RC-1b
Gender, Age, and Age-at-Exposure Effects on Radiation Cancer Risks

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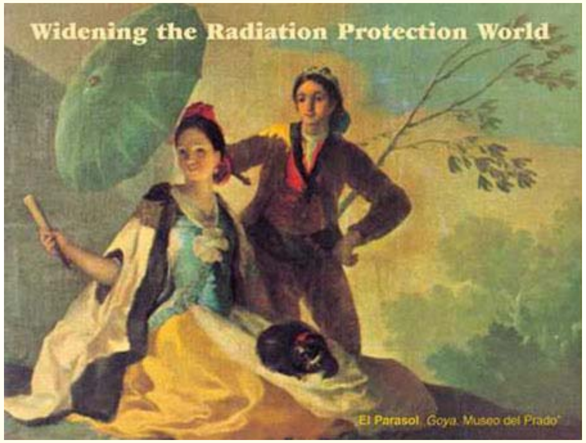


Refresher Course 1b

Gender, Age, and Age-at-Exposure Effects on Radiation Cancer Risks

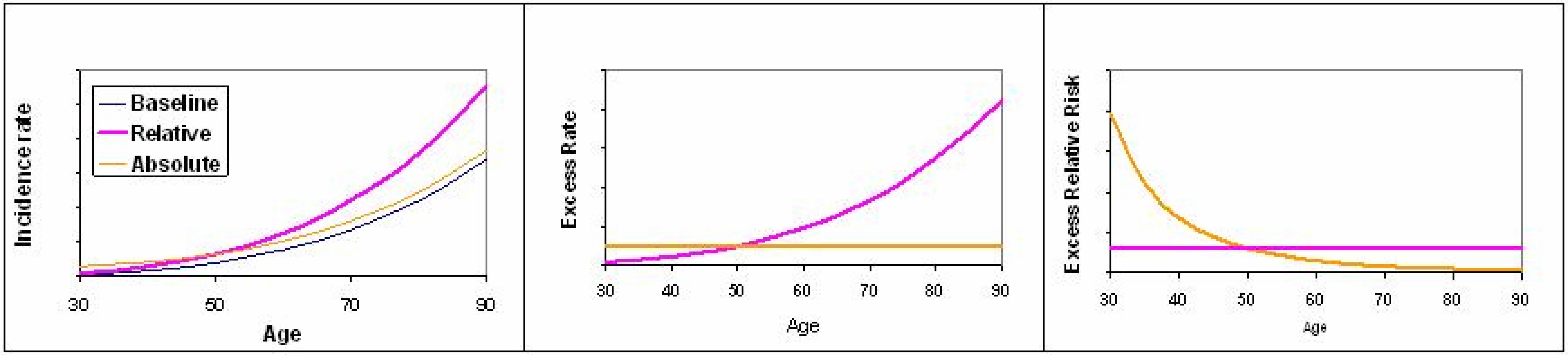
Dale L. Preston

Outline

1. **Issues**
   - Relative versus absolute risks
   - Describing (smoothing) risk patterns
     - ERR or EAR
     - A “simple” descriptive effect modification model
2. **Data**
   - Atomic bomb survivors
     - Solid cancer incidence 1958-94
     - Leukemia mortality 1950-2000
   - Mayak workers
     - Solid cancer and leukemia mortality 1948-1997
   - Pooled breast cancer cohorts
3. **Results**
   - All solid cancers
   - Selected cancer types
   - Leukemia
4. **Related Issues**
   - Time-since-Exposure versus attained age
   - Latent periods
   - Identifying “real” differences

The Old Debate
Relative versus Absolute Risks

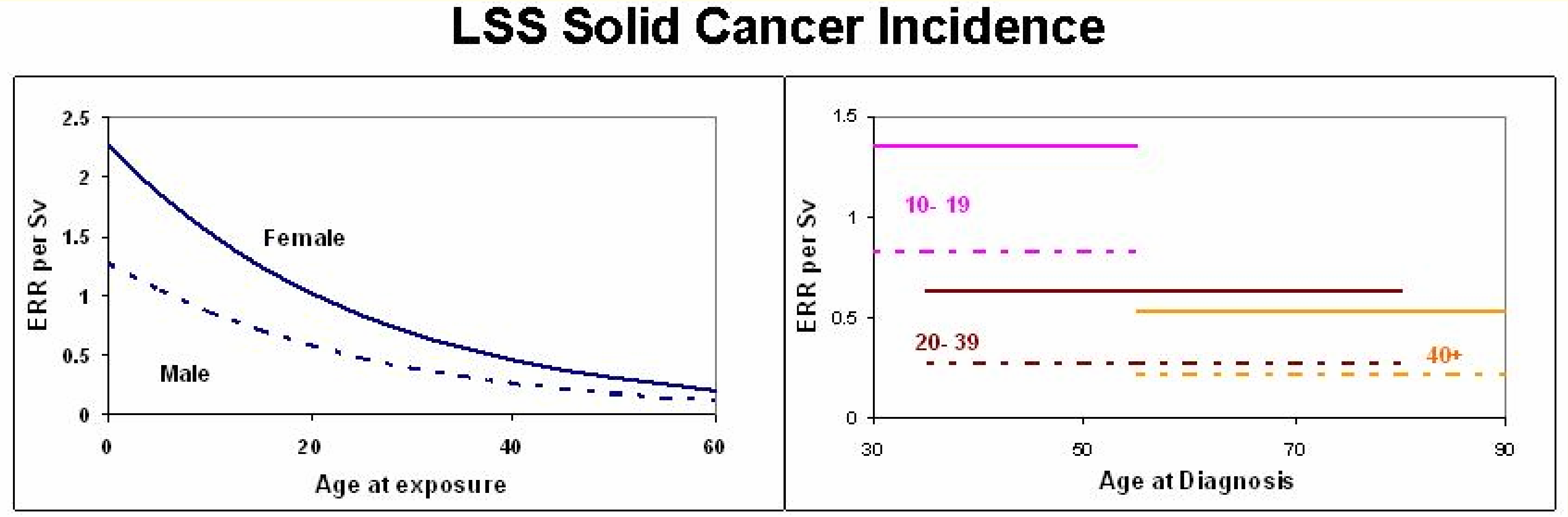
- Do excess risks increase or become relatively less important as time goes by?



- By early 1980's it was agreed that relative risk provided a better description
- Time-constant (excess) relative risk became standard risk summary

Evolving Understandings
Excess Risk is Not a Number

- (Relative) risk depends on gender and age at exposure



- Are excess relative risks constant in attained age (time) given age at exposure and sex?
- How should we interpret gender differences in the ERR?

Evolving Understandings Describing Excess Risks

Excess relative risk (ERR) model

$$\lambda_o(a,s,b)[1 + \rho(d)\varepsilon_R(s,e,a)]$$

Excess absolute rate (EAR) model

$$\lambda_o(a,s,b) + \rho(d)\varepsilon_A(s,e,a)$$

$\lambda_o(a,s,b)$	Baseline (zero dose) risk function *a* age at risk; *s* gender; and *b* birth cohort
$\rho(d)$	Dose-response shape , e.g. linear, linear-quadratic, threshold, …
$\varepsilon(s,e,a)$	Effect modification function *e* age at exposure

Evolving Understandings
ERR versus EAR description

- ERR and EAR are (in principle) equivalent descriptions of the excess risk

$$\varepsilon_R(s,e,a) = \frac{\varepsilon_A(s,e,a)}{\lambda_0(a,s,b)}$$

- Both ERR and EAR descriptions are important
- ERR and EAR provide complimentary information
  - Patterns in ERR effect modifiers may reflect factors such as gender and birth cohort effects in baseline rates
- Description may be simpler or more informative on one scale than the other

Describing Gender and Age-Time Effects

- Smoothing the excess is essential to understanding
  - Subset analyses have little power
  - Uncertainty can make it difficult to see patterns
- Requires choice of variables and model form
  - RERF analyses generally based on log-linear descriptions

$$\varepsilon(s,e,a) = \exp(\beta_s + \theta e + \gamma \log(a))$$

$\exp(\beta_f) / \exp(\beta_m)$	female:male excess (relative) risk ratio
$\exp(10\,\theta)-1$	% change per decade increase in age at exposure
γ	power of age at risk

Describing Gender and Age-Time Effects

- Extensions of basic model possible
  - Sex-dependent age and age at exposure effects
  - More general functions of age and age at exposure
- However, available data usually too limited to support such detailed descriptions

LSS Solid Cancer Incidence 1958-94

By age at exposure					
Age at exposure	**People**	**Person years**	**Cases**	**Estimated Excess**	**AR%**
Male					
0-19	16,533	435,613	1,220	113	9%
20-39	6,117	156,586	1,633	76	5%
40+	9,761	133,347	2,261	60	3%
Total	*32,411*	*725,546*	*5,114*	*249*	5%
Female					
0-19	18,340	511,746	1,234	200	16%
20-39	16,256	472,019	2,880	208	7%
40+	13,173	224,856	2,278	81	4%
Total	*47,769*	*1,208,621*	*6,392*	*489*	8%
Total	***80,180***	***1,934,167***	***11,506***	***738***	***6%***

By colon dose					
Colon Dose	**People**	**Person years**	**Cases**	**Estimated Excess**	**AR%**
< 0.005	35,545	851,102	4,701	3	0%
- 0.1	27,789	676,209	3,787	69	2%
- 0.2	5,527	135,764	827	65	8%
- 0.5	5,935	143,477	1,010	155	15%
- 1	3,173	75,709	611	178	29%
- 2	1,647	38,923	411	172	42%
2+	564	12,982	159	98	62%
Total	***80,180***	***1,934,167***	***11,506***	***738***	***6%***

- Information on gender and age-time patterns depends (only) on radiation-associated (“excess”) cases
- Excess cases not explicitly identified
- Number of relevant cases is relatively small, especially for specific sites

LSS Leukemia Mortality 1950-2000

By age at exposure

Age at exposure	People	Person years	Cases	Estimated Excess	AR%
		Male			
0-19	16,827	783,098	60	24	41%
20-39	6,411	229,330	49	14	28%
40+	12,449	227,441	47	13	28%
Total	*35,687*	*1,239,869*	*156*	*51*	33%
		Female			
0-19	18,569	891,288	42	17	41%
20-39	16,750	702,633	57	17	30%
40+	15,605	350,566	41	9	22%
Total	*50,924*	*1,944,487*	*140*	*43*	30%
Total	***86,611***	***3,184,356***	***296***	***94***	***32%***

By marrow dose

Colon Dose	People	Person years	Cases	Estimated Excess	AR%
< 0.005	38,507	1,415,828	95	0	0%
- 0.1	27,995	1,035,428	62	3	5%
- 0.2	6,907	251,569	17	4	25%
- 0.5	7,359	267,476	32	13	41%
- 1	3,005	112,394	25	16	62%
1+	2,838	101,661	65	57	88%
Total	***86,611***	***3,184,356***	***296***	***94***	***32%***

- Despite smaller number of excess cases, a considerably larger proportion of the cases are radiation-associated

LSS Solid Cancer Incidence Site-Specific Risks

- Interest in gender effects and age-time patterns for specific cancer types – but data are limited
- Real differences may exist, but power to detect them is limited

Site	**Cases**	**Excess Cases**
All Solid	***11,506***	***738***
Stomach	3,229	137
Colon	831	58
Liver	926	45
Lung	1,346	118
Breast	726	136
Thyroid	371	70
Bladder	292	29
Other Solid	3,968	168
Leukemia	***296***	***94***

Mayak Worker Mortality 1948 - 97

Cumulative Dose	Person years	Deaths	Excess Deaths			AR%		
			External	Internal	Total	External	Internal	Total
Solid Cancer								
Zero	236,731	287	0	23	23	0%	8%	8%
-0.5	293,390	598	26	62	88	4%	10%	15%
-1	68,233	193	32	22	54	16%	11%	28%
-3	93,685	472	107	72	179	23%	15%	38%
-5	22,678	130	45	31	75	34%	23%	58%
5+	6,958	50	11	11	22	22%	21%	43%
Total	***721,675***	***1,730***	***220***	***221***	***441***	***13%***	***13%***	***25%***
Leukemia								
Zero	188,178	6	0	0	0	0%	0%	0%
-0.5	322,779	23	3	0	4	15%	2%	17%
-1	75,025	8	3	0	4	43%	3%	45%
-3	103,073	13	11	1	11	82%	4%	85%
-5	24,972	9	5	0	5	58%	1%	59%
5+	7,649	7	3	0	3	39%	0%	39%
Total	***721,676***	***66***	***25***	***1***	***27***	***38%***	***2%***	***40%***
Average external dose			0.8 Gy		21,557 workers			
Average internal (lung) dose			0.2 Gy		No childhood exposure			
24% female								

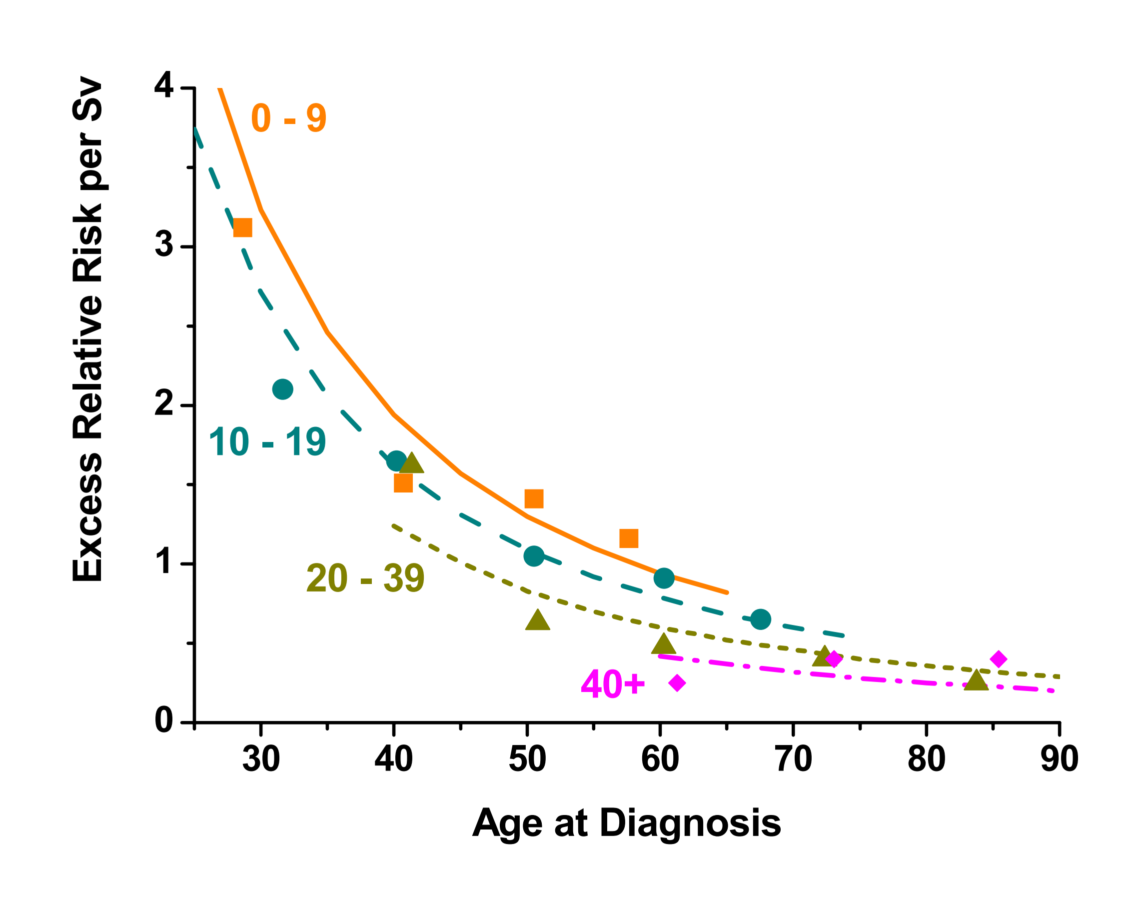
- Internal exposures affect limited set of tissues and may have different temporal patterns
- Separation of internal and exposure efforts complicates use of solid cancer data, but leukemia excess is essentially all due to external exposure

Pooled Breast Cancer

- Pooled analyses provide more information, but
  - Number of cases still limited
  - One must assume patterns are the same for different types of exposure (perhaps not unreasonable)

Cohort	Cases	Excess Cases
LSS	707	128
TB	211	38
Mastitis	114	37
Thymus	34	18
Benign Breast	210	75
Hemangioma	176	-20
Total	**1,452**	**275**

LSS Solid Cancer Excess Relative Risk Temporal Patterns



Age at exposure

-16% per decade
(90% CI -25%; -6%)

Attained age

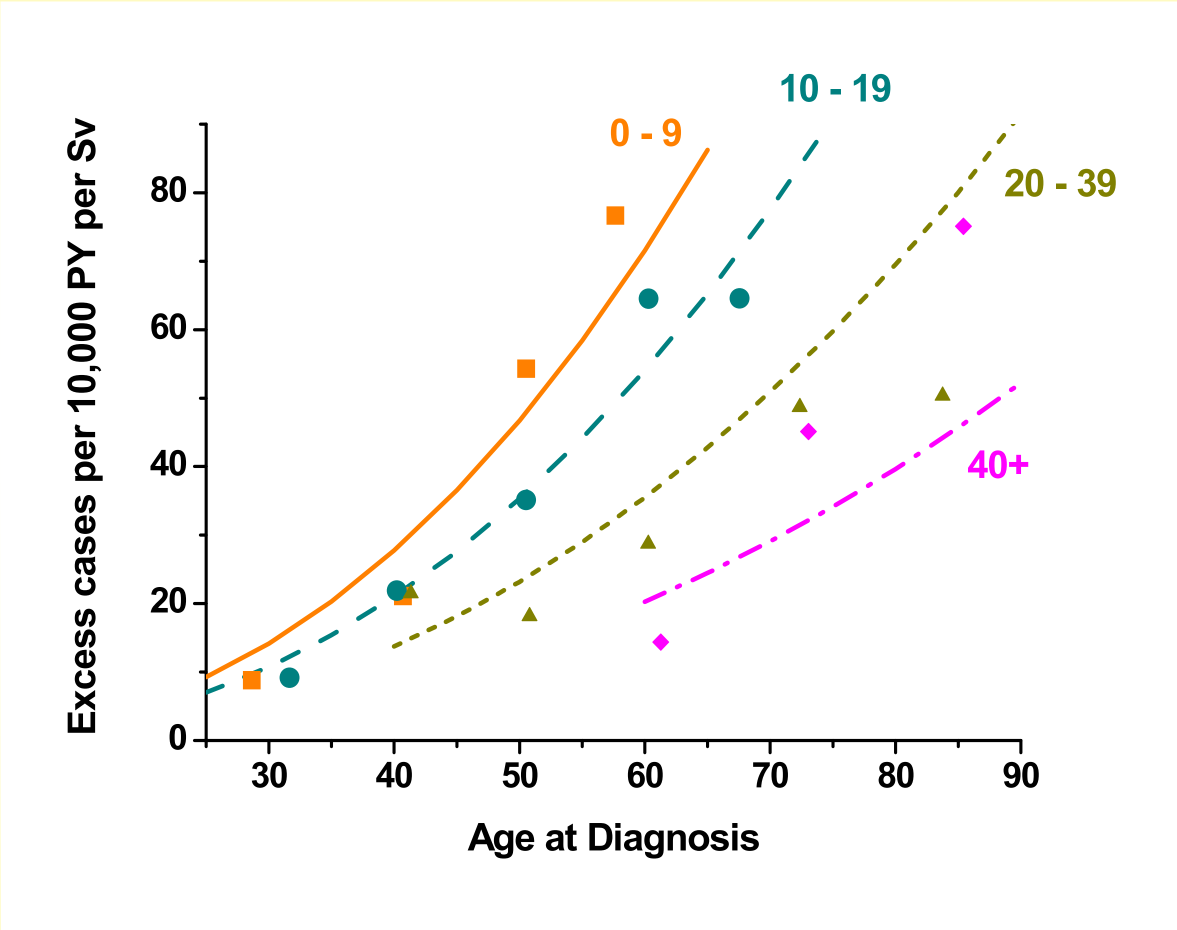
$Age^{-1.8}$
(90% CI -2.3; -1.3)

Gender *

M: 0.35 *(90% CI 0.27; 0.43)*
F: 0.57 *(90% CI 0.47; 0.67)*
F:M: 1.6 *(90% CI 1.3; 2.1)*

* ERR per Sv at age 70 following exposure at age 30

LSS Solid Cancer Excess Rate Temporal Patterns



Age at exposure
+24% per decade
(90% CI 16%; 32%)

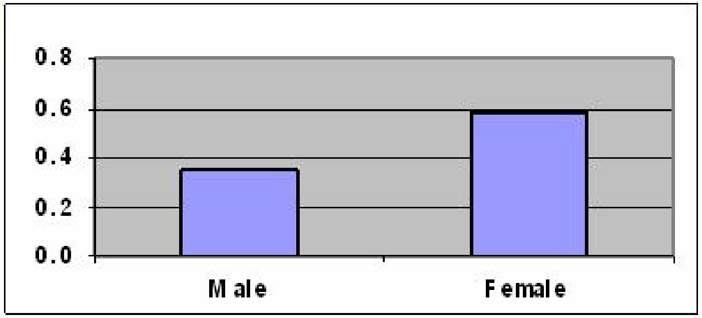
Attained age
$Age^{\mathbf{2.3}}$
(90% CI 1.9; 2.8)

Gender *		
M:	43	*(90% CI 32; 54)*
F:	59	*(90% CI 50; 68)*
F:M:	1.4	*(90% CI 1.1; 1.8)*

* Excess cases per 10000 PY at age 70 following exposure at age 30

Solid Cancer Incidence
Gender Effects

Excess Relative Risk

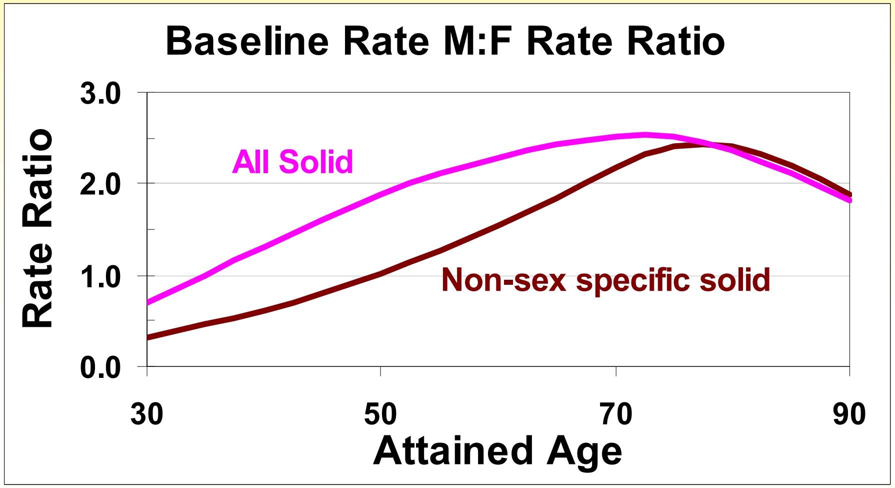


Excess Rate

Risks at age 70 following exposure at age 30

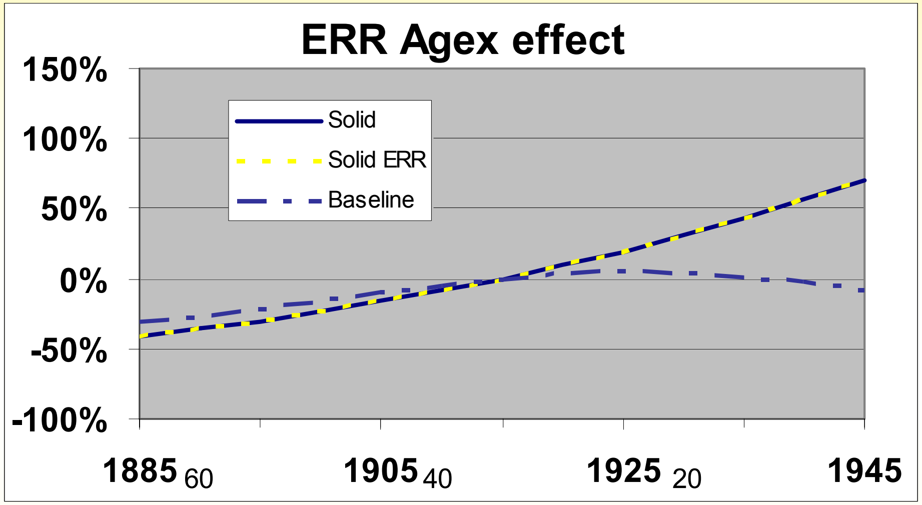
Solid Cancer Incidence Sex Ratio

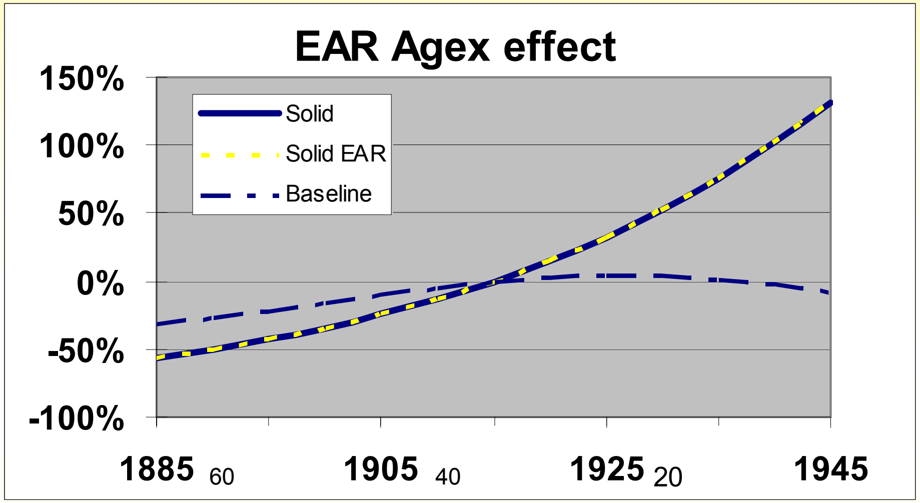
- All solid cancers
  - ERR F:M sex ratio 1.6
  - EAR F:M sex ratio 1.4
  - Baseline **M:F** sex ratio 2
- Non-sex specific solid cancers
  - ERR F:M Sex ratio 1.8
  - EAR F:M Sex ratio 1.0
  - Baseline **M:F** sex ratio 2.2



- **Suggests that ERR sex ratio largely serves to offset baseline rate ratio**

Solid Cancer Incidence
Age-at-exposure and Birth Cohort Effects





Excess risk age at exposure effects relative to age at exposure 30

Solid cancer excess	thick blue line
Solid cancer excess reference	yellow dashed line

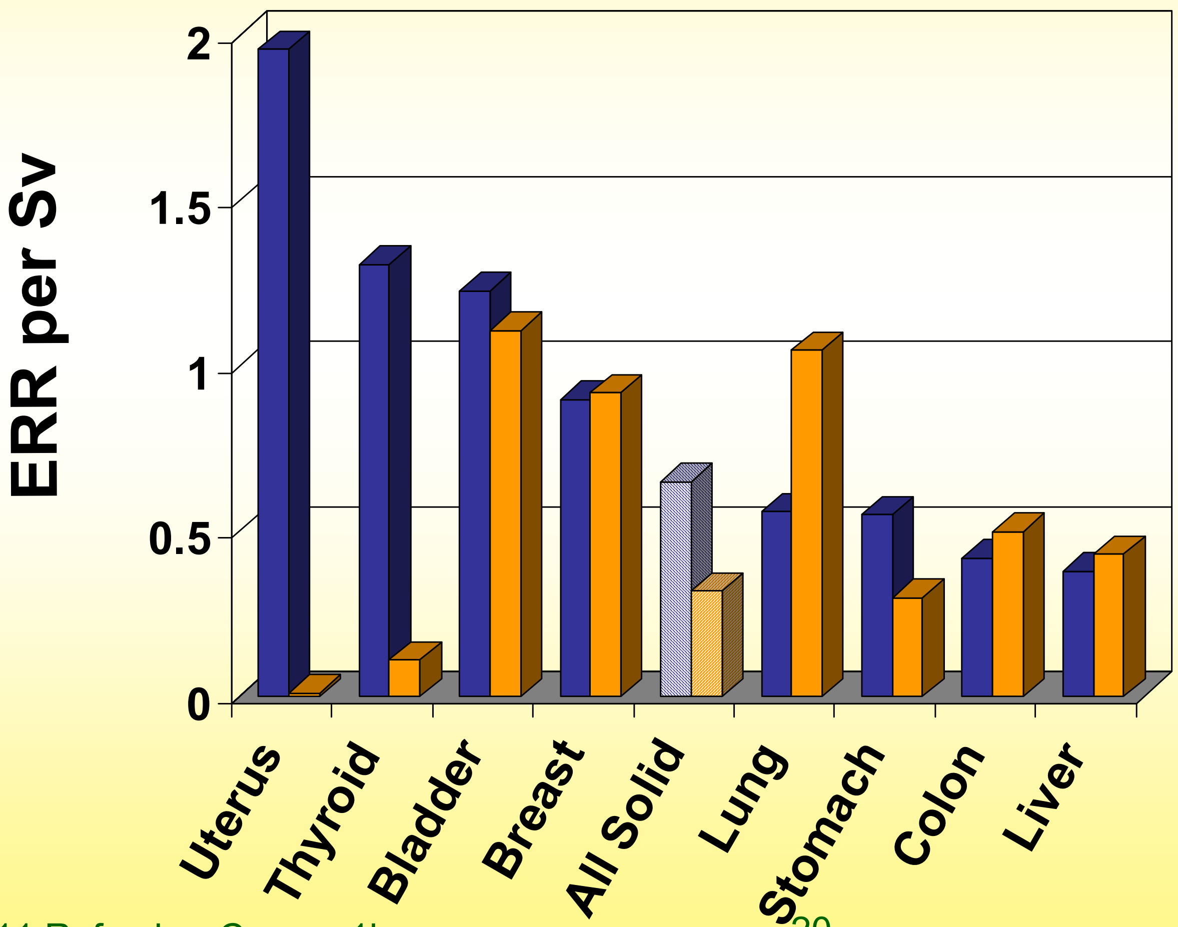
Baseline birth cohort effect relative to 1915 births — dashed blue line

N.B. Birth cohort and age at exposure are equivalent in the LSS

LSS Solid Cancer Risks

- ERR exhibits significant dependence on age at risk (attained age) even after allowance for age at exposure effects
- Despite decreasing ERR, EAR increases rapidly with attained age
- After allowing for attained age effects both ERR and EAR depend on age at exposure and suggest that younger people have higher risks
- ERR gender difference for non-sex specific solid cancers reflects baseline gender differences

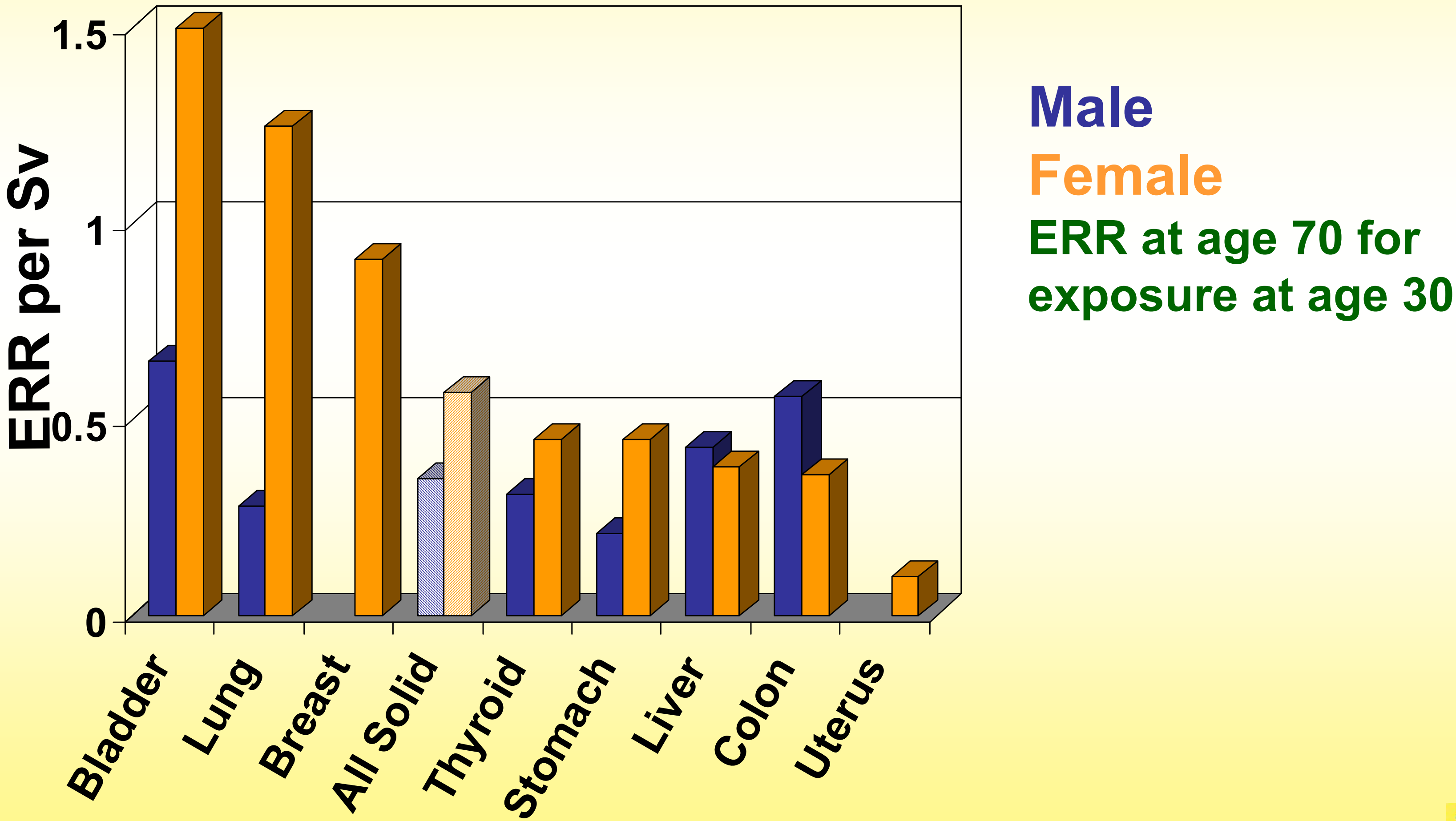
Age at Exposure Effects



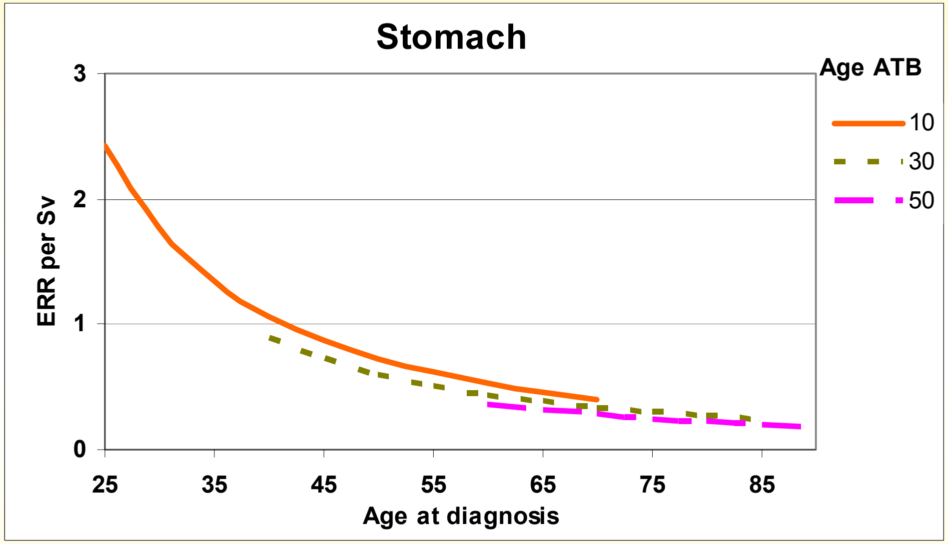
Age at Exposure
Age 10
Age 50

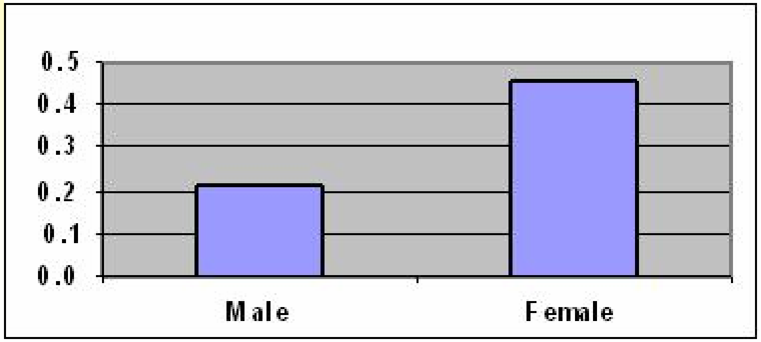
ERR at age 70

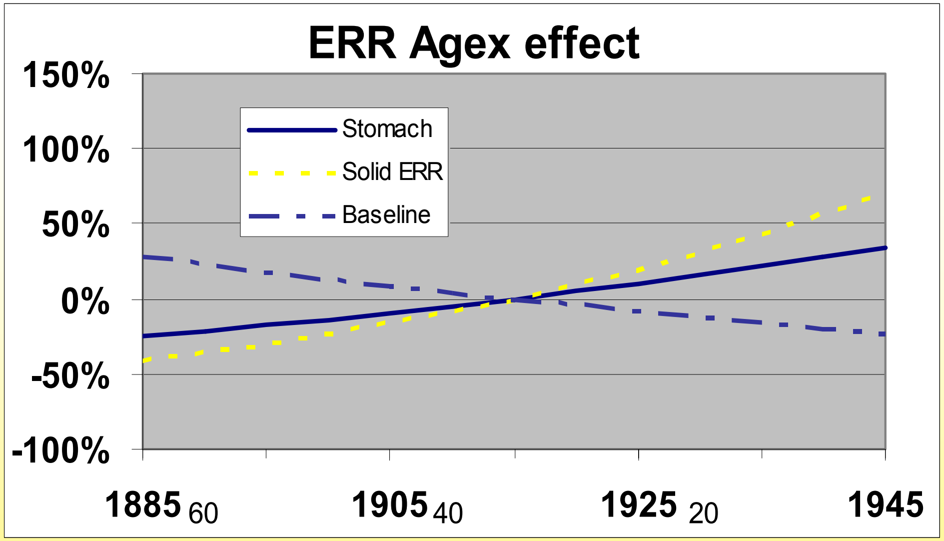
Solid Cancer ERR
Gender Effects



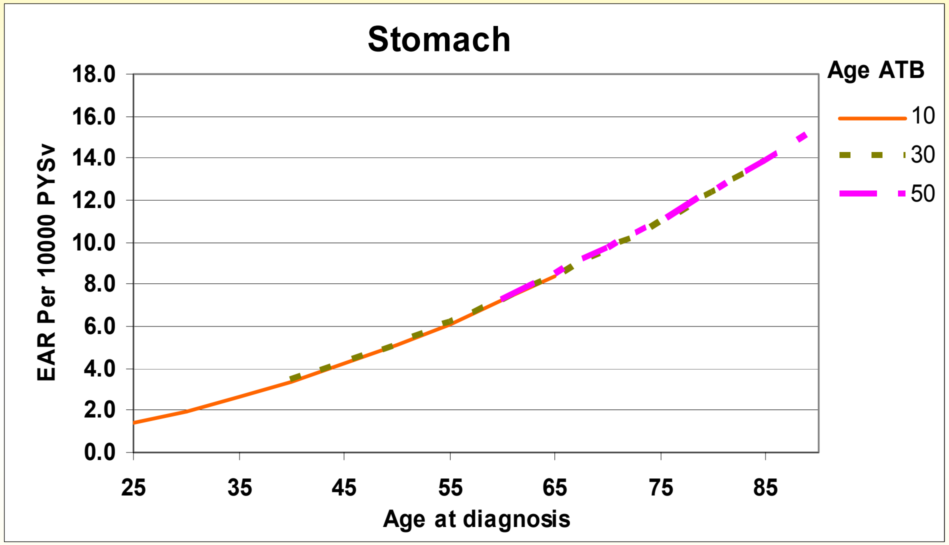
Stomach Cancer Incidence
Excess Relative Risk

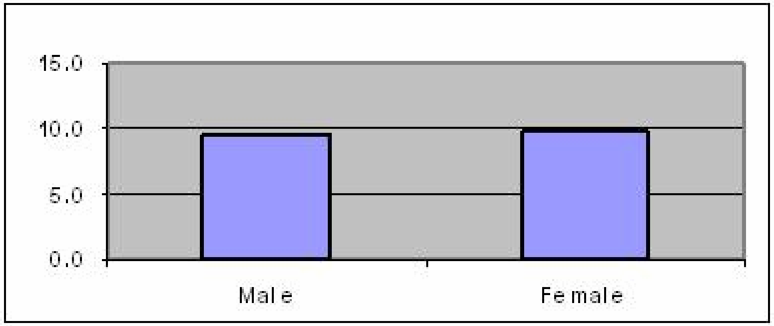


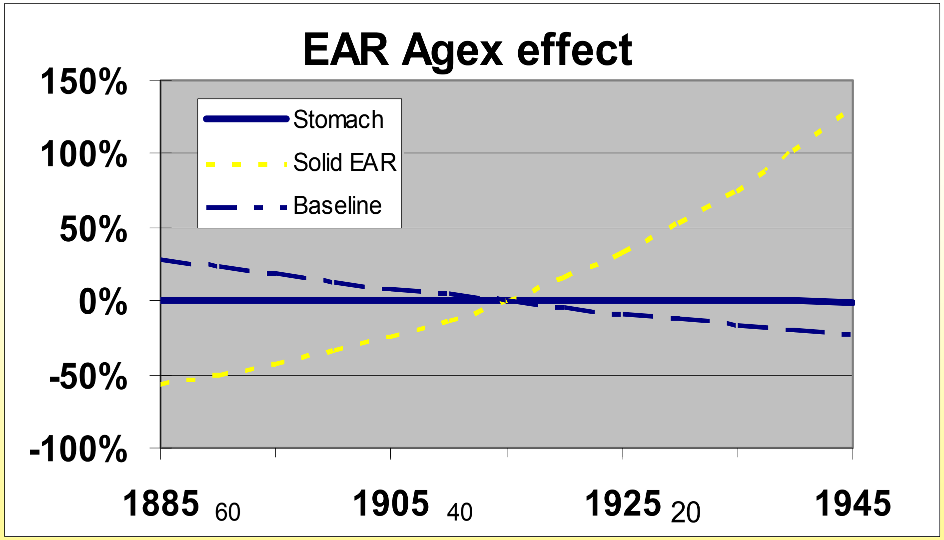




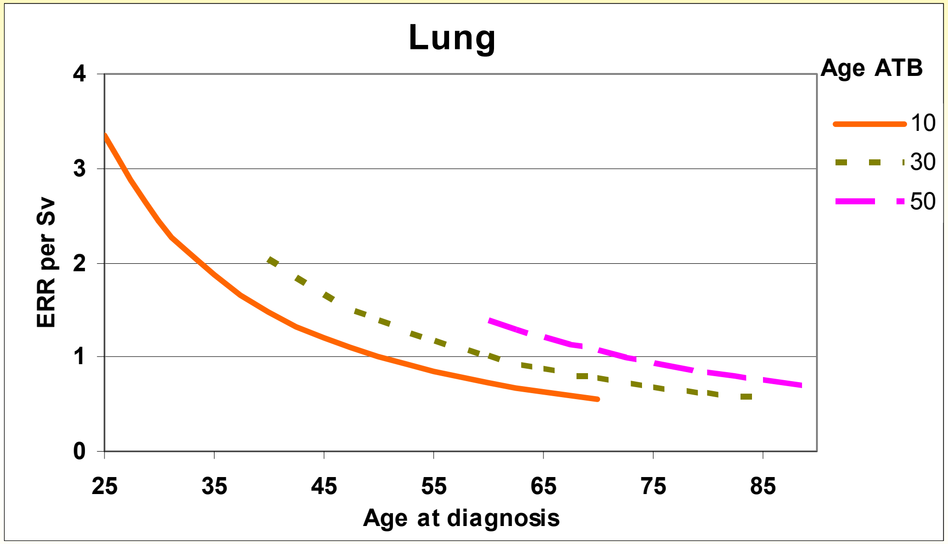
Stomach Cancer Incidence Excess Rate (EAR)

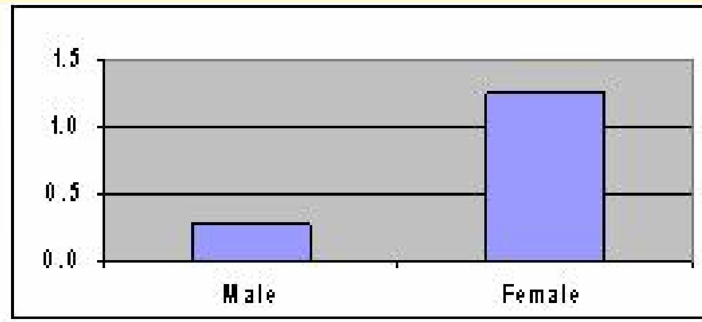


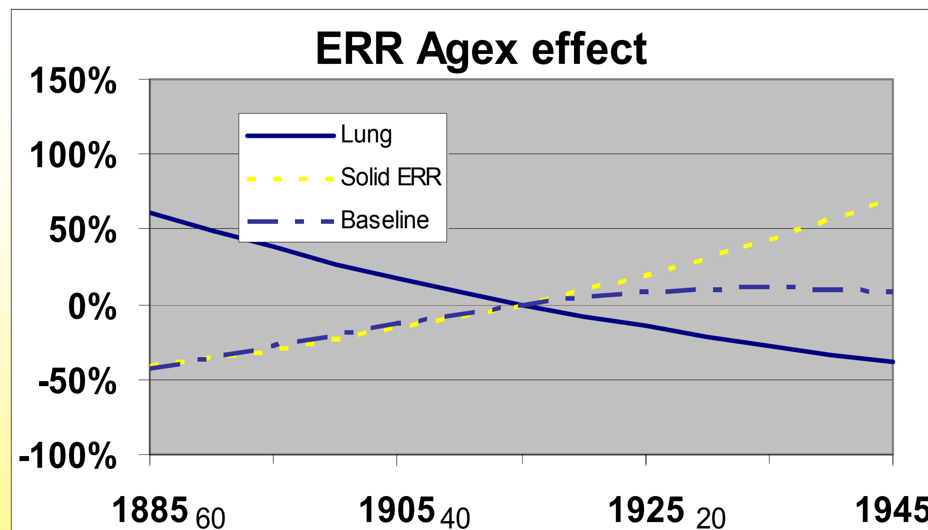




Lung Cancer Incidence Excess Relative Risk

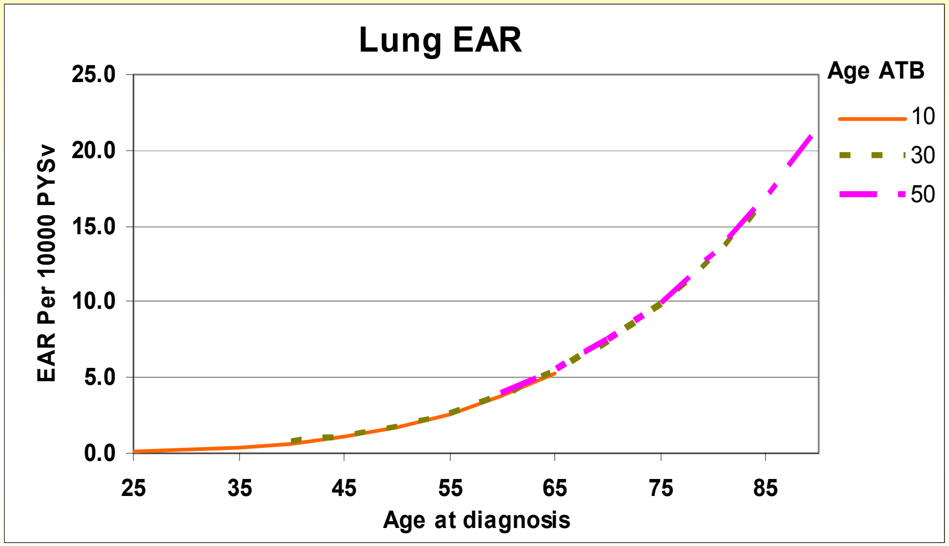


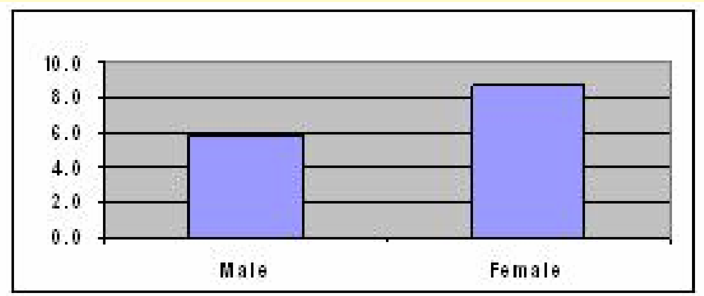


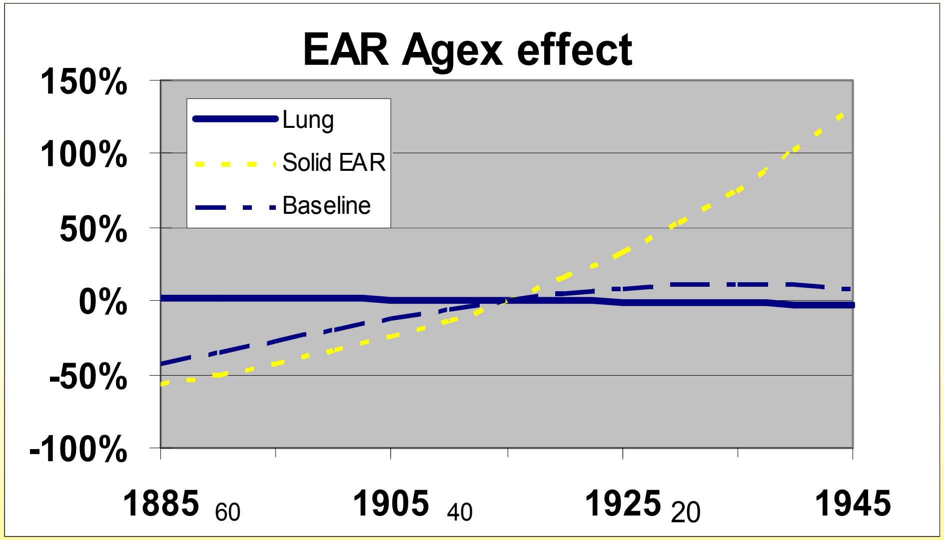


- Age at exposure effect opposite that seen for other solid cancers
- Large gender difference and age at exposure pattern reflect smoking effects on baseline rates

Lung Cancer Incidence Excess Rate





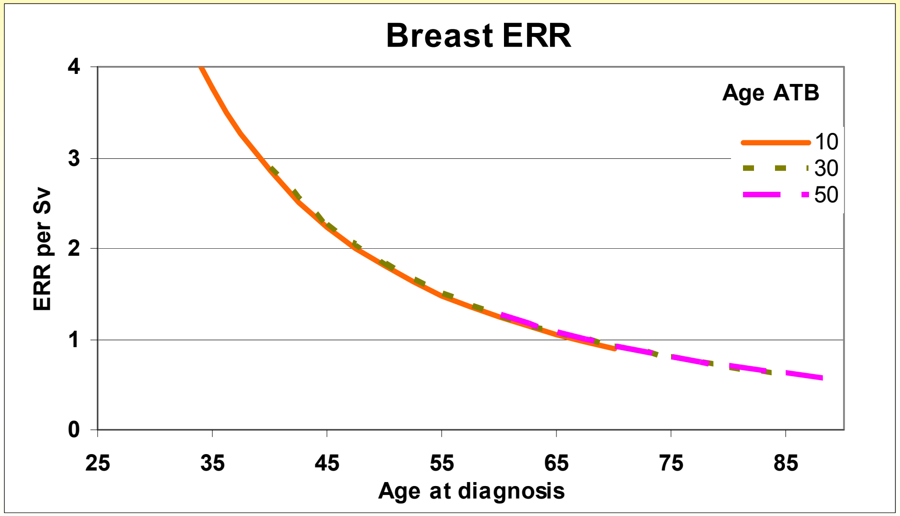


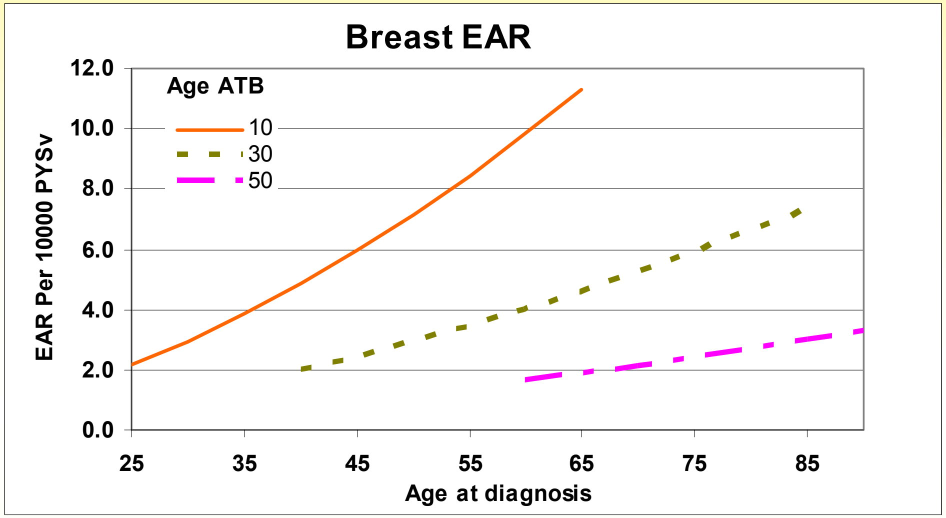
- Lack of age at exposure effect and reduced gender ratio suggest additive joint effect of radiation and smoking (see Pierce et al 2003)

Breast Cancer Incidence
What is "Known"

- Large relative risk
- Large age-at-exposure effect on ERR
- Indications of very high risk (ERR) of early-onset (under attained-age 35) cancer among exposed
- Pooled breast cancer excess risk (EAR) model developed using LSS and 7 other cohorts

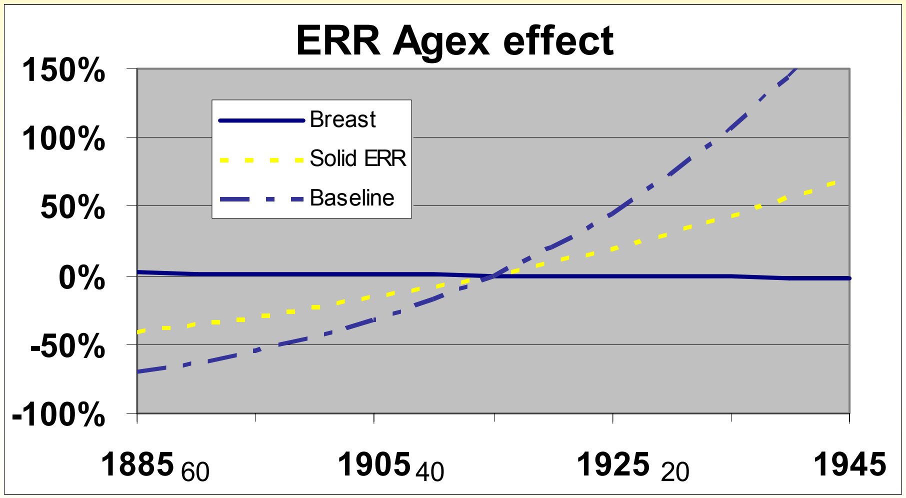
Breast Cancer Incidence
Age and Age at Exposure Effects

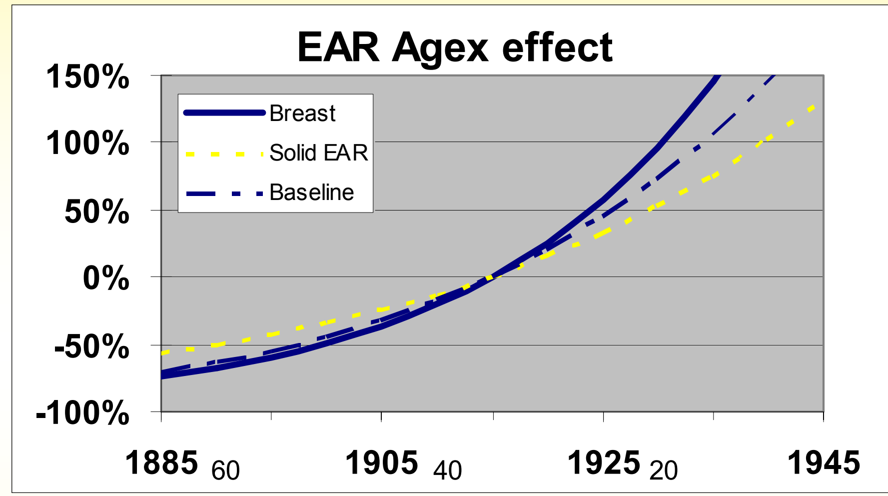




- ERR pattern consistent with large relative risk for early-onset cases
- Large age at exposure effect on EAR
- Is simple EAR pattern adequate

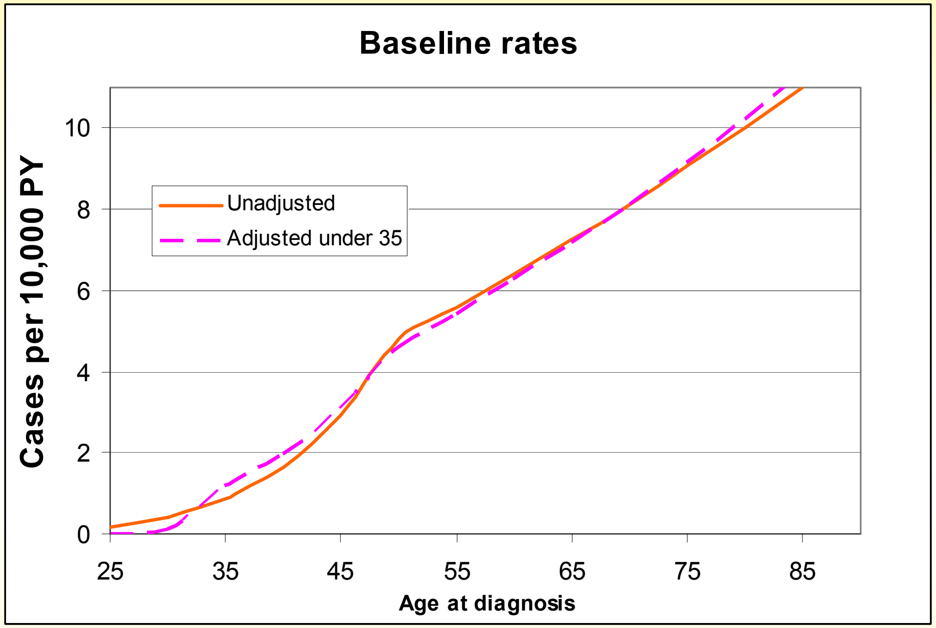
Breast Cancer
Age at Exposure and Birth Cohort Effects

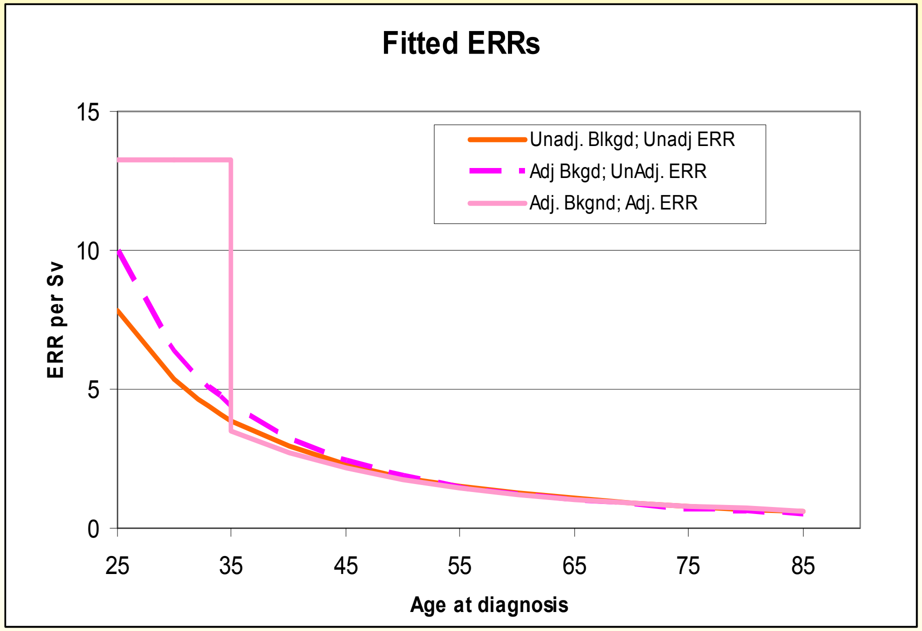




- No apparent age at exposure effect on ERR after allowing for age despite large birth cohort effect
- Large age at exposure effect on EAR parallels the birth cohort effect

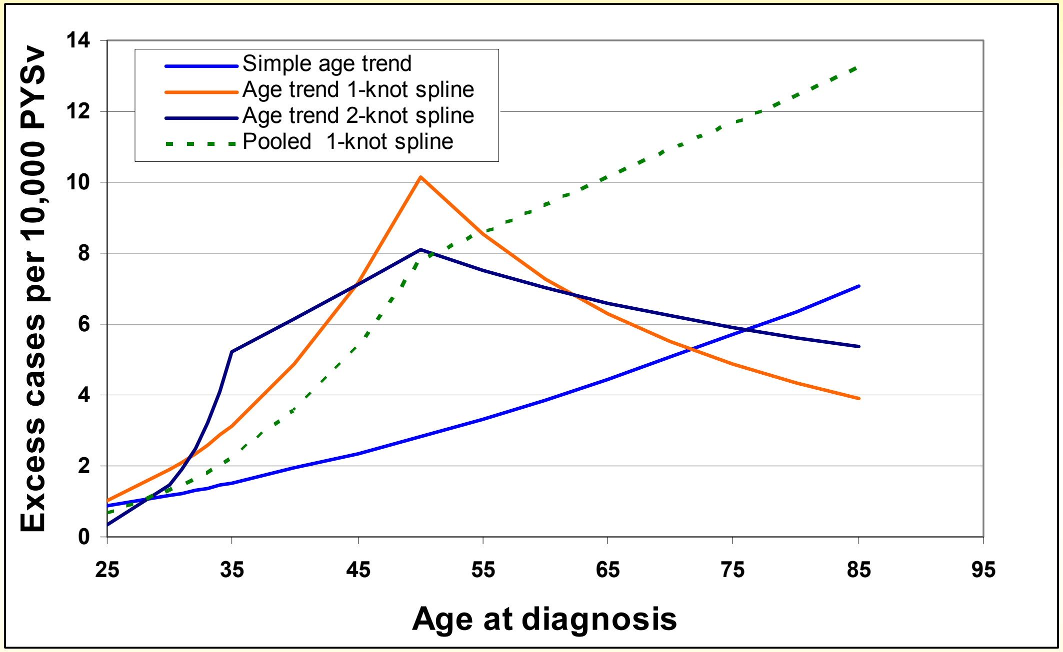
Breast Cancer Incidence Early Onset Effect





- Early onset age confounded with early age at exposure
- Significant ERR early-onset effect only if baseline adjusted for under-35 effect
- Adjustment increases under-35 estimated excess cases by 4 (40%)
- Attained-age remains dominant effect on ERR

Breast Cancer Incidence
EAR Models



- EAR pattern is complex
  - Simple trend improved by addition of EAR change points (ages 35 and 50)
- 8-cohort pooled model predicts higher risks at older ages
- Additional follow-up of youngest birth cohorts essential to understanding post-menopausal excess risks

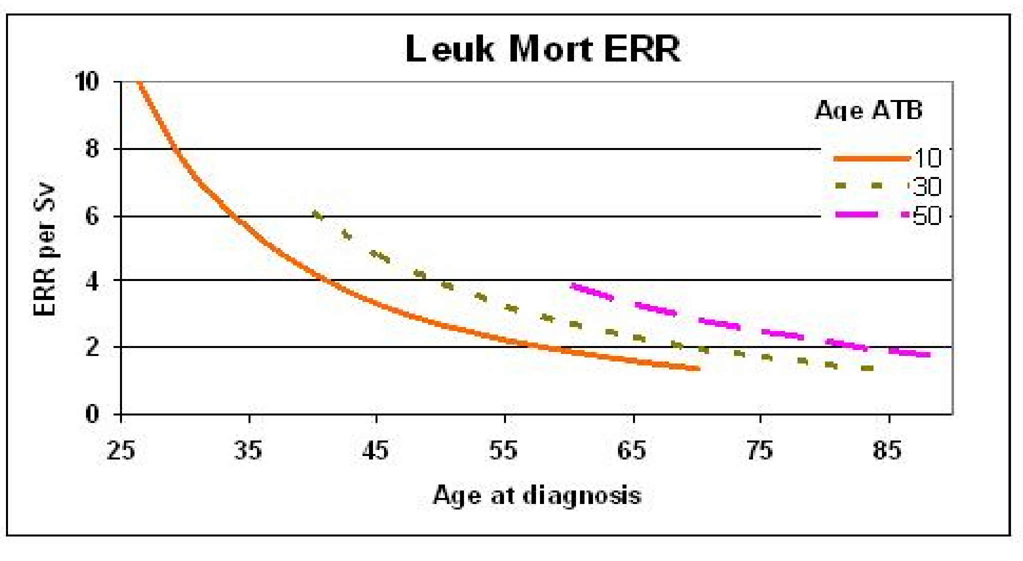
Breast Cancer Incidence

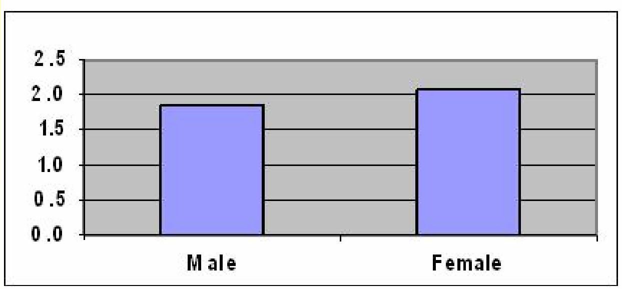
- ERR decreases with increasing attained age
  - Large ERR's may exist for early-onset cases
  - No significant age at exposure effect on ERR
- EAR has complex pattern
  - Strong age at exposure effect
  - Clear change in pattern near age of menopause
  - Basic pattern seen as in other cohorts but LSS changes may be more pronounced

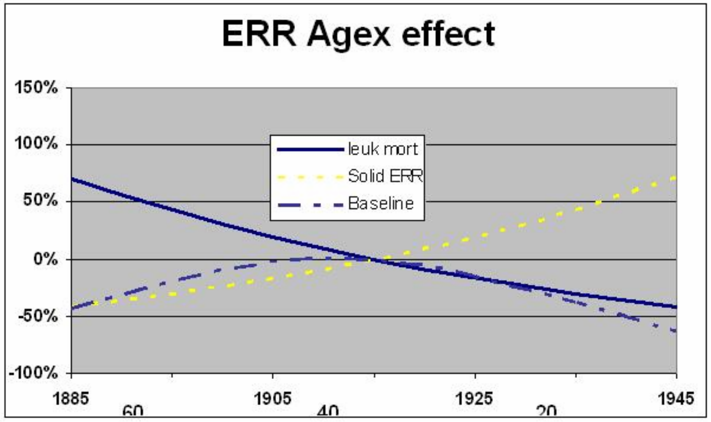
Leukemia

- LSS data usually described in terms of
  - EAR models
  - Time since exposure (TSE) as primary time scale for excess
  - Include age at exposure by TSE interaction
- Descriptive models used here have same form as solid cancer
  - Attained age as primary time scale for excess
  - No need for attained age by age at exposure interaction
- **These models describe data as well as TSE models**

Leukemia Mortality ERR

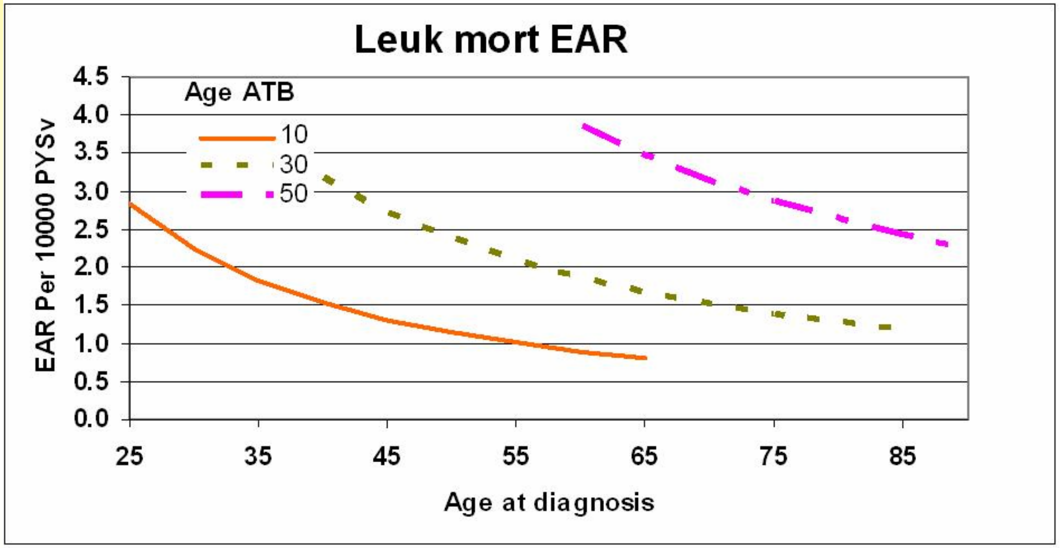


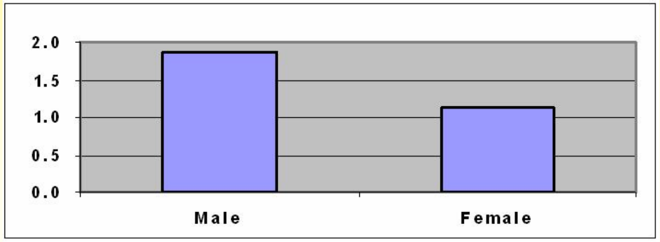




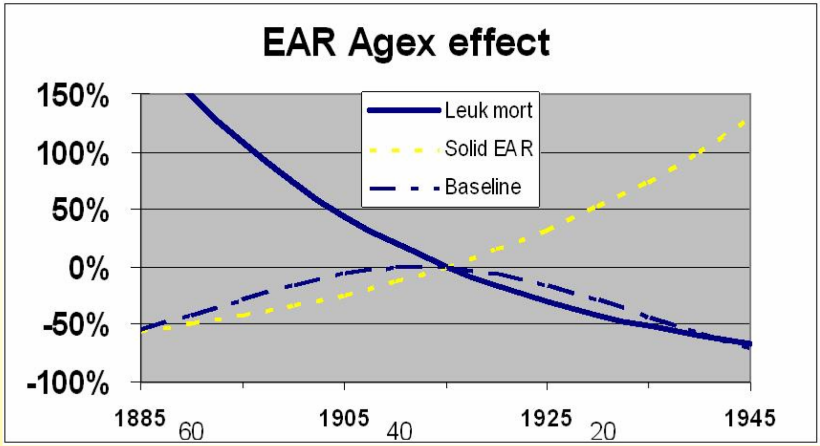
- Age at exposure effect opposite that seen for most solid cancers
- Little gender effect on ERR
- Attained age trend only slightly more marked than that for solid cancers

Leukemia Mortality EAR

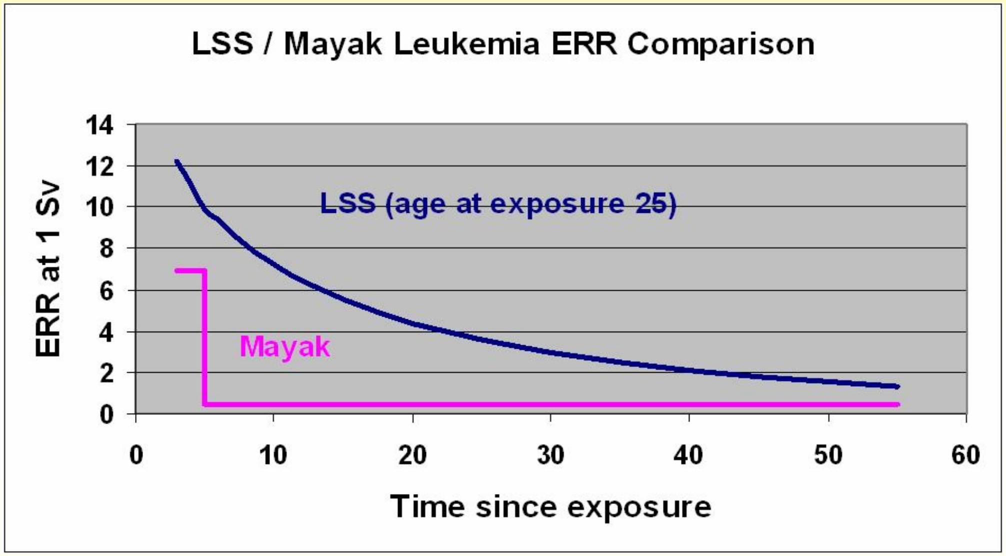




- Declining EAR is in marked contrast to solid cancers



Comparison of LSS and Mayak Leukemia Risks

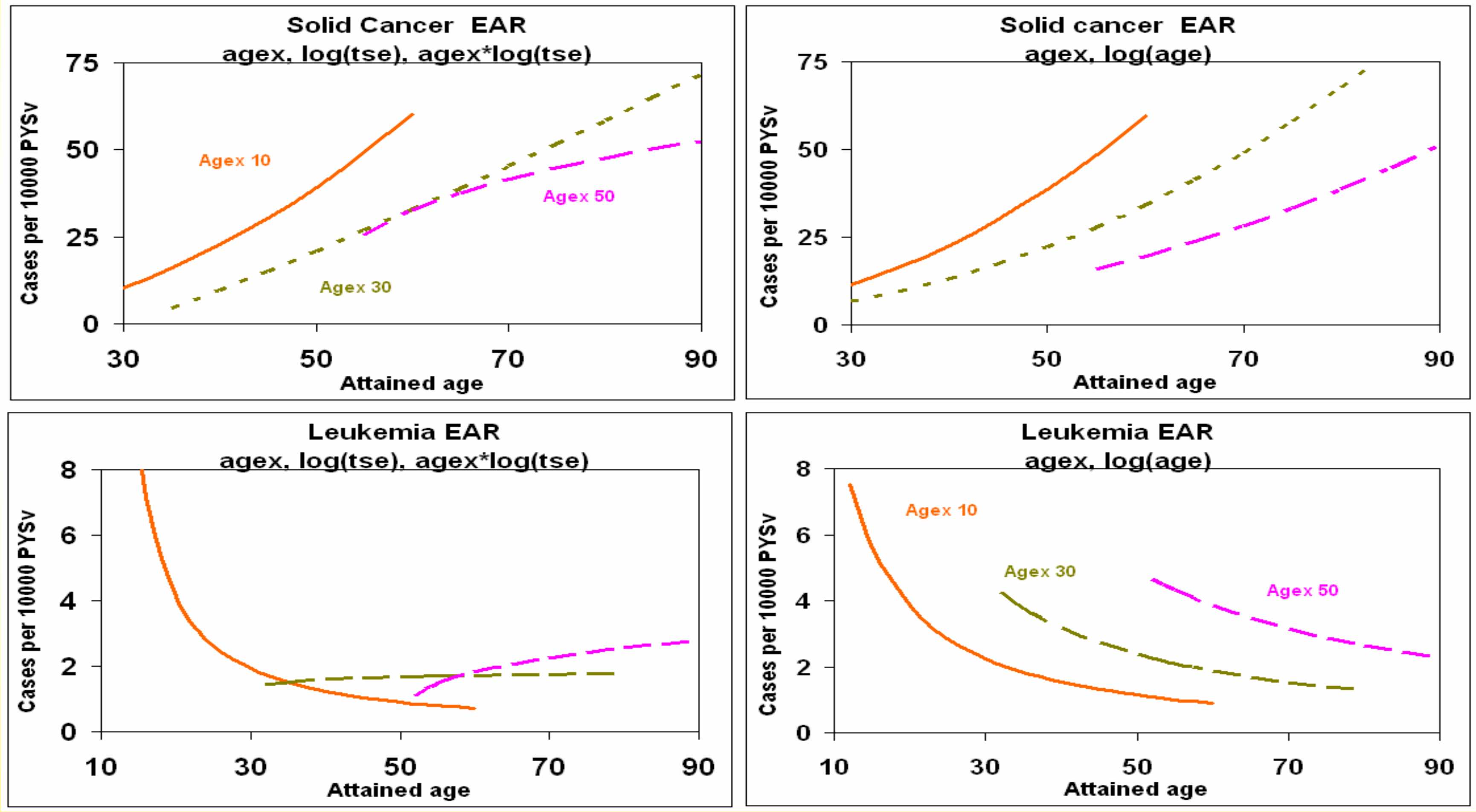


- Large risk for "recent" exposures in Mayak cohort and smaller risks for earlier exposures seems consistent with LSS decline with time
- Mayak 1 Sv risks may be less than LSS risks, but there are large uncertainties in estimates from both cohorts
- LSS clearly has non-linear dose response, but Mayak appears linear

Related Issues
Time-Since-Exposure

- Solid cancer
  - LSS data suggest that largest risks occur late in life regardless of age at exposure
  - EAR TSE model fits worse than attained-age model without an agex-by-TSE interaction
- Leukemia
  - TSE models motivated by EAR decrease and the belief that the excess disappeared after 15 to 20 years
  - TSE models involve significant agex-by-TSE interaction
  - Attained age models provide comparable fit without need for interaction

Comparison of Time-Since-Exposure and Attained-Age Fits



Related Issues
Time-Constant ERR models

- LSS data clearly suggest that the ERR varies with attained age (time since exposure)
- It is difficult to conceive of a radiation carcinogenesis mechanism that would lead to time-constant increases in the ERR

Related Issues
Latency

- Concept of limited usefulness
  - Definition is vague
  - Dose response implies reductions in the expected time from exposure to tumor
  - Minimum latency period is at least time from the final conversion into a malignant cell until diagnosis or death but could be longer
    - Mayak and early a-bomb survivor data indicate that radiation-associated leukemia deaths can occur within two to three years of exposure
    - LSS solid mortality data provide some suggestion of elevated risk 5 to 10 years after exposure for older cohort members
- Better to simply describe age-time patterns

Related Issues
Interpreting Site-Specific Risks

- Difficult to interpret and generalize effect modification
  - ERR gender effects mirror baseline gender effects, but baseline effects may be similar across populations
  - Age at exposure effects in the ERR may depend on birth cohort or period effects on baseline rates
  - Can also be problems in generalizing EAR patterns
- Site-specific differences in patterns are likely to exist
  - However much of observed variability is consistent with random variation
  - Formal statistical tests generally lack power to detect real differences
  - Statistical methods for shrinking estimates toward a central value are likely to lead to improved estimators of risk levels, gender effects and age-time patterns

Summary and Conclusions

- Accumulating data and modern analytical methods make it possible to investigate radiation effect modification in some detail
- Data are limited even in the largest cohort
- Both ERR and EAR descriptions provide equally important and complementary information
  - Attained age is an important factor in both
  - Generalization of age at exposure and gender effects can be difficult
- Pooled analyses may be useful in looking at effect modification