Evaluation of Gene-Environment Interaction for Ovarian Cancer

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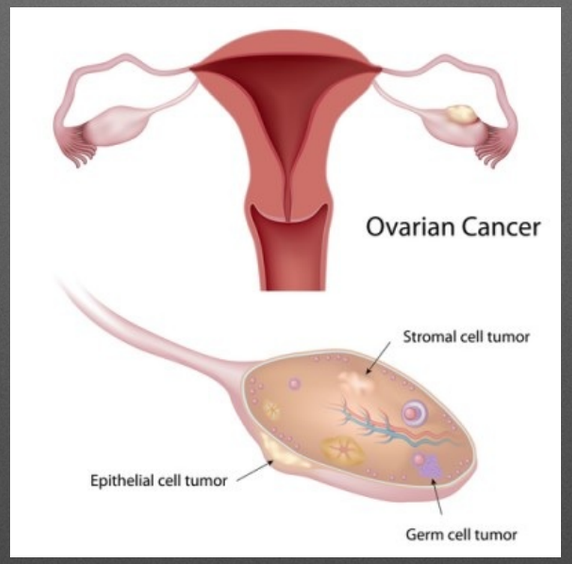
Road Map

- Background
- Gap in Knowledge & Hypothesis
- Study Summary
- Summary Statistics
- Analyses & Results
- Conclusion
- Discussion

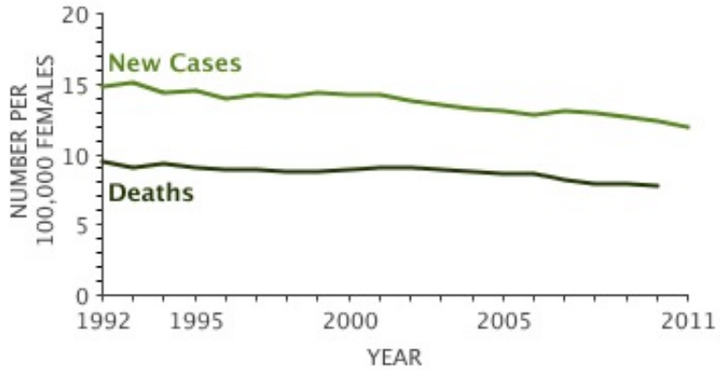
http://www.gpsmagazine.com/2008/02/garmin_nuvi_750_review.php#.U6ZNwxbRy68

Background: General

- Ovarian Cancer
  - Abnormal cell growth in the ovaries
    - Stromal
    - Germ Cell
    - Epithelial
- Treatment
  - Surgery
  - Chemotherapy
  - Radiation Therapy
- Statistics
- Key Mutations



Estimated New Cases in 2014	21,980
% of All New Cancer Cases	1.3%
Estimated Deaths in 2014	14,270
% of All Cancer Deaths	2.4%



Percent Surviving 5 Years
44.6%
2004–2010

http://bionews-tx.com/news/2014/02/03/ovarian-cancer-immunotherapy-at-uthscsa-gets-900000-grant-to-explore-new-treatment-options/
http://www.sgsonline.org/assets/images/Scottsdale_2014/lab%202.jpg
http://www.ovariancancer.org/about/statistics/

Gap in Knowledge & Hypothesis

- Is there an interplay between the BRCA1/2 genes and known reproductive and gynecological risk factors for ovarian cancer?
- Gene-environment interactions work on an multiplicative scale in relation to ovari

http://www.niehs.nih.gov/health/assets/images/hands_holding_two_puzzle_pieces.jpg

Study Summary

- Population: Israeli Women
  - March 1, 1994 - June 30, 1999
- Blood samples
  - Test BRCA1/2 mutation
- Two controls per case
  - Selected from central population registry
  - Matched on age within 2 years
  - Area of birth and place
  - Length of residence

http://supportisrael.us/news/wp-content/uploads/2010/07/israel-map.gif

Study Summary

- Additional Data
  - Age, Ethnicity, Gynecological Surgery, Personal History of Breast Cancer, Family History of Breast or Ovarian Cancer, Parity, and Oral Contraceptive Use
- Environmental factors of specific interest
  - Parity (Dichotomized)
    - 1 child or less (0) VS. More than 1 child (1)
  - Oral Contraceptive Use (Dichotomized)
    - Use for 6 or less years (0) VS. Use for more than 6 years (1)
- Ethnicity: Ashkenazi
  - Large part of data comes from Ashkenazi population
  - Higher rate of BRCA1/2 mutation

http://www.floridaconference.com/iym/wp-content/uploads/2012/09/GodsChildren.jpeg
http://www.gnosticliberationfront.com/yiddish_ashkenazi_traditions_files/image005.jpg

Summary Statistics

Table 1: Characteristics of Women by BRCA1/2 Mutation Status

	Factors	Number of Women with no Mutation (%) n = 1327	Number of Women with Mutation (%) n = 252
1	Cancer	592(45)	240(95)
2	Oral Contraceptive (>6yrs)	56(4)	16(6)
3	No Children	110(8)	21(8)
4	Age (>50)	994(75)	186(74)
5	Ashkenazi	883(67)	219(87)
6	Personal History of Cancer	32(2)	36(14)
7	Undergone Gynecological Surgery	164(12)	19(8)
8	No Family History of Cancer	1,199(90)	192(76)

Table 2: Characteristics of Women by Ovarian Cancer Status

	Factors	Number of Women with No Cancer (%) n = 747	Number of Women with Cancer (%) n = 832
1	BRCA1/2 Mutation	12(2)	240(29)
2	Oral Contraceptive (>6yrs)	41(5)	31(4)
3	No Children	43(6)	88(11)
4	Age (>50)	542(73)	638(77)
5	Ashkenazi	509(68)	593(71)
6	Personal History of Cancer	14(2)	54(6)
7	Undergone Gynecological Surgery	108(14)	75(9)
8	No Family History of Cancer	683(91)	708(85)

Methods for Analyses: Case-Control Design

- Type of observational study
- Compare patients with disease (case) vs no disease (control)
- Retrospective
  - Compare frequency of exposure to a risk factor present in each group
  - Help determine relationship between risk factor and disease

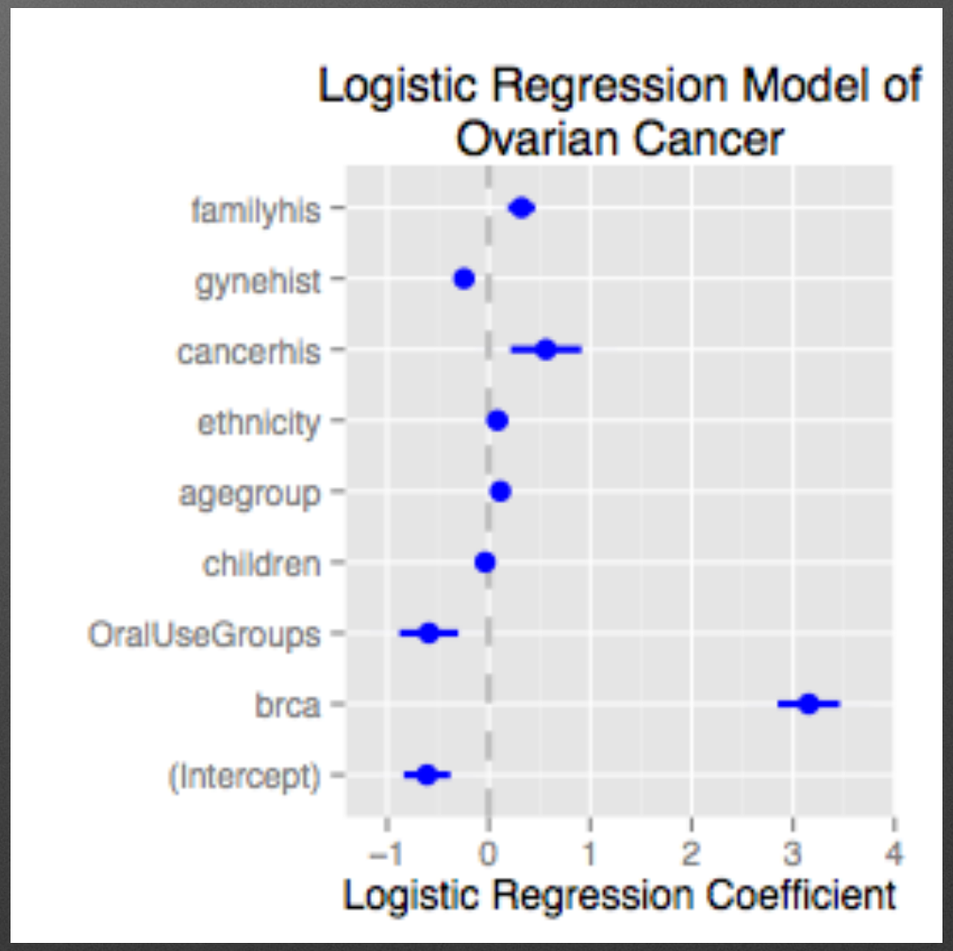
Analysis: Standard Logistic Regression

- Standard Logistic Regression
  - Looks at the effects of covariates on outcome
  - Binary or dichotomous outcome
  - Odds Ratio
    - “How much more likely (or unlikely) it is to be present with y=1 than y=0”

Results:
Standard Logistic Regression

Table 6: Standard Logistic Regression Results Table for Ovarian Cancer

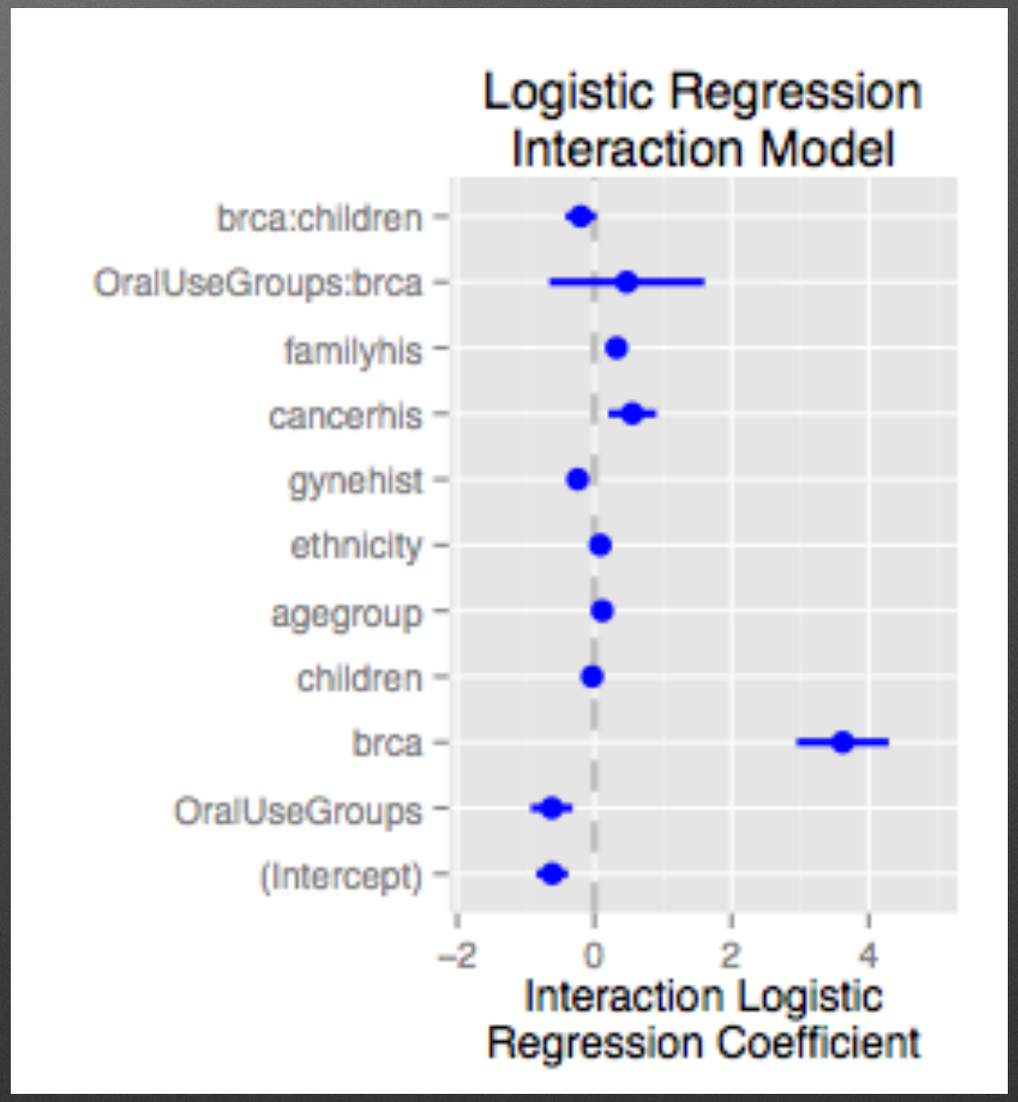
	Factors	Estimate	Std. Error	p-Value	Odds Ratio	95%CI
1	(Intercept)	-0.608	0.229	$7.973e-03$		
2	BRCA1/2	3.153	0.305	$4.934e-25$	23.417	(12.876-42.587)
3	Oral Contraceptive Use	-0.590	0.289	$4.162e-02$	0.555	(0.314-0.978)
4	Parity	-0.035	0.030	$2.477e-01$	0.966	(0.910-1.025)
5	Age Group	0.114	0.046	$1.335e-02$	1.121	(1.024-1.228)
6	Ethnicity	0.085	0.097	$3.813e-01$	1.089	(0.900-1.317)
7	Cancer History	0.564	0.348	$1.052e-01$	1.758	(0.888-3.481)
8	History of Gynecological Surgery	-0.244	0.087	$5.082e-03$	0.784	(0.661-0.929)
9	Family History of Cancer	0.323	0.135	$1.100e-02$	1.381	(1.059-1.801)



Results:
Standard Logistic Regression

Table 7: Standard Logistic Regression on the Interaction Between BRCA1/2 Gene Mutation Given Environmental Factors and that Subjects have Cancer

	Factors	Estimate	Std. Error	p-Value	Odds Ratio	95%CI
1	(Intercept)	-0.616	0.229	$7.230e-03$		
2	Oral Contraceptive Use	-0.623	0.305	$4.127e-02$	0.537	(0.295-0.976)
3	BRCA1/2	3.622	0.670	$6.290e-08$	37.431	(10.076-139.044)
4	Parity	-0.032	0.030	$2.969e-01$	0.969	(0.913-1.028)
5	Age Group	0.114	0.046	$1.334e-02$	1.121	(1.024-1.228)
6	Ethnicity	0.085	0.097	$3.796e-01$	1.089	(0.900-1.317)
7	History of Gynecological Surgery	-0.243	0.087	$5.140e-03$	1.739	(0.661-0.930)
8	Cancer History	0.555	0.349	$1.131e-01$	0.784	(0.877-3.449)
9	Family History of Cancer	0.324	0.135	$1.671e-02$	1.382	(1.060-1.802)
10	Oral Contraceptive Use:BRCA1/2	0.472	1.130	$6.759e-01$	1.604	(0.175-14.681)
11	BRCA1/2:Parity	-0.198	0.219	$3.655e-01$	0.820	(0.534-1.260)



Methods for Analyses: Case-Only Design

- Alternative to case-control design
  - Controls considered to be a sample of the general population
- Used to estimate interaction effect
- Works under two assumptions
  - Rare disease
  - Independence between gene and environmental factor

Methods for Analyses: Case-Only Design

- Back to the two assumptions…
  - Rare disease
    - Case-only estimator is well known to be efficient even when data on unaffected individuals is available
  - G-E independence
    - Condition on additional covariates
    - Also condition on covariates that confound association between disease and the gene and/or environmental factor

Analysis: Logistic Regression-Test for Independence

- Logistic Regression
  - Used to test possible independence
  - Controls only

Results:
Logistic Regression-Test for Independence

- Are the environmental factors independent of the BRC

Table 8: Logistic Regression Results Table for Conditional Probabilities on BRCA1/2 and Each Environmental Factor (Controls Only)

	Environmental Factors	z-score	Alpha	p-Value
1	Oral Contraceptive Use	0.549	0.050	0.583
2	Parity	−0.048	0.050	0.962

Analysis: Case-Only Estimator

- Standard Logistic Regression
- Will only take into account ONLY the cases in our study
- Why can we do this?

Efficiency of the Case-Only Estimator

Goal:

To show that the case-only estimator is a more efficient method to determine interaction effect than a case-control estimator

Variables:

OR = Odds Ratio
Y = Disease outcome [Controls (Y = 0) or Cases (Y = 1)]
G = BRCA1/2 Gene Mutation
E = Environmental Factors (Parity or Oral Contraceptive Use)
GE = Gene-Environment Interaction
C = Confounders

Case-Control Model:

$$Y = \beta_0 + \beta_1 G + \beta_2 E + \beta_3 GE + \beta_p C_p$$

Case-Only Model:

$$G = \alpha_0 + \alpha_1 E_p + \alpha_2 E_O + \alpha_p C_p$$

Consider the use of a logistic regression for analysis in a case-control design, we say that:

$$\ln(OR_{Y \mid C,E,G,GE}) = \ln(OR_{Y=1 \mid C,E,G,GE}) - \ln(OR_{Y=0 \mid C,E,G,GE})$$

Under the rare disease assumption,

$$\ln(OR_{Y=0 \mid C,E,G,GE}) = \ln(OR_{population})$$

Taking into account the independence assumption,

$$\ln(OR_{population}) = 0$$

Thus,

$$\ln(OR_{Y \mid C,E,G,GE}) = \ln(OR_{Y=1 \mid C,E,G,GE}) - \ln(OR_{Y=0 \mid C,E,G,GE})$$
$$= \ln(OR_{Y=1 \mid C,E,G,GE})$$

Efficiency of the Case-Only Estimator

To put it in words,

- The case-only estimator is less variable than the case-control estimator
  - Why?
  - Two key assumptions allow us to NOT take into account extra variability from the log odds ratio of the controls [$\ln(OR_{Y=0 \mid C,E,G,GE})$]

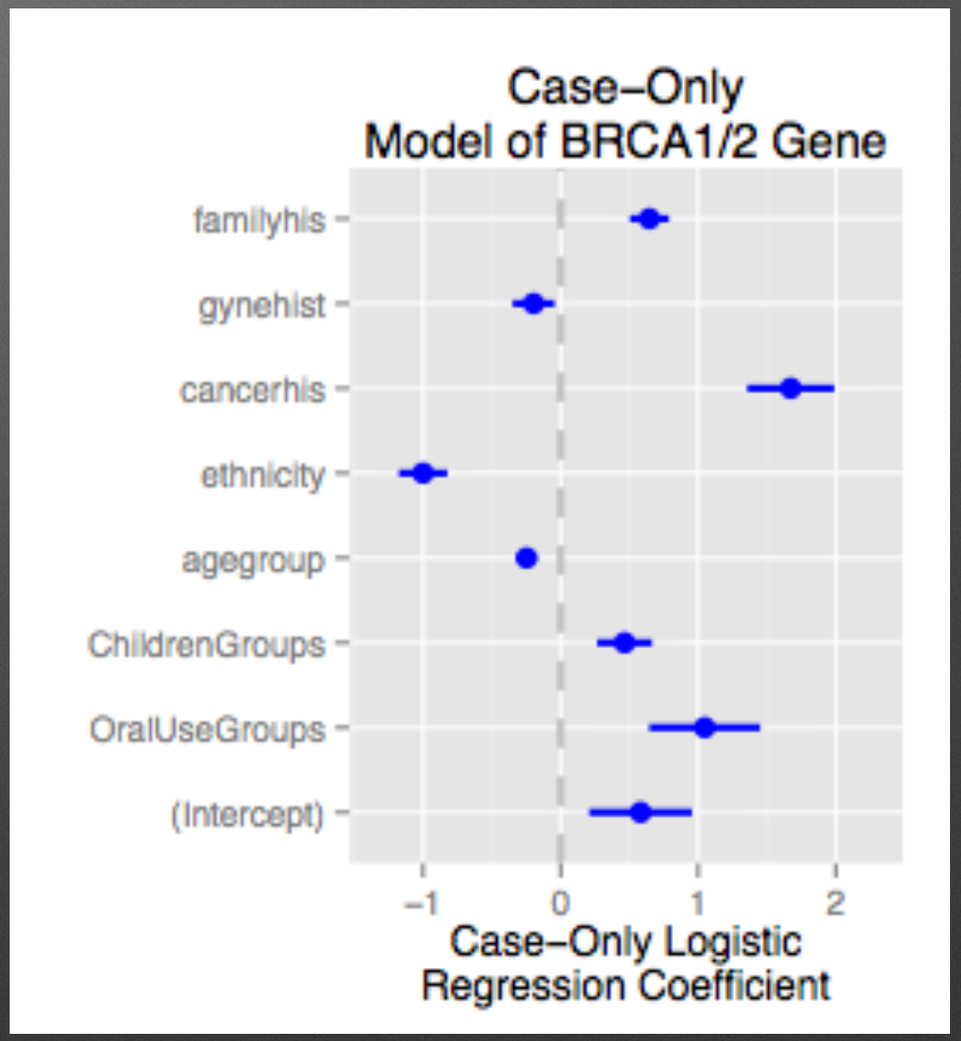
(Note: A detailed proof can be discussed during the lunch break!)

Results:
Case-Only Logistic Regression

Table 9: Case-Only Logistic Regression Assessment on the Interaction Between BRCA1/2 Gene Mutation Given Environmental Factors (Parity Dichotomized) and that Subjects have Cancer

	Factors	Estimate	Std. Error	p-Value	Odds Ratio	95% CI
1	(Intercept)	0.581	0.374	$1.206e-01$		
2	Oral Contraceptive Use	1.047	0.403	$9.434e-03$	2.850	(1.292-6.284)
3	Parity*	0.465	0.200	$1.989e-02$	1.592	(1.076-2.354)
4	Age Group	-0.248	0.073	$6.360e-04$	0.781	(0.677-0.899)
5	Ethnicity	-1.000	0.176	$1.310e-08$	0.368	(0.261-0.519)
6	Cancer History	1.673	0.316	$1.210e-07$	5.327	(2.867-9.897)
7	History of Gynecological Surgery	-0.196	0.152	$1.972e-01$	0.822	(0.609-1.107)
8	Family History of Cancer	0.645	0.141	$5.050e-06$	1.907	(1.445-2.516)

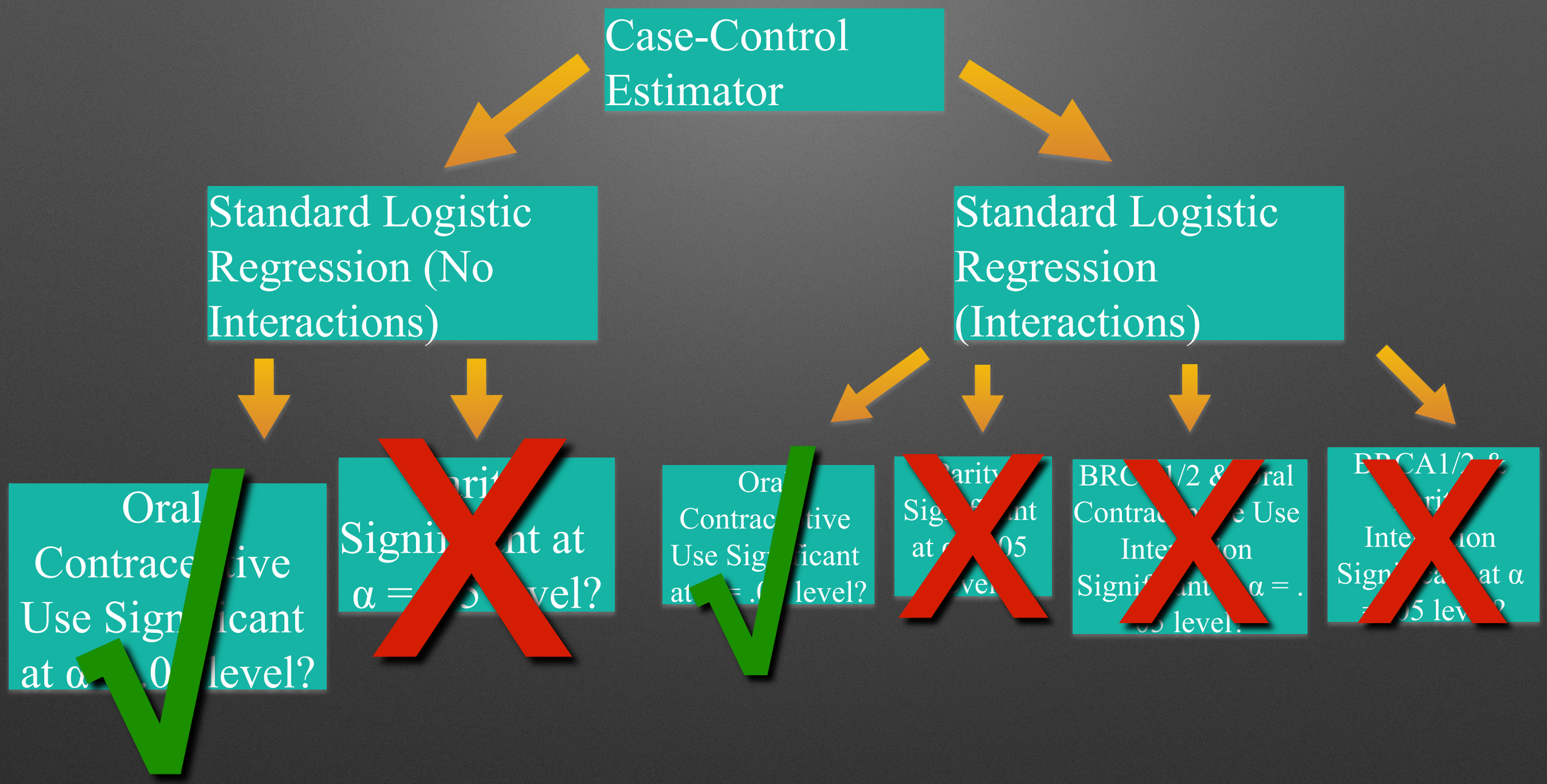
* = Parity Dichotomized



Conclusion

- Objective?
  - Test for an interaction
    - BRCA1/2 vs. Oral Contraceptive Use
    - BRCA1/2 vs. Parity
  - Examine the effect that these factors have on ovarian cancer

Conclusion


Case-Control Estimator
Standard Logistic Regression (No Interactions)
Standard Logistic Regression (Interactions)
Oral Contraceptive Use Significant at α = .05 level?
Parity Significant at α = .05 level?
Oral Contraceptive Use Significant at α = .05 level?
Parity Significant at α = .05 level?
BRCA1/2 & Oral Contraceptive Use Interaction Significant at α = .05 level?
BRCA1/2 & Parity Interaction Significant at α = .05 level?

Conclusion

- Back to the drawing board…
- How do we test for an interaction?
  - We need to check off two important assumptions
    - Assumption 1: Disease under investigation is rare
    - Assumption 2 : Independence between gene and each environmental factor
- Assumption 1
  - Ovarian cancer is, in fact, known to be a rare disease

Conclusion

How do we check for an independence assumption?

Test for Conditional Probabilities with a Logistic Regression (Controls Only)

Is $\alpha > .05$?

YES

Gene and Environmental Factors are INDEPENDENT!

Case-Only Estimator

Case-Only Logistic Regression

Oral Contraceptive Use Significant at $\alpha = .05$ level?

Parity Significant at $\alpha = .05$ level?

Conclusion

- Efficiency of case-only design vs. case-control design
- Use of case-only design
  - Determine that there is indeed an interaction between gene and environment for ovarian cancer
- Oral Contraceptive Use & Parity
  - Not as effective in preventing ovarian cancer with those that have mutation as opposed to those that do not have the mutation

Discussion

- Shortcomings
  - Collection of data
    - Interview bias
    - Recall Bias
  - Generalizability
  - Statistical Power
    - Decreases because of binary/dichotomous variables

Discussion

- Future Studies
  - Run analysis on specific parts(s) of BRCA1/2 gene that are mutated
  - Use continuous data for analysis
  - Increase interests of environmental factors in relation to BRCA1/2 gene
  - Test a different population to increase external validity

Acknowledgements

- We would like to recognize the following people for the support and encouragement throughout the SPQS:
  - Dr. Eric Tchetgen Tchetgen
  - Mr. Caleb Miles
  - Dr. Rebecca Betensky
  - Ms. Tonia Smith
  - Ms. Heather Mattie
  - Ms. Ellie Murray
  - Our fellow SPQS participants

Thank You

- Question?

http://ivyleagueinsecurities.com/wp-content/uploads/2009/10/felt-question.jpg

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