Cohort Studies – Person Time & Bias

Key Words (or Topics)
Confounding by Indication
Fixed or closed cohort
Immortal Person-Time
Incident user
Open or dynamic cohort
Person time
Prevalent user
Residual Confounding
Selection Bias
Target Trial

Objectives
1. Understand the concept of and how to classify person-time.
2. Describe differences between healthy and patient cohorts.
3. Understand how to use study design to minimize immortal-time bias and selection bias in a cohort.
4. Critically appraise potential for bias in published scientific literature.

Assigned Readings
Chapter 7, Rothman, Greenland, & Lash 3rd Edition

Choe, K.S., Cowan, J.E., Chan, J.M., Carroll, P.R., D'Amico, A.V. and Liauw, S.L., 2012. *Aspirin use and the risk of prostate cancer mortality in men treated with prostatectomy or radiotherapy.* Journal of Clinical Oncology, 30(28), pp.3540-3544. https://www.ncbi.nlm.nih.gov/pubmed/22927523

Recommended Reading
Hernán MA et al, *Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses* J Clin Epid, 2016, p.70-72 (or Parts 1-3; NOTE methods discussed in Part 4 are covered in BIO215) https://www.ncbi.nlm.nih.gov/pubmed/27237061

Optional Reading
Emilsson L, García-Albéniz X, Logan RW, Caniglia EC, Kalager M, Hernán MA.
Examining Bias in Studies of Statin Treatment and Survival in Patients With Cancer. JAMA Oncol. 2018 Jan 1;4(1):63-70. doi: 10.1001/jamaoncol.2017.2752. PubMed PMID: 28822996.
https://www.ncbi.nlm.nih.gov/pubmed/28822996

Assignment – Please answer the following questions.

1. For each of the following terms, provide a definition, an example, and explain how each could potentially threaten the validity of a study if not appropriately addressed.

(9 points)

i. Immortal person-time

Immortal person-time occurs when a cohort design requires that everyone must have survived for a specific period and entry into cohort is dependent on survival (Rothman). For example, if a study on survival after cancer treatment requires all eligible individuals to have undergone treatment for at least one year, it excludes all individuals that may have left or died prior to the one-year period (selection bias), or assigns individuals to the unexposed group if they died before reporting the exposure (measurement bias). The presence of immortal time will generally bias the risk ratio if this year period is still included in the denominator of person-time during which an eligible individual could have died, when in fact those that *did* die during that period were excluded. This may affect the effect estimate of this relationship by biasing the estimated disease rate towards the null, by saying that individuals could have died during the one year period when the study design designates that they could not have.

ii. Confounding by Indication

This occurs when a variable is a risk factor for disease and is also an indicator for treatment (with the exposure); and is not an intermediate step in the causal pathway between the exposure and the disease. For example, if you are studying vaccine effectiveness (Y, outcome), it is possible that patients with poor prognoses (L, confounder) will be more likely to be immunized (E, exposure) but also will be more likely to have the health outcomes in your study, introducing confounding into the estimation of the effect size. Another example: Studies of the association between antidepressant drug use (E, exposure) and infertility (Y, outcome). The use of antidepressant medications may appear to be associated with an increased risk of infertility. However, depression itself is a known risk factor for infertility (Depression is a confounder, L). As a result, there would appear to be an association between antidepressants and infertility. (ref: http://sphweb.bumc.bu.edu/otlt/mph-modules/bs/bs704-ep713_confounding-em/BS704-EP713_Confounding-EM4.html)

iii. Reverse Causation

Reverse causation refers to the outcome of interest occurring prior to the exposure of interest. For example, if analgesic use is considered the exposure of interest and disease diagnosis is the outcome, it is possible that the pain medication use (i.e. aspirin) is a result of the disease that is later diagnosed (i.e. liver disease), instead of a cause. As a result, any conclusions of the effect of pain medication use on disease diagnosis would be invalid.

2. Distinguish between latent period and induction time and provide an example of each. (4 points)

Induction time is the period of time from causal action to disease initiation, or the time between exposure and the initiation of disease. Induction time is used to assume the minimum lag time for a disease to develop so that those who develop disease immediately after exposure can be classified as a case unrelated to exposure. For example, the time between exposure to lead in the Flint water crisis to the development of ADHD in children would be considered the induction time.

The latent period is the time between irreversible disease occurrence and detection of disease [though some have used this interchangeably with induction period in the past (Rothman, p. 16), we will be using it as the period after the occurrence of disease]. Building off of the last example, the latent period would be the period from when behavioral deficits occur to when symptoms are noticed and the child is tested for the diagnosis of ADHD. Another example would be the period after prostate cancer occurred to when it was diagnosed.

3. Classify whether the following questions would be better answered using a cohort of patients or healthy individuals. Justify your answer. (6 points)

a. Does hormone replacement therapy protect against osteoporotic fractures?
A healthy cohort would be ideal for this question as the idea would be to protect against fractures by focusing on bone mineral density, which would in turn protect against osteoporosis. However, one could argue that this could be tested in a patient cohort of osteoporotic individuals if you specify that the study population of interest are osteoporotic individuals, and the goal is to prevent fractures in this high risk group. While the healthy cohort is our preferred approach, there is the disadvantage of longer follow-up time to event since all the participants are healthy, so this may not be feasible in some circumstances. It is important to point out that the researchers are often answering different questions when they use patient vs. healthy cohorts.

b. Can hormone replacement therapy increase bone mineral density in osteoporotic individuals?
Patient cohort – note that you are looking in individuals who are already osteoporotic, not trying to prevent osteoporosis in healthy individuals.

c. How much (what dosage of) hormone replacement therapy is needed to protect against osteoporotic fractures?
This could be studied using either a healthy or a patient cohort, similarly to question 3A. In a healthy cohort, you would want to change the exposure from any exposure to HRT to a cumulative or frequency measure of HRT usage. In a patient cohort, this however could be tested using a patient cohort of osteoporotic individuals to see if there were differences in fractures by levels of exposure to HRT, as long as it is specified that osteoporotic individuals are the target audience and that you are looking at protection of a side effect of disease and not the disease itself.

Questions 4 through 9 refer to the following article. Please read and answer the questions below.
Choe, K.S., Cowan, J.E., Chan, J.M., Carroll, P.R., D'Amico, A.V. and Liauw, S.L., 2012. Aspirin use and the risk of prostate cancer mortality in men treated with prostatectomy or radiotherapy. Journal of Clinical Oncology, 30(28), pp.3540-3544.
https://www.ncbi.nlm.nih.gov/pubmed/22927523

4. Describe the study objective and the authors' null and alternative hypotheses. (2 points)

The main objective of this study was to examine the association of anti-coagulant use with prostate cancer-specific mortality (PCSM) in a multi-institutional registry of men treated for prostate cancer with either radiation or radical prostatectomy (surgery). They also examined disease recurrence and bone mets (presumed secondary outcomes).

The null hypothesis is that there is no association between anti-coagulant (AC) use and risk of PCSM (or the other 2 outcomes); while the alternative hypothesis is that there is an association.

5. Describe the study population. Is this an open or fixed cohort? Justify your answer. (2 points)

The CaPSURE population comprises an open cohort because of its registry with no fixed roster. Men with prostate cancer have been continuously enrolled since 1995 from 41 different sites nationwide. As its described in the article, it appears that men are followed until death via surveys and by checking with National Death Index and requests for state issued death certificates. This is an open cohort as enrollment has been going on since 1995.

At the time this paper was written, there were 13,821 men ever-enrolled, and 8,292 men had medication data in the registry database. For this analysis, the authors focused on the following study population: men diagnosed with localized prostate cancer (node negative, non-metastatic), who had data in the database on medication usage, and who were treated with either surgery or radiation. This left 5,955 men for the analysis.

6. For each of the research questions below, make a diagram showing how a sample subject's person time was allotted (2 diagrams total, one for 6a and one for 6b). For each diagram, depict how person time was allocated during the entire study period, including the event that triggered start of follow-up, events that defined eligibility, how exposed and unexposed person-time was allocated for this subject, and include depiction of an outcome in your example. Indicate T_0, E, and A in your diagram, depict/label exposed and unexposed person-time for the subject, and explain what exposure was allocated when the subject experienced the outcome. For examples of visual depictions of person-time allocations, see recorded lecture on Person Time & Bias, part 2. (12 points)

   You may assume the following methods were applied in this study, to help develop the diagrams:

   > "In CaPSURE (the study used for this paper), urologists enrolled eligible patients into the study (after diagnosis of prostate cancer and before treatment), completed medical history at baseline, and recorded recurrence status, treatment, and laboratory results at each office visit. The patient participants completed a baseline questionnaire and follow-up questionnaires periodically (this varied by survey type and could be every 3 to 12 months). You may assume that data on the time-varying exposure (Anticoagulants, AC) was collected at baseline and updated annually. You may assume that the investigators initiated follow-up at the time of treatment for exposures that were not updated over time; and that for analyses using Cox proportional hazards regression, with updating of exposure at each year, that they started follow-up at the return of the first survey after primary treatment."

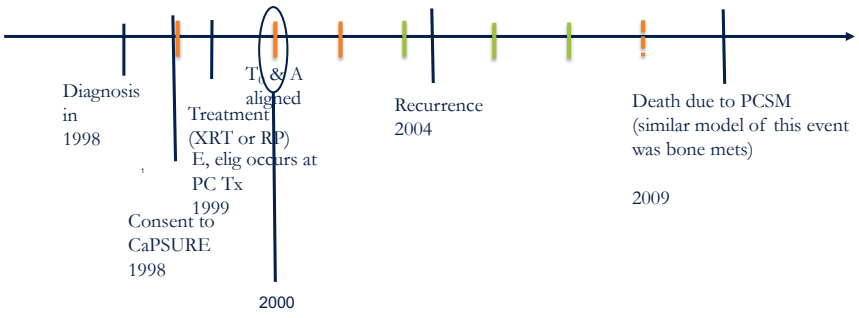
   a) Is time-varying use of anticoagulants associated with prostate cancer-specific mortality?
   b) Is ever or never use of anticoagulants associated with prostate cancer-specific mortality?

(NOTE: you may find this easiest to do on paper or a white-board; to submit, please include your name on the page/board and take a picture that you can submit electronically with the rest of your HW).

Person Time & Bias, Question 6a

Using | Not using

For PCSM or bone mets outcome with time-varying exposure (yes/no): T0 = return of survey after Tx. Eligibility is completed at the time of PC treatment with RP or XRT. T0 =date of return of follow-up survey after PC Tx and this person starts as a non-user. This gets updated as follow-up surveys are administered. Followed until PCSM, but last survey not counted (indicated below with hashed orange line); use the 2nd to last survey as exposure for the last f-up cycle, so this guy is a "user" when he dies. E is not aligned with T0 and A, so opportunity for selection bias, bc people had to live to return the first survey after PC treatment.



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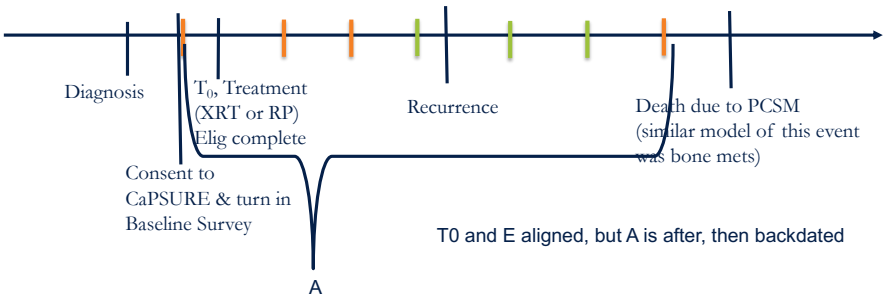
Person Time & Bias, Question 6b

Using | Not using

For PCSM or bone mets with Ever/Never

T0 = treatment. Eligibility is also completed at this time as this is when we know if they had RP or XRT. For the 2-group comparisons using KM curves, T0 started at time of treatment for everyone, but they used data from the entire follow-up interval to classify men into the ever (exposed) or never (unexposed) categories. Thus, the person below would have started T0 at time of treatment and would have contributed all his person-time to the "exposed" category, even though he didn't start using AC until his 4th survey. This creates the potential for "immortal time" in the exposed group, and could lead to bias.



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In general, participants' follow-up contribution ended if they experienced the event of interest (PCSM, or recurrence, or bone mets), or if they were censored due to death due to other causes), lost to follow-up or withdrawal, or end of study (the authors didn't indicate "end of study date"; but probably used last known date of follow-up for each individual).

7. Describe the exposure in the Choe et al. article. When and how was the exposure measured, and how was the exposure classified? Explain at least one way in which measurement error of the exposure could potentially lead to bias in this study. (5 pts)

The exposure was defined as anticoagulant use from any of the following drugs: warfarin, enoxaparin, clopidogrel, and/or aspirin. The exposure was measured via a survey that assessed "ever use" at baseline and at 1 –year intervals for a median of 4 years. It appears that they compared "ever use" with never usage as their main comparison, although they also describe doing a Cox proportional hazard regression model, where they describe allowing the exposure to be updated. These results however are not shown in the figures or tables, but only in text.

Measurement error could lead to bias due to the immortal person-time occurring in the study. Given the ever vs. never classification of exposure used in the analyses, there could be immortal time bias, due to assignment of extra person-time in the exposed group (i.e., people who lived longer had more opportunity to become an "ever user") or in the unexposed group (i.e., people who died to before receiving the exposure).

Another example of measurement bias can be deduced from the ever/never categorization of AC use. It makes assumptions about usage patterns, and implies a rather simple biologic hypothesis. The authors assumed that once someone started using AC, they often stayed on them, and that men who ever-used AC's have different mortality rates than those who never used AC's over follow-up. This puts someone who used aspirin maybe for 6 months and reported "use" during a single survey (but never again) in the same exposure category as someone who was truly a consistent and persistent user over many years. Biologically, this does not seem to be the same, and could have introduced measurement error.

A time varying approach could be employed as solutions to limit these biases. It would avoid extra survival time in the exposed or unexposed groups associated with immortal person-time, and it would improve the accuracy of exposure classification. In the study, the authors report doing a Cox proportional hazard regression with time varying exposure data, and observed a similar result, suggesting that at least in this population, their assumption about 'once a user' → 'continuous use' may have held.

This study also mixes prevalent and incident users, which could lead to selection bias.

8. Assessing bias: (4 pts)

a. Is selection bias a concern in this study? Justify your answer.

Because the study is based on registry data, there is a possibility that those who are less in contact with the healthcare system are under-represented in that study. This could mean that there is an under-representation of patients *not* on anticoagulants. Secondly, patients who have aggressive prostate cancer will develop disease and die rapidly without being sampled by the registry. These two features combined may lead to an under-representation of participants who have aggressive cancer and are not on anticoagulation, which is a bias that would lead to an overestimate of the numeric effect (i.e. in this case, that means a bias towards the null).

This is an example of multiple concerns for selection bias in the study. Although we gave an example of selection bias "at the front end" due to eligibility, there is also concern for selection bias due to exposure classification of prevalent users as "ever users" as well as due to loss to follow-up.

b. Is immortal person-time bias a concern in this study? Justify your answer.

Here is one definition of Immortal Person-time: "Immortal person-time arises in an observational study when follow-up time is included in person-time at risk for the study outcome, even though that time precedes the last event required for entry into the study population or satisfaction of an exposure definition." (Lash & Cole, http://ascopubs.org/doi/full/10.1200/jco.2009.24.1877)

One way for immortal person-time bias to occur is if classification of the exposure occurs ***after*** follow-up begins in at least some of the members of the exposed group. During immortal time, the outcome (in this case, death) cannot occur. In this study, anticoagulant (AC) use was measured yearly immediately at the start of the study and at yearly intervals after that. When considering the ever/never exposure categories, immortal time is not an issue for patients with reported AC use at the start of the study. However, for participants who started taking AC at the one-year mark or later, there is immortal time between the time of the start of the study and when the patients reported taking anticoagulation. Therefore, immortal time is present in a subset of the exposed patients in the study, and could lead to bias. This seems akin to Emulation Failure 4 in the Hernan article (J Clin Epid 2016) or slide 12 from the 4th segment of the recorded lecture.

To minimize immortal person-time and selection bias, we can align T0, eligibility and assessment of exposure. We use the diagrams from Q6 to exemplify successes and failures. For the outcome of PCSM with time-varying exposure (q6a diagram), T0, eligibility, and assignment of exposure all occurred at the return of the first follow-up survey. For the recurrence outcome with time-varying exposure and the analyses of PCSM (or bone mets) with updating of ever/never exposure, T0 was at treatment, eligibility was completed at treatment, and the exposure assessment was based on a survey returned prior to treatment. This may be susceptible to some selection bias because there is a space of time between when exposure is assigned (baseline survey) and T0 (tx), and usage of AC or aspirin could have influenced whether someone survived until T0. When conducting analyses with the ever/never categorization for the PCSM and bone mets outcomes *(*q6b diagram), there is a risk that immortal person time was counted for a subset of exposed (those who started after baseline), and this could introduce bias.

9. State the author's conclusion. Based on your assessment of potential biases, are you confident in the author's conclusion of whether aspirin use is associated with prostate cancer mortality? Please justify your answer. Consider how a "target trial" might have addressed the research question and describe what the authors could have done to strengthen their study design. (4 pts)

Authors' conclusion: AC therapy, particularly aspirin, was associated with reduced risk of prostate cancer-specific mortality in men treated with RT or RP for prostate cancer.
Answers may vary. We are mostly looking for how you justify your response. This is an observational study and we can never rule out the possibility of residual confounding. Furthermore, as mentioned above, there is the

possibility of immortal person time and selection bias. Given this, I think the estimates are optimistically strong, or that the true association is more moderate.

Areas of improvement:

- The authors could have been clearer on their "time varying analysis". We do not see any of the results of this analysis or if they did present it, it was unclear. This is to ensure we avoid immortal time bias.
- They could have excluded patients who were prevalent users before study entry and only include patients who were incident users. Combining prevalent with incident users may introduce selection bias.
- The authors could have measured dose of AC to assess for a dose-response in AC-use and PCSM. This is also tricky because we know that too much AC can cause bleeding and put you at risk for mortality regardless of PC status.
- Was exposure status blinded during outcome ascertainment? If not, this could have been done. What percentage of outcomes was from "local study coordinators"? (see questions 7-8)
- Some argue the use of "cancer specific mortality" is flawed and the use of all-cause mortality is preferred. The use of cancer-specific mortality could lead to differential misclassification, although this is more of an issue for the assessment of screening interventions (makes them look falsely "bad").
- Covariables were selected based on PCSM and not by AC-use. Again, this could lead to unmeasured confounding. It is certainly possible that cardiovascular disease, which is related to AC-use, could also affect PCSM. Thus, they could have measured more possible confounders (i.e. CV disease, diabetes status, other medication use, etc).

48 points total, +optional 4 extra credit points

Extra credit (4 pts):

In the *Statistical Analysis* section of Emilsson et al. 2017 (Optional Reading), the authors write the following:

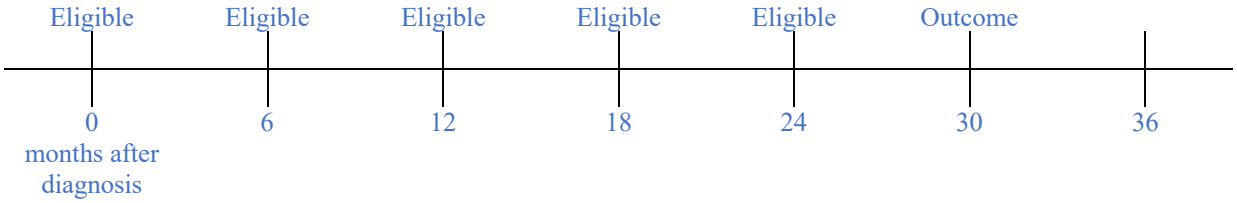
We explicitly emulated a target trial of statin therapy initiation among patients with cancer using observational data from the SEER-Medicare database. To do so, we created a data set with 2 copies of each eligible individual at baseline and assigned each of the replicates to 1 of the treatment strategies. Replicates assigned to the statin strategy were artificially censored at 6 months if they had not initiated statin therapy by then. Replicates assigned to the no-statin strategy were censored if and when they initiated statin therapy at any time during the follow-up period. This approach avoided both selection bias due to the inclusion of prevalent statin users and immortal-time bias due to defining statin therapy initiation among survivors.

Draw a diagram depicting how person time was represented in this study. Include at least two participant examples to show replicates for a patient that initiated statin therapy and a patient that did not. See Part 2 of the recorded lectures for Person-time & Bias for an example of a visual depiction of person-time.

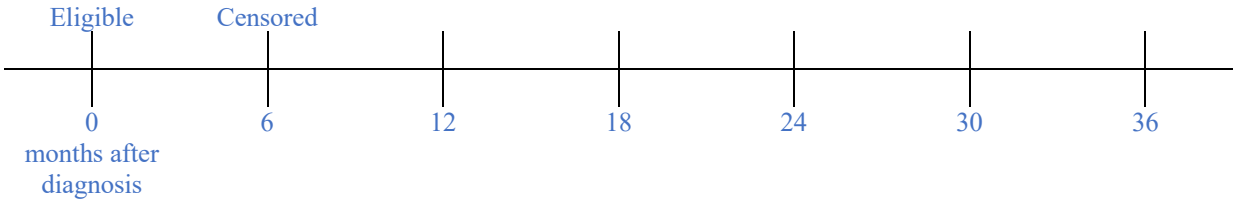
Answer: Eligible means the individual contributes person time to the indicated category of treatment (assigned to statin therapy within 6 months after diagnosis) or no treatment (assigned to no statin therapy).

Patient A started statin therapy at month 2 and died at month 30

Copy 1 (assigned to statin therapy initiation within 6 months after diagnosis; this person did do this, so s/he contributes person time until death at 30m):

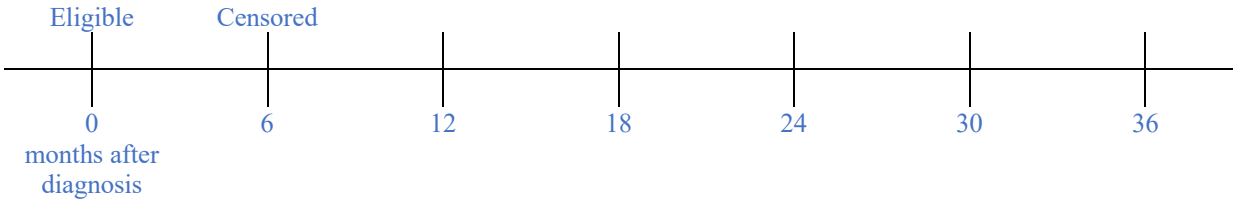


Copy 2 (assigned to no statin therapy initiation; this person did not do this so is artificially censored at 6m per the Methods):



Patient B never started statin therapy and died at month 18

Copy 1 (assigned to statin therapy initiation but censored at 6 months after diagnosis because never started statin therapy in real life):



Copy 2 (assigned to no statin therapy initiation; this matches what the person actually did, and they contribute follow-up until censored at death at 18m):