Multiple Primary - Standardized Incidence/Mortality Ratios (MP-SIR/SMR)

Sara Schonfeld and Rochelle Curtis

Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics

NCI Analytic Tools SEERies

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Objectives

Introduce methods for conducting analyses within SEER*Stat MP-SIR/SMR

- Multiple primary malignancies (SIR)
- Standardized mortality ratios (SMR)

By the end of the webinar:

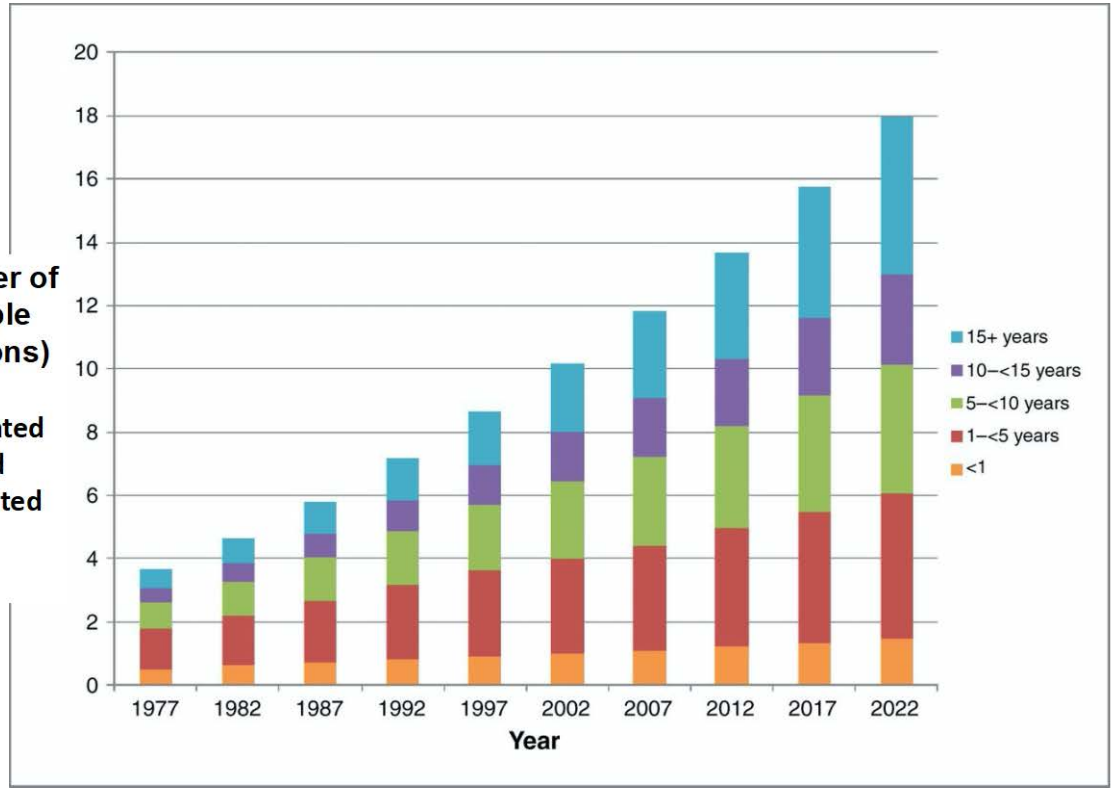
- Define SIR and SMR
- Generate SIRs and SMRs in SEER*Stat
- Interpret SIRs and SMRs generated in SEER*Stat
- Awareness of challenges and common pitfalls

Outline

1. *Background: Cancer Survivors*
2. *Statistical Measures*
3. *SEER*Stat MP-SIR/SMR*
4. *Study Examples*
5. *Key Limitations and Strengths*

Background

Growing Population of Cancer Survivors

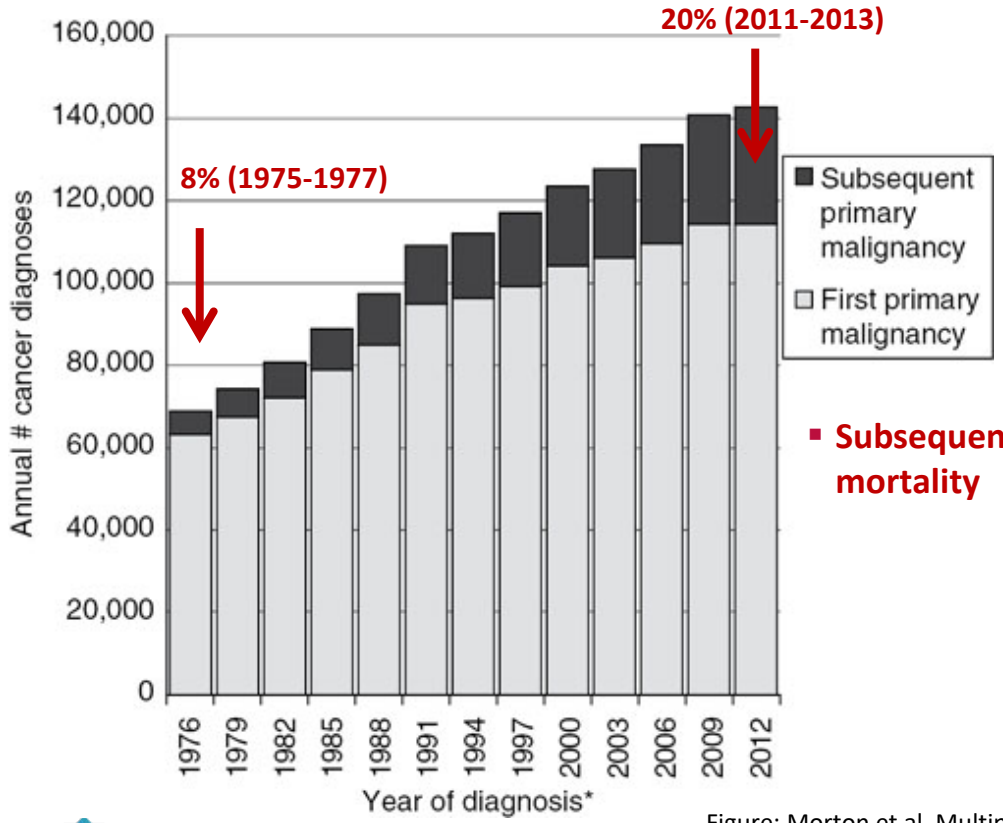


- Improved survival
- Aging population

de Moor JS et al. *Cancer Epidemiol Biomarkers Prev* 2013

Rising Number of Subsequent Malignancies

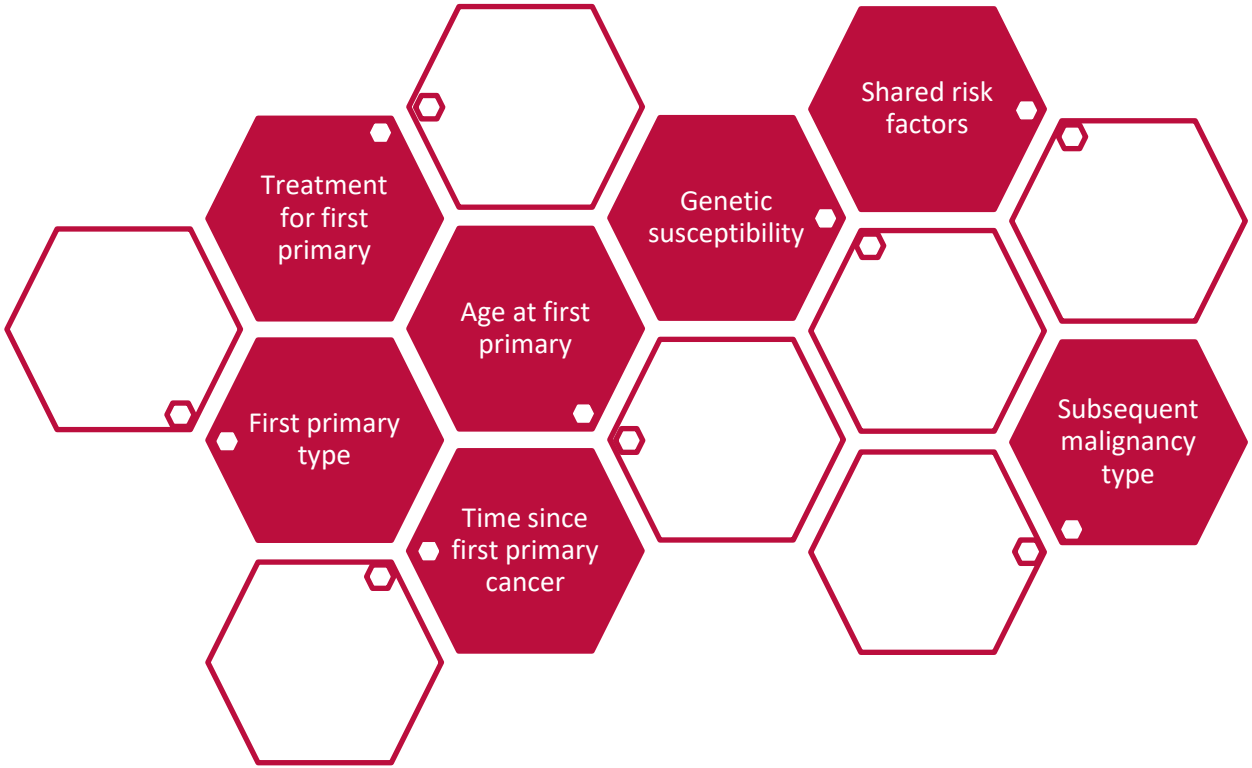
SEER 9: (1975-2013)



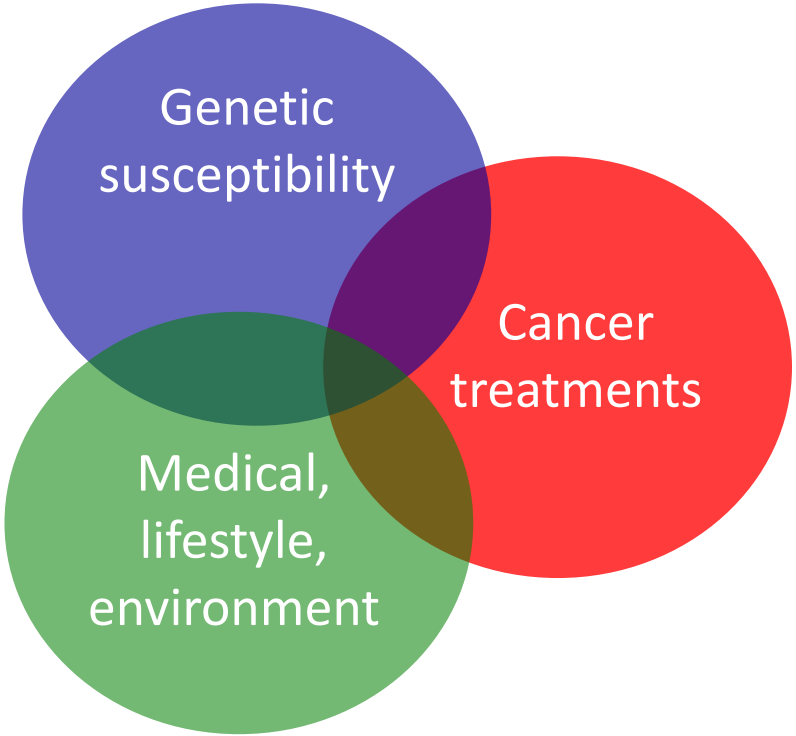
- **Subsequent malignancies → morbidity, mortality**

Figure: Morton et al. Multiple Primary Cancers (chapter 60) in Cancer Epidemiology and Prevention 2018

Variation in subsequent cancer risks



SEER*Stat MP-SIR/SMR: multiple primaries and mortality among cancer survivors



- Describe patterns of multiple primary cancers and mortality among survivors
  - Identify high-risk subsets
  - Quantify burden
- Etiologic clues - Hypothesis generating
  - Treatment
  - Age
  - Race
  - Latency
  - Reciprocal risks

Figure: Morton & Chanock. *Nat Med* 2011

Sample questions we seek to answer with MP-SIR/SMR

MP-SIR

Are cancer survivors at increased risk for developing new primary* malignancies compared with the general population?

- How do risks vary by patient-, tumor- and treatment- characteristics?

MP-SMR

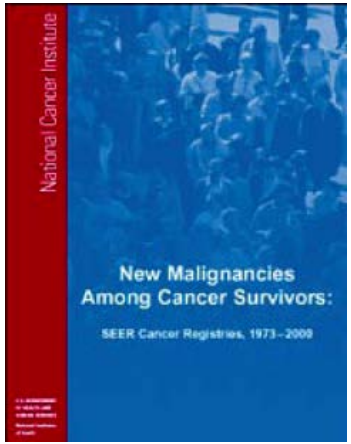
Are cancer survivors at increased risk of death (overall excluding deaths due to initial cancer, cause-specific)?

*not recurrence or metastasis

New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000 (Published 2006)

9 SEER cancer registries

- Population-based (10% of U.S.)
- High quality
- 2 million cancer survivors
- Nearly 30-year period (1973-2000)
- 185,000 subsequent cancers



Systematic, comprehensive evaluation subsequent cancer risk

- 50 adult and 18 childhood cancer types, including data on less common cancers
- Over 350 data tables risk by:
  - Time since initial diagnosis
  - Sex
  - Age
  - Treatment (RT vs no RT)
  - Cell type
- **Key resource for methodologic considerations**

Curtis et al. 2006 https://seer.cancer.gov/archive/publications/mpmono/index.html

Statistical Measures:

SIR, SMR, EAR

Standardized incidence/mortality ratios (SIR/SMR): Concept

- Indirect standardization for age, calendar-year, race, sex, and other factors
  - ➢ How many cases would I expect in my population if my population had the same rate of disease as some standard population?
- SEER*Stat
  - SIR: Compare to general population (SEER data)
  - SMR: Compare to US mortality data

SIR/SMR: Source of observed and expected cases

- Study population* followed for defined period of follow-up
- Person-years of follow-up can be stratified by age, sex, calendar year, race and other factors
  - Observed cases of subsequent cancers or deaths within strata
  - Expected cases of subsequent cancers or deaths
    - Stratum-specific SEER cancer incidence rates or US mortality rates multiplied by stratum-specific person-years
- Stratum-specific observed and expected values summed to generate totals

*Selected from SEER when using MP-SIR/SMR

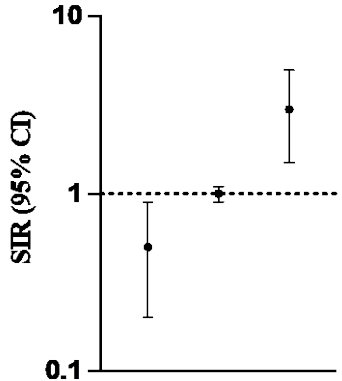
Observed and Expected: Relative and absolute measures

Standardized incidence/mortality ratio

- Ratio: Observed/Expected
- Measure of relative risk
- Measure the strength of association

Excess absolute risk (EAR)

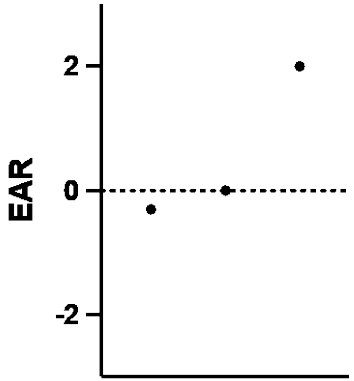
- Difference: (Observed-Expected)/PYR
- Often expressed per 10,000 PYR
- Measure of absolute risk, burden



Risk in study population > referent population

Risk in study population = referent population

Risk in study population < referent population



Interpretation

- Consider magnitude and not only statistical significance
- Can have high SIR and low EAR when baseline risk is low (rare event)
- Moderate, low SIR but high EAR possible when baseline is high

SEER*Stat MP-SIR/SMR

SEER Solid Tumor and Hematologic Malignancy Rules

Purpose: Instructions for registrars

- Rules for differentiating between new primaries vs metastasis or recurrence
- Number of primaries to abstract and histology
- General and site-specific rules for selected sites

Impact for MP-SIR users

- Important to understand coding rules for outcome sites of interest
- Understand changes over time
  - Cases coded according to rules at time of diagnosis
  - May need to review multiple versions depending on time frame of your study

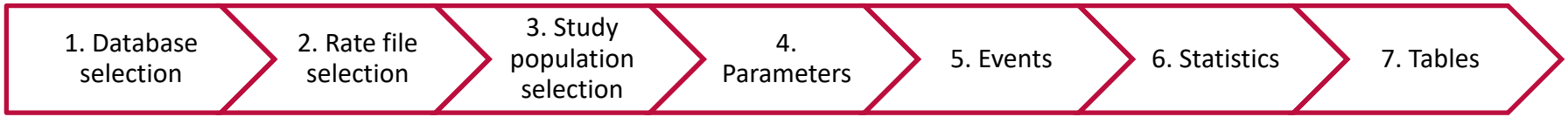
Resources

- https://seer.cancer.gov/tools/solidtumor/
- https://seer.cancer.gov/tools/heme/

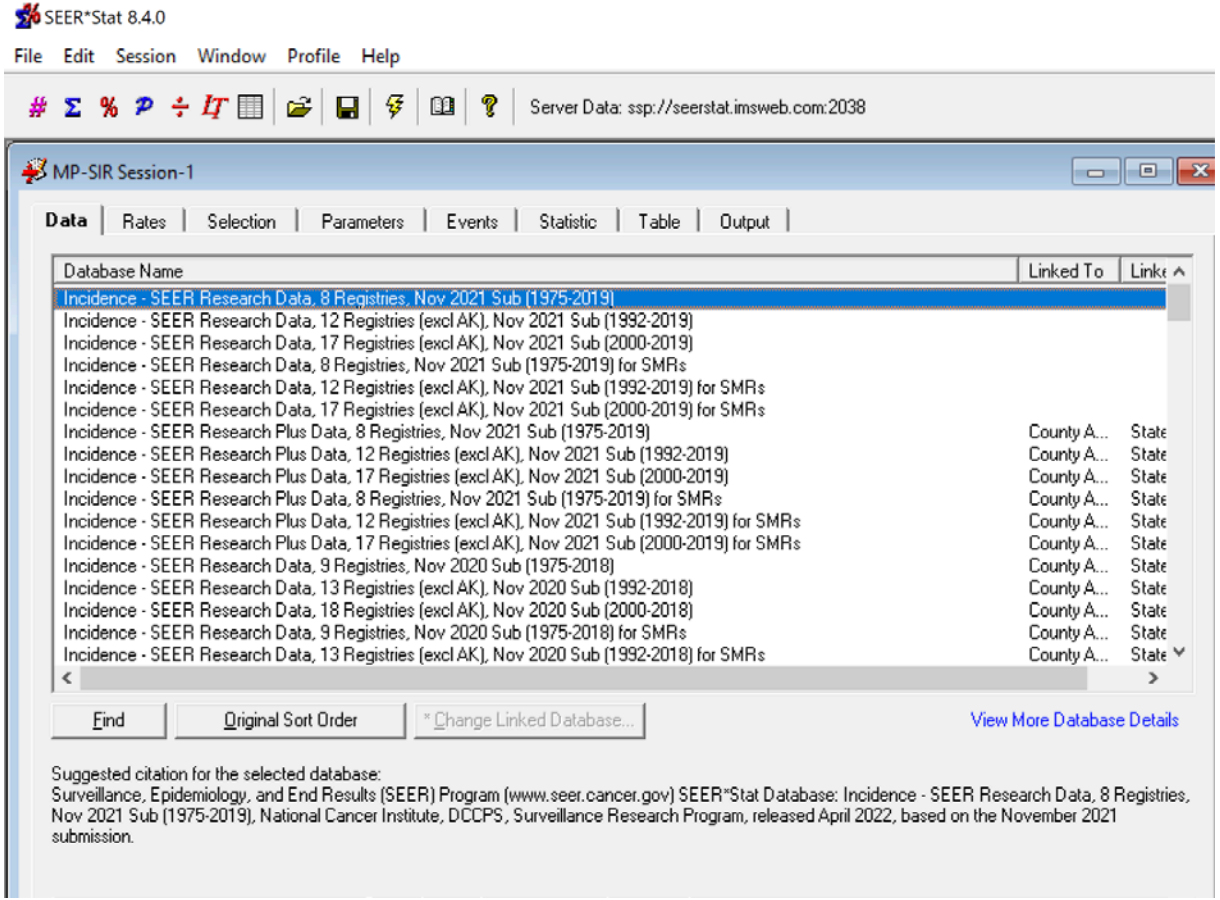
Steps for Running MP-SIR

Our objective: walk through the considerations for setting up analysis

Steve Scoppa from IMS will give live tutorial next



1. Database selection



1. Database selection

Overview of databases available for MP-SIR/SMR

Characteristics	Incidence – SEER 8 Previously SEER 9	Incidence - SEER 12 (exc. AK) Previously SEER 13 (exc. AK)	Incidence - SEER 17 (exc. AK) Previously SEER 18 (exc. AK)
Registries *Change in latest submission – Detroit no longer included	San Francisco-Oakland SMSA Connecticut Hawaii Iowa New Mexico Seattle (Puget Sound) Utah Atlanta (Metropolitan)	**SEER 8** plus San Jose-Monterey Los Angeles Rural Georgia Alaska Native Tumor Registry (AK)*	**SEER 12** plus California excluding SF/SJM/LA Kentucky Louisiana New Jersey Greater Georgia
Proportion of US population covered	8.3%	12.2%	26.5%
Calendar years of diagnosis	1975-2019	1992-2019	2000-2019
Total number of tumors	4,765,822	5,021,215	8,712,246

*Excluded from MP-SIR/SMR

https://seer.cancer.gov/registries/data.html

1. Database selection

Limit to one database

- Different registries – different populations
- Different length follow-up
- Databases not intended to be combined – can distort results

Remember differences across the databases

SEER 8 : 1975- 2019

SEER 12 : 1992- 2019

SEER 17 : 2000- 2019

Trade-offs

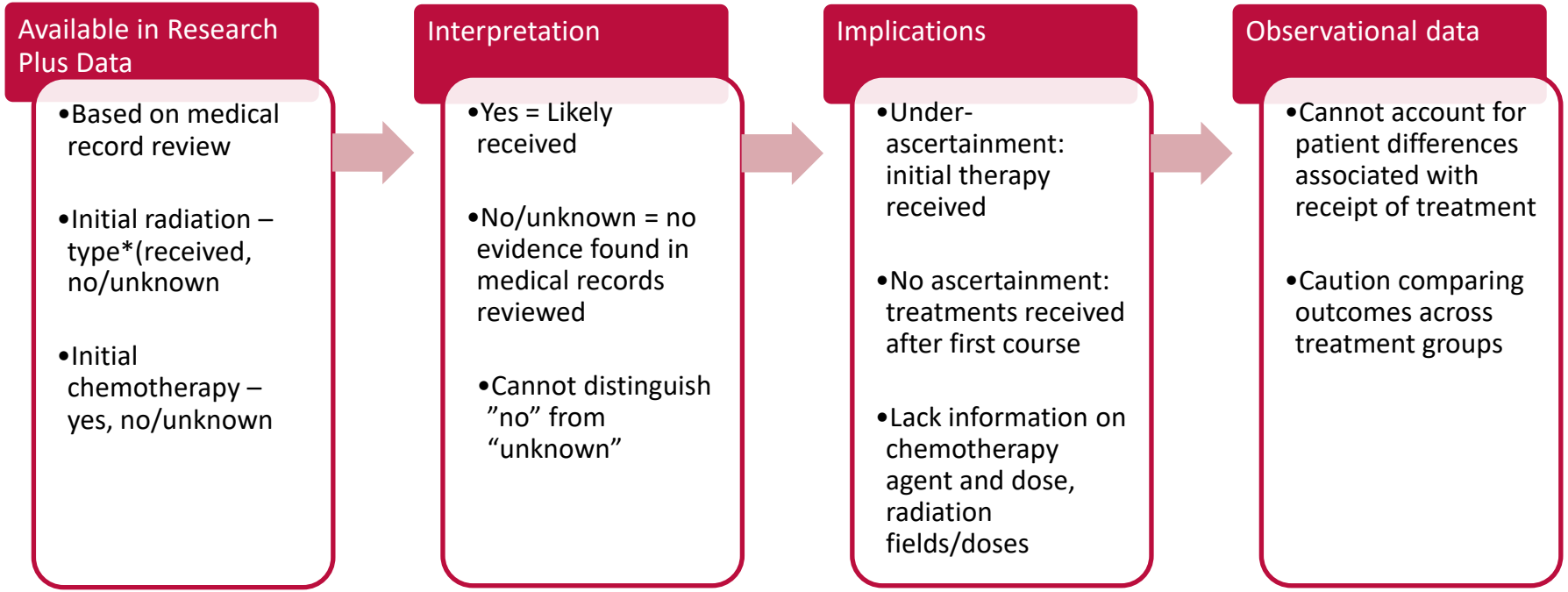
- Longer follow-up data vs larger set of registries
- Variation in variable availability
  - Example: Expanded versus more limited race variables
- Changes in classification over time
  - Example: WHO Classification of Lymphoid Neoplasms 2000
- Database selection depends on key research questions

Additional notes

- SIRs – select “incidence files for SIRs”
- SMRs – select “incidence files for SMRs”
- Research vs Research Plus
    - Research Plus includes additional variables such as:
        - Geography
        - Months in dates
        - Other demographic fields
        - Treatment information

See https://seer.cancer.gov/data/product-comparison.html

Registries ascertain radiation and chemotherapy given for first course of therapy



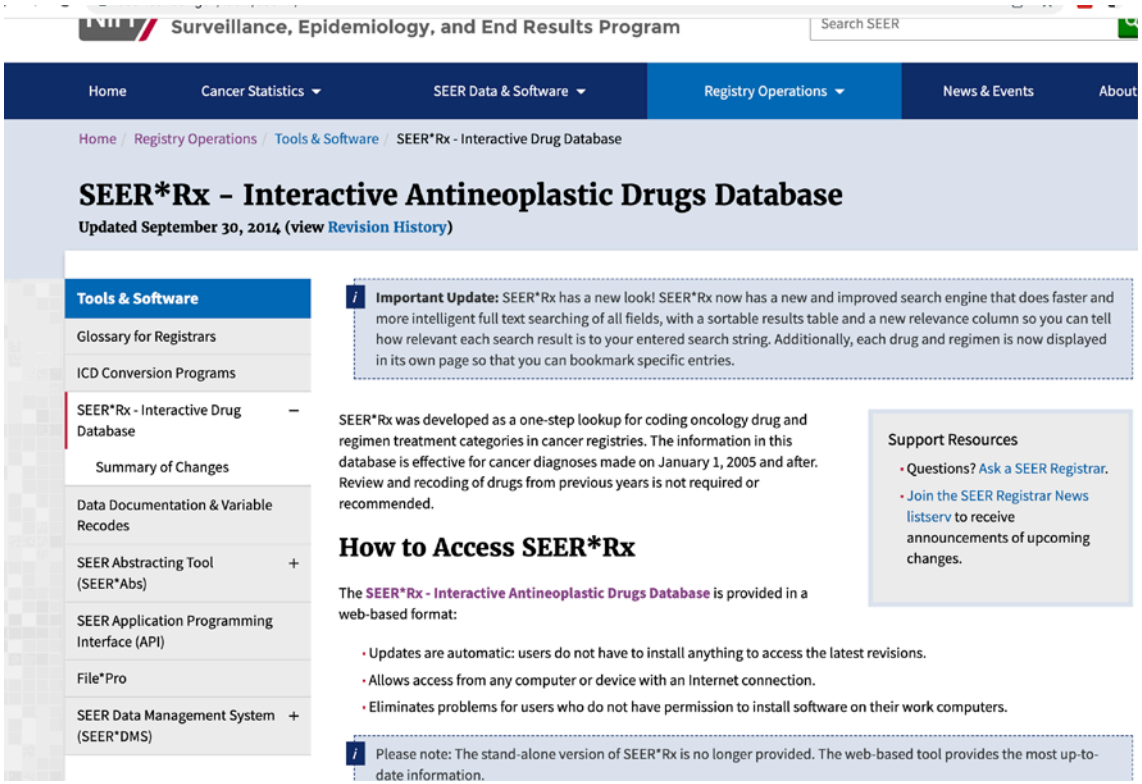
* Broad categories (none/unknown, beam, radioisotopes, radioactive implants…)
https://seer.cancer.gov/data-software/documentation/seerstat/nov2020/treatment-limitations-nov2020.html

SEER*Rx

Understand what is included in “chemotherapy” recode (since 2005)

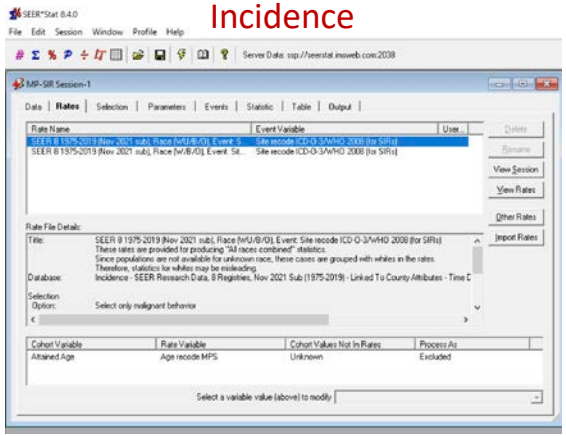
Understand changes (since 2005)

Access at: https://seer.cancer.gov/tools/seerrx/

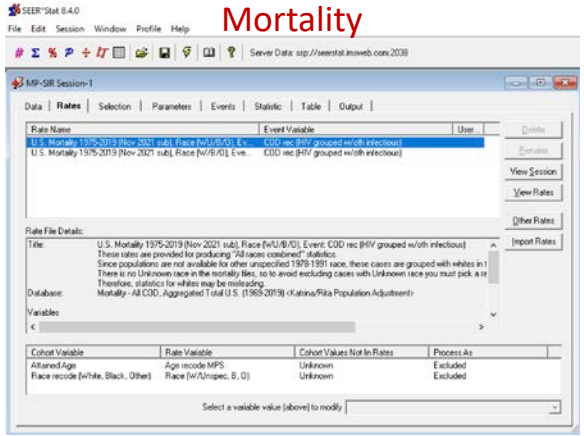


2. Rate file Selection

Incidence



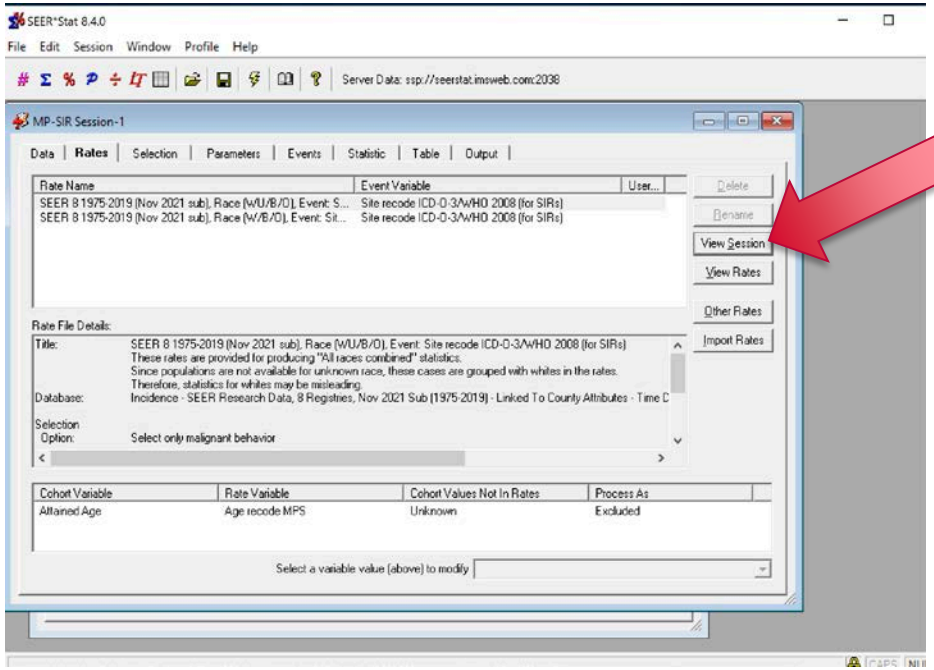
Mortality

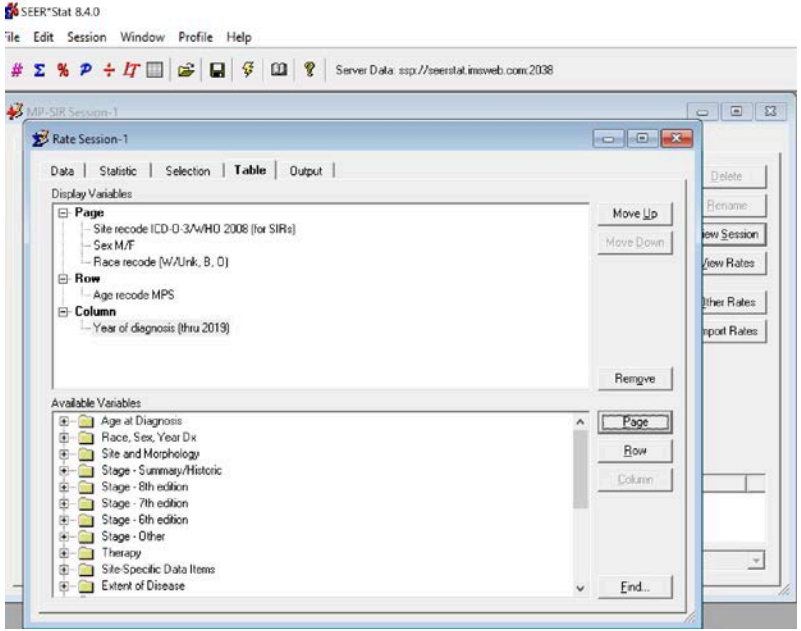


Standard rate files		
Incidence (SIR)		**Mortality (SMR)**
Site recode ICD-O-3/WHO 2008 (for SIRs) https://seer.cancer.gov/siterecode/ *Rate file should come same database selected in Step 1*		Mortality: Cause of death recode https://seer.cancer.gov/codrecode/1969_d03012018/index.html
Race (WU/B/O): Unknown race included with white Race (W/B/O): Use for analyses where you plan to stratify by race		

2. Rate file Selection

Take time to know the rate file





2. Rate file Selection

Outcome classification: Defined in rate file

Rate file: stratify by population characteristics by which you plan to calculate SIRs/SMRs

- Example: Race, sex, calendar year, age

2. Rate file Selection

Create customized rates within SEER rate session, export to MP-SIR

Events customized by combinations of site, histology, behavior, etc…

- Example: Lung cancer incidence by histologic type
- Example: Thyroid cancer incidence by stage at diagnosis
- Example: Soft tissue sarcoma defined by histology and not only topography

Events based on other SEER recodes such as:

- AYA Site Recode
- International Classification of Childhood Cancer
- Lymphoma Subtype Recode

Alt. grouping population characteristics

2. Rate file Selection

Create customized rates within SEER rate session, export to MP-SIR

Reminder:
Use same database for rate file and study population

Observed and expected cases:

- Same source population*
- Same outcome classification
- Same stratification by population characteristics

Events customized by combinations of site, histology, behavior, etc…

- Example: Lung cancer incidence by histologic type
- Example: Thyroid cancer incidence by stage at diagnosis
- Example: Soft tissue sarcoma defined by histology and not only topography

Events based on other SEER recodes such as:

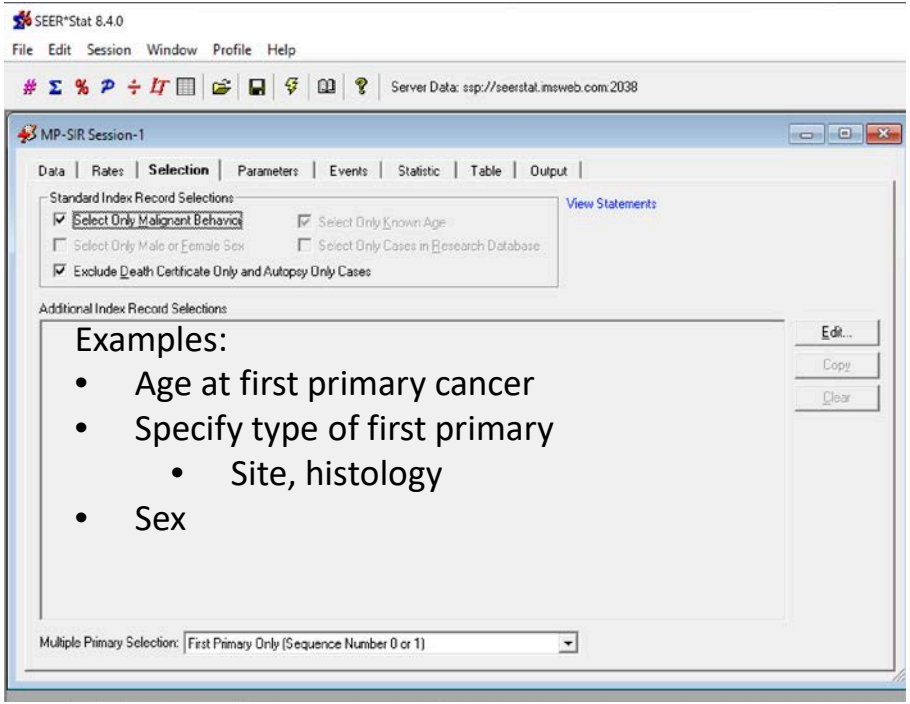
- AYA Site Recode
- International Classification of Childhood Cancer
- Lymphoma Subtype Recode

Alt. grouping population characteristics

*Applies only to SIR

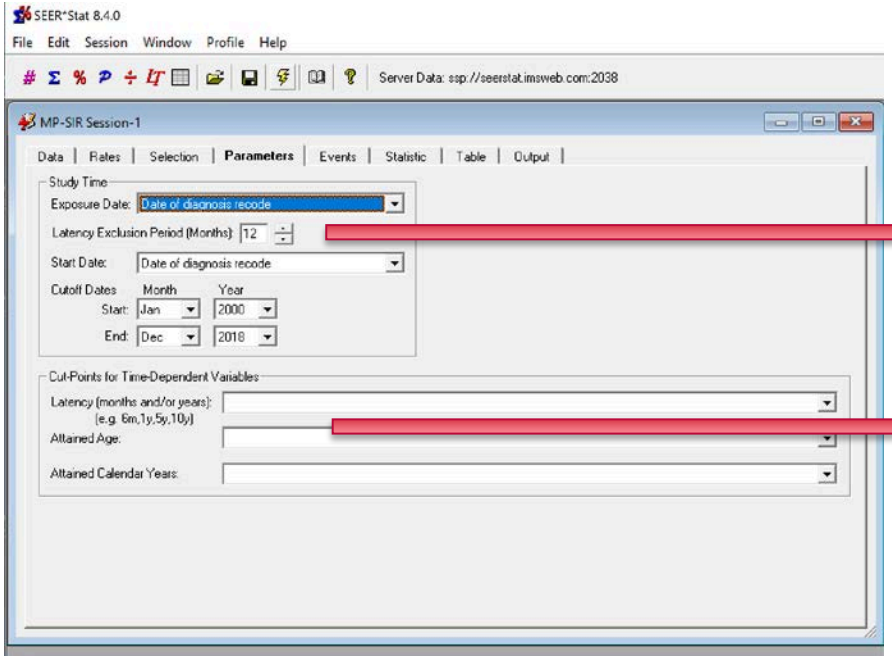
3. Study population selection

Define study population (first primary cancer group)



- Select only malignant behavior (uncheck to include patients with in situ)
- Exclude death certificate only or autopsy cases
- Multiple Primary Selection: First primary only (sequence 0 or 1)
  - Selecting a population of individuals at the time of their <u>first</u> known malignancy when resident of SEER registry catchment area
    - Reason: Cannot account for treatments prior to the baseline cancer

4. Parameters



- Latency exclusion (default 2 months)
  - Reasons for different latency exclusions
    - Minimize surveillance bias
    - Minimum latency for treatment exposure (e.g., radiotherapy and subsequent neoplasms)
- Risk estimates by latency, attained age, attained calendar year

Multiple vs Single Outcome Analysis (SIR only)

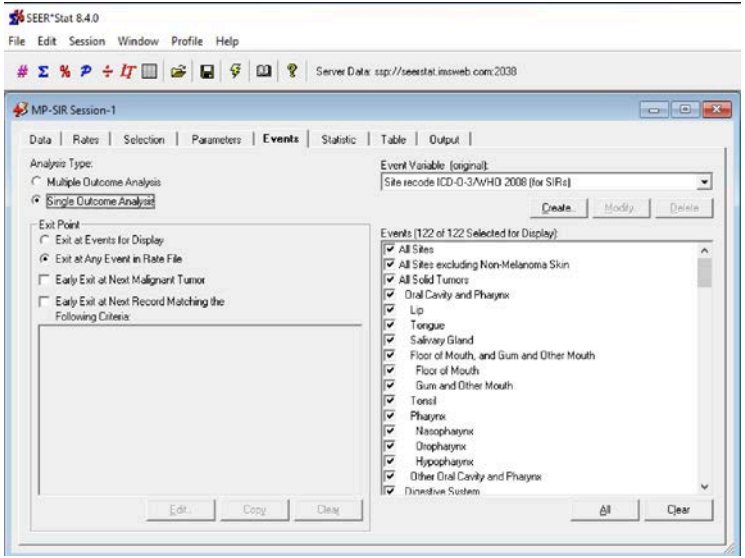
Multiple Outcome (default)

- Follow until earliest of end of study, death, date of last vital status
- Events include all subsequent (2nd, 3rd, …) primary cancers
- More complete estimate of risk among long-term survivors
  - Comparable to SEER incidence rates

Single Outcome

- Follow-up censored at second primary cancer diagnosis
- Count 2nd primary cancers only

➢Preferable for evaluating risk of treatment related second cancers



5. Events

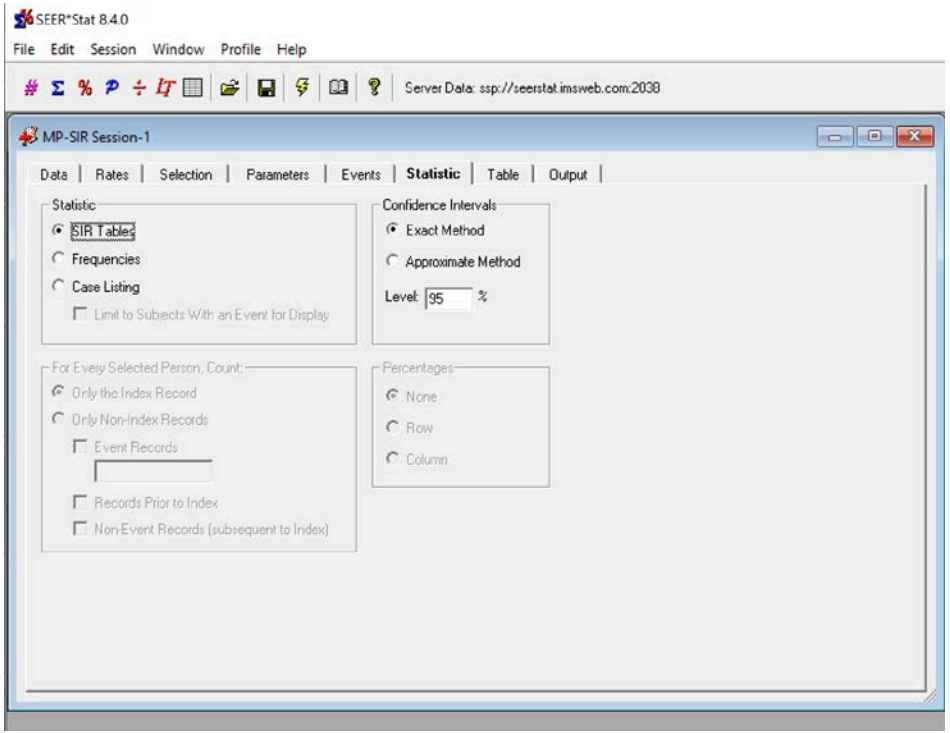
Example: Subsequent cancer incidence after first primary thyroid cancer

Single outcome:
Count second colon only

Multiple outcome: Count all subsequent cancers including colon, breast

6. Statistics

- SIR Tables
- Frequencies
- Case Listing



More to come during live tutorial…

Study examples

Risk of second primary papillary thyroid cancer among adult cancer survivors in the United States, 2000-2015

Rationale

- Known: Elevated risk of subsequent thyroid cancer after spectrum of first primary malignancies
- Factors contributing to risk among adult cancer survivors unclear

Objective

- Quantify risk of second papillary thyroid cancer (PTC) among adult cancer survivors by:
  - Stage of second PTC
  - Time since first primary (latency)
  - Treatment for first primary cancer

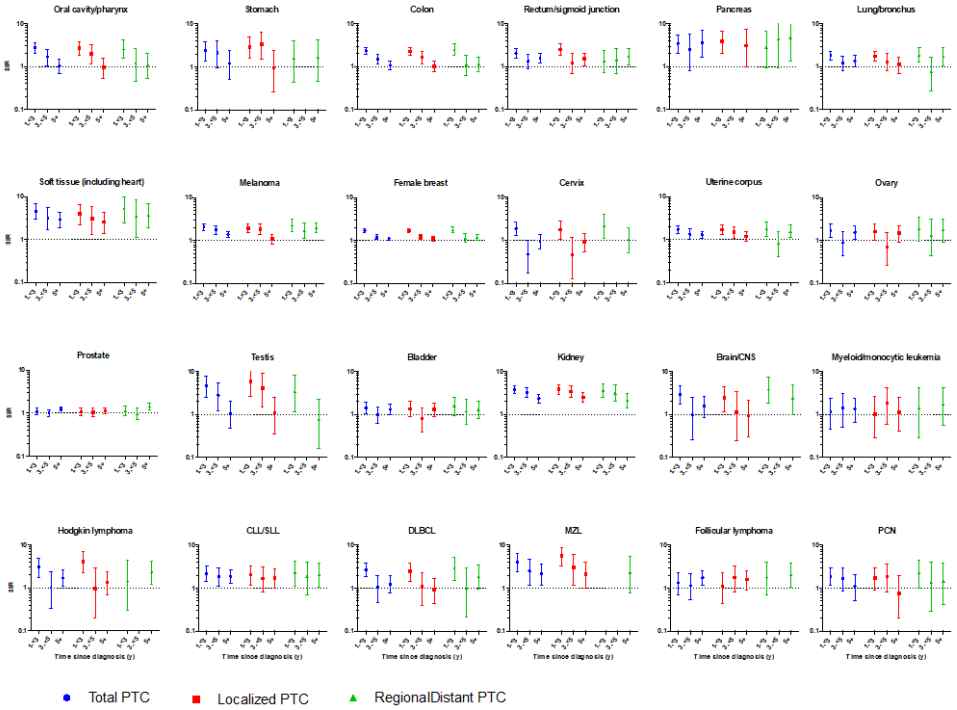
Population

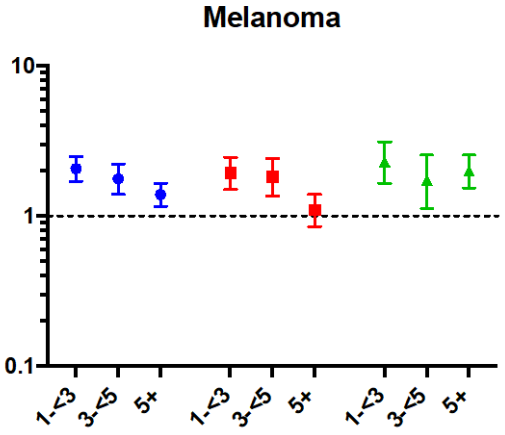
- 3,175,216 ≥ 1-year adult survivors of non-thyroid malignancies
- First primary diagnosis: 2000-2014, followed through 2015 (SEER 18)
- Ages 20-84 at first primary diagnosis

Statistical analyses

- SIRs (second cancer)
- Poisson regression – tests of trends, heterogeneity (not in SEER*stat)

SIRs by latency and stage of PTC

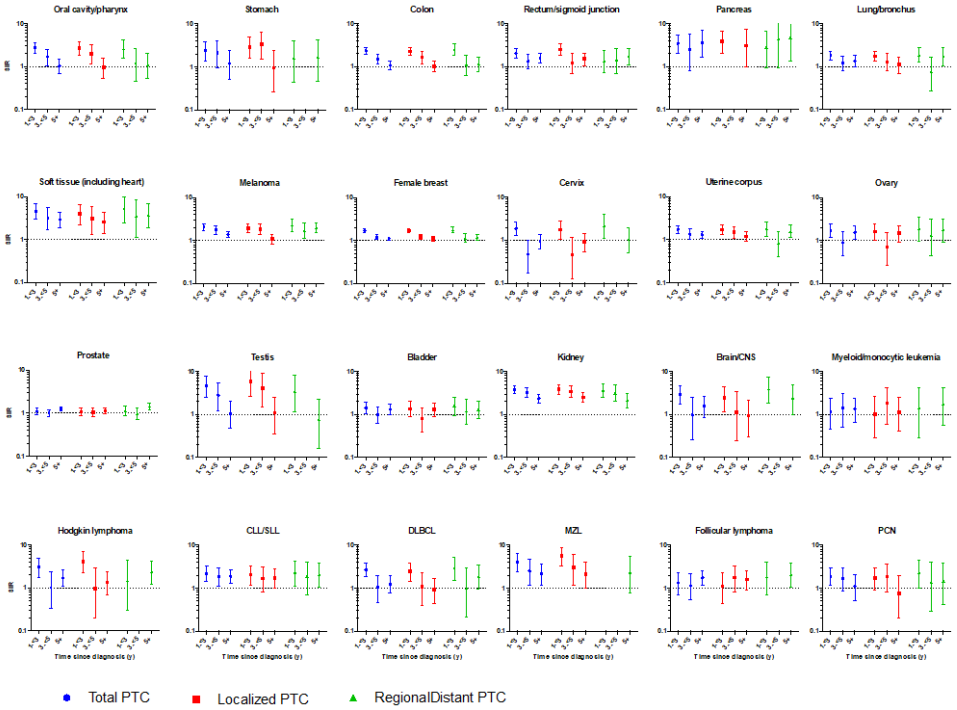




Total PTC
Localized PTC
Regional/distant PTC

Schonfeld et al. Cancer Epidemiology 2020

SIRs by latency and stage of PTC



- SIRs elevated following broad range first primary cancers
- SIRs tend to decrease with time since first primary diagnosis
- SIRs generally similar for localized and regional/distant PTC
- No clear patterns with treatment (not shown)

Schonfeld et al. Cancer Epidemiology 2020

Cause-specific mortality after classical HL (cHL)

Rationale

- Changes in treatment over time
  - ABVD replaced MOPP
  - Decreasing use radiotherapy
- Comprehensive assessment of mortality after cHL lacking

Objective

- Characterize stage- and cause-specific mortality risks after diagnosis of classical Hodgkin lymphoma (cHL) in current treatment era

Population

- 24,985 adults diagnosed with cHL
- Diagnosis: 2000-2015 (SEER 18)
- Follow-up through 2016
- Restricted to patients treated with chemotherapy

Statistical analyses

- SMRs and EARs for >40 different causes of death

Dores et al. JCO 2020

Leading causes of excess deaths after cHL

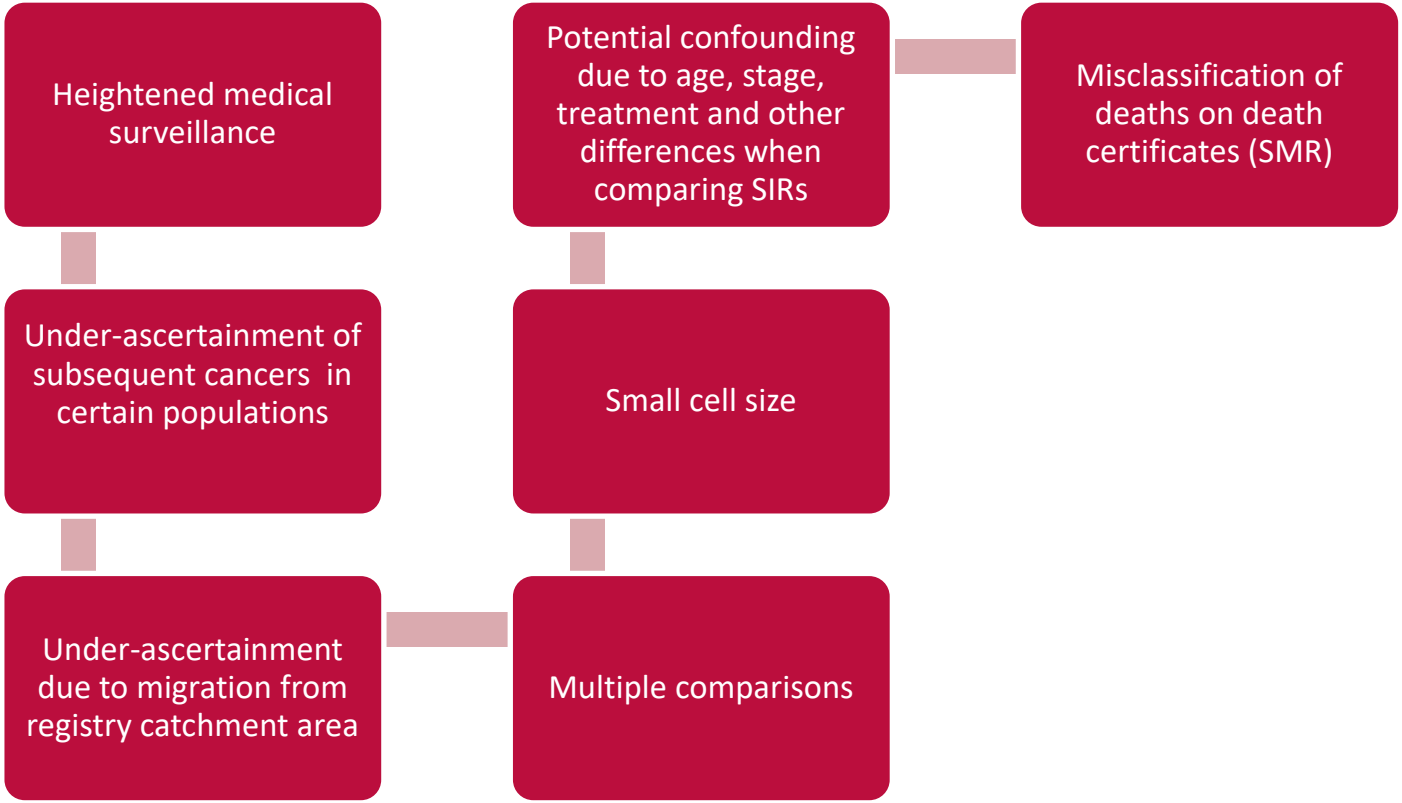
Cause of death	Stages I/II		Stages III/IV	
	SMR	EAR	SMR	EAR
All	3.3 (3.2-3.5)	103.1	6.0 (5.8-6.3)	310.3
All, excluding lymphoma	1.5 (1.4-1.6)	21.7	2.2 (2.0-2.4)	71.7
Heart disease	1.7 (1.5-2.0)	6.6	2.1 (1.8-2.5)	15.1
Interstitial lung disease	13.1 (9.2-17.9)	3.7	22.1 (16.6-28.8)	9.7
Infections	2.2 (1.6-2.8)	3.1	3.9 (3.1-4.9)	10.6
AEs due to medication/drug exposure	2.3 (1.7-3.2)	2.5	5.0 (3.7-6.7)	7.4

- Risk estimates increased with stage
- SMRs decrease with age
- EARs increase with age

Dores et al. JCO 2020

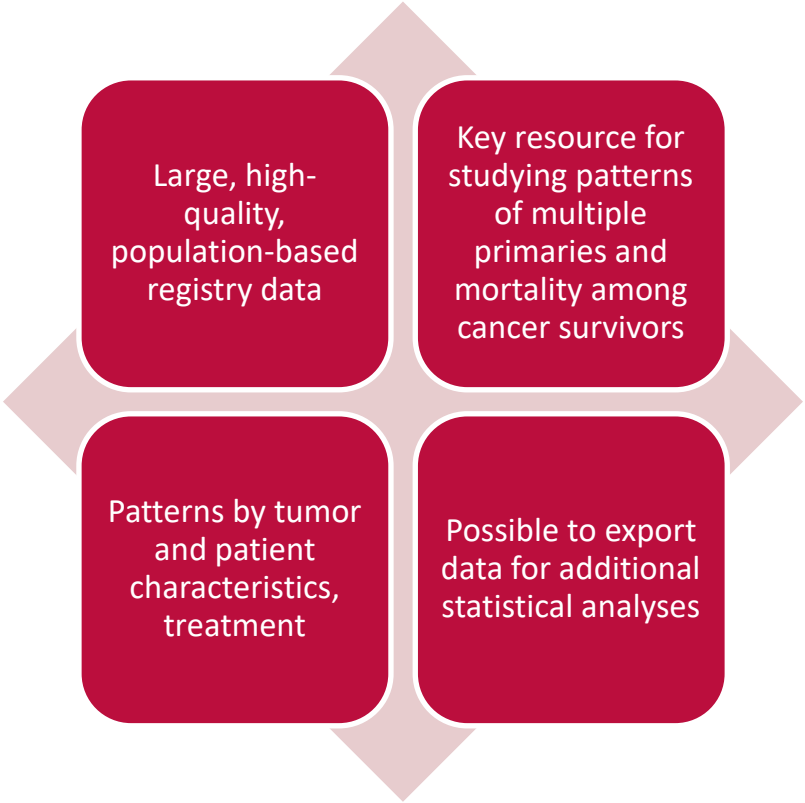
Summary of limitations and strengths

Be Mindful…

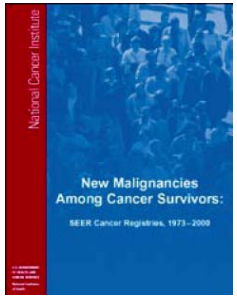


Curtis et al. 2006

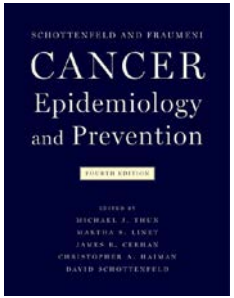
SEER MP-SIR has great strengths!



Resources



Curtis et al. 2006 https://seer.cancer.gov/archive/publications/mpmono/index.html



Chapter 60: Multiple Primary Cancers

SEER*stat Tutorials (https://seer.cancer.gov/seerstat/tutorials/advanced.html)

Migration issues for multiple primary analyses in SEER

Migration from SEER catchment area

- Under-ascertain subsequent malignancies among long-term survivors

Migration into SEER catchment area

- Previous malignancies ascertained outside of SEER catchment area (or prior to start of registry) not captured

Relocation between SEER registry catchment areas:

- Separate IDs in SEER (one per registry)
- Sequence numbers correct if both registries have the person's full cancer history.

Live Demonstration

Steve Scoppa

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