Competing Risks: *Application to Osteoporosis*

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MrOS

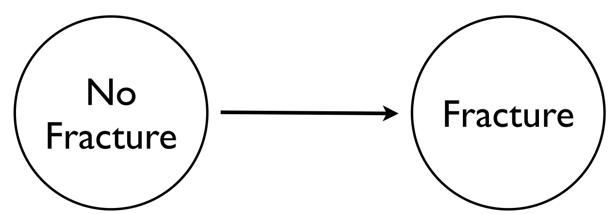
- 5,995 men over 65
- Given baseline DEXA to determine BMD
- Follow for the onset of fractures

Two Questions

- Does BMD predict the risk of fractures?
- Does BMD predict one type of fracture better than another?

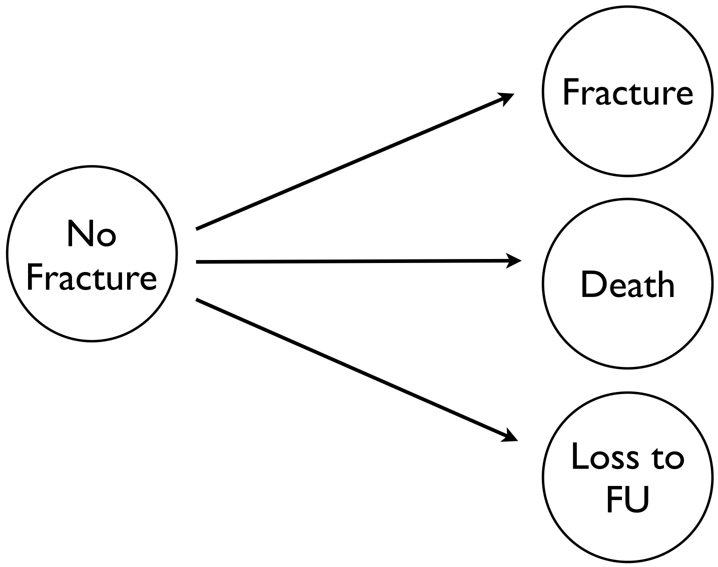
Take on first question, can apply that strategy to second

Survival Analysis



The data we wish we'd observed

Real Data



Survival Framework

- Two states (no fracture v. fractured)
- Everyone starts with no fracture
- No repeat fractures
- *Binary* paradigm
- Amenable to survival analysis

Actual Data

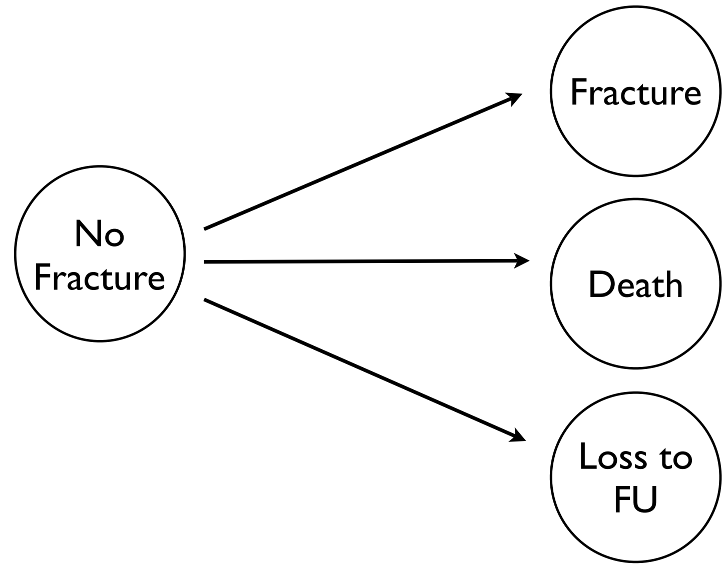
- Everyone starts with no fracture
- Many states (death, fracture, LFU)
- Any event precludes a fracture
- *Multistate* paradigm
- Survival analysis doesn't handle multiple states

Extend Our Framework

Competing Risks

- Identify all the possible events
  are they of interest, artifact or inherent
- Consider their meaning in the analysis:
  eliminate v. accommodate
- This guides approach to analysis

Real Data



Events

- Fracture
- Death
- Loss to Follow-up

Types of Events

- Of interest: an event which is directly under study. Example: fracture.
- Inherent: not under study but a part of the broader biological process. Example: death.
- Artifact: not under study. Censored by external process. Example loss to FU

Inherent v. Artifact

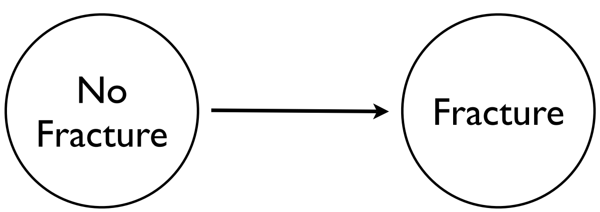
- Possible to alter study to eliminate death?
  No! Then, it is inherent.
- Possible to alter study to eliminate LFU?
  Yes, at least in theory. It is an artifact.

Difference guides goals of analysis.

Analysis Objective

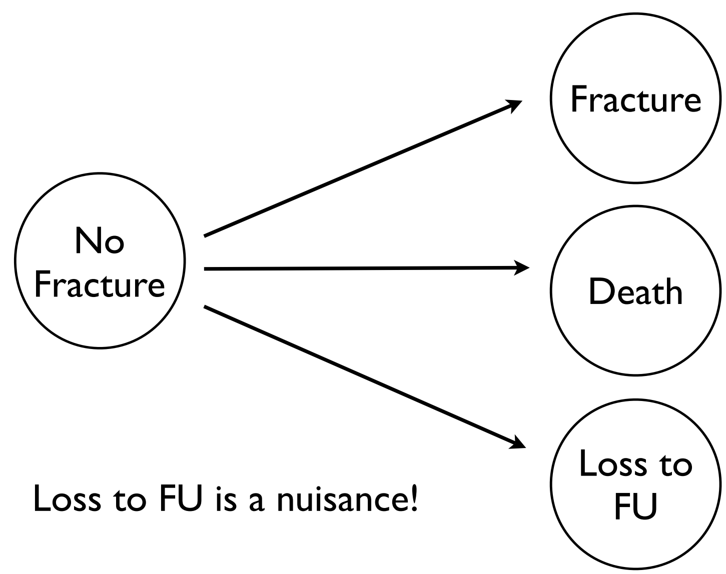
- Eliminate:
  What if event could be prevented?
- Accommodate:
  Allows for the competing event

Unrealistic



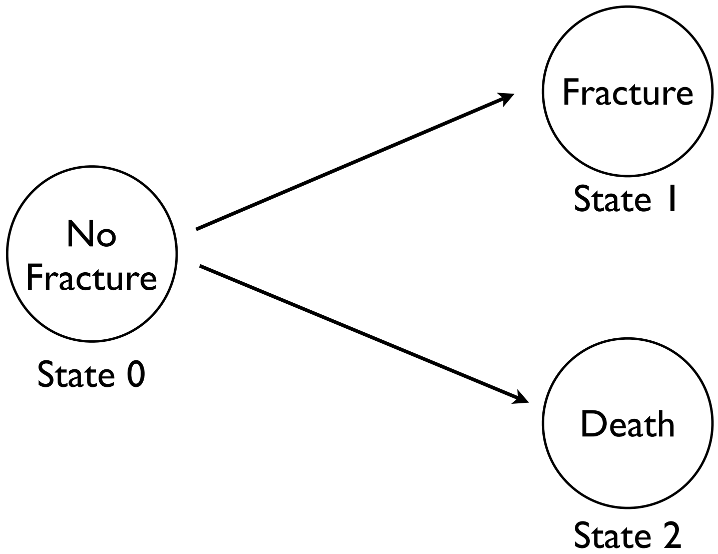
How can we eliminate death?
Requires speculation!

Observed Data



Loss to FU is a nuisance!

Realistic Data



Censoring/LFU

- Censored survival data
  alive v. dead or censored
- Censoring is competing risk
- Goal: eliminate from the analysis
- Assumption: independent censoring

Independence

- Censoring: risk death/fracture not higher in censored subjects
- Standard survival analysis depends on this assumption
- Can't verify this assumption
- If dependent, detailed and unverifiable assumptions are required

Analysis

Survival Summaries

- <u>Incidence:</u> hazard rate
  rate of development of fracture
  model: Cox proportional hazards function
- <u>Prevalence:</u> survivor function
  proportion without fracture over time
  estimated by Kaplan-Meier

Attuned to a binary framework!

Analyses

- Exploratory: Something like a Kaplan-Meier
- Modeling: Something like a Cox model

Hazards

- In survival analysis, hazard, $\lambda(t)$, is rate of event in period $[t,t+h)$
- Rate of moving between states at time t
- Estimated using Nelson-Aalen estimator
- Modeling using a Cox model
- Needs extension to competing risks

Cause-Specific Hazards

- Hazards for competing risk data
- One for each event (e.g., fracture)
- Rate of fracture among those alive and unfractured at time t
- Estimated by Nelson-Aalen estimator

Nelson-Aalen Estimator

- Estimates cumulative hazard
- Sum over time of
  - number of events at t
  - divided by "risk set at t"
- Risk set at t : uncensored, alive and unfractured
- "Censors" both death and loss to follow-up

Death v. Loss to Follow-Up

- We are not treating death and LFU the same
- LFU: trying to eliminate as cause,
  assume censoring is independent
- Death: trying to accommodate as cause,
  dead people not at risk for fracture
  conditioning on death
  no independence assumption

Cox Models

- Effect of BMD on risk of fracture
- Cox model for *cause-specific* risk of fracture
- Model fit:
  - Censor subjects at time of death
  - Fit Cox model

Cox Model for Fracture

```
Cox regression -- Breslow method for ties

No. of subjects =         5993                     Number of obs   =      5993
No. of failures =          531
Time at risk    =     11134085
                                                   LR chi2(2)      =    200.96
Log likelihood  =   -4402.4215                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         bmd |   .4735806   .0319467   -11.08   0.000     .4149289    .5405229
      giage1 |   1.047036   .0075624     6.36   0.000     1.032318    1.061964
------------------------------------------------------------------------------
```

BMD in 0.20 g/cm^2 units

Age in years

Cox Model for Death

```
Cox regression -- Breslow method for ties

No. of subjects =         5993                     Number of obs   =      5993
No. of failures =          657
Time at risk    =     11134085
                                                   LR chi2(2)      =    293.75
Log likelihood  =    -5392.0439                    Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         bmd |   .9689049   .0554886    -0.55   0.581     .8660308    1.083999
      giage1 |   1.114373   .0070559    17.10   0.000     1.100629    1.128288
------------------------------------------------------------------------------
```

BMD in 0.20 g/cm^2 units

Age in years

BMD on Fracture Type

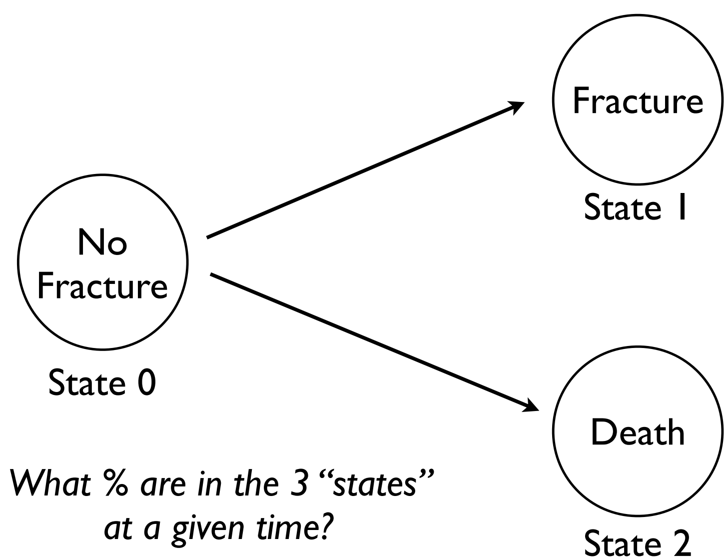
	HR*	95% Conf Int	
Hip	0.20	0.14	0.27
Wrist	0.39	0.26	0.60
Lumbar	0.36	0.26	0.49
Rib	0.53	0.40	0.70
Ankle	0.61	0.44	0.85
Other	0.66	0.55	0.80

*Adjusted for age

Survival v. Competing Risks

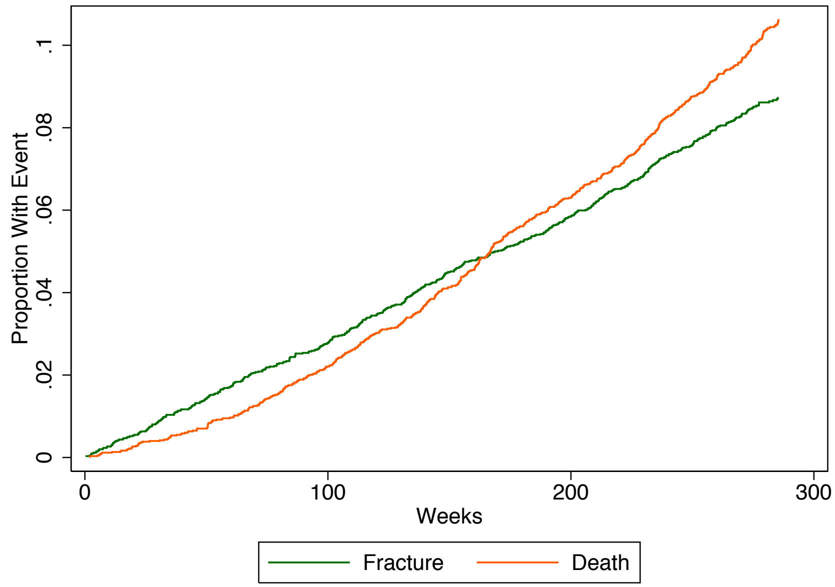
- Censoring other causes works for
  - Cox model on cause-specific hazards
  - logrank test for cause-specific hazards
- It <u>does not</u> work for Kaplan-Meier curves
- Concept of "survival" curve needs to be extended
- Extended version: *cumulative incidence function*

Cumulative Incidence



What % are in the 3 "states" at a given time?

Cumulative Incidence



Event Curves

- KM curve: proportion alive over time
- Cumulative incidence: proportion in a given state with time
- Curves for death, fracture and alive without fracture

Calculating Cumulative Incidence

$F_2(t)$ = pr(in state 2 at time t)

Text

Pr(in state 2 at t_{k-1})

Pr(in state 0 at t_{k-1})

$$F_2(t_k) = F_2(t_{k-1}) + F_0(t_{k-1}) * \lambda_{02}(t_k)$$

Pr(in state 2 at t_k)

rate of moving from 0 to 2 at t_k

Calculating Cumulative Incidence

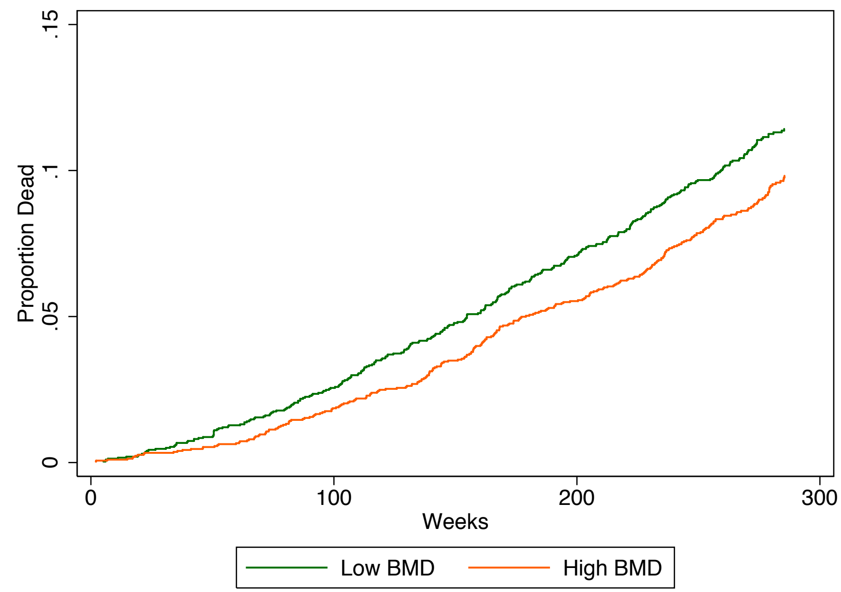
$F_0(t)$ = pr(in state 0 at time t)

Equal to Kaplan-Meier if death+fracture pooled

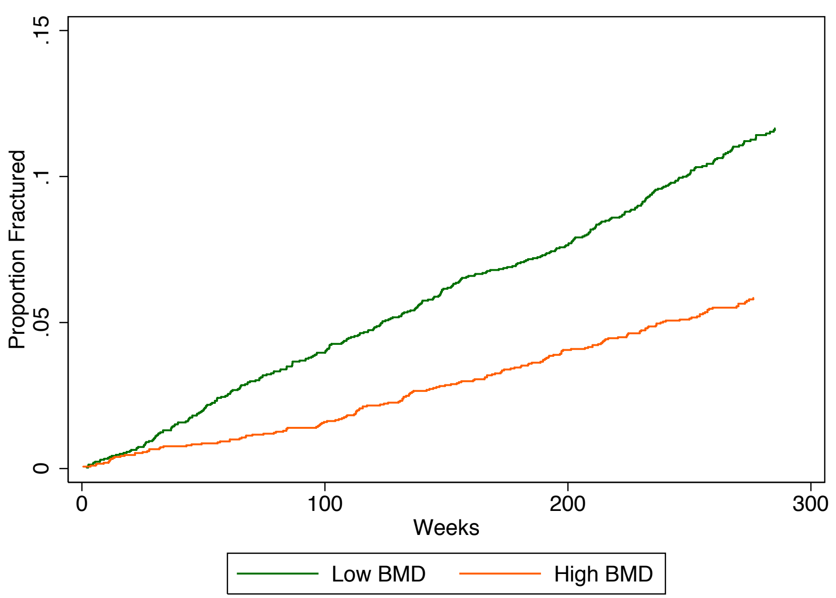
Exploring BMD Effects

- Suppose we make BMD into a binary variable
- Above the median (about 0.95 g/cm^2): high
- Below the median: low

Proportion Dead



Proportion Fractured



Indirect Effects

- Suppose fracture rates unaffected by BMD
- But death rates much higher in low BMD
- Cumulative incidence of fracture will be lower in the low BMD group
- *Why? Because more low BMD subjects will have died first.*

BMD would have indirect effect on fracture incidence

Software

- SAS does not have built in CI functions
- Can obtain macro from

  http://www.biostat.mcw.edu/software/SoftMenu.html

Summary

- Competing risks extends survival data
- Hazard extension: cause-specific hazard
  - easily modeled in standard software
- KM extension: cumulative incidence fn
  - requires special software