an Italian regulatory agency suspended the use of AstraZeneca52 AZD1222 for safety monitoring more than doubled, from 8.6% to 19.7%.[9] An additional concern—perhaps even more alarming for the lasting damage it may cause—is self-defeating distrust of public health recommendations. The most effective remedy for this distrust is education. Widespread dissemination of results such as those reported in this study will ensure that a safe and effective COVID-19 vaccine—justly celebrated as a scientific and medical triumph—is provided to the patients, including those with cancer, who stand to benefit from it most.

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