Point-by-Point Response to Reviewers

We thank the reviewers for their thoughtful, detailed, and constructive evaluation of our manuscript, and appreciate their recognition of the importance and timeliness of this topic. Below, we provide a point-by-point response and indicate how the manuscript has been revised or clarified accordingly.

We believe these revisions strengthen the manuscript by sharpening its scope, clarifying its intent as a scoping review, while also preserving the central scientific motivation.

Reviewer #1

Kuperwasser and El-Deiry
COVID vaccination and post-infection cancer signals: Evaluating patterns and potential biological mechanisms
This review is a well written comprehensive approach to one of the most critical questions on the horizon bridging SARS-CoV2 infection, and mRNA vaccination across the globe linked to the promotion or initiation of a range of different cancers. It takes a difficult but first attempt at elucidating many of the underlying complexities that now exist and the critical need to address this evolving issue in the world after such a difficult and highly disastrous pandemic.
The authors have done a stringently addressed this question based on current literature, which in itself was difficult due to the lack or searchable indices. I believe it will be important and timely review that will have wide readership in infectious disease and cancer fields. I have some suggestions to help enhance the overall ease of reading as well as its balance.

1. some mention should be made about the other major neurological, autoimmune and inflammatory consequences due to the mRNA vaccine a bit more and state that this will be focused on cancer. It mentions them but does not really help put them in context. Discuss them early in a paragraph so that the reader have a more complete view of the major problems that are now being dealt with in the medical field due to vaccination.

We agree and have revised the first paragraph of the Introduction to briefly contextualize the manuscript within the broader spectrum of post-vaccination neurological, autoimmune, and inflammatory syndromes that have been reported in the literature, while clearly stating that the present review focuses specifically on oncologic outcomes.

2. page 7, fix fractions and percentages across the 69 studies with fractions first followed by percentages to be consistent across the statements.

This has been revised.

3. It may be good to examine the differences in vaccination, infection and both with what differences they may entail on page 10 so that it's clear that there are key differences in how individuals may respond to each.

We agree that distinguishing responses to vaccination alone, infection alone, and combined

exposure is important and highly relevant. However, the current literature does not provide sufficiently detailed or standardized individual-level data to support a such a comparison. Most published reports are case-based and lack consistent documentation of prior infection status, timing relative to vaccination, cumulative exposure, baseline immune status, or relevant clinical covariates, precluding meaningful stratified analysis.

Accordingly, while we describe vaccination-associated, infection-associated, and combined exposure reports where available, we feel that attempting to infer differential biological responses across these groups is beyond the scope of the paper.

We have a comment in the paper about this limitation.

4. Some mechanisms in HHV-8 may lead to bypass of cell cycle arrest during abortive lytic infection and expression of some lytic antigens including VGPCR (Mesri etal) or Spike induced lytic reactivation.

We thank the reviewer for this important insight.

5. I would suggest to discuss the examples of cancers based on categories in figure 2 with better organization of the figure panels in figure 3 (separate into groups based on cancer types). It's a bit difficult to follow as arranged. The table should be separated out of the figure.

We have reorganized Figure 3 into panels grouped by cancer type (lymphoma, sarcoma, carcinoma, melanoma, glioblastoma and other) based on categories in figure 2. We have also moved the tabular content into a standalone table to improve readability. We have also revised the revised text to parallel the grouping of the cancer types .

6. HIV is a major contributor but I don't believe its accepted as yet that it's a direct causative agent of cancer. Some thinks that way and others still have not accepted this as true.

We have revised this to "*HIV is strongly associated with Kaposi's sarcoma, cervical cancer, lymphoma, anal cancer, and other malignancies, largely though immunosuppression and co-infection with oncogenic viruses."*

7. HCMV has strong evidence in its association with glioblastoma and breast. See the use of ganciclovir for treatment of glioblastoma in the NEJM paper). The work unproven should be removed and replaced with a more nuanced statement that geographic and molecular methodological differences across studies have hampered consistency across findings.

We revised the wording to reflect available evidence linking HCMV to glioblastoma and breast cancer.

8. Page 173rd paragraph. I would suggest stating that vaccinations were mandated across many countries limiting unvaccinated cohorts. This was basically directly linked to the livelihood of many individuals to take a vaccine.

We appreciate (and agree) with the reviewer's point regarding the impact of vaccine mandates on the availability of unvaccinated comparison groups. This issue is already addressed conceptually in the manuscript through discussion of the limited size and representativeness of unvaccinated cohorts and the resulting constraints on epidemiologic inference. We also agree that widespread vaccination policies influenced cohort composition in many countries, but our intent was to describe this limitation in neutral methodological terms rather than to expand into policy or socioeconomic considerations, which fall outside the scope of the present review. We believe the current framing appropriately captures the relevant study-design implications without detracting from the manuscript's scientific focus.

9. Page 21, great point, which should also focus on connecting with the known prolonged recovery for many individuals after vaccinations. Can this be a cytokine storm that existed in these individuals?

It is indeed plausible that immune dysregulation and sustained inflammatory signaling are potential contributors in some individuals, the current literature does not provide sufficient evidence to conclude that a classical or persistent cytokine storm underlies these prolonged recovery states, nor to directly link such mechanisms to the oncologic observations discussed here.

Given the speculative nature of this hypothesis and the absence of consistent mechanistic or longitudinal data connecting prolonged post-vaccination recovery, cytokine dynamics, and cancer-related outcomes, we chose to limit the discussion to well-described immune perturbations supported by the existing literature. We believe this approach maintains appropriate scientific restraint and keeps the manuscript focused on cancer-related observations and mechanisms directly relevant to the scope of this review.

10. Figure 1, please label the color palates for completeness across the vent diagram. You labeled 6 palates and I could 9 or maybe 10 color palates. Please also complete in the legend.

Addressed

11. Figure 2, reorganize into panels A, B, C, D as well as the color palates and cancer types across the 4 panels. Two top and 2 bottom. Its organized with wasted space as

shown now.

Addressed

12.Figure 3, remove table (panel D) into a separate table. Reorganize this into cancer types and different figures. It will be easier to navigate as you reorganize the text to match as well.

We appreciate the reviewer's suggestion to reorganize Figure 3 for navigability. We have done this.

13. Figure 4, Can data be included from other cancers besides the hematologic malignancies? It may make it more complete if its available.

Figure 4 is the data from the US Armed Forces Health Surveillance Division (AFHSD) report. They only looked at NHL.

14. Figure 5, include viral antigens from oncogenic viruses that can drive paracrine and other tumor promoting effects...in the bot I suggest you include VGEF, MMPs, TNF signaling know pathways driving oncogenic activities (place next to the vessel and tumor)

We thank the reviewer for the suggestion. We already indicated TNFα as well as IL1β and IL6 but have included the text "viral antigens" and "MMPs" in the revised figure.

Reviewer #2

This scoping review by Kuperwasser and Deiry identified 69 peer-reviewed publications (January 2020-October 2025) describing cancers temporally associated with COVID-19 vaccination or infection. The evidence base consisted mainly of 333 case-level reports from 27 countries, along with two large population-based cohort studies and one longitudinal cohort study of U.S. military personnel.

Although the authors frame these findings as hypothesis-generating rather than causal, the review does not adequately account for multiple key confounding factors. In addition, their analysis lacks the denominators and reference comparisons needed to estimate risk or incidence. Hence, the claim that the observed temporal patterns are "difficult to attribute to background incidence alone" is not supported by the data.

We thank Reviewer #2 for their detailed critique and for raising important points regarding epidemiologic interpretation, confounding, and study design. We agree that the available literature does not permit estimation of cancer risk or incidence, nor does it allow adjustment for key confounders using denominators or reference populations.

Importantly, however, this manuscript was not designed to estimate risk or to draw causal inferences. Rather, it is a scoping review intended to systematically assemble, categorize, and contextualize published reports of malignancies temporally associated with COVID-19 vaccination or SARS-CoV-2 infection, and to outline biologically plausible mechanisms that could warrant further investigation. We specifically state in the introduction "*The goal of this article is to provide factual information from published literature without bias, and without intent to influence any individual's choices regarding vaccines or risk mitigation***."We recognize that case reports and small series are inherently subject to reporting bias and lack appropriate denominators.**

In fact, these issues are explicitly addressed in the Limitations section of the manuscript, where we state that the predominance of case reports and small series precludes estimation of incidence or relative risk, that observations are highly susceptible to reporting bias, and that the absence of appropriate control populations limits inference regarding background rates or causality.

Thus, the intent of this scoping review is not to control for confounding or to estimate population-level risk, but to catalog and synthesize published reports for early signal detection and hypothesis generation. Accordingly, all mechanistic interpretations are explicitly described as speculative, and the manuscript states that no causal relationship has been demonstrated. We believe the existing Limitations section accurately and transparently frames these constraints but have added the following sentence to the start of the Results section to avoid any confusion "*This scoping review covering the period of January 2020 until April 2025 was not designed to estimate cancer risk or incidence, nor to draw causal inferences, but rather to systematically assemble, categorize, and contextualize published reports of malignancies temporally associated with COVID-19 vaccination or SARS-CoV-2 infection***." In addition, we have added the following statement in the conclusion section:** "*The goal of this review is not to estimate population-level cancer risk but to provide a structured synthesis of the existing peer-reviewed literature, identify recurring clinical and biological themes, and delineate critical gaps that require rigorous epidemiologic and mechanistic follow-up. This will enable a better understanding of the full spectrum of immune responses to inform safer immunization strategies and illuminate previously underappreciated links between immunity and cancer biology*."

To address this issue (and the subsequent comments below) we have revised the statement in the introduction to state: "*The goal of this article is to systematically synthesize and contextualize findings from the published literature regarding malignancies temporally associated with COVID-19 vaccination or SARS-CoV-2 infection, without attempting to estimate risk, establish causality, or inform individual clinical or vaccination decisions."*

Major Comments:

1. Overall evidence base: The Results section is dominated by counts of case reports and small series (333 patients across 69 publications), but there is no corresponding denominator (e.g., number of vaccinated or infected individuals) or comparison to

expected background cancer incidence. Without such reference rates, these data cannot support any inference about increased risk.

We agree with this comment, which is why we explicitly state in the conclusion " *The goal is to understand the full spectrum of immune responses to inform safer immunization strategies and illuminate previously underappreciated links between immunity and cancer biology*.**" The goal of this review is not to estimate risk or incidence or provide denominators as this is beyond the scope of the current literature base. As stated above, we have also revised the language in the introduction to explicitly frame the manuscript as a scoping review for early signal detection and hypothesis generation, consistent with established methodologies and does not interpret the evidence nor make claims as to what they may or may not imply. Nowhere in the manuscript are there claims that vaccination increase risk of cancer. We have strengthened or added language throughout to avoid any implication of risk quantification.**

2. Geographic distribution: The authors state that the broad geographic distribution "indicates that the reported temporal associations... are not confined to a particular region or healthcare system." Given global COVID spread and vaccine rollout, it is expected that cases be reported from multiple countries. Without the proper denominators (e.g., country-level vaccination rates) or standardized incidence comparisons, the geographic spread primarily reflects patterns of case reporting, not evidence of a biological signal.

Again, as stated above, geographic distribution of the published literature simply reflects reporting breadth rather than evidence of differential risk. The intent of this section is to demonstrate that published observations are not confined to a single healthcare system or region.

3. Exposure types: The breakdown of case reports by vaccine platform is purely descriptive. Counts of reports is not the same as risk by platform. The author does not compare the fraction of global doses by platform to the fraction of reported cases.

We agree that the vaccine platform breakdown is descriptive only and reflects vaccine availability and uptake rather than comparative risk. We have added the following language to avoid confusion on this point "*This distribution indicates that the published literature is heavily weighted toward mRNA vaccine platforms, particularly Pfizer-BioNTech and Moderna, which together account for the vast majority of vaccine-associated reports. This pattern closely mirrors global vaccination practices where mRNA vaccines were most widely deployed. The relatively smaller representation of adenoviral vector vaccines and inactivated platforms likely reflects both their more limited use in certain regions and differential reporting practices, rather than a comparative assessment of biological risk."*

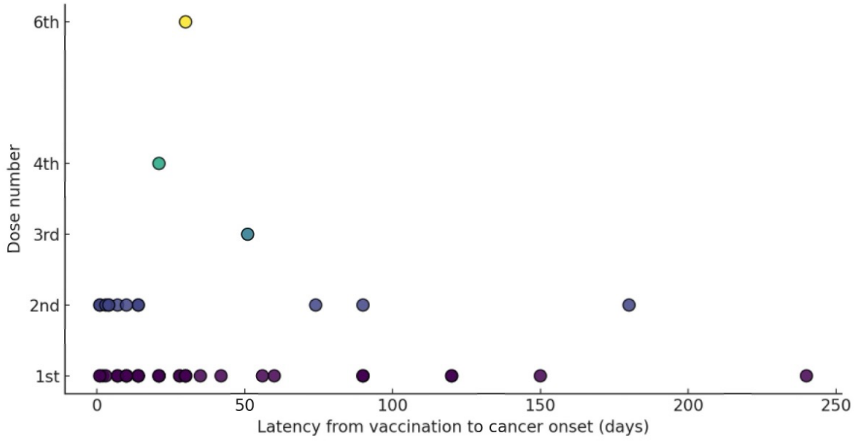
4. Cancer types: The statement that, "... making their temporal clustering around vaccination events unusual and difficult to attribute to background incidence alone" is not supported by data. Their argument is based primarily on case reports, which are inherently biased toward unusual reports. Moreover, the authors are counting

publications (e.g., 43% of publications reported lymphoid malignancies) rather than patients, and there is no formal analysis of the time from vaccination/infection to diagnosis, nor any comparison with reference distributions or expected numbers of cases in specific post-exposure windows.

We have revised the wording of this to emphasize that observations are reported as unusual by the original authors and are hypothesis-generating, rather than evidence of excess incidence beyond background rates.

5. Timing of onset: The description of latency intervals is purely descriptive and based on a highly selected set of case reports, which are more likely to be chosen when timing is short. The observed clustering of diagnoses within a few weeks of vaccination does not in itself provide evidence of causality.

We agree this section is purely descriptive- but was compiled and plotted from data extracted from all of the case reports that included the information (see data below). Because this was derived from case reports in a qualitative way, nowhere do we state that the latency intervals and timing between vaccination and diagnosis establishes causality. Nowhere in this review do we state or establishes causality of cancer from vaccination.



6. Population-level studies: The two retrospective population-level studies are mentioned, but their actual findings (e.g., effect estimates, cancer types) and extent of confounding control are not summarized. It is difficult to claim "the signal warrants further prospective evaluation" without supporting evidence.

We agree that additional information and synthesis of the population level studies is needed. We have therefore, expanded the summary of population-level studies to describe their design, endpoints, and limitations more explicitly, including confounding control and follow-up duration.

7. For the AFHSD report, the analysis is an ecological time-trend in a specific and highly selected population, and may not be suitable for drawing individual-level inferences about vaccine-related risk. The review highlights an increase in certain NHL subtypes,

but does not present absolute counts or rates. It does not address alternative explanations such as changes in diagnostic practices, force composition, or pandemic-related healthcare disruptions.

We agree and do not cite this study to draw individual level inferences about vaccine related risk. This section explicitly states, "*The authors did not analyze or attribute the changes in NHL incidence to vaccination or infection, but the temporal sequence provides an epidemiologic framework for future comparative analyses.***" We agree that these data could be confounded by diagnostic practices and healthcare disruptions during the pandemic and explicitly discuss this limitation in the revised manuscript.**

8. Related to the comment above, a 2025 meta-analysis clearly documents widespread interruptions in cancer screening, underscoring the importance of considering this confounder. This could also be true for DoD dataset (figure 4) that the authors highlight. https://doi.org/10.1038/s43018-024-00880-4

We agree and acknowledge as a limitation.

9. The authors indicate that most of the oncologic effects were associated with vaccination. Could this be due to the inclusion of REACT19 in their database search?

Yes, the REACT19 database was one of several resources used in our search strategy, and when filtered for "Oncology" it contains approximately 199 references. Many of the reverences overlap with the peer-reviewed literature identified through PubMed, Scopus, Web of Science, and Google Scholar but could not be found using conventional searching on those platforms.

Thus, the rationale for including REACT19 was not to preferentially capture vaccine-associated outcomes, but rather to address a well-recognized limitation in the discoverability of peer-reviewed publications on SARS-CoV-2 infection, COVID-19 vaccination, and cancer. As noted in the Methods and Limitations sections, much of the relevant literature is not consistently indexed with standard Medical Subject Headings (MeSH) or cross-referenced using conventional oncology or vaccinology search terms. Consequently, reliance on traditional database queries alone fails to retrieve a substantial portion of the existing peer-reviewed case literature.

We explicitly acknowledge in the manuscript that this reliance on publicly available but incompletely indexed literature imposes inherent limitations, including potential reporting bias, incomplete capture, and challenges in verification. We emphasize that this affects both infection- and vaccination-associated reports and reflects structural limitations of current indexing systems rather than an a priori focus on vaccination. Accordingly, the predominance of vaccination-associated reports in the assembled literature should be interpreted as descriptive of the published record to date, not as evidence of differential risk.

Comments on the Methods

1. Aim and estimand: The inclusion criterion of "temporally associated" malignancy after vaccination or infection is reasonable for collecting case materials, but the methods do not clearly distinguish between (i) describing temporal clustering and clinical patterns, and (ii) estimating causal effects on cancer incidence or progression.

The manuscript does not seek to estimate causal effects on cancer incidence or progression. Its aim is explicitly descriptive and hypothesis-generating, consistent with established scoping-review methodologies. We have clearly stated this at the start of the Results section to avoid any implication of risk quantification and to clearly state that incidence estimation lies beyond the scope of the available literature.

2. Use of AI-generated summaries: The methods section describes a general Google search that returned an AI-generated summary stating CDC and NCI statements about vaccine safety. These AI-generated summaries are not curated scientific databases and can be unreliable. They are more as contextual background rather than as part of the primary evidence base.

The reference to an AI-generated Google summary was included strictly as contextual background to illustrate prevailing public-health messaging and the contrast with the peer-reviewed literature. These summaries were not used as data sources, nor were they incorporated into the evidentiary base of the review. All included findings derive from peer-reviewed publications. We have removed this from the paper.

3. Handling of heterogeneous study designs: The authors list the types of studies included but do not provide an analytic plan that describes: (i) how studies will be stratified by design, (ii) which designs are considered suitable for estimating risk versus providing biological plausibility, and (iii) whether any quantitative synthesis of effect measures is planned, and if so, how heterogeneity will be addressed.

Given the dominance of case reports and small series, no quantitative synthesis or meta-analysis was planned or performed. Study designs are described and categorized to contextualize evidentiary weight, with population-level studies clearly distinguished from case-level reports. Only the former are potentially informative for incidence estimation, and even these are discussed cautiously due to confounding and limited follow-up.

4. Confounding assessment: There is no evaluation of confounding in the included observational studies (e.g., adjustment for age, sex, comorbidities, prior cancer, immunosuppressive treatment, infection status, calendar time).

Formal confounding adjustment was not feasible or appropriate given the nature of the underlying literature and the scope of this review. The lack of adjustment for age, comorbidities, prior cancer history, immunosuppression, infection status, and calendar effects is not relevant and we have described the limitations of this review.

The goal of this review is not to control for confounding or to estimate population-level cancer risk, but to provide a structured synthesis of the existing peer-reviewed literature, identify recurring clinical and biological themes, and delineate critical gaps that require rigorous epidemiologic and mechanistic follow-up. We believe the manuscript's Methods and Limitations sections accurately and transparently frame these constraints and appropriately limit inference.