

# Contraceptives

Week 9

# Objectives

1. Comprehend confounding and calculate unbiased estimates
2. Learn about the history of oral contraceptives
3. See how study designs and measures of association are used to study contraceptives
4. Practice being a health consumer; critique a study

# Introduction

- Millions of women have used the pill or oral contraceptives (OCs) since 1957 debut
- #1 most prescribed drug among 18-44 year olds
- One journalist wrote in 1960 that the pill's development *“ranks in importance with the discovery of fire...and hunting”*



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# Introduction

The pill gave women power over their biological sex

- Altered gender roles

Highlights countless issues

- Physician-patient relationship
- Health effects
- Backlash

Current research

- Breast cancer
- Thrombotic events
- HIV
- Fetal Outcomes
- Mortality
- Health disparities

# Pill Development

“No woman can call herself free who does not own and control her own body... It is for women the key to liberty.”

-Margaret Sanger, activist and nurse 1922

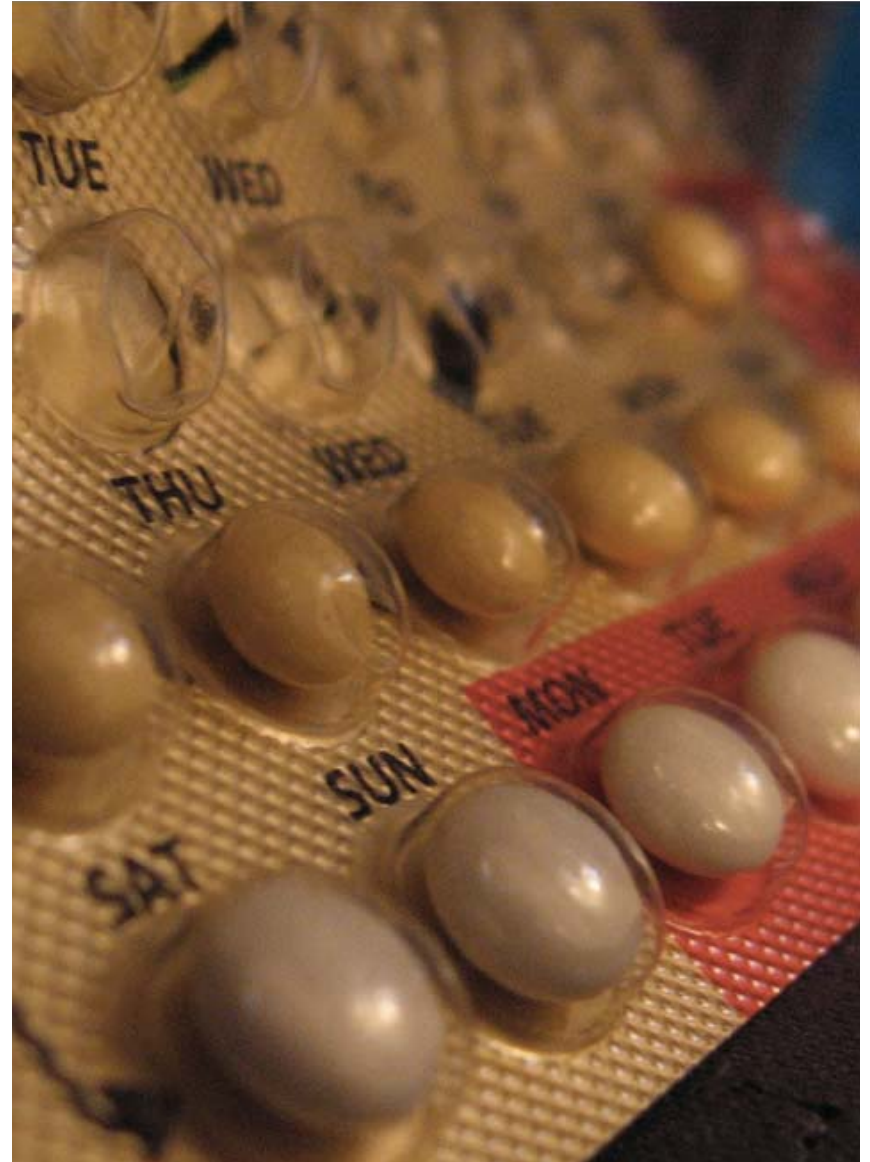


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# Women in 1950s

Post-depression, post-WWII

- Upsurge in domesticity & consumerism
  - All time marriage rate high & age low (women median: 19 yrs)
  - Women worked out of necessity and to enjoy more money for goods
    - Needed more control
      - Space pregnancies
      - More reproductive years post-childbearing

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# Birth control in 1950s

Most effective: diaphragm

- Need to be fit by physician
  - Implicit permission to plan family
- Need to touch genitals

Others: condom, withdrawal, douching

- Need partner cooperation



Image Courtesy of Axefan2.  
Source: [Wikimedia Commons](#).

# Birth control in 1950s

- Contraception generally accepted in marriage
- Stigma of premarital use
  - Denial as a way to cope
    - *“It never entered my mind to use birth control. It never really occurred to me that I could get pregnant. I knew birth control existed, but I didn’t know anything about it. To go out and actually get it would mean that I planned to do these things, to have sex. Since I knew it was wrong, I kept thinking I wasn’t doing it, or I wasn’t going to do it again. Each time was the last time. Birth control would have been cold-blooded.”*



# Birth control in 1950s

- Legal barriers enforced norms
  - Married women should be childbearing
  - Unmarried women not having sex
- 1960: 30 states restricted sales/ads
  - “Comstock laws”
- 1965: Supreme Court protects married couples “right to privacy” (via CT case)
- 1972: Extended to unmarried women (via MA case)

# Influencers

# Female vs. Male Contraceptive

- Economic, scientific, and sociocultural factors contributed
- Sanger and McCormick insisted women control method
  - *“Birth control should be the right and responsibility of women.”*
- Social convention agreed
  - Number of male research volunteers and the demand inadequate
- Scientists claimed to be *“daunted by the task of inactivating the millions of sperm produced by the human male each day.”*
- Directed focus to manipulating women’s bodies

# Development Challenges

- Recognized exogenous estrogen/progesterone disrupt ovulation
- Two issues prevented development
  - Inactivity of compounds given orally
  - High cost of progesterone

# Development Challenges

Pincus and Rock convinced Searle to market Enovid as the first OC

Over time pill has changed

- Dosages of estrogen and progestins lowered
- New “generations” of progestins developed
- New usage patterns

# Future Developments

Spectrum of hormonal contraception now includes

- Various OCs
  - Monophasic, bi-, or triphasic OCs, progesterone only pills
- Injectables (Depo-provera, Lunell)
- Vaginal rings and skin patches containing estrogen and progesterone
- Implantable rods and IUDs with progesterone

# Pill Novelty

- Novelty in that it was taken orally and at a separate time from intercourse
  - Control reproductive system without the knowledge of male partners
  - Separated the act of sex and contraception
- More power over their bodies, they physically endured this responsibility
  - Dr. Nancy Kreiger's ecosocial theory (embodiment)

# Physician-Patient Relationship



# Popularity

- Within 5 years, OCs most popular birth control
- Several contributing factors
  - Physicians
  - Planned Parenthood
  - Media
  - Patient Requests

# Physicians

- Viewed of OCs
  - Convenient, easy to prescribe
  - Prescription status increased authority/control
  - Financial incentive (biannual visits)
- Influenced by
  - Direct mail, journal ads, popular press
  - Pharmaceutical industry
    - *“The physician wants to be convinced that Enovid is...His drug; control of his patient on a month-to-month bases if he desires...Making the role of the physician assume greater importance in family planning.”* Searle in-house newsletter

# Planned Parenthood

- Within days of FDA approval
- Calderone negotiated direct sales with Searle, cutting price in half
  - *“There will be many poor patients who will not be able to afford the drug in any way for whom we will have to raise funds to cover cost.”*
- Endorsement allow affiliate clinics to prescribe at discount

# Media

- Women relied on popular media
- Generally positive, shortcomings to be remedied
- Pincus and Rock portrayed as heroes
  - *“The biologist and the physician joined forces” in the interest of progress.*
- Initial reports of severe side effects taken seriously 1961
  - Post-thalidomide->birth defects
- FDA conducted initial study: no affect
- Lay press promoted

*Playboy* cartoon promoting causal acceptance of pill



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# Patient Requests

- First time patient request drug
  - Know problem and solution, only need prescription
  - No longer passively receiving care
  - More power, can go to another physician
- Letters poured into physicians, Planned Parenthood, and Dr. Pincus
  - *“I have been reading in one of the magazine books about your address of the birth control pills, and I wish you would help me very much. I sure need your help. You see sir I already have 9 children from age 13 to 1 years old, and about to have one in this days of August and I am only 29 years of age and I get very sick having babies one after another and I read about the birth control pill that could help someone like me, and make my life worth living.”*
- Frequently offered to be test subjects
  - *“I read of your experiments which have resulted in a pill that will induce sterility...If it is at all possible, I would like to secure some of the pills, whatever the cost. I would also be more than glad to offer myself as a subject if you are still conducting experiments.”*

# Health Effects

# Political Climate Changing

- End of 1960s, counterculture and public begin to question authority
- Began to question pill's safety
- Simultaneous consumer protection movement
  - Demanded full disclosure
- All drugs carry risk but why is the pill a different scenario?

# Role of Press

- Press played main role publicizing results
  - Heightened concern
  - Called into question medical profession's authority
    - Physicians also frustrated with lack of information
- Cannot forget the pharmaceutical industry's role
  - Made large profits, different motives/actions
- General attention to long-term health effects
  - Radioactive fallout, pesticides, etc.



# Technical/Public Debate

- Especially challenging
  - 1) technical product and process
  - 2) “expert” witnesses (physicians, researchers) also key players
  - 3) “experts” disagree over evidence
- Above layperson’s understanding
- Millions affect so press attempted to translate
- As reports flourished, physicians began to listen to women
  - *“Medical specialists at first tended to discount such unscientific comments [women’s descriptions of physical discomfort], attributing them to the known vagaries of women. But now doctors are listening intently.” New York Times, 1969*

# Side Effects

- Early trials showed side effects
  - Nausea
  - GI disturbances
  - Breast tenderness
  - Weight gain
  - Breakthrough bleeding
    - Some enough to stop using
- Physicians didn't seem concerned with "side effects"
- Did note death and "serious disease"

# Challenging to Study

- Data collection
  - Study design: different choices (Prospective cohort, Case-control)
  - Exposure assessment: May start, stop repeatedly for various reasons (side effects, pregnancy intention)
    - Users are self-selecting group (high risk patients may be screened out)
  - Effects: rare in women of reproductive age, long latency
  - Impetus for large studies (e.g., Nurses' Health Study I and II)
- Weighing risk/benefit
- Communication across medical field
  - Increased medical specialization limits communication
  - OB/GYN prescribes but other specialists see side effects

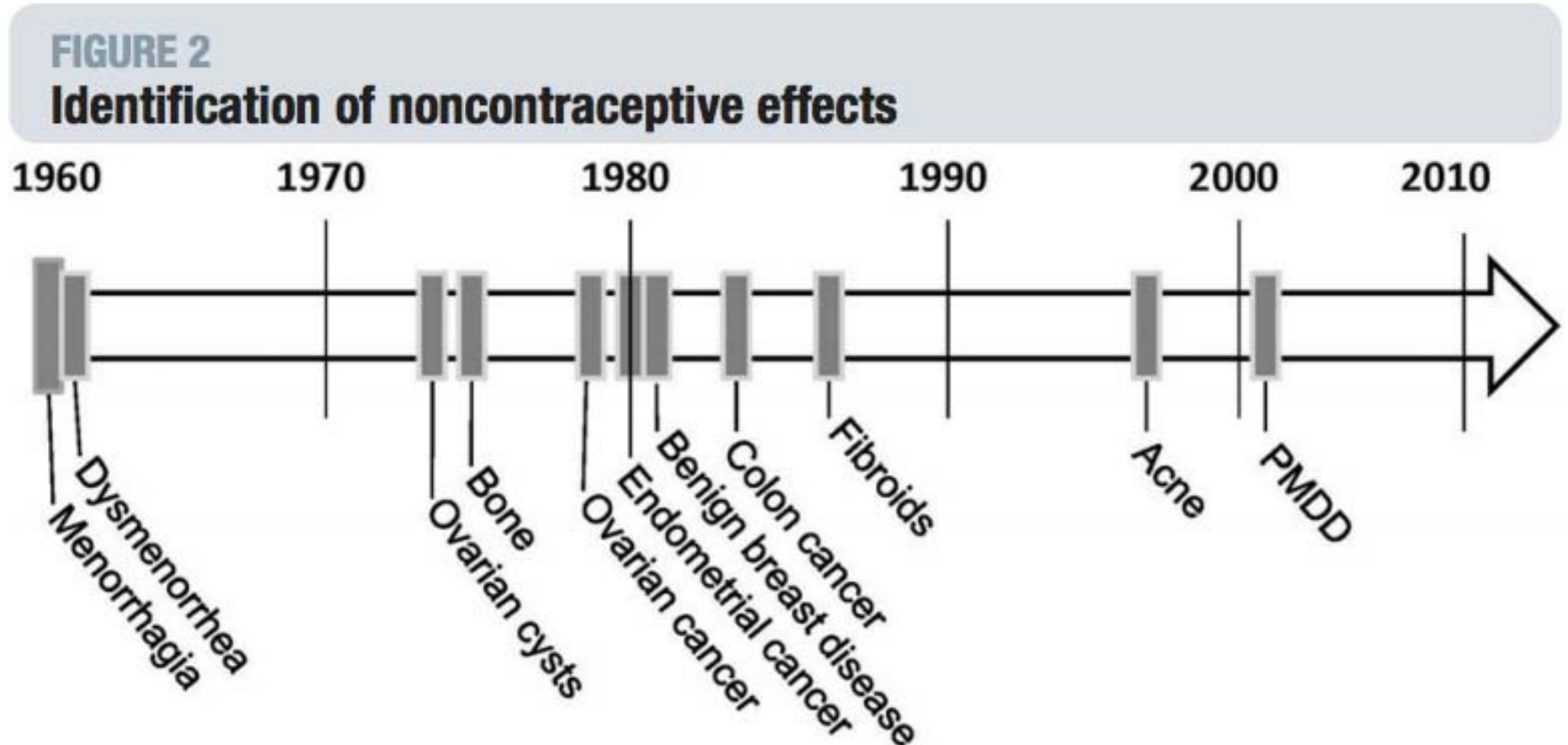
# Women's Responses

- Not all women were eager to use
- Often blamed physician for serious side effects claiming negligent treatment
  - *“I was sitting in the waiting room of the intensive-care unit...when I read your article on the dangers of the pill. It was a little late for me to read it since my wife had just been operated on for massive clotting in her leg. She had been taking the pill for five months when the attack occurred. She had been ill for two weeks with sharp pains traveling through her body, and we had been to our family doctor twice and he had not found the cause of her illness.”*
- Nonetheless, other women were willing to accept the risk
  - *“I don't care if you promise me cancer in five years, I'm staying on the pill. At least I'll enjoy the five years I have left. For the first time in eighteen years of married life I can put my feet up for an hour and read a magazine...If you refuse to give me the pill, I'll go get it from someone else.”*
- Regardless of response, media reports reduced isolation, created a shared experience

# Physician Responses

- Physicians also frustrated with lack of information
- Nonetheless, frequently withheld available information disempowering women from making informed choice
  - *“Some women just aren’t comfortable on oral contraceptives... These are the women who make the phone calls that drive us crazy.”*
- Medical advice often was class dependent
  - Middle- or upper-class white women often steered toward “safer” options since they were “conscientious”

# Noncontraceptive Benefits



Identification of noncontraceptive effects of combination oral hormonal contraceptives: a time line.

Maguire. *Noncontraceptive health benefits*. *Am J Obstet Gynecol* 2011.

Courtesy of Elsevier, Inc., <http://www.sciencedirect.com>. Used with permission.

# Backlash

# Barbara Seaman

1969: *The Doctors' Case Against the Pill* published

- Wealth evidence against safety
- Built off consumer protection and feminist movements



# Senate Hearings Overview

Senate subcommittee formed

- Span of two years
- Produced 14 volumes
- <1 year later, FDA ordered manufacturers to include drug insert

# First Round of Hearings

- First hearing last five days, almost all were covered by three major TV networks
- Included many of Seaman's experts so no "new" information but new press
  - *"Although very little of the information presented here or perhaps none of it was new to the experts in the field, quite obviously a lot of it was not know to the the practicing physician who prescribes the pill and the public which consumes it."* -Senator Gaylor Nelson, Chairperson
- Despite relying heavily on Seaman's experts and advice, she was not invited to testify because *"she wasn't a primary source."* -Sen. Staff
- Nor were any women with pill experience asked to testify because *"Nelson...didn't like that way of doing things...He wanted to keep the hearings on a high level."* -Senate Staff

# First Round of Hearings

- Feminist groups attended
  - *“When we got there, we were both frightened, really frightened, by the content and appalled by the fact that all of the senators were men and all of the people testifying were men. They did not have a single woman who had taken the pill and no women scientists.”-Alice Wolfson*
- Regular protests became the norm
- Almost all agreed on major tenants
  - FDA allowed companies to market pill without adequate testing (met standards of the time)
  - Likened women to unsuspecting guinea pigs in a massive experiment
  - Didn't advocate ban and recognize contraceptive need
  - All women needed information to make informed decision
- Disagreed in solution
  - Senate chair: Informed consent solved by improving communication among drug company, FDA, physicians, patients
  - Feminist groups: Tip of iceberg for larger women's health issues, can't be solved within context of contemporary system of male dominated professionals

# Second Round of Hearings

- One month later, second round of hearings
  - Included three female physicians and one female former director of non-profit
- Post hearings: OC use dropped, increase use of IUDs, diaphragms, vasectomies, etc.
- Result: package insert
  - Feminists generally pleased with more information
  - Medical professions felt it intruded on doctor-patient relationship

# Current Research

Breast cancer  
Thrombotic events  
HIV  
Fetal Outcomes  
Mortality

# OCs and Breast Cancer

- Initially large concern but mixed results
- Meta-analysis: premenopausal breast cancer, positive association
  - OR=1.19 (1.09-1.29)<sup>1</sup>

# OCs and Breast Cancer

- Challenging with formulation differences
- Nurses' Health Study II<sup>1</sup>
  - Current use marginally significant higher risk, RR=1.33 (1.03-1.73)
  - One specific formulation accounted for the excess risk
    - Current use of triphasic preparations with levonorgestrel, RR=3.05 (2.00-4.66)

# OCs and Thrombotic Events

- Complex topic especially with exposure issues
- 3<sup>rd</sup> vs. 2<sup>nd</sup> generation pills
  - Meta-analysis: RR=1.70 (1.40 to 2.00)<sup>1</sup>
- Progesterone-only pills vs. never-user
  - Meta-analysis: RR=1.03 (0.76 to 1.39)<sup>2</sup>

<sup>1</sup>Kemmeren, BMJ, 2001  
<sup>2</sup>Manta, BMJ, 2012



# OCs and HIV

- Two-fold increases in the risks of both HIV acquisition and HIV transmission among women in HIV-discordant couples using hormonal contraceptives<sup>1</sup>
  - Particularly the progestin-only injectable
- WHO and others putting large amount of resources to understand mechanism
- Serious public health implications

# Conclusion

- Pill serves as barometer of change: attitudes about science, technology, & medicine
- Gave way to caution, concern, trust, and confidence issues
- By 1990, 80% of American women used pill at some point
- Feminist movement moved onto other issues
  - DES, IUDs, Depo-Provera, Norplant, abortion, etc.
  - More self-help books on menopause, pregnancy, and childbirth
- Pill debates continue on over various issues
  - Formulations
  - Continuous use, especially before first birth
  - Over-the-counter status

# Study Critique

Greer, Julia B., Francesmary Modugno, et al. "Short-Term Oral Contraceptive Use and the Risk of Epithelial Ovarian Cancer." *The American Journal of Epidemiology* (2005).

# Introduction

1. What was the **objective(s)** of the study?
  - To determine whether short-term OC use is associated with decreased risk of ovarian cancer.

# Introduction

2. What was the **rationale** for performing the study? Given the state of the evidence on this topic, what was the need for this particular study?

- Ovarian cancer is the most fatal gynecologic cancer in the U.S.
- OCs have consistently been associated with a reduced risk of ovarian cancer, with increasing duration of use linked to greater risk reduction. Some studies have shown a protective effect with as little as 6 months of OC use.
- Studies have been limited by a small number of short-term users.

# Methods

3. What was the primary **outcome** of interest? Briefly explain how the outcome was measured. Was this accurately measured?

- Diagnosis of epithelial ovarian cancer, confirmed by pathology.
- The outcome seems to be accurately measured.

# Methods

4. What was the primary **exposure** of interest? Briefly explain how the exposure was measured. Was this accurately measured?

- A standardized 1.5-hour in-person interview of cases and controls provided detailed demographic data as well as information on a subject's gynecologic and obstetric history
- A "life" calendar marked with important events that each participant recalled during her lifetime was used to enhance memory of distant events. The reference date was calculated as 6 months prior to diagnosis (cases) or interview (controls).
- All contraceptive information was recorded, including the type, frequency of use, and duration of use. Additional details obtained for hormonal contraceptives included the brand, reason for use, and reason for stopping use. Picture books with photographs of OCs available in the United States (courtesy of Dr. Ruth Peters, University of Southern California, Los Angeles, California) were used to help women specify the formulations used.
- This exposure seems to be accurately measured.

# Methods

5. What **type of study** was conducted? Was the study design appropriate to approach the study question?

- Used data from a large, case-control study of epithelial ovarian cancer.
- The study design was appropriate especially because ovarian cancer is a rare disease.



# Methods

6. What was the **sample population**? How was it selected? Depending on the study design, what was the ratio of cases:controls (case-control study) or ratio of exposed:unexposed (cohort study)? Was this sample population appropriate?

- Cases 20–69 years of age whose epithelial ovarian cancer was diagnosed within the 6 months prior to interview were ascertained from 39 hospitals in the Delaware Valley surrounding Philadelphia, Pennsylvania, between May 1994 and July 1998.
- For all cases, the diagnosis of epithelial ovarian cancer was confirmed by pathology.
- 767 completed interviews.
- Controls aged 65 years or younger were ascertained by random digit dialing and were frequency matched to cases by race, 5-year age groups, and three-digit telephone exchange.
- 1,367 completed interviews.
- Inclusion and exclusion criteria were outlined and appeared appropriate.
- The sample population seemed appropriate.

# Methods

7a. Prior to the analysis, what study design provisions were made to minimize the influence of potentially **confounding** factors?

- Frequency-matched control selection.

7b. At the analysis stage, what methods were used to control confounding bias? Were these sufficient?

- Regression models to adjust for any additional effects of potential confounding variables.

# Methods

8. What **measure(s)** of disease frequency, association, and/or public health impact was calculated? Was this appropriate? How was the role of chance assessed?

- Odds ratios, with corresponding 95% confidence intervals, were calculated as the primary measure of effect size.
- All tests of statistical significance were two tailed and were considered significant at  $p < 0.05$ .
- All seem appropriate.

# Results

9. What was the major **result(s)** of this study? Do you believe it? Why or why not?

- Women who had used OCs for less than or equal to 6 months had reduced odds of ovarian cancer (OR=0.73, 95% CI: 0.54, 0.99).
- When stratified by reasons for stopping OC use, this protective effect was observed in only the group who had used OCs for less than or equal to 6 months and stopped because of side effects (OR=0.59, 95% CI: 0.40, 0.87 for side effects and OR=0.91, 95% CI: 0.60, 1.37 for non-side-effects). Women who used OCs for >6 months were at a reduced risk independent of their reason for stopping.
- Results were similar when stratifying by parity and hormone therapy use. Thus, OC use for as little as 6 months provides significant protection against ovarian cancer risk, protection that appears limited to those women who stop using OCs because of side effects. Mediating factors may reflect endogenous hormone levels, OC metabolism, or OC bioactivity.
- The results seem believable based on limited bias and significant associations. However, seeing a linear dose-response might make the results more believable.

# Discussion

10. Did the discussion section adequately address the **limitations** of the study? Was the final conclusion of the paper a balanced summary of the study findings?

- Discuss other plausible hypotheses.
- State there is no biological mechanism for differences by reason for stopping.
- Do not mention lack of dose-response especially in the 7-13 months exposure category.
- The final conclusions seem to be balanced.

# Discussion

11. What **public health action** would you recommend based on these results?

- The take away: women who use OCs for as little as 1–6 months can achieve a reduction in the risk of ovarian cancer, but only if they stop use because of side effects.
- There is not likely to be any major public health action from these findings.
- What about in women with a family history of ovarian cancer?
- What about in women with a genetic mutation (e.g., BRCA mutations)?

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