Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers: Study Design and Analysis Issues

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Variable Characteristics of BRCA1/2 Mutation Carriers

- Age at Diagnosis
- Cancer Occurrence
- Tumor Site
- Tumor Stage or Type
- Prognosis
- Efficacy of Prevention

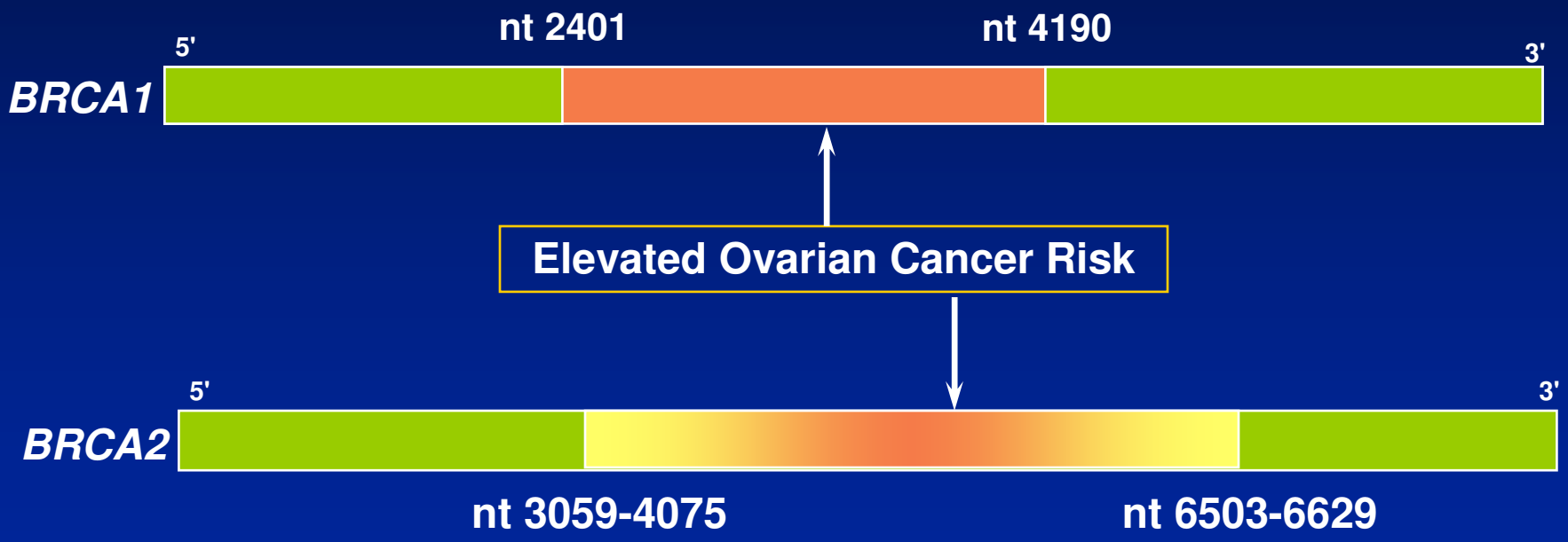
Questions

- What predictors may be required for personalized risk assessment?
- What design and analysis issues need to be faced?
  - Hypothesis testing
  - Point estimation

What Kinds of Predictors May Be Useful?

- **Mutation Location**
- **Exposures**
- **Genes at Other Loci**
- **Interactions of Genotypes and Environments**

Mutation Location and Cancer Risk



Gayther 1995, 1997;
Easton 2001, BCLC 2002

Risk Modifying Exposures in BRCA1/2 Mutation Carriers

	Effect on Cancer Risk		
Factor	**Breast**	**Ovarian**	**Reference**
High Parity	70% ↑	-	Jernström 1999
	0	40% ↑	Narod 1995
	0	-	Rebbeck 2001
Late AFLB	0	0	Narod 1995
	300% ↑	-	Rebbeck 2001
OC Use	-	50% ↓	Narod 1998
	-	0	Modan 2001
Smoking	50% ↓	-	Brunet 1998

Risk Modifying Genes in BRCA1/2 Mutation Carriers

	Maximum Odds/Risk Ratio		
Gene	Breast	Ovarian	Reference (Abstract)
*AIB1**	5.8	-	Rebbeck 2001,
	1.8	-	Kadouri 2003
*PR**	-	2.4	Runnebaum 2001
AR	3.5	-	Rebbeck 1999
	0	-	Kadouri 2001
*CYP1A1***	0.4	-	(Narod 1998)
*NAT2***	0.4	-	(Rebbeck 1997)
HRAS1	-	2.0	Phelan 1996
RAD51	3.5	-	Levy-Lehad 2001, Wang 2001

* Interaction with reproductive factors, OC Use, or BMI; ** Interaction with smoking

Questions

- **What predictors may be required for personalized risk assessment?**
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Generic Algorithm

- **Model relationship of predictors to risk**
- **Generate risk estimates**
- **Create computational algorithm to translate risk estimates into clinical practice**

Problems

- ***BRCA1/2*** **mutations are rare in the general population**
- **Mutation screening is costly**
- **Population based studies may not represent the correct target group in which to make inferences**

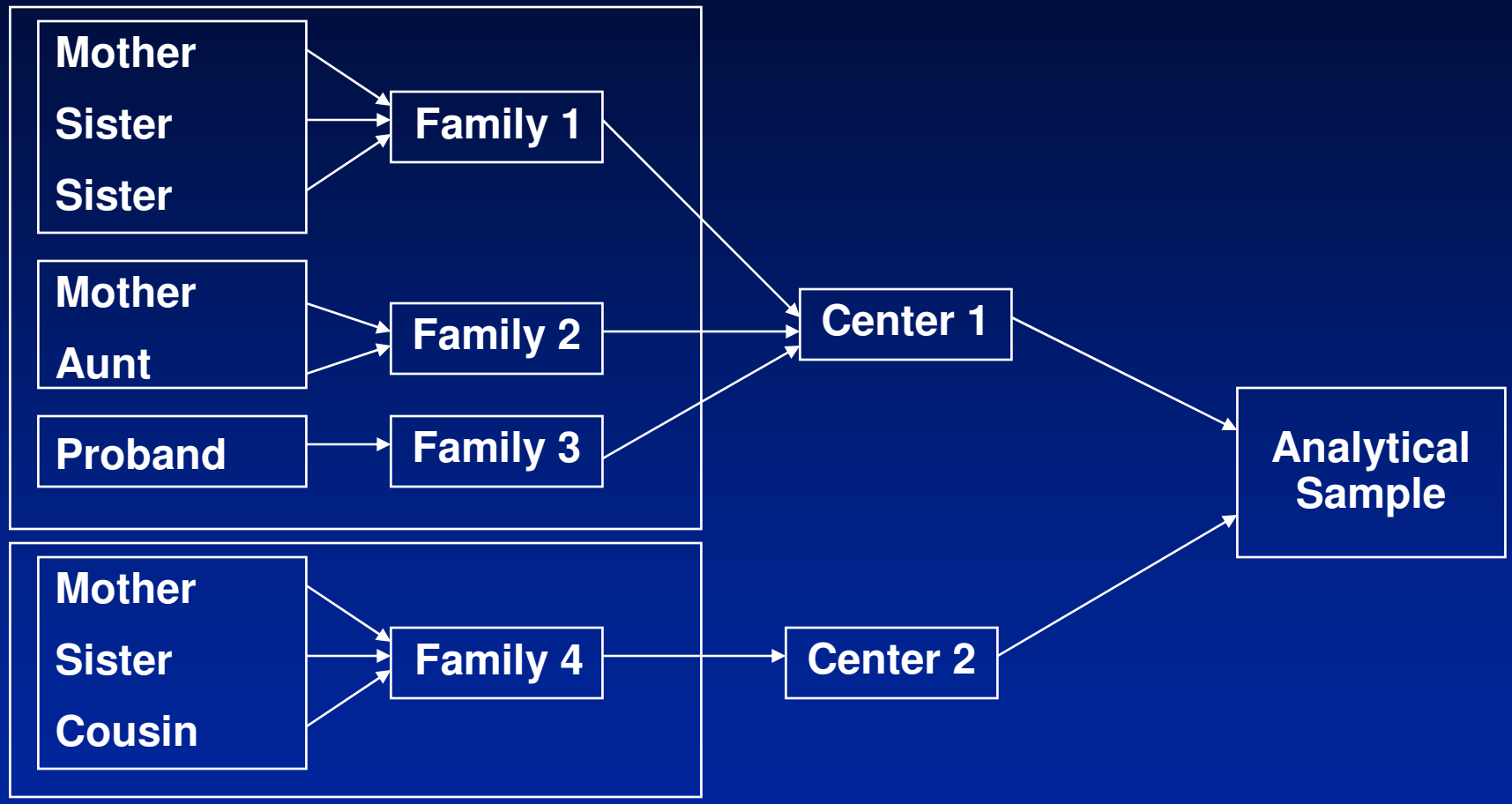
More Problems

- **Multicenter studies of high risk referral populations may be required in which subject ascertainment is inconsistent or not well defined**

…And Even More Problems

- **Correlated Data**
- **Information Bias**
- **Right Censoring**
- **Left Truncation**

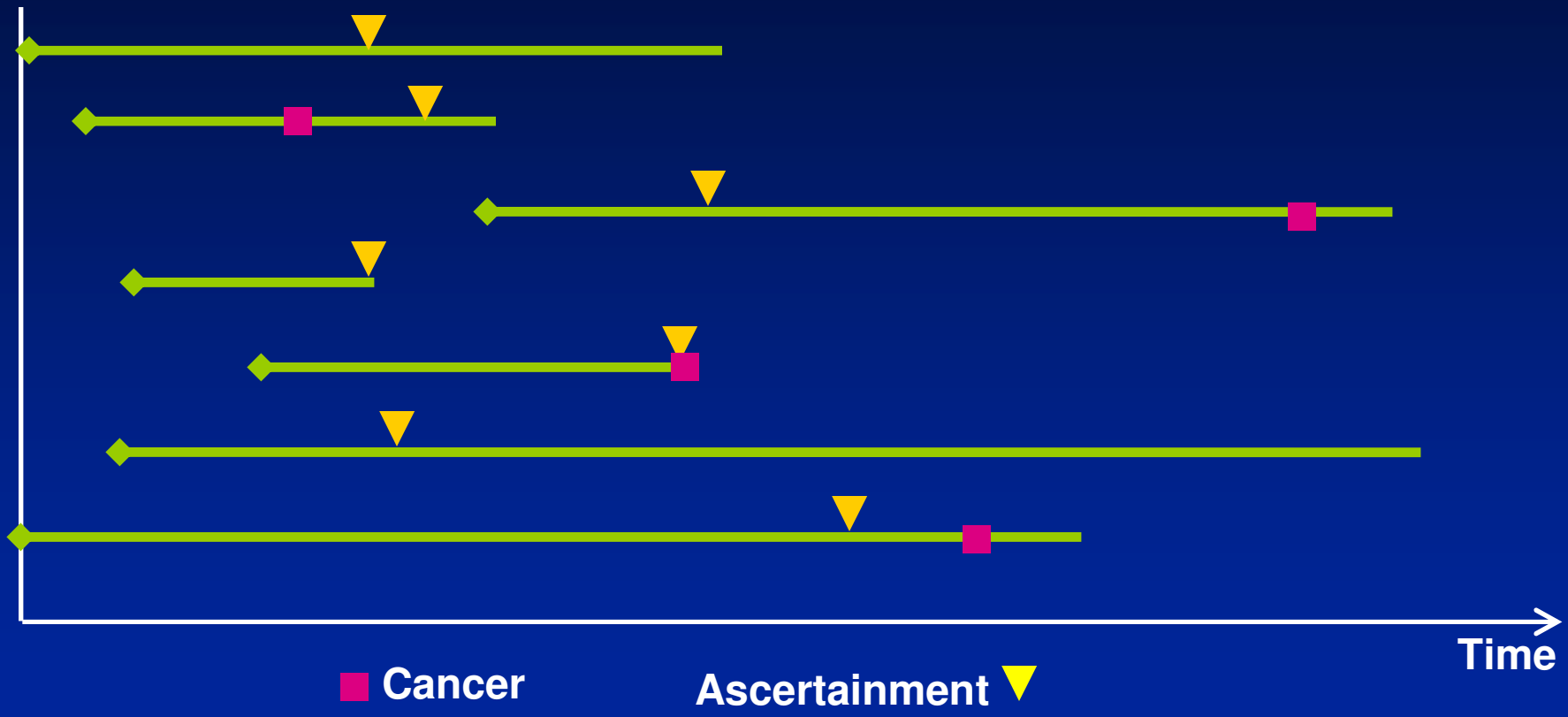
Hierarchical (Nested) Clustered Data



Implications: 1) Potential for confounding by family and/or center

2) Assumption of independence among observations is violated

Left Truncated, Right Censored Data



***Implications*: Survival and Information Bias**

Analysis Option 1: "Nested" Case-Control Sample

Sampling Design:	**Incidence density sampling relative to ascertainment date**
Cases:	**Women "recently" diagnosed with breast cancer and no prior BPM**
Controls:	**Women without breast cancer; No prior BPM, alive and cancer free at the age the case was diagnosed.**
Confounders:	***BRCA1/2*; Birth cohort; Center; BPO or total ovarian hormone exposure time**

Analysis Option 2: Failure Time Approach

Sampling Design:	**Left truncated right censored prevalent cohort**
Follow-Up:	**From the time of ascertainment**
Events:	**Breast cancer**
Censoring:	**Prophylactic surgery, death, last contact**
Confounders:	***BRCA1/2*; Birth cohort; Center**

Effect of AIB1 by Reproductive History: Case-Control vs. Failure Time Approaches

Stratum	Case-Control OR* (95% CI)	Failure Time HR* (95% CI)
Nulliparous	2.7 (1.1-6.8)	1.8 (1.0-2.1)
Parous	1.6 (1.0-2.7)	1.5 (1.1-2.1)
Early Menarche (<13)	1.4 (0.9-2.2)	1.4 (1.1-1.8)
Late Menarche (≥13)	2.7 (1.0-7.6)	1.8 (1.0-3.2)
Early AFLB (<30)	1.7 (1.0-2.7)	1.5 (1.1-2.0)
Late AFLB (≥30)	5.8 (1.0-35.7)	2.7 (1.0-7.1)

*Adjusted for Year of Birth and Parity or Age at Menarche

Other Methodological Considerations

Left Truncation:	**Weighting by Selection bias functions (e.g., Wang et al. 1993; Bilker and Wang 1997)**
Nested Sampling:	**Linear Correction for Confounding (e.g., Neuhaus and Kalbfleisch 1998)**
Correlated Obs:	**Robust 95% CI (e.g., Lin and Wei 1989)**

High Parity and BRCA1-Associated Breast Cancer Risk

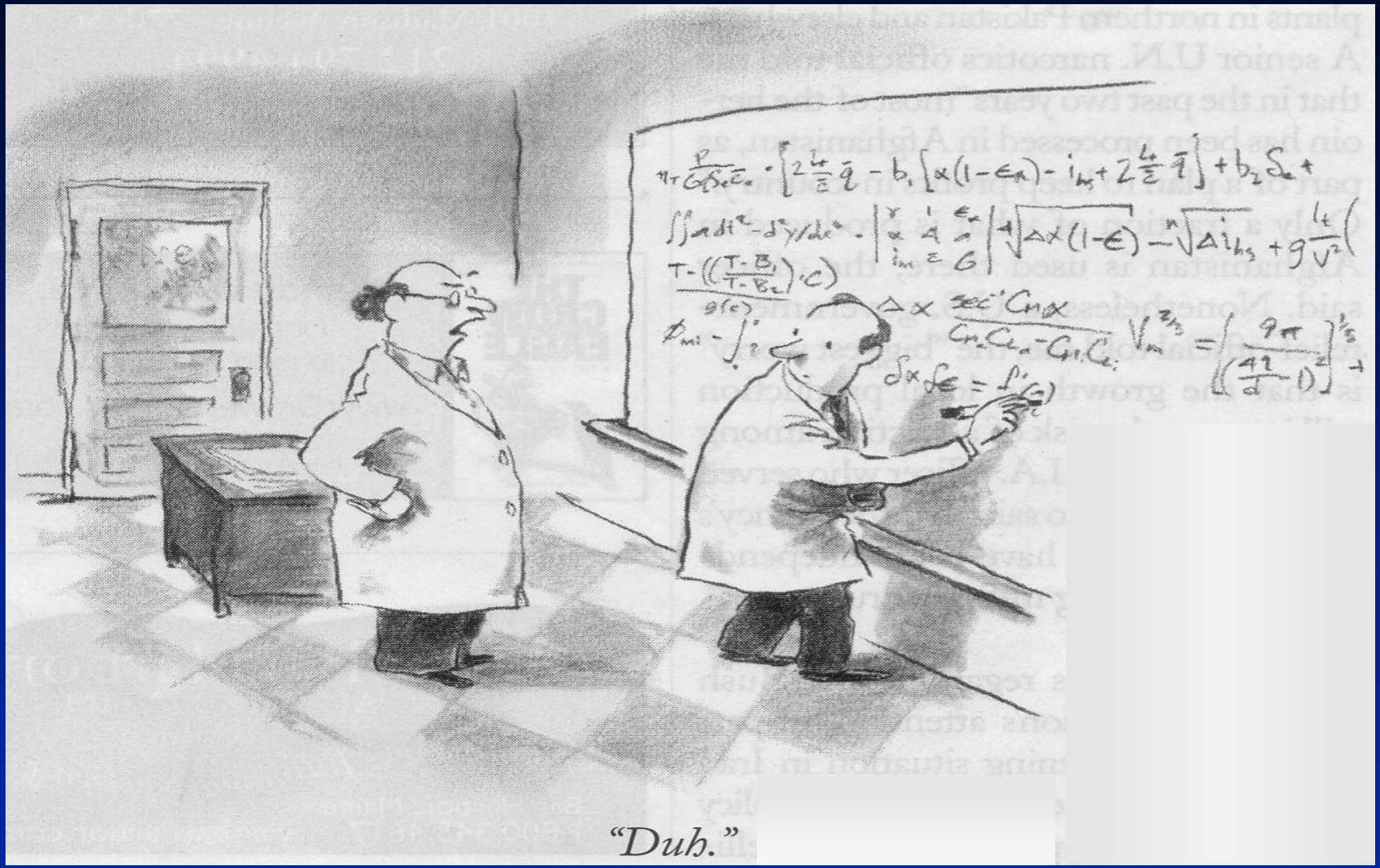
Confounding by Family/Center, Dependence of Observations

Adjustment	HR*	Variance	
		Naïve	Robust
None	0.54	0.36-0.82	0.36-0.80
Center	0.54	0.35-0.82	0.35-0.82
Family	0.63	0.37-1.06	0.39-1.01
Family+Center	0.61	0.36-1.03	0.37-0.99

*Also adjusted for birth cohort, age at first live birth, and age at menarche

Conclusions

- **Modifiers of cancer risk in *BRCA1/2* mutation carriers may exist**
- **These factors should be considered in future risk models**
- **Appropriate epidemiological and statistical methods are required to obtain “correct” risk estimates**



"Duh."

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