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Preclinical Circulating Tumor DNA (ctDNA) Shedding Duration and Prognostic Implications of Modeling 3669 Participants From American Cancer Society Cancer Prevention Study-3 (CPS-3) and Circulating Cell-Free Genome Atlas Substudy 3 (CCGA3)

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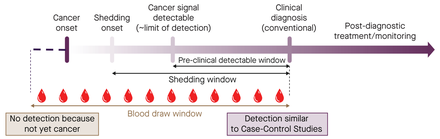
INTRODUCTION

- Early detection of cancer can occur in the preclinical phase (i.e., prior to clinical diagnosis), when development of cancers is unobservable (**Figure 1**)
- Shedding of ctDNA has previously been associated with aggressive cancers,[1–3] suggesting these tumors may develop rapidly before diagnosis
- The duration of the detection window for cancers is expected to vary among cases
  - Similar to prior reports, we assume an exponential distribution of this detection window governed by a timescale parameter[4]
- Previous studies have assessed dwell time largely in only a few commonly screened for cancers, but not in the subset of cases where ctDNA positivity occurs[5–7]
- Assessing ctDNA status in blood samples from prospective cohort studies collected at various lead times (i.e., the time between blood draw and diagnosis) allows probing the timescales of preclinical cancer development, as well as prognosis

Figure 1. Early detection of cancer can occur in the preclinical detectable window.



OBJECTIVES

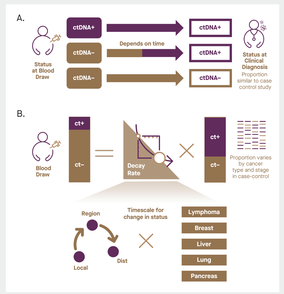
- Estimate timescales for the detectable window of cancer in the preclinical phase
- Estimate hazard ratio (HR) for ctDNA- and ctDNA+ cancers compared to expected survival for the cancer type and stage

METHODS

Timescales for changes in cancer shedding, as measured by signal detection rates

- We used a targeted methylation assay and the associated locked classifier for cancer signal detection (CSD) on samples from two large prospective biobank studies:
  - 1) CPS-3, where blood draw at enrollment (occurring between 2006 and 2013) occurred ≤3 years before clinical diagnosis (n=1065)[10]
    - A cohort of cancer cases with matched non-cancer cases were sampled from over 300 000 participants between the ages of 30 and 65 years[11]
    - This healthy, young population (50% aged <50 years, ~70% nonsmokers, 75% female) had a lower cancer incidence (~0.32) than SEER[8] participants matched for age and sex (0.46)
    - Individuals with defined, stageable, single cancer types were chosen for this analysis
  - 2) CCGA3 (NCT02889978), where blood draw (occurring between 2016 and 2019) was concurrent with clinical diagnosis (n=2604)
    - Demographics of this case-control study have been previously described[12]
    - Individuals matching the cancer types and stages of the sampled subset of CPS-3 cohort were used for joint modeling

Figure S1. Sketch of computational model. A. Theory of ctDNA shedding behavior over time. B. Computation of probability of detection at blood draw compared to clinical detection (above) and the dependence of exponential decay of detection on cancer type and stage (below).



- We constructed a model for detectability including the following factors (**Figure S1**):
  - Study, including any experimental effects due to differences in sample handling
  - Inherent ctDNA detectability (probability of shedding) at clinical diagnosis
  - Effect of lead time (time between blood draw and diagnosis) by cancer type and stage
- We used a published model of natural history of cancer[8] to predict detection rates over time based on the rate of interval cancers for various screening intervals, and compared the predictions to the observed data

Impact of ctDNA status on indicating clinically significant cancers and prognosis

- In addition, we evaluated prognosis stratified by ctDNA status (CSD positivity) and compared to expected CSS matched by age, cancer type, and stage for up to 9 years of follow-up, noting that ctDNA status may change during lead time

Supporting Data

- Models for detection and prognosis were fitted using the Stan Bayesian modeling language using the rstan package[14] - probability of detection depended on study, cancer type and stage, and a time-dependent rate also dependent on cancer type and stage
- For prognosis, this detection model was extended to fit a HR at clinical diagnosis depending on both the observed ctDNA status at blood draw and the time-dependent probability of changing ctDNA status between blood draw and diagnosis
- We report posterior credible intervals and medians as approximate confidence intervals in figures and tables

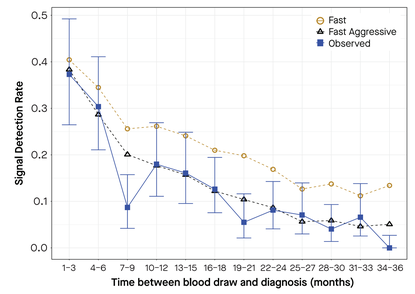
DWELL TIMES FOR ctDNA-POSITIVE CANCERS WITHIN THE DETECTION WINDOW ARE SHORT, CONSISTENT WITH MODELED AGGRESSIVE TUMOR GROWTH.

Cancer signal detection rates

- The detection rate in observed data (CPS-3) and fitted results changes with lead time in a predictable way (**Figure 2**)
  - Compared to estimates derived from CCGA3 data (0 lead time) for the same cancers and stages at each time after blood draw, we noted that fitted and observed detection rates resemble CCGA3 estimates at very short lead times (**Figure 2**)
- Observed detection rates closely resemble detection rates predicted for a fast-aggressive cancer case by a previously published model[8] (**Figure 3**)

Figure 2. Observed detection rate over time (blue squares) changes with time between blood draw and clinical diagnosis (95% pointwise confidence intervals using Jeffrey's method shown). Fitted line (green line connecting triangles) shows (median) output from the fitted model. The naive expected detection rate using sensitivities from the CCGA case-control study (all at 0 lead time) applied to the cancers seen in CPS-3 in each time window with no change over time due to natural history is shown as a reference (red line connecting circles). The difference can be explained by cancer progressing through its natural history and consequently changing shedding behavior.

Figure 3. In the model fitted to the observed data, the resulting estimates for the duration of the detectable window are short. However, the observed data matches predicted detection rates and the change through time given the natural history assumptions for a fast-aggressive tumor growth scenario of cancer of a previously published model.[8] This suggests that the observed data is largely consistent with the previously published model's natural history assumptions and therefore is consistent with potential for stage shift.



Timescales for changes in ctDNA

- CCGA3 and CPS-3 studies did not differ statistically in estimates of inherent ctDNA detectability at clinical diagnosis, although the confidence interval is broad
  - 95% confidence interval [CI] for difference is [-8.2%, 4.6%] and spans zero
- Median [CI] detection timescales by type ranged from 0.49 [0.26, 0.88] years for pancreas to 2.45 [1.14, 4.87] years for lymphoma (**Figure 4**)
- As stage increased, median [CI] detection timescales increased (assuming exponential decay of detection over time) (**Table 1**)

Figure 4. Estimated timescales for the average duration of detectable window stratified by cancer (sorted by median timescale). For example, pancreatic cancer has a shorter expected duration of shedding detectable ctDNA than lymphoma does.

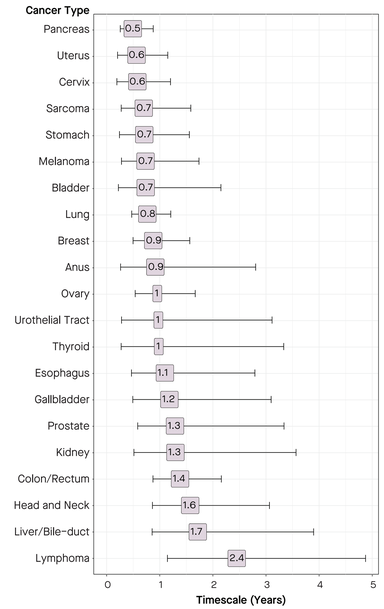


Table 1. Estimated timescales for the average duration of detectable window stratified by stage. For example, the expected average duration of shedding detectable ctDNA is shorter for localized stage than for distant stage.

Stage	Time [CI], years
Localized	0.8 [0.5, 1.3]
Regional	0.9 [0.6, 1.3]
Distant	1.2 [0.8, 1.7]

Impact of ctDNA status on indicating clinically significant cancers and prognosis

- For CPS-3, the estimated cancer-specific survival (CSS) at 9 years from blood draw was 54% for ctDNA+ and 79.5% for ctDNA- participants (**Figure 5; Table 2**)
  - Although these unadjusted survival curves show that ctDNA status can indicate cancer types and stages that are clinically significant, they do not take into account known differences in cancer type, stage in survival, and shedding behavior
  - Further, in this data set, ctDNA detection status is predicted to change between blood draw and clinical diagnosis, complicating analysis of HRs
- Compared to synthetic controls for age, cancer type, stage, and lead time in Surveillance, Epidemiology, and End Results (SEER) data, CSS was better in each group (see Methods; **Figure 5**)
  - ctDNA+ fitted HR at clinical diagnosis: 0.63 (CI: 0.54, 0.74)
  - ctDNA- fitted HR at clinical diagnosis: 0.45 (CI: 0.22, 0.74)

Figure 5. Survival data separated by ctDNA detection at blood draw. Cancer types, stages, and lead times are different in ctDNA+ and ctDNA- cases; therefore, direct comparison is not recommended for prognostic purposes. In each case, a reference (solid) curve of expected survival via SEER data is computed given the cancer type, stage, and lead time. Because the probability of converting from ctDNA- at blood draw to ctDNA+ at clinical diagnosis changes with lead time, the prognostic effect of ctDNA status at blood draw changes depending on the test time. Fitted (dashed) curve adjusts the reference curve for this variable HR.

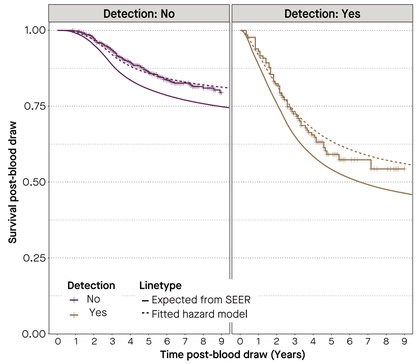


Table 2. HR [CI] for ctDNA+ vs ctDNA- status at blood draw as a single factor predicting CSS. This shows the ability to indicate clinically significant cancers by ctDNA detection. As this study is retrospective and not interventional, we cannot determine whether survival can be altered due to early detection. As cancer type, stage, and lead time vary, this HR at blood draw is not directly usable as a prognostic factor.

Years to diagnosis after blood draw	HR [CI]
≤1	7 [4.2, 12.2]
≤2	4.2 [2.9, 6.0]
≤3	3.5 [2.5, 4.7]

CONCLUSIONS

- To our knowledge, these results are the first to provide estimates for the duration of the average preclinical detection window of cancers shedding ctDNA across multiple cancer types and stages, including numerous cancer types with no current screening paradigm
  - The first time a population is screened, there is a backlog of cancers to be detected, proportional to the average preclinical duration of the detection window. Cancers with long detection windows, such as lymphoma, may be over-represented in the first screening rounds of studies compared to faster-growing solid tumors or later rounds of screening
  - Long dwell times may allow for early detection of lymphoid neoplasms, which lack current screening paradigms and are the fourth most common cancer and the sixth leading cause of cancer death in the US
  - Previous literature suggests that screening intervals should be similar to the average detection window;[9] in this case, it suggests that an appropriate screening interval is approximately one year
- Taking lead time into account, preclinical ctDNA status indicated individuals who developed clinically significant cancers, limiting potential for overdiagnosis
- Despite indicating clinically significant cancers, participants with ctDNA+ cancers still had survival comparable to SEER for their cancer type and stage, even up to 9 years of follow-up, consistent with previous reports with shorter follow-up duration[3]
  - ctDNA- cancers in the first year consist largely of cancers effectively managed by standard of care at early stage and have good survival even if clinically diagnosed
- Strikingly, the picture of cancer natural history here is similar to that predicted from a previously published model of cancer natural history and detection[8]
  - This is consistent with the potential to achieve stage shift by long-term screening

Strengths

- Access to preclinical blood draws
- Use of a locked classifier not tuned on CPS-3 data
- Explicit modeling of timescales across multiple cancer types and stages
- Use of reference data from SEER to account for differences in cancer type and stage on survival
- Linkage between case-control study and preclinical data set

Limitations

- The duration of time when cancers are growing but not detectable by ctDNA cannot be estimated in this study
- The potential for stage shift cannot directly be examined in this data set because this is not an interventional study, and so cancer status, including detailed staging information was not collected at blood draw
- Since ctDNA+ and ctDNA- cancers comprise very different cancer types, stages, and lead times in this study, direct comparison of ctDNA status alone should not be used for prognosis
- Credible intervals are too large in this study to recover differences in HRs due to ctDNA status, after accounting for differences in cancer type, stage, and lead time

Future Considerations

- Results require confirmation in future prospective analyses
  - Differences in sample handling and storage exist between CPS-3 and CCGA3
  - Although these studies performed statistically similarly in detection rate when clinical diagnosis matched blood draw, we cannot rule out potential reductions in performance that would shorten timescales for cancer detection and/or reduce sensitivity
  - Younger populations may have more aggressive cancers with differing prognoses than populations of typical screening age

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Disclosures

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