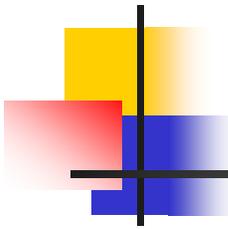


Potential modification of the effect of alcohol on breast cancer risk by variation in genes involved in alcohol metabolism



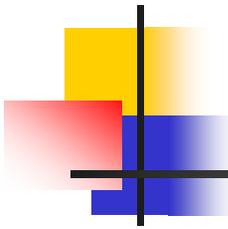
Alcohol and breast cancer

- Initial results inconsistent
- Pooled and meta-analyses more consistently suggested small increased risk from alcohol consumption
 - Approximately 10% increased risk per drink per day
- Alcohol a potentially modifiable risk factor



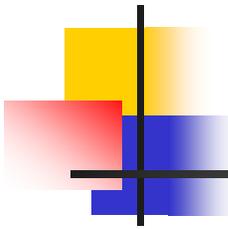
Alcohol metabolism

- Several possible mechanisms for alcohol
- Alcohol dehydrogenase (ADH) catalyses the oxidation of about 80% of ethanol to acetaldehyde
- Acetaldehyde is carcinogenic
- ADH gene has several loci encoding subunits
 - Several with functional polymorphisms



Previous case-control studies

- Increased risk for fast metabolizers (esp. with higher alcohol intake) in premenopausal women only (Freudenheim et al., 1999)
- No effect in mostly postmenopausal women (Hines et al., 2000)
- Terry et al. (in press) consistent with Freudenheim
 - Increased risk for fast metabolizers/15-30g/d and effect greater in premenopausal women



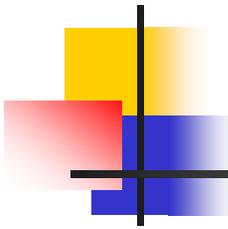
Rationale

- Effect of alcohol may vary across population
 - Overall effect small
 - Sizable subgroups could be at greater risk
- Evidence of gene-environment interaction
 - Support evidence of biological mechanism
 - Alcohol effect less likely to be confounding



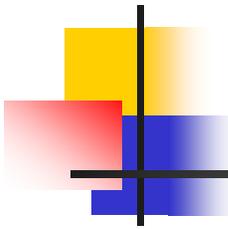
Pilot project

- Funded in 2004 by Program of Research to Integrate Substance Abuse Issues into Mainstream Healthcare (PRISM)
- Funding received to genotype ADH1C I349V polymorphism in BCFR and conduct analysis



Design

- Sister sets with affected and unaffected sisters (New York, Ontario, Northern California, Fox Chase, Utah)
- Cases vs. population controls (Ontario)
- Focus on interaction between genotype and alcohol consumption

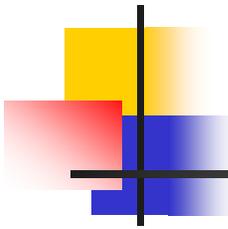


Analysis

- Unconditional logistic regression for population case-control (Ontario)
- Conditional logistic regression for sister sets (only cases with unaffected sister)
- Also for all cases + all sisters
 - Unconditional regression
 - Generalized estimating equations

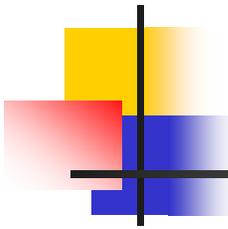
	Genotype	Number of cases	Number of sisters	OR	95% CI
New York Sister Sets					
	GG	21	26	1.00	
	GA	121	135	1.37	0.53-3.53
	AA	130	158	1.2	0.45-3.16
Ontario Sister Sets					
	GG	49	72	1.00	
	GA	170	241	0.86	0.51-1.47
	AA	108	172	1.32	0.69-2.55
California Sister Sets					
	GG	36	54	1.00	
	GA	140	215	1.07	0.60-1.91
	AA	149	194	0.90	0.45-1.81
Fox Chase and Utah Sister Sets					
	GG	10	10	1.00	
	GA	31	35	0.37	0.07-2.02
	AA	35	32	0.24	0.04-1.54

All cases and sisters

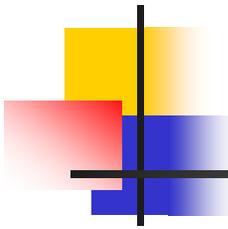


	Unconditional Model	Conditional Model	GEE
Fast, non-drinker	1.0	1.0	1.0
Intermediate, non-drinker	1.0 (0.9-1.2)	0.9 (0.7-1.3)	1.0 (0.9-1.2)
Slow, non-drinker	0.8 (0.6-1.1)	0.9 (0.5-1.6)	0.8 (0.6-1.1)
Fast, < 7 g/d	0.9 (0.7-1.1)	1.2 (0.9-1.7)	0.9 (0.7-1.1)
Intermediate, < 7 g/d	0.8 (0.7-1.0)	1.0 (0.7-1.4)	0.8 (0.7-1.0)
Slow, < 7 g/d	0.9 (0.6-1.2)	0.9 (0.5-1.5)	0.9 (0.7-1.2)
Fast, ≥ 7 g/d	0.8 (0.6-1.1)	1.1 (0.7-1.7)	0.8 (0.6-1.1)
Intermediate, ≥ 7 g/d	0.9 (0.7-1.1)	1.1 (0.7-1.8)	0.9(0.7-1.1)
Slow, ≥ 7 g/d	0.9 (0.6-1.5)	1.6 (0.7-3.7)	0.9 (0.6-1.4)

Premenopausal cases and sisters

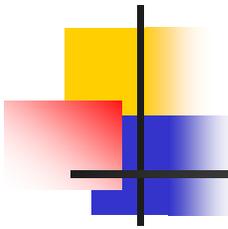


	Unconditional Model	Conditional Model	GEE
Fast, non-drinker	1.0	1.0	1.0
Intermediate, non-drinker	0.9 (0.7-1.1)	0.9 (0.6-1.3)	0.9 (0.7-1.2)
Slow, non-drinker	0.6 (0.4-0.9)	1.5 (0.7-3.5)	0.6 (0.4-0.8)
Fast, < 7 g/d	0.8 (0.6-1.0)	1.3 (0.8-2.2)	0.8 (0.6-1.0)
Intermediate, < 7 g/d	0.7 (0.5-0.9)	1.4 (0.9-2.3)	0.7 (0.5-0.9)
Slow, < 7 g/d	0.8 (0.6-1.2)	0.9 (0.4-1.8)	0.8 (0.6-1.2)
Fast, ≥ 7 g/d	0.8 (0.5-1.1)	1.2 (0.6-2.3)	0.8 (0.5-1.2)
Intermediate, ≥ 7 g/d	0.7 (0.5-1.0)	1.8 (0.9-3.5)	0.7(0.5-1.0)
Slow, ≥ 7 g/d	1.0 (0.6-1.7)	2.6 (0.9-8.4)	1.0 (0.6-1.7)



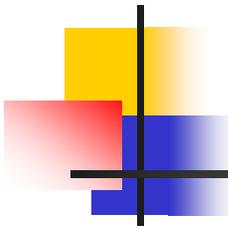
Issues to consider

- Potential for bias
 - Participation related to alcohol consumption
 - Note: Ontario controls marginally more likely to provide blood if they consumed alcohol
- Relationship of genotype to alcohol intake
 - Slow metabolizers more likely to drink
 - True for Ontario cases, but not controls
 - True in Long Island controls



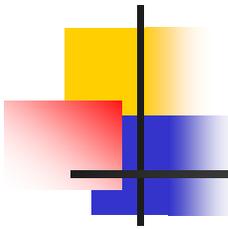
More issues

- Potential differences between cases with participating unaffected sisters and those without
- Heterogeneity across sites with respect to participation and alcohol consumption
- Ethnic differences



Next steps

- More analysis with consideration of the complex issues
- Also, genotyping of additional variants
 - Currently genotyping ADH1B Arg47His



Acknowledgements

- PI's: Mary Beth Terry and Julia Knight
- Genotyping: Regina Santella
- Other co-I's on PRISM pilot: Esther John, Hilmi Ozcelik, Debra Hasin, Laurent Briollais
- Analysis: Lydia Zablotska, Suzanne Thompson, Nayana Weerasooriya
- BCFR