The Effects of Environmental Factors and the BRCA Genetic Mutation on Ovarian Cancer Risk

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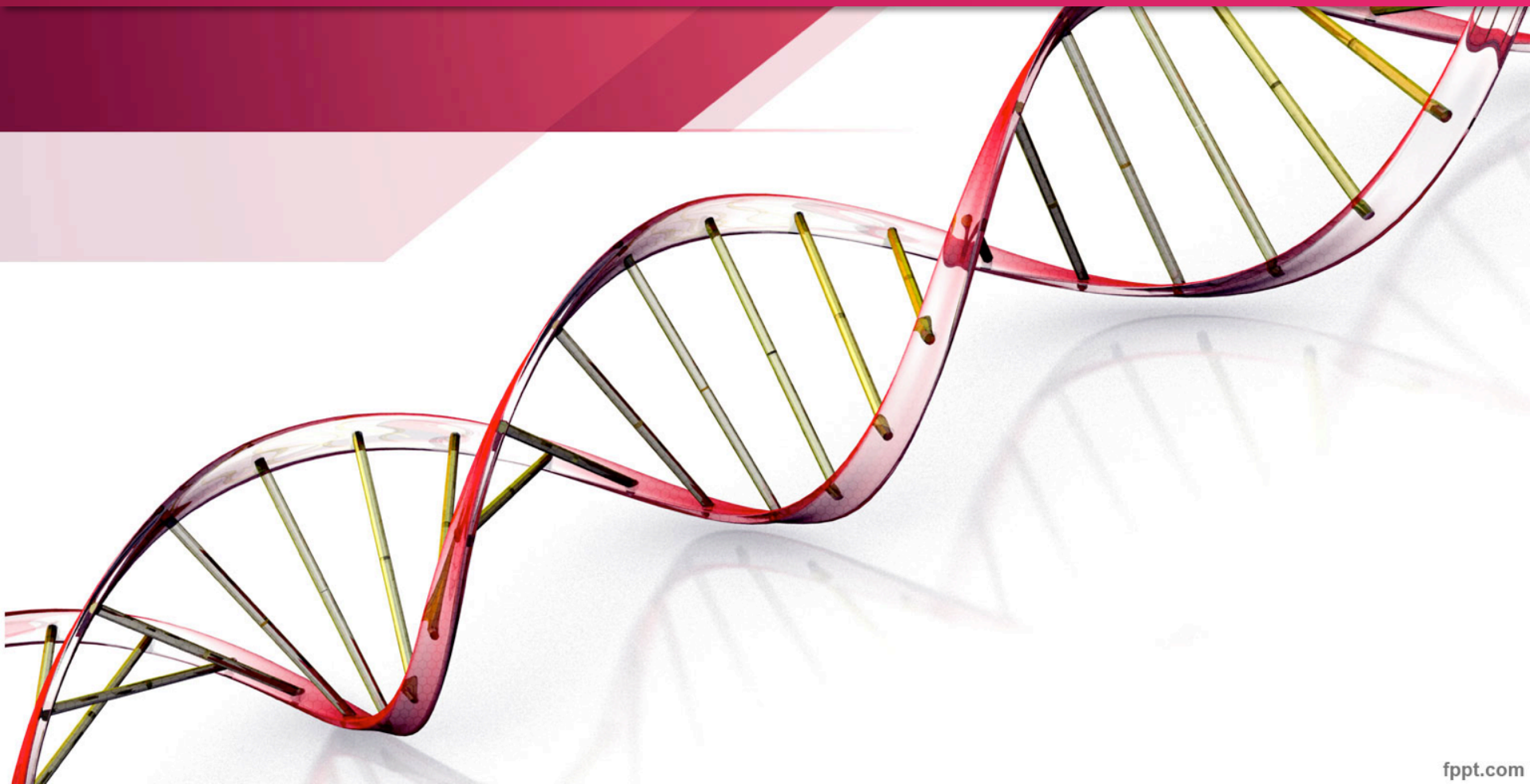
Talk Outline

- Background info & study design
- Analysis methods
- Results, conclusions, moving forward

Part 1: Background



Ovarian Cancer

- Ovarian cancer is a cancer that originates in the tissue of the ovaries, female reproductive gland that produces eggs.

- “The American Cancer Society estimates that in 2015, about 21,290 cases of ovarian cancer will be diagnosed and 14,180 women will die of ovarian cancer in the United States”

- “The overall five-year survival rate for women with ovarian cancer is 45%”

Known Risk Factors

- Genetics
  - Breast Cancer Genetic mutations (BRCA1 and BRCA2)
  - Lynch Syndrome
- Reproductive History and Infertility
  - Oral Contraceptive Use
  - Parity
- Family History
  - Ovarian Cancer
  - Other female reproductive cancers
- Increasing Age
- Hormone Replacement Therapy
- Obesity

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Research Question

Are there any significant interactions between the BRCA mutation and the environmental factors: parity and oral contraceptive use?

Research Study

- Population
  - Women in Israel (Ashkenazi Jews)
  - 1994-1999
- Case-control Design
  - Ovarian cancer is rare
- Covariates
  - Parity, Oral Contraceptive use, BRCA mutation, Age, Ethnicity, Family History, Gynecology History, Cancer History

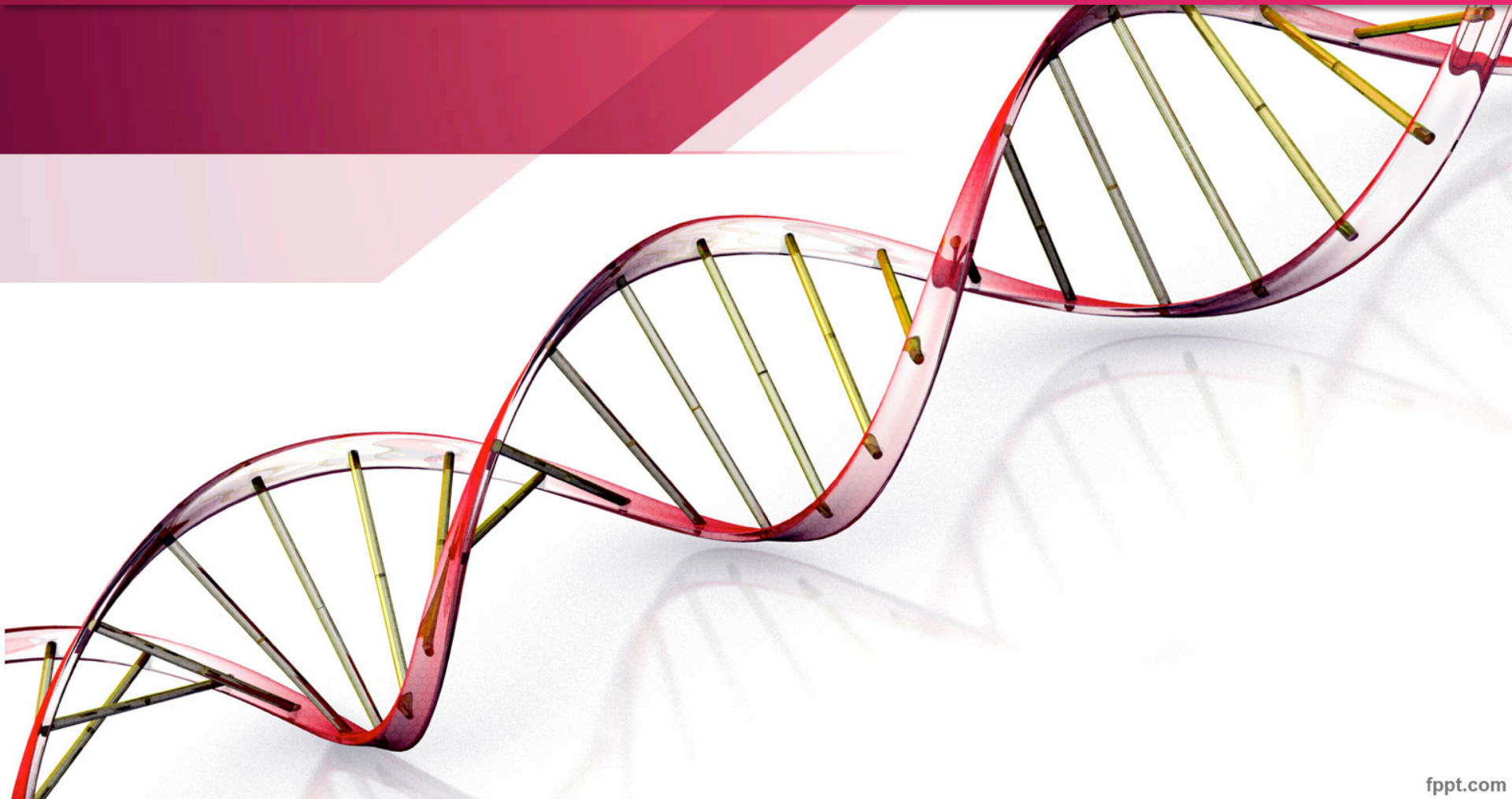
Descriptive Statistics

Characteristic	Cases (N = 832)	Control (N = 747)
	Mean (Std)	**Mean (Std)**
Use of Oral Contraceptives (yrs)	0.70 (2.47)	0.89 (2.48)
Number of Children	2.61 (1.88)	2.81 (1.84)
BRCA Mutation	**N (%)**	**N (%)**
Present	240 (29)	12 (1.7)
Not Present	592 (71)	735 (98.3)
Age Group	**N (%)**	**N (%)**
< 40	31 (3.73)	68 (9.10)
40s	163 (19.59)	137 (18.34)
50s	205 (24.64)	155 (20.75)
60s	240 (28.85)	218 (29.18)
⩾ 70	193 (23.20)	169 (22.62)

Descriptive Statistics

Ethnicity	**N (%)**	**N (%)**
Ashkenazi	593 (71.27)	509 (68.14)
Non-Ashkenazi	193 (23.20)	183 (24.50)
Mixed ancestry	46 (5.53)	55 (7.36)
Cancer History		
Yes	54 (6.49)	14 (1.87)
No	778 (93.51)	733 (98.13)
History of breast or ovarian cancer in at least one first- degree relative		
None	708 (85.10)	683 (91.43)
1 relative	70 (8.41)	54 (7.23)
> 1 relative	54 (6.49)	10 (1.34)
Gynecological History		
0	757 (90.99)	639 (85.54)
2	75 (9.01)	108 (14.46)

Part 2: Analysis



Logistic Regression Models

1. Isolating variables of interest and examining interaction terms

$$logit(P(Y=1)) = \beta_0 + \beta_1 G + \beta_2 E_1 + \beta_3 E_2 + \beta_4 G E_1 + \beta_5 G E_2$$

Variable	Estimate	p-value
Intercept	-0.097	0.32
BRCA	3.67	<0.0001
Oral Contraceptives	-0.32	0.025
Parity	-0.021	0.46
BRCA*Oral Contraceptives	0.36	0.61
BRCA*Parity	-0.21	0.33

$\alpha = 0.05$

Logistic Regression Models

2. Model with all variables

$$logit(P(Y=1)) = \beta_0 + \beta_1 G + \beta_2 E_1 + \beta_3 E_2 + \beta_4 C + \ldots + \beta_8 C$$

Variable	Estimate	p-value
(Intercept)	-0.55	0.021
BRCA	3.13241	<0.0001
Oral Contraceptives	-0.19	0.21
Parity	-0.033	0.27
Age	0.10	0.037
Ethnicity	0.080	0.41
Cancer History	0.59	0.093
Gynecological History	-0.24	0.0062
Family History	0.34	0.013

Logistic Regression Models

3. Model with all variables and interaction terms

$$logit(P(Y=1)) = \beta_0 + \beta_1 G + \beta_2 E_1 + \beta_3 E_2 + \beta_4 G E_1 + \beta_5 G E_2 + \ldots + \beta_{10} C$$

Variable	Estimate	p-value
Intercept	-0.56	0.019
BRCA	3.59	<0.0001
Oral Contraceptives	-0.20	0.20
Parity	-0.030	0.32
Age	0.10	0.036
Ethnicity	0.080	0.41
Cancer History	0.57	0.10
Gynecological History	-0.24	0.0062
Family History	0.33	0.013
BRCA*Oral Contraceptives	0.28	0.69
BRCA*Parity	-0.21	0.35

Problem with Interaction

$$logit(P(Y=1)) = \beta_0 + \beta_1 G + \beta_2 E + \beta_3 GE$$

$$e^{\beta_3} = \frac{OR(G,E \mid Y=1)}{OR(G,E \mid Y=0)}$$

1. Sample size issue (Controls with BRCA)

2. Not the best estimate of interaction coefficient

Case – Only Assumptions

1. Ovarian cancer is a rare disease

$$OR(G,E \mid Y=0) \approx OR(G,E)$$

2. The BRCA genetic mutation and environmental factors are independent

$$OR(G,E) = 1$$

$$\Rightarrow \quad OR(G,E \mid Y=0) = 1$$

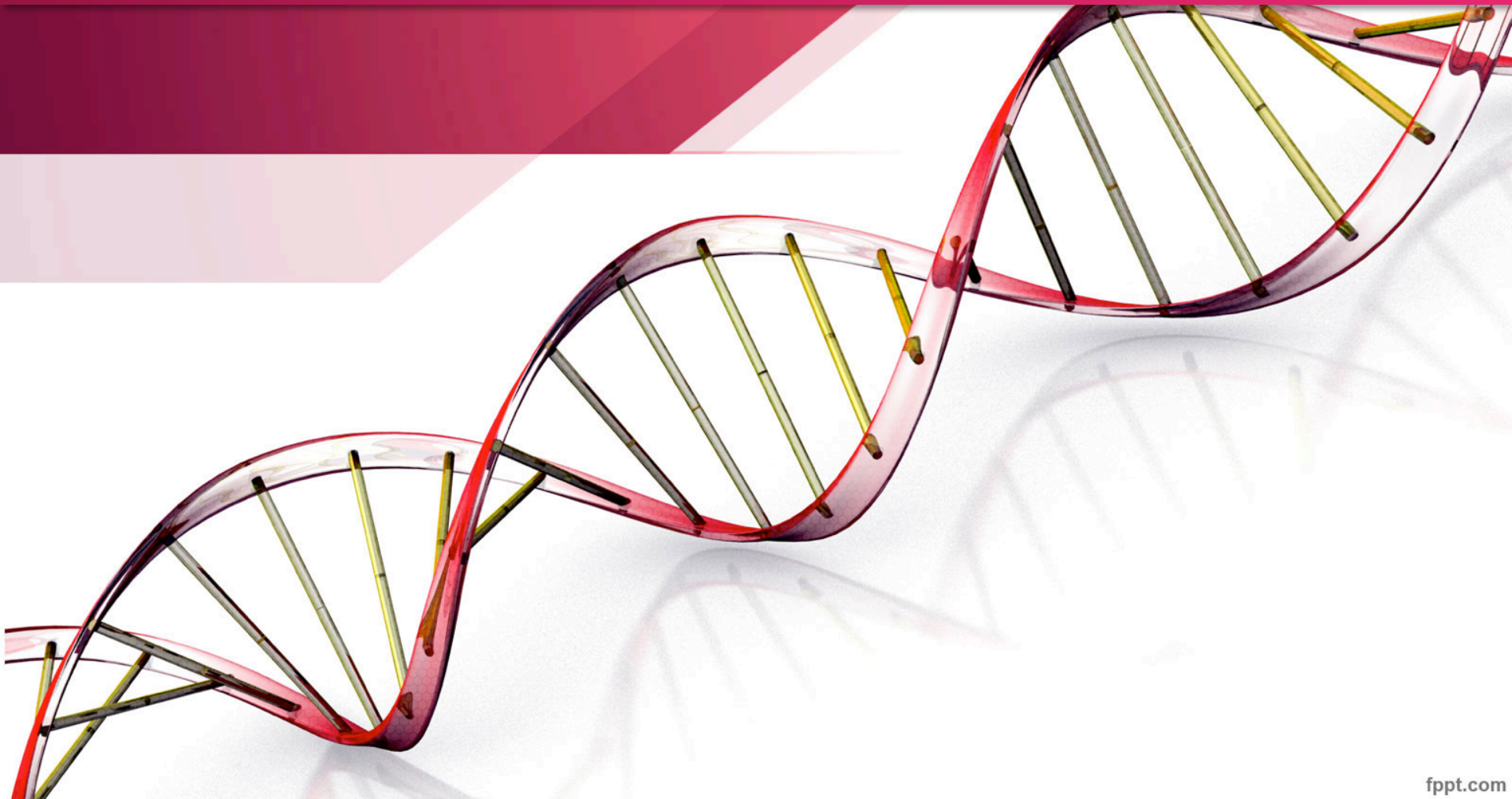
Case - Only Model

Now we need to estimate: $OR(G,E \mid Y=1)$

$$logit(P(G=1)) = \beta_0 + \beta_1 E$$

β_1 In the case-only model = β_3 in the general model

Part 3: Results



Research Question - Revisit

Are there any significant interactions between the BRCA mutation and the environmental factors: parity and oral contraceptive use?

Results : Interactions

- Interaction 1: BRCA and Oral Contraceptive Use

Variable	Estimate	95 % CI	p-value
Intercept	-0.99	(-1.16, -0.82)	<0.0001
Oral Contraceptives	0.43	(0.055, 0.79)	0.023

- Interaction 2: BRCA and Parity

Variable	Estimate	95 % CI	p-value
Intercept	-0.60	(-0.86, -0.34)	<0.0001
Parity	-0.12	(-0.21, -0.035)	0.0070

Results: With Covariates

Interactions Accounting for Covariates (N = 832)

Variable	Estimate	95% CI	p-value
(Intercept)	0.81	(0.065, 1.56)	0.034
Oral Contraceptives	0.24	(-0.18, 0.70)	0.27
Parity	-0.038	(-0.14, 0.061)	0.46
Age	-0.21	(-0.37, -0.061)	0.0061
Ethnicity	-0.91	(-1.28, -0.57)	0.0001
Cancer History	1.59	(0.99, 2.23)	0.0001
Gynecological History	-0.17	(-0.48, 0.12)	0.27
Family History	0.60	(0.33, 0.88)	0.0001

Conclusions

- Overall, the interaction between BRCA and the environmental variables were not significant at the 0.05 level
- Estimate for the interaction between BRCA mutation and use of oral contraceptives is positive, indicating increase in the risk of ovarian cancer
- Estimate for the interaction between BRCA mutation and parity is negative, indicating decrease in the risk of ovarian cancer
- Data suggests use of oral contraceptives reduces risk of ovarian cancer in the overall population
- BRCA mutation is the biggest indicator for ovarian cancer risk

Limitations

- Retrospective studies
  - Self-reported data
- Case-control study
  - Cannot estimate risk or rate, only odds ratio
- Case-only analysis
  - limited to analysis of interactive coefficient
- Generalizability

Future Research

- More generalizable study population
- Relating environmental factors to other types of cancer
- Better understanding of biological mechanisms

References

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