

Cancer Epidemiology

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Goals

- Answer the question:
“What is cancer epidemiology?”
- Understand the key issues for critically evaluating a cancer epidemiology journal article
- Calculate and interpret an odds ratio and 95% confidence interval
- Examine some examples of cancer epidemiology results

What is Epidemiology?

- It is not the study of skin!
- Originally, the study of spread of disease (epidemics)
- The study of factors that influence the frequency and distribution of diseases, such as cancer, in an effort to find the cause and therefore prevent them

What is Cancer Epidemiology?

- The study of how risk factors may contribute to the development of cancer
 - Environment
 - Occupational hazards
 - Personal characteristics/habits
 - ▣ Demographics
 - ▣ Genetics
 - ▣ Diet
 - ▣ Smoking
 - ▣ Lifestyle

Types of Epidemiologic Studies

- Observational
 - Cross-sectional
 - Case-Control
 - Cohort
- Experimental
 - Clinical Trial

Case-Control vs. Cohort Study Design

- Case-Control Study
 - Select sample from a population of people with the disease (cases)
 - Select a sample from a population at risk that is free of the disease (controls)
 - Measure the exposures
- Cohort Study
 - Select a sample from the population
 - Measure exposures variables
 - Follow-up the study population over time
 - Measure outcome variables (disease present or absent)

Case-Control vs. Cohort Study Advantages

- Case-Control Study
 - Useful for studying rare conditions
 - Short duration
 - Relatively inexpensive
 - Yields odds ratio (a good approximation of relative risk when disease is rare)
- Cohort Study
 - Establishes sequence of events
 - Avoids bias in measuring exposures
 - Can study several outcomes
 - Yields incidence, relative risk

Case-Control vs. Cohort Study

Disadvantages

- Case-Control Study
 - Does not guarantee temporal sequence of events
 - Potential bias in measuring exposures
 - Potential recall bias
 - Limited to one outcome variable
 - Does not yield disease incidence
- Cohort Study
 - Often requires large sample size
 - Long follow-up time is often required
 - Often more costly
 - Not feasible for rare outcomes

Measures of Association

Odds Ratio and Relative Risk

- A statistical comparison between two groups of people
- Used to determine if a specific risk factor is related to a disease
- Case-Control Study
 - Odds Ratio (OR): the odds of disease in exposed population divided by the odds of disease in unexposed population
- Cohort Study
 - Relative Risk (RR): the disease rate in the exposed population divided by the disease rate in the unexposed population

Critically Evaluating a Cancer Epidemiology Journal Article

- Research Objectives
- Study Population
- Exposure Assessment
- Sample Size and Statistical Analysis
- Evaluation of the Results

Critically Evaluating a Cancer Epidemiology Journal Article

- Research Objectives
 - What is the primary study hypothesis?
 - Are there secondary hypotheses?
 - ▣ If so, what are they?

Critically Evaluating a Cancer Epidemiology Journal Article

- Study Population
 - Is the study "population-based" or "hospital-based"?
 - Who are the study population?
 - 📁 How is a "case" defined?
 - Are incident cases or prevalent cases selected?
 - Who was excluded from the pool of possible cases?
 - 📁 How were the controls selected?
 - Do the controls form an appropriate comparison group?

Critically Evaluating a Cancer Epidemiology Journal Article

- Exposure Assessment
 - What is the exposure variable of primary interest?
 - How is information about exposure obtained?
 - How accurate is the assessment of exposure?
 - Who constitute the "exposed" and "unexposed" groups?
 - Are other potential exposures that are risk factors for the outcome of interest controlled?

Critically Evaluating a Cancer Epidemiology Journal Article

- Sample Size and Statistical Analysis
 - Is the sample size adequate to answer the question being asked?
 - Is statistical power assessed?
 - Are the methods of statistical analysis appropriate to answer the research question?

Critically Evaluating a Cancer Epidemiology Journal Article

- Evaluation of the Results
 - What are the main findings of the study?
 - Are the findings generalizable to other populations?
 - What are the study strengths and limitations?

In-Class Hypothetical Study

- The Hypothesis
 - M&M exposure is associated with developing Peanut Butter Cup disease (PBC)
 - ☐ PBC is considered a rare disease

Choose Your Study Design

- Rare disease
- Short amount of time to conduct study
- Limited funds available
- Small sample size available

CASE-CONTROL STUDY

- Define a case
 - Has PBC
- Define a control
 - Does not have PBC
- Assess exposure among cases
 - Has M&M's?
- Assess exposure among controls
 - Does not have M&M's

Calculating the Odds Ratio: Step One

- Cases
 - How many have PBC disease?
 - How many cases have M&M's exposure?
- Controls
 - How many do not have PBC disease?
 - How many controls have M&M's exposure?
- Fill in the 2 x 2 table

The Classic 2 x 2 Table

PBC
Disease

No PBC
Disease

M&M's
Exposure

No M&M's
Exposure

A	B
C	D

Calculating the Odds Ratio: Step Two

- Using the data in the 2 x2 table:
 - Calculate the odds of PBC disease among the people with M&M's exposure
 - Calculate the odds of PBC disease among the people without M&M's exposure

Calculating the Odds of PBC among those with and without Exposure

$$\text{Odds of PBC among those with M\&M's exposure} = \frac{\# \text{ with PBC among those with M\&M's exposure}}{\# \text{ without PBC among those with M\&M's exposure}}$$

$$\text{Odds of PBC among those without M\&M's exposure} = \frac{\# \text{ with PBC among those without M\&M's exposure}}{\# \text{ without PBC among those without M\&M's exposure}}$$

Calculating the Odds Ratio: Step 3

- Take the ratio of the two odds

	PBC	No PBC
M&M's	A	B
No M&M's	C	D

$$\text{Odds Ratio} = \frac{\text{Odds of PBC among the exposed}}{\text{Odds of PBC among the unexposed}}$$

$$= \frac{\frac{A}{B}}{\frac{C}{D}} = \frac{A * D}{B * C}$$

Calculating the 95% Confidence Interval

	PBC	No PBC
M&M's	A	B
No M&M's	C	D

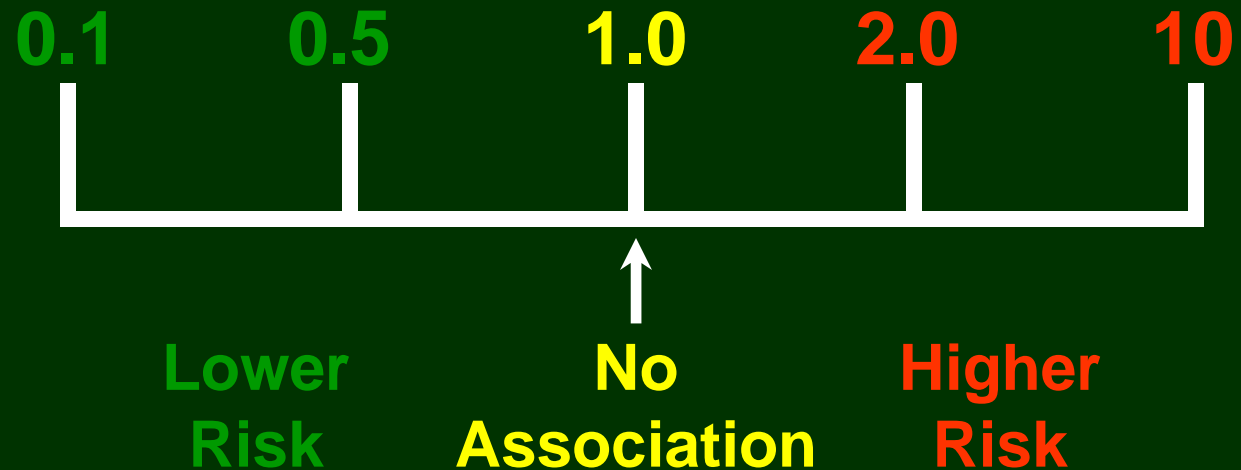
Standard Error of the Ln(OR) =

$$\sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}$$

95% Confidence Limit for the Odds Ratio =

$$\exp \left(\ln \left(\frac{A * D}{B * C} \right) \pm 1.96 * \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}} \right)$$

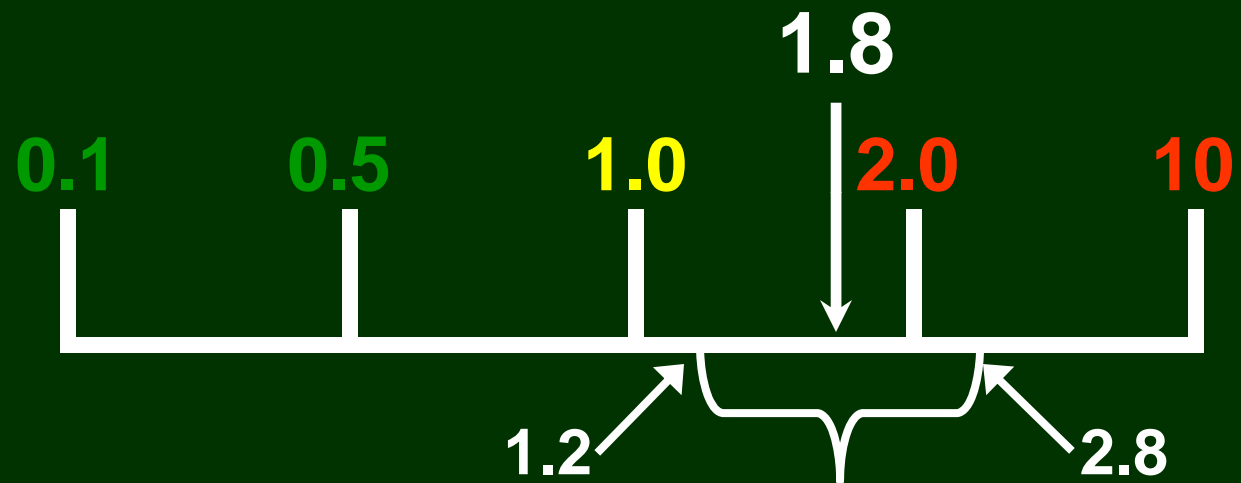
How to Interpret an Odds Ratio



OR > 1.0: People with exposure are more likely to develop disease than people without exposure

OR < 1.0: People with exposure are less likely to develop disease than people without exposure

How to Interpret a 95% Confidence Interval (CI)

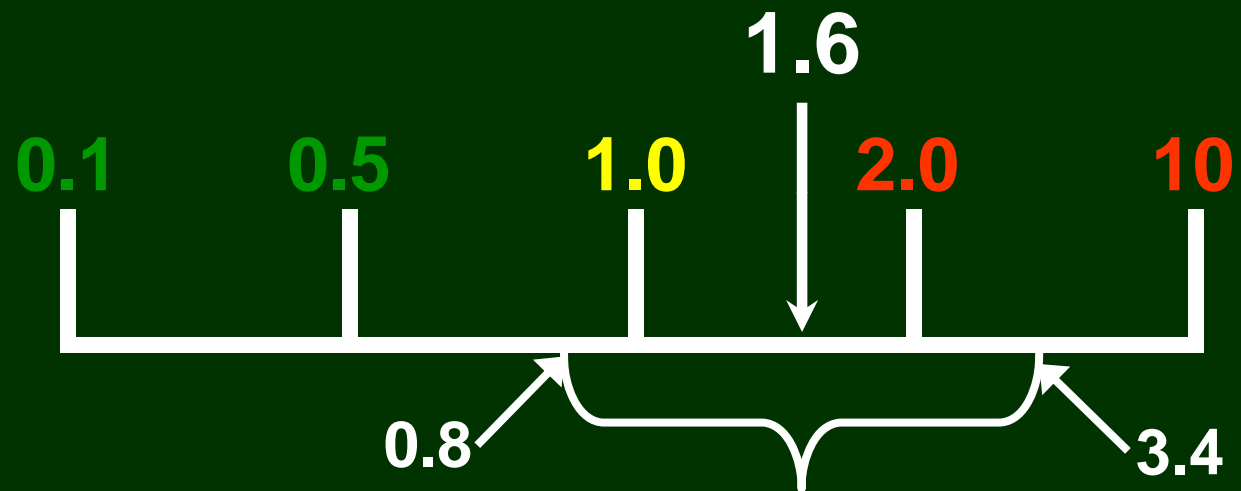


OR=1.8 95% CI (1.2, 2.8)

Confidence Interval does not include 1.0

The OR is statistically significant → people with exposure are 1.8 times more likely to develop disease than people without exposure

How to Interpret a 95% Confidence Interval (CI)



OR=1.6 95% CI (0.8, 3.4)

Confidence Interval includes 1.0

The OR is not statistically significant

The Long Island Breast Cancer Study Project

- Case-Control Study of the Environment and Breast Cancer
- Cases
 - LI residents newly diagnosed with breast cancer between 7/96 and 8/97
- Controls
 - LI residents never diagnosed with breast cancer
 - Randomly selected from the LI population

The Long Island Breast Cancer Study Project

- Exposure assessment
 - Questionnaire
 - Biomarkers measured in urine and blood
 - Diet through a food frequency qx
 - Environmental samples
 - ▣ Dust
 - ▣ Soil
 - ▣ Water
 - Genetic polymorphisms

LIBCSP Primary Hypotheses

- Higher levels of organochlorine compounds (e.g., DDT) are associated with increased risk of breast cancer
- Higher levels of PAH DNA adducts (biomarker of exposure to PAH) are associated with increased risk of breast cancer

LIBCSP Additional Hypotheses

Growing List

- Electromagnetic fields and breast cancer
- Electric blanket use and breast cancer
- Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk
- Myeloperoxidase genotype, fruit and vegetable consumption, and breast cancer risk
- Polymorphism in the DNA repair gene XPD, polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, and breast cancer risk
- Polymorphisms in XRCC1 modify the association between polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, dietary antioxidants, and breast cancer risk
- Body size changes in relation to postmenopausal breast cancer
- MGMT genotype modulates the associations between cigarette smoking, dietary antioxidants and breast cancer risk
- Associations between breast cancer risk and the catalase genotype, fruit and vegetable consumption, and supplement use
- MnSOD Val-9Ala genotype, pro- and anti-oxidant environmental modifiers, and breast cancer
- IGF1 CA repeat polymorphisms, lifestyle factors and breast cancer risk
- ADH3 genotype, alcohol intake and breast cancer risk
- Estrogen metabolism and breast cancer
- Fruits, vegetables, and micronutrient intake in relation to breast cancer survival
- Catechol-O-methyltransferase haplotypes and breast cancer among women

LIBCSP Additional Hypotheses

Growing List

- Relationship between urinary 15-F2t-isoprostane and 8-oxodeoxyguanosine levels and breast cancer risk
- OGG1 polymorphisms and breast cancer risk
- Effects of glutathione S-transferase A1 (GSTA1) genotype and potential modifiers on breast cancer risk
- Shift work, light at night, and breast cancer
- Dietary flavonoid intake and breast cancer risk among women
- Reported residential pesticide use and breast cancer risk
- Genetic polymorphisms in the cyclooxygenase-2 gene, use of nonsteroidal anti-inflammatory drugs, and breast cancer risk
- Preeclampsia, pregnancy-related hypertension, and breast cancer risk
- Age and menopausal effects of hormonal birth control and hormone replacement therapy in relation to breast cancer risk
- Polymorphisms of one-carbon-metabolizing genes and risk of breast cancer
- A functional 19-base pair deletion polymorphism of dihydrofolate reductase (DHFR) and risk of breast cancer in multivitamin users
- Cooked meat and risk of breast cancer--lifetime versus recent dietary intake
- Genetic variation of TP53, polycyclic aromatic hydrocarbon-related exposures, and breast cancer risk
- Interactions among GSTM1, GSTT1 and GSTP1 polymorphisms, cruciferous vegetable intake and breast cancer risk
- Polymorphisms in Nucleotide Excision Repair Genes, Polycyclic Aromatic Hydrocarbon-DNA Adducts, and Breast Cancer Risk

LIBCSP Study: Organochlorines & BRCA

- Concern among LI residents about effects of widespread spraying of pesticides, especially DDT, a persistent organochlorine compound (OC)
- DDT used for mosquitoes and gypsy moth control was banned in 1972
- DDT and its metabolite DDE as well as other OCs have been shown to have estrogenic and antiestrogenic action
- Studies conducted in the 1990's observed increased breast cancer risk in relation to OC levels

LIBCSP Study: Organochlorines & BRCA

- LIBCSP was the largest study at that time to address the hypothesis that higher OC levels are associated with increased risk
 - 1508 cases and 1556 controls
- Blood samples were collected from 73% of participants (cases and controls)
- 646 cases and 429 controls were selected from participants who provided blood samples
 - OC concentrations were measured in plasma

Organochlorine Compounds and Breast Cancer

Gammon MD et al. 2002 CEBP; 11:686-97

Table 3. Age-adjusted ORs and 95% CIs for breast cancer in relation to log-transformed serum organochlorine levels adjusted for serum lipid levels among breast cancer cases and controls, Long Island Breast Cancer Study Project, 1996 –1997

Organochlorine compound	Quintile cutpoints (ng/gm lipid)	Cases	Controls	OR	(95% CI)	
DDE	Quintile 1	306.91	122	84	1.00	
	Quintile 2	306.91–515.00	110	83	0.84	(0.56–1.26)
	Quintile 3	515.01–798.24	127	84	0.91	(0.60–1.36)
	Quintile 4	798.25–1,373.48	123	85	0.82	(0.54–1.25)
	Quintile 5	1,373.49–11,818.78	150	83	0.95	(0.62–1.46)
DDT	Quintile 1	44.79	129	81	1.00	
	Quintile 2	44.79–61.43	96	82	0.72	(0.48–1.08)
	Quintile 3	61.44–81.20	123	82	0.94	(0.63–1.39)
	Quintile 4	81.21–108.03	134	82	1.00	(0.67–1.48)
	Quintile 5	108.03–747.92	133	82	0.97	(0.66–1.44)

Organochlorine Compounds and Breast Cancer: Conclusion

- Little evidence of an increased risk of breast cancer in relation to DDT, DDE or other OCs
- Consistent with findings of studies that had been published after the LIBCSP had been conducted
- Strengths
 - Large population-based sample
 - Comprehensive assessment of potential and established breast cancer risk factors
- Limitations
 - Less than optimal response among the controls
 - Single blood sample used to assign exposure level

LIBCSP Study: Reported Pesticide Use

- A wide variety of pesticides other than DDT and other OCs were used on LI
- Many of these pesticides have the potential to influence breast cancer risk but have not been studied
 - Biomarkers may be short term or not available
- To assess exposure to other residential pesticides, pesticide use for 15 pest problems was ascertained
- Patterns of pesticide use was assessed
 - Who applied
 - Type of product applied
 - Frequency of application
 - Duration of use

LIBCSP Study: Reported Pesticide Use Questionnaire

C33. Did you or others use products to control (PEST)?	C37. On average, about how many times per year were these products applied?	C38. About how many years in your lifetime were these products applied?
a. Ants, carpenter ants or cockroaches YES.....1 NO.....2 (C33b) DONT KNOW...8 (C33b)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
b. Bees or wasps YES.....1 NO.....2 (C33c) DONT KNOW...8 (C33c)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
c. Flies or mosquitoes YES.....1 NO.....2 (C33d) DONT KNOW...8 (C33d)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
d. Moths, silverfish, or caterpillars YES.....1 NO.....2 (C33e) DONT KNOW...8 (C33e)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
e. Mice, rats, gophers or moles YES.....1 NO.....2 (C33f) DONT KNOW...8 (C33f)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
f. Fleas or ticks, except on pets YES.....1 NO.....2 (C33g) DONT KNOW...8 (C33g)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
g. Termites YES.....1 NO.....2 (C33h) DONT KNOW...8 (C33h)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
h. Any other type of pest in your home YES (SPECIFY) . 1 NO.....2 (C33i) DONT KNOW...8 (C33i)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS

C39. Did you or others apply ...	C42. On average, about how many times per year were these products applied?	C43. About how many years in your lifetime were these products applied?
a. Weed killers? YES.....1 NO.....2 (C39b) DONT KNOW...8 (C39b)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
b. Lawn insecticides? YES.....1 NO.....2 (C39c) DONT KNOW...8 (C39c)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
c. Chemicals for insects or diseases of trees? YES.....1 NO.....2 (C39d) DONT KNOW...8 (C39d)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
d. Pesticides on a vegetable or fruit garden? YES.....1 NO.....2 (C39e) DONT KNOW...8 (C39e)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
e. Chemicals for insects or diseases of other outdoor plants? YES.....1 SPECIFY..... NO.....2 (C39f) DONT KNOW...8 (C39f)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
f. Any other type of pesticides used outdoors? YES.....1 NO.....2 (C39g) DONT KNOW...8 (C39g)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS
g. Chemicals for diseases or bugs of indoor plants? YES.....1 SPECIFY..... NO.....2 (C44) DONT KNOW...8 (C44)	TIMES PER WEEK.....1 MONTH.....2 YEAR.....3	YEARS

Reported Pesticide Use and Breast Cancer

Teitelbaum SL et al. AJE 2007; 165: 643-51

Table 1. Age-adjusted odds ratios (OR) and 95 percent confidence intervals (CI) for breast cancer, according to lifetime applications of pesticides, among 3,058 women in Nassau and Suffolk Counties, NY, 1996-1997

	Lifetime applications		Number		OR	95% CI
	Min	Max	Case	Control		
Lawn and Garden (LG) Pesticide Use						
Never used LG pesticides			240	305	1.00	(reference)
Quartile 1	1	15	282	303	1.25	0.99, 1.59
Quartile 2	16	44	341	313	1.45	1.15, 1.83
Quartile 3	45	108	301	307	1.29	1.02, 1.63
Quartile 4	109	20820	330	308	1.38	1.10, 1.74
Nuisance Pest (NP) Pesticide Use						
Never used NP pesticides			100	117	1.00	(reference)
Quartile 1	1	8	290	364	0.97	0.71, 1.33
Quartile 2	9	29	338	358	1.19	0.87, 1.61
Quartile 3	30	96	393	357	1.34	0.99, 1.82
Quartile 4	97	9608	383	357	1.29	0.95, 1.75

Reported Pesticide Use and Breast Cancer: Conclusion

- Higher overall use of lawn and garden pesticides was associated with increased breast cancer risk
 - No observed dose response with increasing reported use
- No association with overall nuisance pest pesticide use
- Interpretation of these findings in the context of other studies is difficult
- Popular pesticides that replaced OCs have been classified as probably carcinogens and others have been shown to have some hormonal potential

LIBCSP Study: Nucleotide Excision Repair Genes

- DNA is regularly damaged by mutagens
- Reduced DNA repair capacity may lead to genetic instability and carcinogenesis
- Genes involved in DNA repair have been proposed as candidate cancer susceptibility genes
- Nucleotide excision repair (NER) pathway repairs a wide variety of DNA damage
- Reductions in DNA repair capacity in the NER pathway may be associated with increased susceptibility to breast cancer

Nucleotide Excision Repair Genes and Breast Cancer

Crew et al. CEBP 2007;16:2033-41

Table 1. Genotype frequency for polymorphisms in NER pathway genes, Long Island breast cancer study project, 1996-1997

Gene	Genotype	Cases, N (%)	Controls, N (%)	Odds Ratio* (95% CI)
<i>ERCC1</i>	CC	551 (52.1)	606 (54.9)	1.00
	CA	434 (41.1)	436 (39.5)	1.09 (0.92-1.30)
	AA	72 (6.8)	62 (5.6)	1.29 (0.90-1.85)
<i>XPA</i>	GG	488 (46.1)	488 (44.3)	1.00
	GA	466 (44.0)	477 (43.3)	0.97 (0.81-1.17)
	AA	105 (9.9)	137 (12.4)	0.77 (0.58-1.02)
<i>XPD</i>	GG (Asp/Asp)	415 (40.2)	490 (45.2)	1.00
	GA (Asp/Asn)	478 (46.4)	454 (41.9)	1.25 (1.04-1.50)
	AA (Asn/Asn)	138 (13.4)	139 (12.8)	1.16 (0.89-1.52)
<i>XPF</i>	GG (Arg/Arg)	859 (84.4)	888 (83.4)	1.00
	GA (Arg/Gln)	156 (15.3)	167 (15.7)	0.99 (0.78-1.26)
	AA (Gln/Gln)	3 (0.3)	10 (0.9)	0.27 (0.07-1.00)
<i>XPG</i>	GG (Asp/Asp)	562 (56.3)	571 (54.3)	1.00
	GC (Asp/His)	371 (37.1)	409 (38.9)	0.94 (0.78-1.13)
	CC (His/His)	66 (6.6)	71 (6.8)	0.98 (0.69-1.41)

* Adjusted for age.

Nucleotide Excision Repair Genes and Breast Cancer Gene-Environment Interaction

		Odds Ratio* (95% CI)	
		PAH Adduct	
		Non-Detectable	Detectable
XPD	GG	1.00	1.45 (1.05-2.00)
Asp312Asn (G/A)	GA	1.57 (1.07-2.30)	1.56 (1.13-2.15)
	AA	0.71 (0.39-1.29)	1.83 (1.22-2.76)

*Adjusted for Age

Nucleotide Excision Repair Genes and Breast Cancer: Conclusion

- Modest 25% statistically significant increase in breast cancer risk associated with having one XPD Asp³¹²Asn variant allele
- Examination of the interaction between XPD genotype and PAH DNA adducts:
 - Heterozygotes are at increased risk of breast cancer regardless of the detection of PAH DNA adducts
 - Homozygotes are only at increased risk of breast cancer if adducts were detected
 - There is an indication of an increasing trend in risk according to the number of variant alleles among women with detectable adducts