Intro - current

* Cancer and dementia co-exist, cancer patients have impaired cognitive function, but observational studies have shown the opposite
* Selection bias can come in three ways: 1. Survival bias (conditioning on participants who have survived up to the moment of study assessment), 2. Inmortal time bias (starting point for cancer patients over follow up) , 3 CR of death (as in independent censoring assumption).
* How study design and analytical decisions can lead to bias. 1) visual explanation of the potential problems of selection bias due to study design, 2) replicate analytical desions, 3) two ways to address CE plus inmortal time bias

Intro-new

* Cancer and dementia coexist, and observational studies have shown opposite results
* Current methodological studies are discussing how the competing event of death can be partly explain these results, though focus has been centered in statistical methods (ref) and selective survival (ref). However, a missing piece is that there is no one single way to define the question(ref JY) around of death, and bias will depend on the question, and hasn’t been addressed yet in this topic.
* Most importantly, studies have used “history of cancer or incident cancer” as the key exposure, but there are many causal structures that could be framed in order to understand the sources of bias.
* We want to 1) the different ways in which selection bias is present in current studies 2) discuss how confounding should be addressed depending on what proxy is cancer dx. representing?

Methods- current

* Data info
* Statistical analysis:
  + Replication of previous studies:
    - cohort study with cox and cancer as time-dependent, plus sensitivity analysis on those who survived up to 80 yo.
    - Cohort study using cox-ph and cancer as time-dependant
    - Nested case-control study using cox ph and cancer as time-dependant
    - Cross-sectional case-cohort

Correcting for age, sex, educational level, smoking, bmi, SBP, hypertension, 15 years of follow-up

Current thoughts: Something I realized with how the CR paper has progressed is that now I would prefer to prevent replications of unclear analysis (such as ignoring censoring, presenting hazards, not being clear about the question (even only in terms of the competing event) just to show that selecting on survival up to certain point, and considering ever vs. never show a range of “protective effects”.

* + Inmortal time bias: we fail to align the start of follow-up, those who survive longer have a higher probability to be dx. with cancer than those with short follow-up.
  + Death is considered as uninformative censoring event
    - Crude risk
    - Net risk
    - IPW for cancer dx
    - Cloning and censoring
  + LTFU was considered from skipping/missing visits

Methods-new

Start with clear points:

* Acknowledge that cancer cannot be considered as a causal question for several reasons (DAG as Figure 1. different causal structures) (Could this work as in the methods section?)
* After being explicit about cancer, we can now focus on the different descriptive questions where we want to see the distribution of dementia, and show how results change depending on how cancer is defined in terms of time\* for the net risk and crude risk
* Be clear that censoring for death is conditional on time-varying covs and how much it changes if unconditional censoring is considered.
  + Cancer ever vs. never
  + Cancer as time-varying
  + Cancer as time-varying emulating that over time, those who are diagnosed with cancer at a certain time point are similar (and alive) to those who remain alive and free of cancer dx. (ipw for time to cancer) (Does this make sense?)
  + No LTFU

Results-old

* Table 1: baseline characteristics
* Figure 2: transition stages
* Replication: Table 2. All results, Figure 3: illustration of desing
* Figure 4: Risk of death among participants with cancer and without cancer
* Figure 5A-F: cumulative incidence curves

Results-new:

Table 1. baseline characteristics

Figure 2. distribution of event-status over time

Table 2. Key results

|  |  |  |  |
| --- | --- | --- | --- |
|  | Crude risk dif or rr | Net risk dif or rr (unconditional) | Net risk dif or rr (conditional) |
| Ever vs. Never |  |  |  |
| Time-var cancer |  |  |  |
| Time-var cancer weighted for cancer |  |  |  |

Figure 3. Cumulative incidence curves

Discussion-old

* Direction and magnitude of the risk of dementia is affected by study desing and statistical analysis
* Replication of analysis (but reporting hr). Cross-sectional is the worse
* Longitudinal studies: time-independent vs time dependant (Hanson et al), though cox-ph for independent cov handle inmortal time bias, they are presented as Hazards, and death is considered as uninformative
* Assumption is not examined (!). Death matters, Hanson et al. studies used negative control diseases, cancer types, stratify follow-up (21). Tumor marker as proxy of cancer, cancer might increase dementia risk
* Pathology-confirmed cancer dx is used as exposure, it can represent multiple causal pathways, cancer dx. itself does not cause dementia. Ill-defined question may result in wrong interpretations. Explanation of several pathways, each may require different confounding structures.
* Conclusion: study design and analytical decisions matter. Given the ill-defined definition we cannot answer the causal effect. Future studies need to get this better

Discussion-new

* Results show how different results are depending on what question we are asking, and when we address the question with regards to eliminate death…assuming independent censoring is wrong.
* Clarify that competing event is a characteristic of the data structure, not a bias. Selection bias can be present in different ways…surviving up to cancer dx, presenting results as hazards, independent censoring assumption.
* The independent censoring assumption is a big one, and although results conditional and unconditional are different results this is a rough approximation since interventions to prevent death will be different among those who are free of cancer (intervening on cardiovascular related deaths) vs. eliminating death from cancer in the cancer group… so again a lot of embedded assumptions in this point, and better questions will clarify some of this.
* To understand the causal effect one has to first acknowledge what “cancer dx.” stands for. That is the first step to understand the confounding structures.