



# RESEARCH DESIGN AND METHODOLOGY

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# Why Do We Need Research

To increase our knowledge and understanding about diseases (their prevention, diagnosis, treatment, natural history,....)

To provide evidence for informed decision-making in health care policy

To test new ideas for the advancement of the medical profession

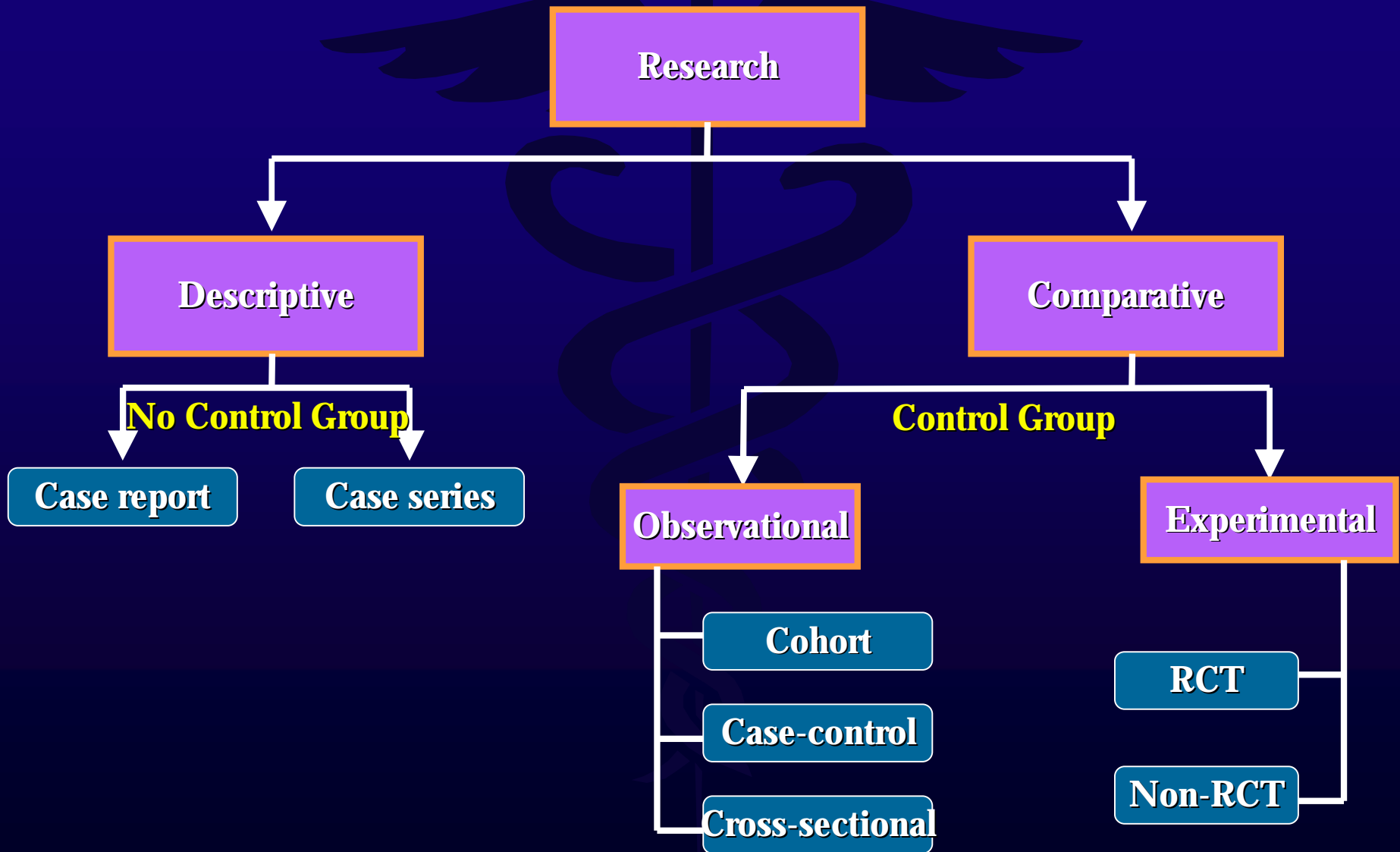


**But  
Research  
is not all the same**

# The Evidence Pyramid



# The Hierarchy Of Research



# Clinical Problem

- **Patient:** 30 years old
- **Complaint:** Primary infertility 2 years
- **Investigations:** Anovulation
- **Management Plan:** Ovulation Induction
- **Question:** ovarian cancer risk?

**Does induction of ovulation increase the risk of OVARIAN CANCER?**

# Case Reports

## Isolated Reports Of Unexpected Conditions

- 1: [Acta Obstet Gynecol Scand. 1982;61\(3\):261-3.](#)

**Massive hyperstimulation and borderline carcinoma of the ovary. A possible association.**

[Atlas M, Menczer J.](#)

A patient with persistent ovarian cysts subsequent to clomiphene-induced severe hyperstimulation was found to have borderline ovarian carcinoma. Since several endocrine and epidemiological studies implicate hormonal factors in the genesis of ovarian tumors, a possible association between ovarian hyperstimulation and neoplasia is suggested.

PMID: 7124357 [PubMed - indexed for MEDLINE]

# Case Reports

After 1982, case reports were published on 66 women with malignant or borderline ovarian tumors **during or after infertility treatment** have been published

## Limitations of case reports

- Coincidental findings that can not establish association
- Generate hypothesis that calls for further studies

# Case Series

□ 1: [Acta Obstet Gynecol Scand](#), 1997 Feb;76(2):177-81.

**Malignant tumors of the ovary or the breast in association with infertility: a report of thirteen cases.**

[Unkila-Kallio L](#), [Leminen A](#), [Tiitnen A](#), [Lehtovirta P](#), [Wahlstrom T](#), [Ylikorkala O](#).

Department of Obstetrics and Gynecology, Helsinki University Hospital, Finland.

**BACKGROUND:** Many questions have been raised recently about the relationship between infertility, fertility drugs and cancer. This prompted us to evaluate our patients having ovarian or breast cancer with a known history of infertility. **METHODS:** We report thirteen women who had been examined and/or treated for infertility before the occurrence of malignant tumors of the ovary or the breast at an age under 50 years in 1990-1995 in our unit.

**RESULTS:** Mean age of the patients was 35 years (s.d. 5.9 years, range 28-47 years). Of the 11 ovarian tumors, one was a malignant teratoma, two were granulosa cell tumors and eight epithelial ovarian cancers. Ten women had received either clomiphene citrate alone or together with gonadotrophins, one had used only gonadotrophins, and in two patients ovarian cancer was detected during an infertility work-up but before any treatment. Four women had used clomiphene for more than twelve cycles. Two patients had ductal breast cancer. **CONCLUSIONS:** Our patients emphasize the need for follow-up and long-term prospective studies in infertile women who have been evaluated or treated for infertility.

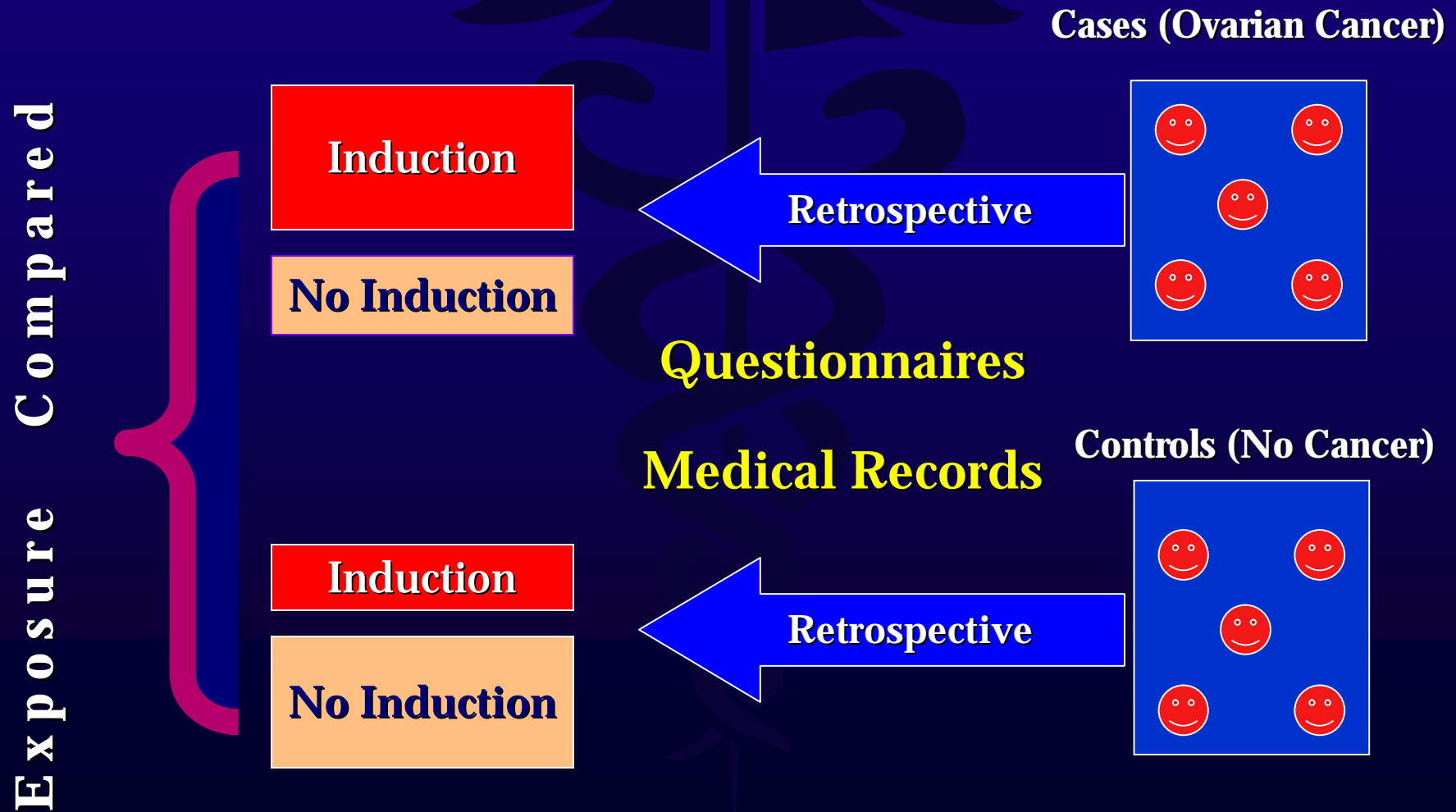
# Case Series



Descriptive analysis of a number of subjects receiving a new therapy or having a particular disease or condition.

**Infertility treatment or detection bias?**

# Case Control Studies



# Case Control Studies

Whittemore et al., 1992

Analysis of 12 case-control studies

- No fertility drugs à **No** increased risk
- Fertility drugs use à **2.7-fold** increased risk
- Fertility drugs use & nulliparity à **27-fold** increased risk

# Case Control Studies

Ness et al., 2002

Analysis of 8 case-control studies:

Among nulligravid women:

- Fertility drug use à **No** increased risk
- Attempts for 2-5 & 5 vs. 1 year à **2 & 2.7-fold** increased risk
- Fertility drug use (subtype analysis) à **2.4-fold** increased risk of border-line serous tumors

# Case Control Studies

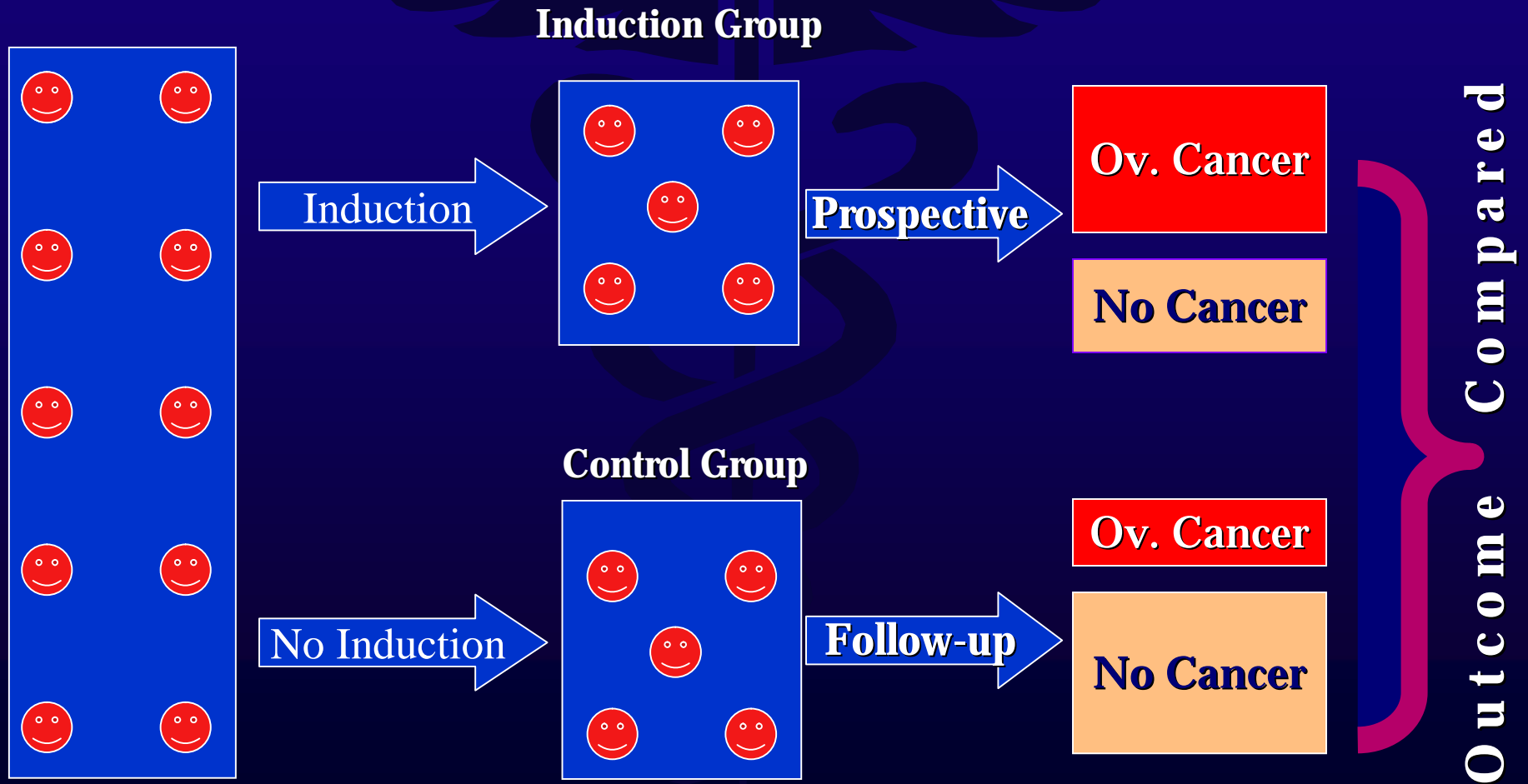
## Advantages of Case-Control Studies

- Quick and cheap
- Allow studying rare and harmful disorders
- Allow studying diseases that develop after long time

## Limitations of Case-Control Studies

- **Recall Bias:** Questionnaires, interviews, records, ..
- **Difficult matching** between cases & controls

# Cohort Studies



**Infertile  
Females**

# Cohort Studies

Brinton et al., 2004

12193  
Infertile  
women from  
5 units  
in USA  
Between  
1965 - 1988

Infertile

8429

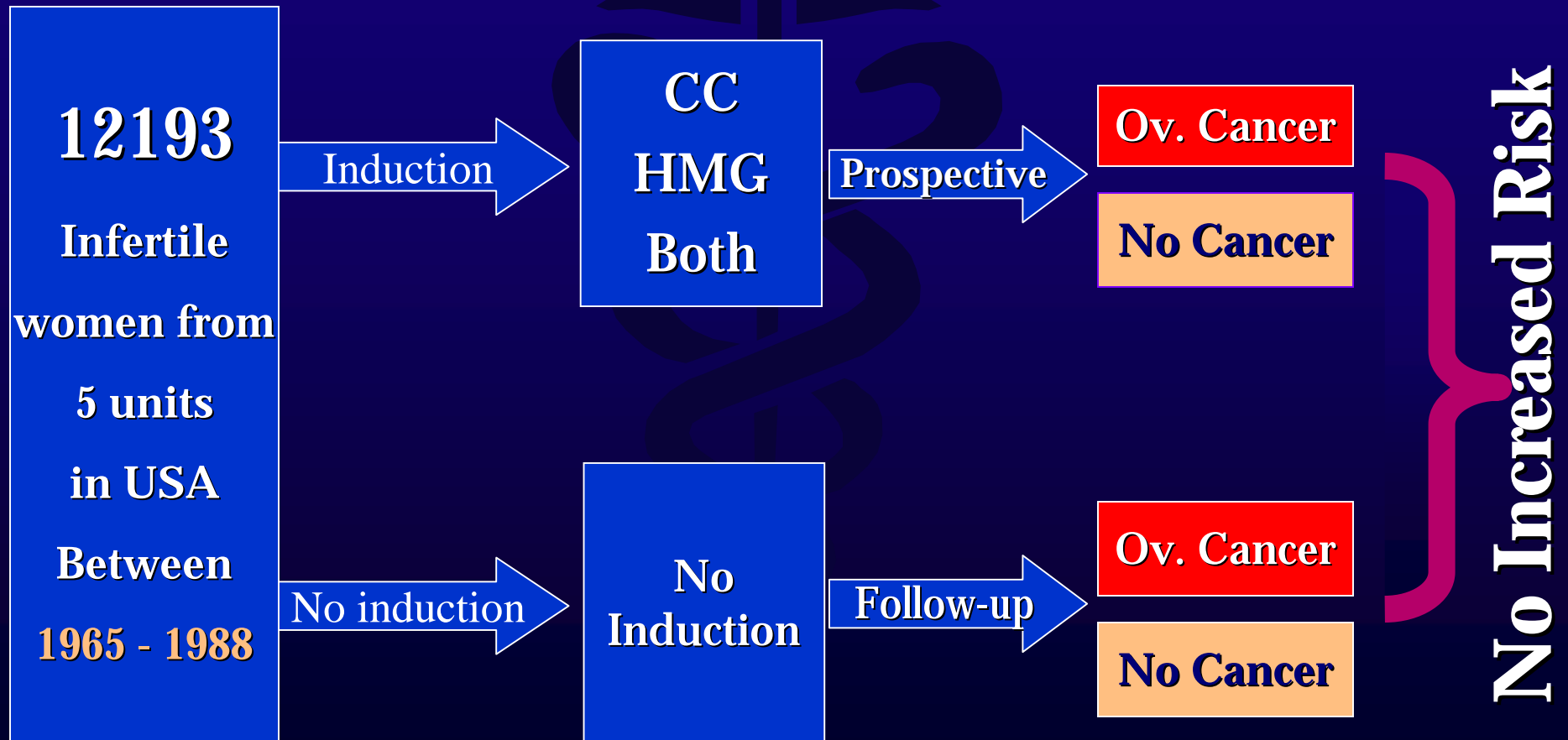
Population

Incidence  
In  
Population

SIR 1.98, 95% CI 1.4 - 2.6

# Cohort Studies

Brinton et al., 2004



# Cohort Study



## Advantages:

- § Ethically safe
- § Can establish causality

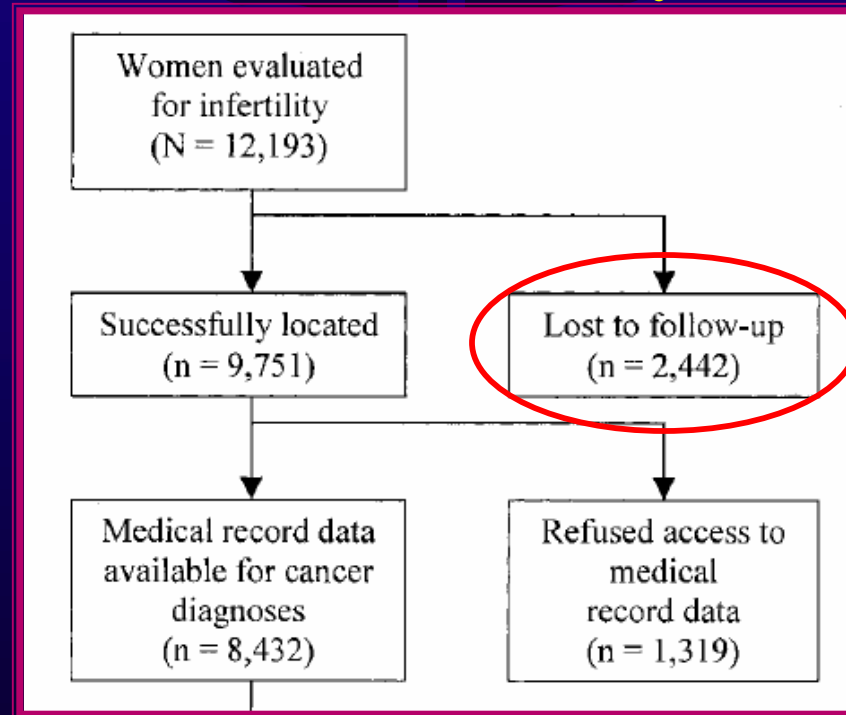
## Disadvantages:

- § Rare diseases needs large sample size
- § Not suitable when the time between exposure and disease manifestation is very long
- § Long follow-up (many dropouts)

# Cohort Studies

Brinton et al., 2004

## Problems in the study



Very low  
event rate  
(45 cases)

This very high rate of drop outs and loss to follow-up in comparison with very low event rate may seriously affect the study results

# Cohort Studies

Mahdavi et al., 2006

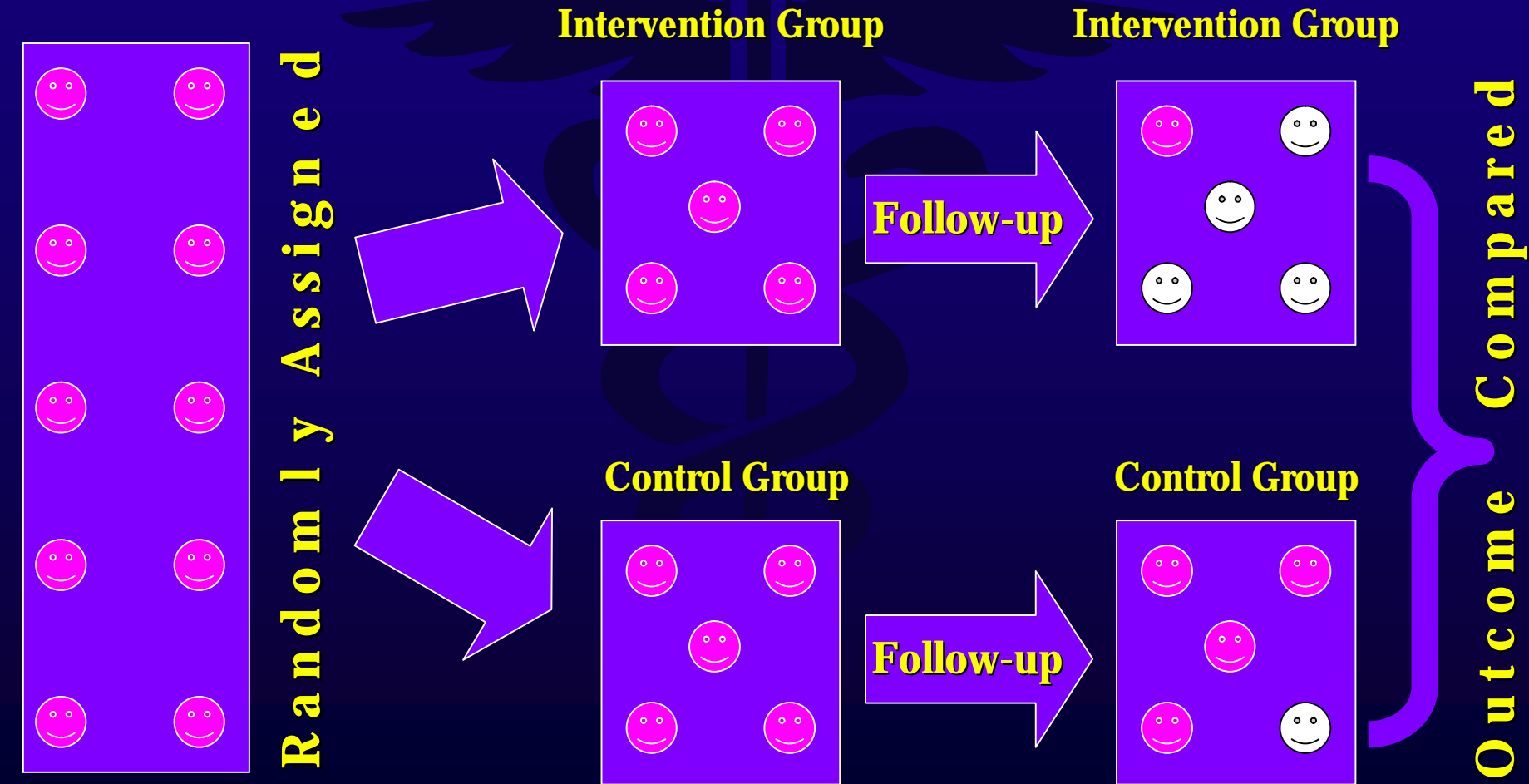
**TABLE 1**

Selected cohort studies of ovarian cancer risk and fertility drugs.

Author	Median age at end of follow-up (y)	Mean length of follow-up (y)	Total cohort size (no. of ovarian cancer)	SIR (95% CI): comparison with general population		RR (95% CI): drug use vs. no use		Confounding control
Rossing et al. 1994	41.5	11.6	3,837 (11)	No drug	1.4 (0.2–5.0)	Clomiphene	2.3 (0.5–11.4)	Parity, oral contraceptive, weight, cause of infertility
				Clomiphene	3.1 (1.4–5.9)	>12 cycles	11.1 (1.5–82.3)	
				hMG	5.6 (0.1–31.0)	hCG	1.0 (0.2–4.3)	
				hCG	2.8 (0.6–8.0)			
Venn et al. 1995	39	7	29,666 (13)	No IVF	1.2 (0.5–2.6)			Cause of infertility
				IVF	0.9 (0.4–1.8)			
Modan et al. 1998	50	21.4	2,496 (12)	No drug	1.6 (0.6–3.5)			Not indicated
Potashnik et al. 1999	44.8	17.9	1,197 (2)	Clomiphene	2.7 (0.9–5.8)	Treatment	0.5 (0.02–7.49)	Not indicated
				No drug	1.35 (0.02–7.49)			
				Treatment	0.68 (0.01–3.80)			
Doyle et al. (2002)	46	15.5	5,556 (6)	No drug	1.7 (0.2–6.0)	Treatment	0.6 (0.1–3.0)	Parity
				Treatment	0.8 (0.2–2.2)			
Brinton et al. (2004)	47	19.4	12,193 (45)	No drug	2.1 (1.4–3.0)	Clomiphene	0.8 (0.4–1.5)	Oral contraceptive, family history, parity
				Clomiphene	1.8 (1.0–3.0)	hMG	1.1 (0.4–2.8)	
				hMG	2.3 (0.7–5.3)			

Mahdavi. Induction of ovulation and ovarian cancer. Fertil Steril 2006.

# Randomized Controlled Trial



Participants

# Randomized Controlled Trial



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and the National Institutes of Health

PubMed

Nucleotide

Protein

Genome

Structure

for "Ovulation Induction"[MeSH] AND "Ovarian Neoplasr"   [Save](#)

Limits

Preview/Index

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Details

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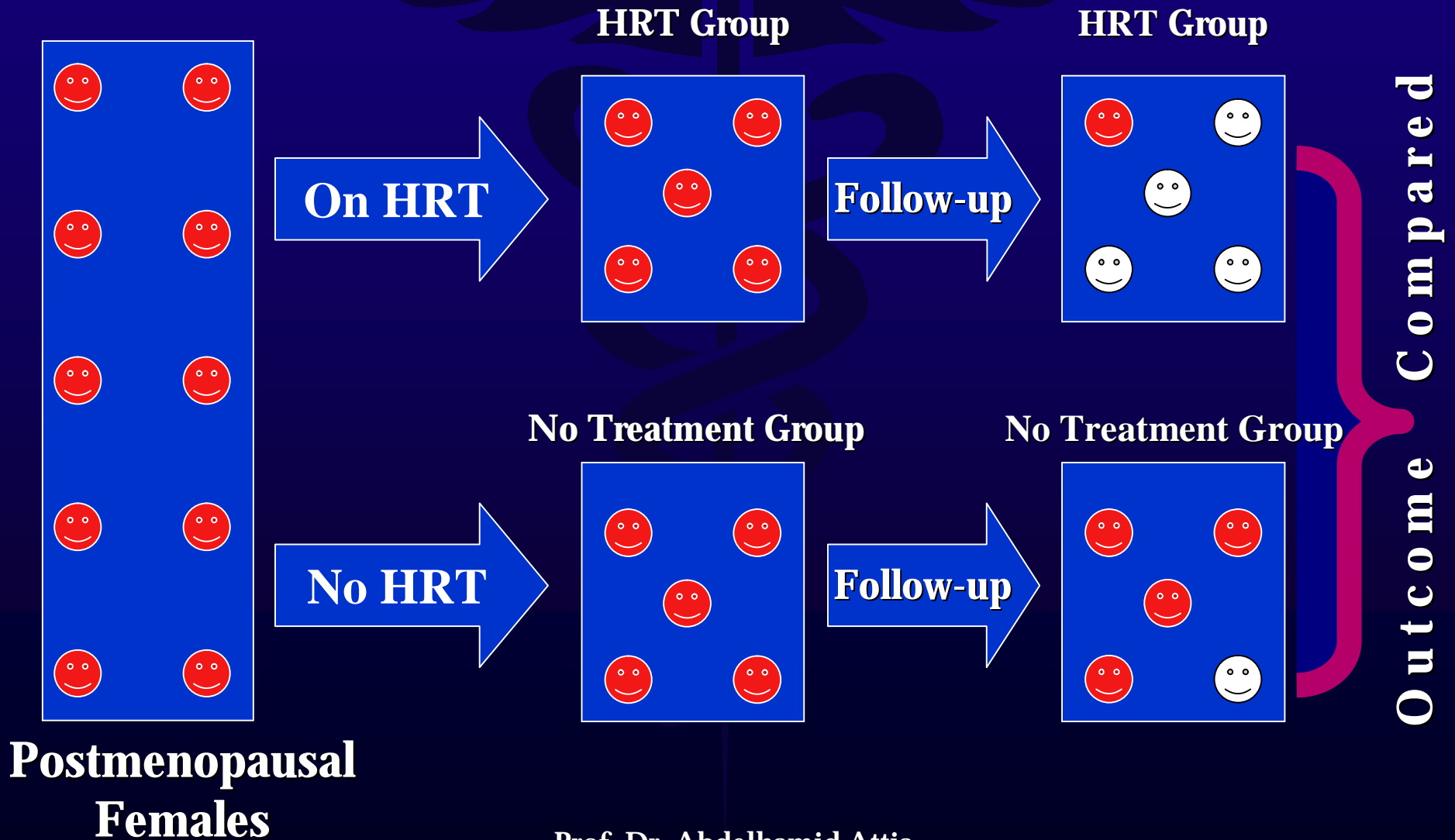
# Importance Of RCT



**> 4 Decades of HRT use based on observational studies**

**Observational studies have a good deal of bias**

# A Cohort Study On HRT



# Cohort Study

**Menopausal Females  
Already On HRT**

**Follow-up**

**Outcome**

**Menopausal Females  
Not On HRT**

**Follow-up**

**Outcome**

# Cohort Study

**HRT Group**  
**Less Risk Factors**

**Follow-up**

**Less CHD**  
**& BCA**

**No Treatment Group**  
**More Risk Factors**

**Follow-up**

**More**  
**CHD BCA**

**Selection Bias**

# Cohort Study

**HRT Group  
Monitored Better**

**Follow-up**

**Better  
Care  
Better  
Outcome**

**No Treatment Group  
Less Monitored**

**Follow-up**

**Less  
Care  
Poorer  
Outcome**

**Prevention Bias**

# Cohort Study

HRT Group  
On Treatment

Follow-up

Placebo  
Effect  
Better  
Outcome

No Treatment Group  
On No Treatment

Follow-up

No  
Treatment  
Poorer  
Outcome

**Compliance Bias**

# Cohort Study

**HRT Group**  
Doesn't include those  
who stopped it (SE)

Follow-up

**Less Side  
Effects**

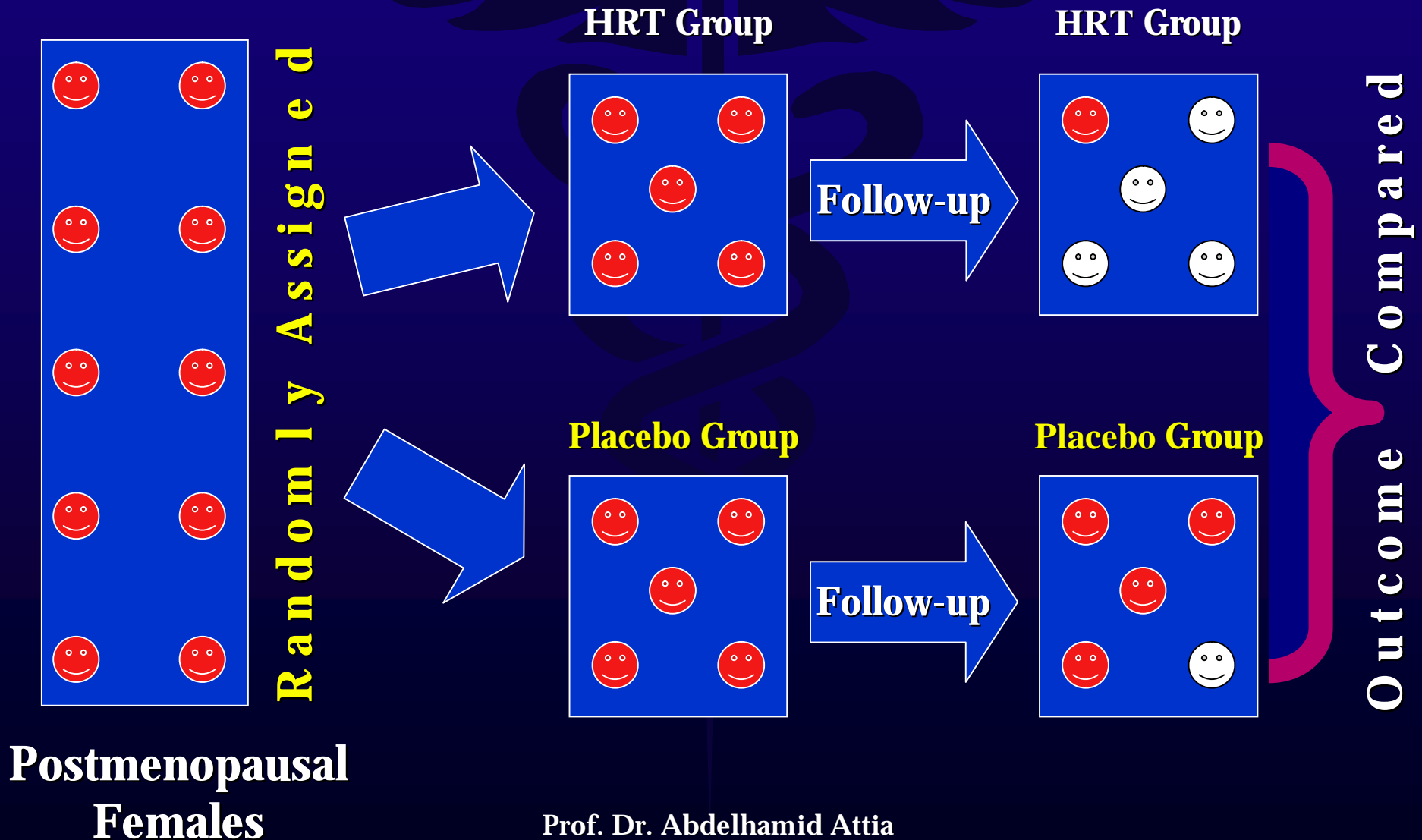
**No Treatment Group**

Follow-up

**Outcome**

**Survivor Bias**

# Randomized Controlled Study



Postmenopausal  
Females

# Randomized Controlled Study

Menopausal Females  
Randomized To HRT

Follow-up

Outcome

Menopausal Females  
Randomized To  
Placebo

Follow-up

Outcome

**R.C. Study**

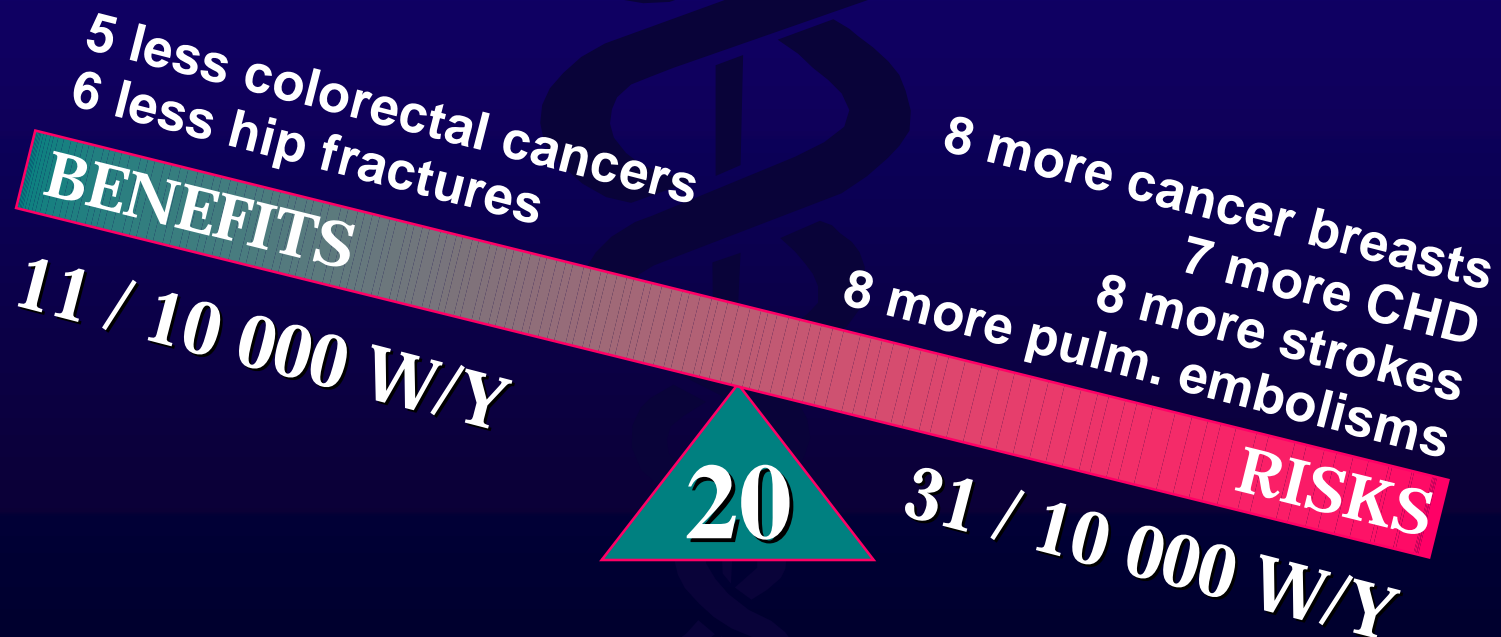
JAMA. 2002 Jul 17;288(3):321-33.

**Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.**

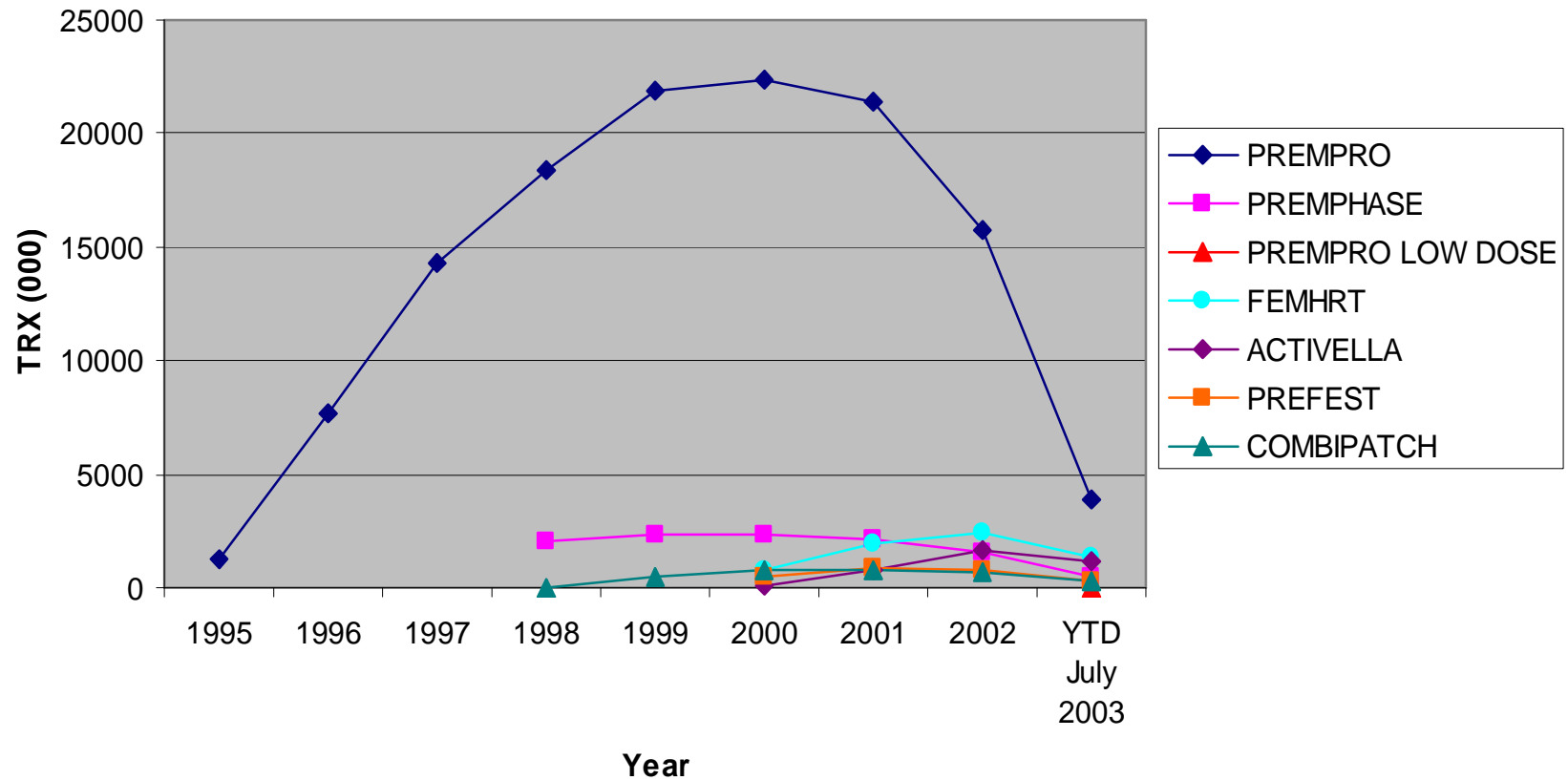
**Ro** CONTEXT: Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy  
**Ho** postmenopausal women remains uncertain. OBJECTIVE: To assess the major health benefits and risks of the most commonly used  
combined hormone preparation in the United States. DESIGN: Estrogen plus progestin component of the Women's Health Initiative,  
a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16608 postmenopausal women aged 50-79  
**Div** years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998. INTERVENTIONS: Participants  
**300** received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or placebo (n  
= 8102). MAIN OUTCOMES MEASURES: The primary outcome was coronary heart disease (CHD) (nonfatal myocardial  
infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of  
risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip  
fracture, and death due to other causes. RESULTS: On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety  
monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast  
cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This  
report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence  
intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke,  
1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases;  
endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes,  
0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total  
cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures,  
0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10 000 person-years  
attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers,  
while absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute  
excess risk of events included in the global index was 19 per 10 000 person-years. CONCLUSIONS: Overall health risks exceeded  
benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women.  
All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements  
for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or  
continued for primary prevention of CHD.

# The WHI Study CEE+MPA

Global Index  
10 000 W / Y



### Total Prescriptions Dispensed for Combination Estrogen/Progestin Products, 1995 - July 2003



*IMS Health, National Prescription Audit Plus™, 1995 – July 2003, extracted August 2003.*

# Thank You & Join



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