



INFERTILITY, OVULATION INDUCTION AND CANCER INCIDENCE

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November 2015



OVARIAN CANCER

BREAST CANCER

ENDOMETRIAL CANCER

OVARIAN CANCER

Ovarian
Cancer

Fathala

**Relationship between
ovarian cancer and
“incessant ovulation”.**



Lancet 1971;ii:163

Casagrande et al.

The number of ovulatory cycles between menarche and menopause is directly proportional to a women's risk of ovarian cancer.

Lancet 1979;ii:170-173

Case Reports

Bamford & Steele	1982	Balasz & Barri	1993
Atlas & Menczer	1982	Willemssen et al.	1993
Ben Hur et al.	1986	Karlan et al.	1994
Carter & Joyce	1987	Komatsu et al.	1995
Kulkarni & McGarry	1989	Salle et al.	1997
Dietl	1991	Unkila-Kallio et al.	1997
Goldberg & Runowicz	1992	Lopes & Mensier	1993
Nijman et al	1992	Grimbizis et al	1995

Summary of Case control Studies

Any fertility drug Vs. none

Ovarian
Cancer

Author	Year	OR	CI
Shu	1989	2.1	0.2-22.7
Whittemore	1992	2.8	1.3-6.1
Franceschi	1994	0.73	0.2-3.3
Shushan	1996	1.3	0.6-2.7
Mosgaard	1997	0.8	0.4-2.0
Parazzini	1997	1.1	0.4-3.3
Parazzini	2001	1.3	0.7-2.5
Ness	2002	0.97	0.8-1.3
Kurta	2012	0.93	0.6-1.35
Merritt	2013	1.05	0.8-1.4
Asante	2013	0.64	0.37-1.1

Summary of Cohort Studies

Author	Year	Cohort size	RR/SIR	95% CI
Ron	1987	2632	3.2	0.3-32.9
Rossing	1994	3837	2.3	0.5-11.4
Venn	1995	10,358	1.45	0.28-7.55
Modan	1998	2,498	1.6	0.8-2.9
Potashnik	1999	1,197	0.68	0.01-3.8
Venn	1999	29,700	0.99	0.57-1.7
Doyle	2002	5,556	0.59	0.1-3.0
Dor	2002	5,026	0.57	0.01-3.2
Brinton	2004	12,193	0.8	0.4-1.5

Summary of Cohort Studies- cont'

Author	Year	Cohort size	RR/SIR	95% CI
Calderon-Margalit	2009	15,030	0.61	0.08-4.42
Sanner	2009	2,768	5.28	1.7-16.65
Jensen	2009	54,362	0.83	0.50-1.37
Lerner –Geva	Unpublished	5788	0.9	0.4-1.9
van Leeuwen	2011	19,146	1.35	0.91-1.92
Kallen	2011	24, 058	2.09	1.39-3.12
Yli-Kuha	2012	9,175	2.57	0.69-9.63
Stewart	2013	21, 646	1.36	0.71-2.62
Brinton	2013	87, 403	0.90	0.45-1.79
Trabert	2013	9,825	1.34	0.86-2.07
	CC+Nulligravid		3.64	1.36-9.72

Summary of Cohort Studies- cont'

Author	Year	Cohort size	RR/SIR	95% CI
Kessous (Borderline ?)	2015	106,031	3.9	1.20 – 12.6
Reigstad	2015	812,986	1.43	0.83 – 2.45
	Nulliparity		1.80	1.04 – 3.11
Sutcliffe	2015	255,786	1.37	1.24 – 1.51
	Nulliparity		1.54	1.34 – 1.76

**Ovarian
Cancer**

"most analyses of this huge dataset suggest that this increased risk was principally because of the nature of women needing these treatments in the first place (their underlying risk factors) and not due to the hormone drug treatments themselves"

Dr Sutcliffe told Medscape Medical News.

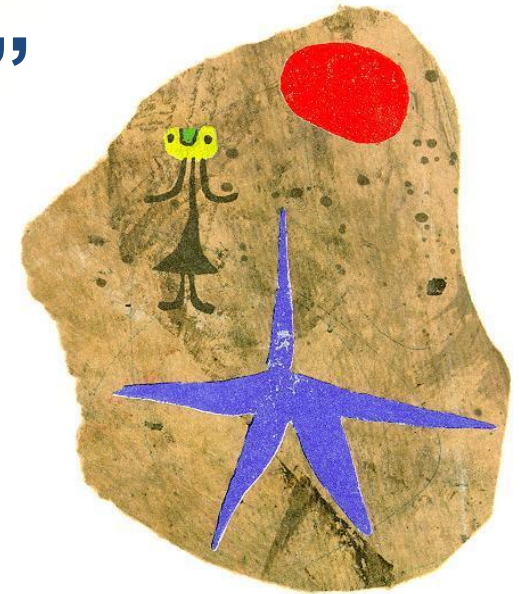
*American Society for Reproductive Medicine (ASRM) 2015 Annual Meeting:
Abstract O-93. Presented October 20, 2015.*

Kashyap et al.2004

- **Meta-analysis**
- **7 Case control design**
OR =0.99; 95% CI 0.67-1.45
for treated vs. untreated
- **3 Cohort design**
RR =0.67; 95% CI 0.32-1.41
for treated vs. untreated



**“infertility drugs do not increase
the risk of ovarian cancer
when compare with
infertile controls ...”**



Siristatidis et al 2012

- **Meta-analysis**
- **9 cohort studies, 109 969 women**
- **RR = 1.5; 95%CI 1.17-1.92**
(ref: general population)

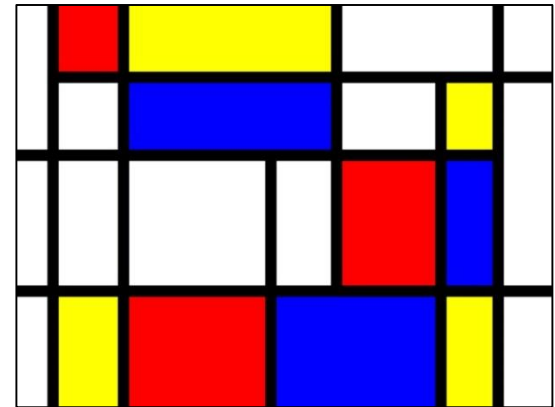
- **RR = 1.26; 95%CI 0.62-2.55**
(ref: infertile women)



Zhao et al 2015

- **Systematic review and Meta-analysis**
- **167,640 Women**
- **10 Cohort design**

OR=1.06; 95%CI 0.85-1.32
for IVF vs non-IVF



“A significant increased ovarian cancer risk was not found in women undergoing ovarian stimulation for IVF.”



***ARE INFERTILITY TREATMENTS
A POTENTIAL RISK FACTOR
FOR OVARIAN CANCER ?
PROSPECTIVE OF 30 YEARS OF FOLLOW – UP
Gynecol Endocrinol, 2012***



Objective

To evaluate the possible association between infertility, ovulation induction treatments and cancer development.

Cohort Study

Population:

- **Women evaluated for infertility 1964-1974.**
- **Sheba Medical Center, Tel Hashomer, Israel**

Methods:

- **Abstraction of medical records.**
- **Linkage to National Population Registry.**
- **Linkage to National Cancer Registry updated to 31.12.1981, 31.12.1991, 31.12.1996, and 31.12.2005.**
- **Verification of original histopathological reports.**

CANCER INCIDENCE IN A COHORT OF INFERTILE WOMEN TREATED BETWEEN 1964-1974

Sheba Medical Center	Ron et al 1987	Modan et al 1998	2003	2010
No of Women	2575	2496	2431	2431
Mean age at first visit	28.7	28.7	28.6	28.6
Women years of follow-up	31,622	56,140	64,762	84,191
Mean years of follow-up	12.3	21.4	26.1	33.8
End of follow-up	31.12.1981	31.12.1991	31.12.1996	31.12.2005
Mean age at the end of follow-up	41.0	50.0	54.7	62.7
Cancer Incidence Observed, Expected (SIR; 95%CI)				
All Sites	42, 37.4 1.1; 0.8-1.5	143, 116.1 1.2; 1.0-1.5	189, 181.7 1.0; 0.9-1.2	350, 338.4 1.0; 0.9-1.2

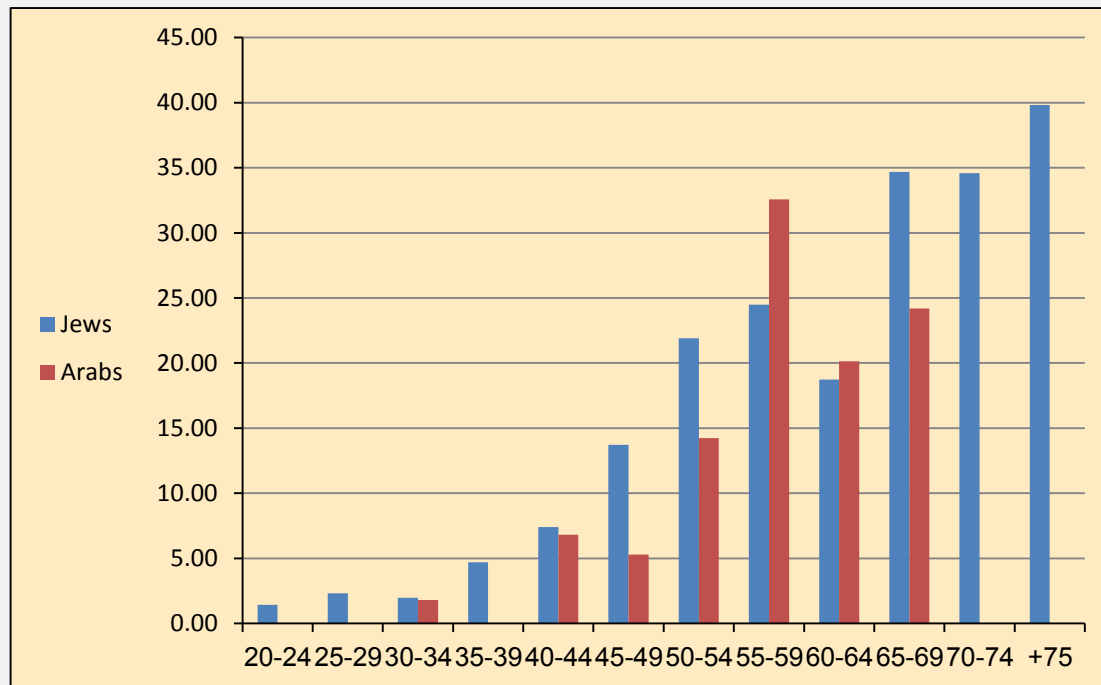
Statistical Methods

- **Standardized incidence ratio (SIR) was calculated as the ratio between observed cancer and expected rates in the general population matched for sex, age and continent of birth.**
- **Relative Risk (RR) was calculated as the ratio between cancer incidence among women who were treated with ovulation induction and cancer incidence among those who were not treated.**
- **Multivariable analysis using Poisson regression model adjusted for independent variables and with diagnosis of cancer as the outcome variable was performed.**

Ovarian Cancer in Israel by Age

Age Specific Rate/ 100, 000

2010



Israeli National Cancer Registry, 2013

CANCER INCIDENCE IN A COHORT OF INFERTILE WOMEN TREATED BETWEEN 1964-1974

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Ovary	4, 1.93 2.1; NS	12, 7.2 1.6; 0.8-2.9	13, 10.4 1.3; 0.7-2.2	18, 18.1 1.0; 0.6-1.6

Observed ovarian cancer cases as compared to expected Diagnosis of infertility

	N	Obs.	Exp.	SIR	95%CI
Hormonal	1340	7	9.92	0.71	0.28-1.45
Non-hormonal	1061	11	8.17	1.35	0.67-2.41

Observed Ovarian cancer cases as compared to expected

Presence of Estrogen and Progesterone

Ovarian
Cancer

	N	Obs.	Exp.	SIR	95%CI
Estrogen+ Progesterone-	935	4	6.60	0.61	0.16-1.55
Estrogen+ Progesterone+	671	9	5.11	1.76	0.80-3.34
Estrogen- Progesterone-	129	1	1.09	0.92	0.01-5.10

Observed ovarian cancer cases as compared to expected Treatment for infertility

Ovarian
Cancer

	N	Obs.	Exp.	SIR	95% CI
CC+ hMG	238	0	1.77	-	-
CC	884	8	6.00	1.33	0.57-2.63
hMG	159	1	1.35	0.74	0.01-4.12
No treatment	1150	9	8.96	1.00	0.46-1.91

Poisson model for multivariable analysis

	Hazard Ratio	95%CI
Non- hormonal Vs. Hormonal	2.3	0.8-6.9
Treated Vs. Untreated	1.5	0.5-4.1

Borderline tumors of the Ovary

Summary of studies Borderline tumors of the Ovary

Author	Year	Design	OR/ SIR/RR	95%CI
Harris	1992	Grouped analysis case-control	4.0	1.1-13.9
Rossing	1994	Cohort	3.3	1.1-7.8
Shushan	1996	Case- control	3.5	1.1-10.1
Parazzini	1998	Case- control		0.004
Ness	2002	Pooled analysis case- control	2.43	1.01-5.88
Sanner	2009	Historical cohort	3.61	1.45-7.44

Summary of studies

Borderline tumors of the Ovary – cont'd

Author	Year	Design	OR/SIR /RR	95%CI
Van Leeuwen	2011	Historical cohort	1.76	1.16-2.56
Yli-Kuha	2012	Historical cohort	1.68	0.31-9.27
Bjornholt	2015	Historical cohort	1.00	0.67-1.51

Invasive Ovarian Cancer Vs. Borderline tumors of the Ovary

why different?

- **Ascertainment bias**
- **Two different entities**

	Borderline	Invasive
Family history	2.9-4.3%	13%
BRCA	4%	30%
ER	76%	30%
Age of diagnosis <50y	59%	24%
5 years survival	90%	39%

Harding, Cancer, 1990

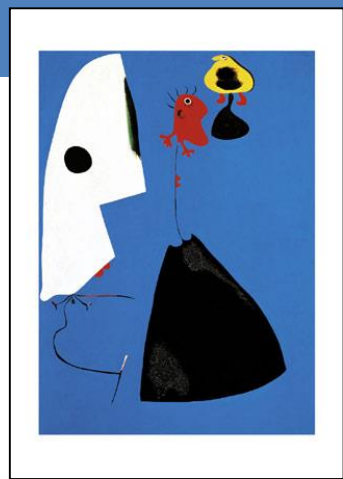
Shushan, Am J Obstet Gynecol, 1996

Abu-jawden, Gynecol Oncol, 1996

Hirsh-Yechezkel, Gynecol Oncol, 2003

Gotlieb, Gynecol Oncol, 2005





“ovarian cancer (especially **invasive epithelial carcinoma** and non-epithelial neoplasia) risk associated with fertility drug treatment are reassuring, but not definitive

A stronger association has been observed between fertility drug use and **borderline tumors of the ovary**”

“We found no convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment.

There may be an increased risk of **borderline ovarian tumours in subfertile women treated with IVF.**

Studies showing an increase in the risk of ovarian cancer had a high overall risk of bias, due to retrospective study design, lack of accounting for potential confounding and estimates based on a small number of cases.”

BREAST CANCER

Health

The connection between fertility treatments and breast cancer

By: Rose Levy - Barzilay, Ha'aretz

Friday, 24 December 2004, 14:10

Studies found no association between fertility treatments for breast cancer, but doctors now say that they are convinced that when young women is "fired upon" with hormones the chance of cancer is more likely Patients also believe this.....



"Do gynecologists fear that if they warn a woman that she may fall sick with breast cancer she will decide not to become a mother"

Israel in the last decade has done extensive research, headed by Prof. Baruch Modan (who died three years ago), and Dr. Liat Lerner Geva of the Gertner Institute. A comprehensive study of 5788 women, including 2,500 women undergoing fertility treatments was performed in 1964-198. Dr. Lerner Geva reports that by taking into account age, and breast cancer incidence compared to the general population, they expected to find 115 breast cancer patients, however 131 cases were reported. She says that this finding "is not statistically significant," and therefore "In principle we concluded that no association has been shown".The minimal increase in cancer cases diagnosed Dr. Lerner Geva attributed to the fact that the research participants are under constant medical surveillance.

Ovulation Induction & Breast Cancer

Case - Control Studies

No Association	Possible Association
<p>Gammon et al (Am J Epidemiol. 1990) 4,730 Breast Cancer 4,688 Controls</p>	<p>Burkman et al (Fertil Steril. 2003) 4,575 Breast Cancer 4,682 Controls hMG > 6 months OR = 2.1 (95% CI ; 1.0-4.4) hMG > 6 cycles OR = 2.7 (95% CI ; 1.0-6.9)</p>
<p>Braga et al (Hum Reprod. 1996) 2,569 Breast Cancer 2,588 Controls</p>	
<p>Ricci et al (Hum Reprod. 1999) 3,415 Breast Cancer 2,916 Controls</p>	
<p>Fei et al (JNCI 2012) 1,422 Breast Cancer <50 1,669 Control sisters</p>	

Ovulation Induction & Breast Cancer - Cohort Studies

No Association	Possible Association
<p>Ron et al (Am J Epidemiol. 1987) 2,575 Infertile Women</p>	<p>Cowan et al (Am J Epidemiol. 1981) 1,083 Infertile Women Hormonal Vs. Nonhormonal Premenopausal RR = 5.4 (95% CI ; 1.1-49.0)</p>
<p>Brinton et al (Am J Epidemiol. 1989) 2,335 Infertile Women</p>	<p>Coulam et al (Obstet Gynecol. 1983) 1,270 Infertile Women Anovulation Vs. General Population Postmenopausal RR = 3.6 (95% CI ; 1.2-8.3)</p>
<p>Rossing et al (Gynecol Oncol. 1996) 3,837 Infertile Women</p>	<p>Potashnik et al (Fertil Steril. 1999) 1,197 Infertile Women CC 1-2 cycles RR = 2.6 (95% CI ; 1.2-5.0) CC ≤ 1000 mg (cumulative dose) RR = 2.6 (95% CI ; 1.2-4.6)</p>

Cohort Studies (cont.)

No Association	Possible Association
<p>Modan et al (<i>Am J Epidemiol.</i> 1998) 2,496 Infertile Women</p>	<p>Ganthier et al (<i>Hum Reprod.</i> 2004) 6,602 Infertile Women Treated with family history RR = 1.37 (95% CI ; 0.99-1.87)</p>
<p>Doyle et al (<i>Hum Reprod.</i> 2002) 5,556 Infertile Women</p>	<p>Brinton et al (<i>Hum Reprod.</i> 2004) 12,193 Infertile Women CC ≥ 20 years of follow-up RR = 1.60 (95% CI ; 1.0-2.5)</p>
<p>Terry et al (<i>Arch Intern Med</i> 2006) 5,798 Infertile Women</p>	<p>Lerner-Geva et al (<i>Breast Cancer Res Treat.</i> 2006) 5,877 Infertile Women Treatment with CC HR = 1.5 (95% CI ; 1.0-2.2)</p>

Cohort Studies (cont.)

No Association	Possible Association
<p>Jansen et al (Cancer Epidemiol Biomarkers Prev 2007) 54,362 Infertile Women</p>	<p>Calderon-Margalit et al (Am J Epidemiol. 2009)</p> <p>Any treatment HR=1.65 (95%CI;1.15-2.36)</p> <p>Treatment with CC HR = 1.48 (95% CI ; 0.93-2.37)</p>
<p>Lerner-Geva et al. (unpublished data) 5,877 infertile women treated with CC. HR=0.9 (95%CI 0.6-1.2)</p>	
<p>dos Santos Silva et al (British J Cancer, 2009) 7355 Infertile Women</p>	<p>Brinton et al (Cancer Epidemiol Biomarkers Prev, 2014) 12,193 infertile women Nulligravid HR=1.98 (95% CI; 1.04-3.60)</p>
<p>Brinton et al (Fertil Steril, 2013) 87, 403 Infertile Women</p>	

Meta-analysis : *Kashyap et al.*

- **Case control design**
10,559 cases and 10,175 controls
OR = 1.01; 95% CI 0.86-1.22
for infertility drugs
- **Cohort design**
33,393 subjects
OR = 0.74; 95% CI 0.67-0.97
for treated vs. untreated

Meta-analysis : *Zreik et al.*

- **Case-control design**
6,347 cases and 7,408 controls
RR = 1.06; 95% CI 0.91-1.23
for clomiphene exposure
- **Cohort design**
158,972 subjects
RR = 1.09; 95% CI 0.96-0.1.24
for clomiphene exposure

IVF and Breast Cancer

No Association	Possible Association
Venn et al (Lancet 1995) 10,358 Infertile Women	Brzezinski et al (Gynecol Oncol. 1994) 950 Infertile Women RR =2.2 (95% CI ; ?)
Venn et al (Lancet. 1999) 29,700 Infertile Women	Pappo et al (Ann Surg Oncol 2008) 3,375 infertile women ≥ 4 IVF cycles HR =1.9 (95% CI 0.95-3.81)
Dor et al (Fertil Steril. 2002) 5,026 Infertile Women	
Lerner-Geva et al (Int J Gynecol Cancer 2003) 1,082 Infertile Women	
	Katz et al (Breast J, 2008) 28 IVF BC 140 IVF non BC 114 non IVF BC IVF> age 30 RR= 1.24; 95% CI 1.03-1.48

IVF and Breast Cancer (cont.)

No Association	Possible Association
Kristiansson et al (Hum Reprod. 2007) 8,716 Infertile Women	Stewart et al (Fertil Steril 2012) 21,025 infertile women IVF at age ≤ 24 HR =1.56 (95% CI 1.01-2.40)
Tsafrir et al (AYALA 2008) 582 Infertile Women ≥ 40	
Kallen et al (Human Reprod, 2011) 24,058 (After first delivery)	
Yli-Kuha et al (Hum Reprod 2012) 9175 Infertile women	
Brinton et al (Fertil Steril 2013) 87,401 Infertile women	
Brinton et al (Cancer Epidemiol Biomarkers Prev 2014) 12,193 Infertile women	

Meta-analysis: *Sergentanis et al*

8 Cohort Studies –

Venn, 1999

Dor, 2002

Lerner Geva, 2003

Pappo, 2008

Kallen, 2011

Yli Kuha, 2012

Stewart, 2012

Brinton, 2013

Cohort size: 1,554,332 Women

**576 incident Breast Cancer cases among women
exposed to IVF**

Meta-analysis: *Sergentanis et al*

- **8 Cohort design**

RR = 0.91; 95%CI 0.74-1.11

(ref: general population)

RR= 1.02; 95% CI 0.88-1.18

(ref: infertile women)

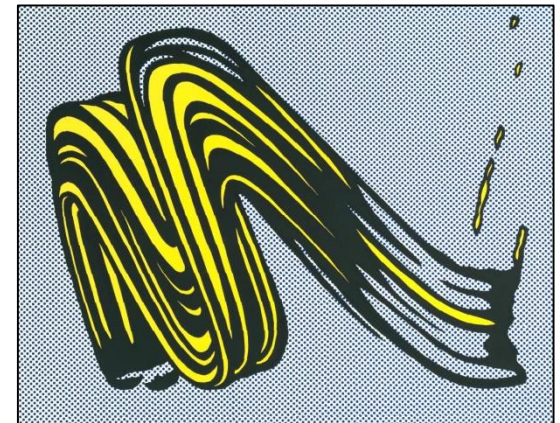


Zhao et al 2015

- **Systematic review and Meta-analysis**
- **10 cohort design**
- **151,702 women**

OR = 0.69; 95%CI 0.63-0.75

for IVF vs non-IVF



“ Studies treating the general population and the infertile women as reference group did not point to a statistically significant association between IVF and breast cancer risk”

Gennari 2015

- **Meta-analysis**
- **7 Cohort design**

SRR = 0.96; 95%CI 0.80-1.14

**(ref: general population 6 studies,
1 study infertile women)**

**“...no increased risk was observed
in women undergoing IVF”**

Breast Cancer Res Treat 2015





***ARE INFERTILITY TREATMENTS
A POTENTIAL RISK FACTOR
FOR BREAST CANCER ?
PROSPECTIVE OF 30 YEARS OF FOLLOW - UP
Gynecol Endocrinol, 2012***

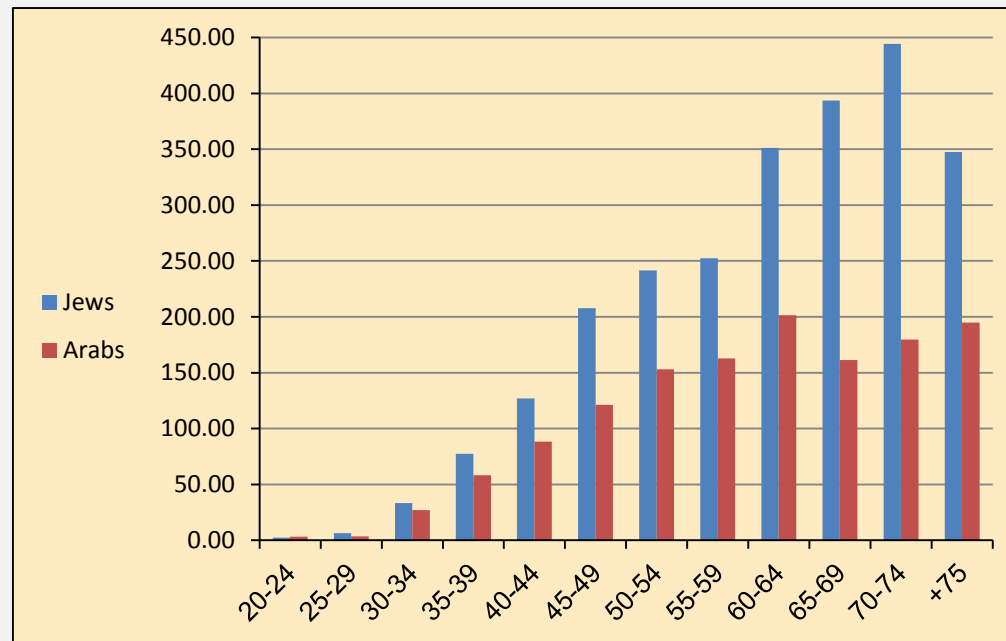
Breast Cancer

- **Breast cancer is the leading cancer in women with an incidence of (ASR) 91/100,000 (Jewish) and 53/100,000 (Arab) cases per year in Israel.**
- **In 2010, there were 3510 (Jewish) and 300 (Arab) new cases.**
- **In 2010, breast cancer accounted for 930 deaths in women.**

Breast Cancer in Israel by Age

Age Specific Rate/ 100, 000 2010

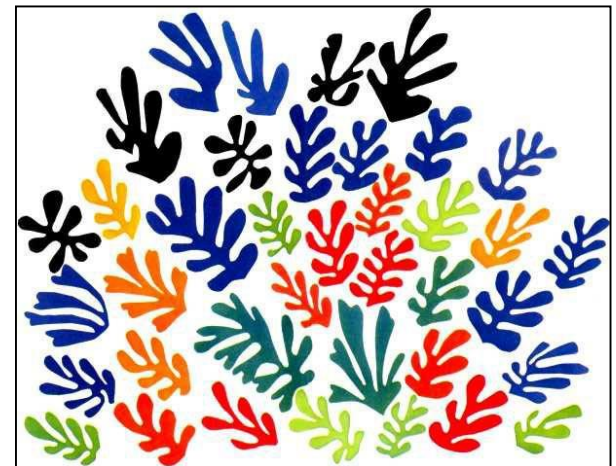
(Females, Invasive)



Israeli National Cancer Registry, 2013

Rationale

- **Infertility in itself is an established risk factor for breast cancer.**
- Estrogen is a potent hormone. It promotes the **proliferation** of epithelial breast cells.



CANCER INCIDENCE IN A COHORT OF INFERTILE WOMEN TREATED BETWEEN 1964-1974

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Mean years of follow-up	12.3	21.4	26.1	33.8
End of follow-up	31.12.1981	31.12.1991	31.12.1996	31.12.2005
Mean age at the end of follow-up	41.0	50.0	54.7	62.7
Cancer Incidence Observed, Expected (SIR; 95%CI)				
Breast	15, 14.14 1.1; NS	59, 46.6 1.3 0.96-1.6	76, 75.2 1.0; 0.8-1.3	153, 131.9 1.2;0.98-1.4

Observed breast cancer cases as compared to expected Diagnosis of infertility

Breast
Cancer

	N	Obs.	Exp.	SIR	95%CI
Hormonal	1,340	70	72.8	0.96	0.75-1.22
Non-hormonal	1,061	83	59.1	1.4	1.12-1.74

Observed breast cancer cases as compared to expected

Presence of Estrogen and Progesterone

Breast
Cancer

	N	Obs.	Exp.	SIR	95%CI
Estrogen+ Progesterone-	935	54	48.4	1.11	0.84-1.45
Estrogen+ Progesterone+	671	47	37.4	1.26	0.92-1.67
Estrogen- Progesterone-	129	3	7.92	0.38	0.08-1.11

Observed breast cancer cases as compared to expected

Treatment for infertility

Breast
Cancer

	N	Obs.	Exp.	SIR	95% CI
CC+ hMG	238	12	12.9	0.93	0.48-1.63
CC	884	54	44.7	1.21	0.91-1.58
hMG	159	4	9.9	0.4	0.11-1.6
No treatment	1150	83	64.4	1.29	1.03-1.6

Poisson model for multivariable analysis

	Hazard Ratio	95%CI
Treated Vs. untreated	0.9	0.6-1.5
Estrogen+ Progesterone- Vs. Estrogen- Progesterone-	2.9	1.1-11.9
Estrogen+ Progesterone+ Vs. Estrogen- Progesterone-	3.2	1.1-13.5
Live birth Yes Vs. No	1.2	0.8-1.8

Brinton et al.

“ Results regarding effects of fertility drugs on breast cancer risk are conflicting.”

Reprod BioMed 2007; 15: 1; 38-44.



Lo Russo et al

“In conclusion, data currently available are in general reassuring. There is not a certain correlation between ovarian stimulation and the risk of breast cancer. However, the lack of long-term follow-up and the inherent confounding factors present in all the published studies do not allow a definitive answer”

Lo Russo et al

“None of the works commented provides an indisputable evidence about a link between ovarian stimulation and breast cancer risk. On the contrary, most of them actually suggest a lack of interaction between them or even a protective role of ovarian stimulation”.



ENDOMETRIAL CANCER

Haaretz 24.05.2012

HAARETZ.com

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Fertility drugs increase uterine cancer by 69%, Israeli study shows

A research team at the Gertner Institute for Epidemiology and Health Policy Research reveals no link found between treatment and breast or ovarian cancer.

By Dan Even | 20:23 24.05.12 | 0

[Tweet](#)

Fertility drugs increase the risk of cancer of the womb by 69%, according to an Israeli study that tracked women who underwent fertility treatments for 30 years. In contrast to previous studies, however, no link was found between the treatments and the incidence of breast and ovarian cancer.

The research team, headed by Dr. Liat Lerner-Geva who heads the Women and Children's Health Research Unit at the Gertner Institute for Epidemiology and Health Policy Research, tracked 2,431 female patients who began receiving fertility drugs between the years 1964-1974, over the course of 30 years. These drugs, which stimulate female hormone production, have been available in Israel since the early 1960s, and were later included in external fertility treatments.

By crosschecking the women's details with the information that appears in the Health Ministry's national cancer registry, it was found that the morbidity rate due to cancer of the womb was higher among the women than the rest of the population.

According to the study, 30% of the women developed cancerous tumors in the mucous membrane of their uterus, in comparison to a forecast percentage of 17.8, based on the prevalence of the tumor in the general population. Thus, it was found that these women had a 69% higher chance of being diagnosed with cancer, in comparison with the rest of the population.

Nevertheless, the researchers believe that the results are not necessarily attributable to the risk of uterine cancer treatment, but rather can be attributed to the original cause of infertility among the women. A number of previous studies have already identified a link between infertility and a higher likelihood of developing uterine cancer. However, researchers also state that one cannot separate between the problem of infertility and the medicine as a cause for cancer, as an overwhelming number of women in Israel who suffer from infertility use the medicine for treatment (especially in light of the fact that the drug is nationally subsidized). The researchers state that the danger of uterine cancer is less problematic than other dangers that have been diagnosed in previous studies, including the development of breast cancer, as uterine cancer may be cured through the removal of the uterus.

Likewise, the researchers found that as opposed to many previous studies, women who are in treatment are not in danger of developing invasive cancer. Furthermore, no statistical connection was made between the medicine and breast cancer.

Summary of Case control Studies

Any fertility drug Vs. none

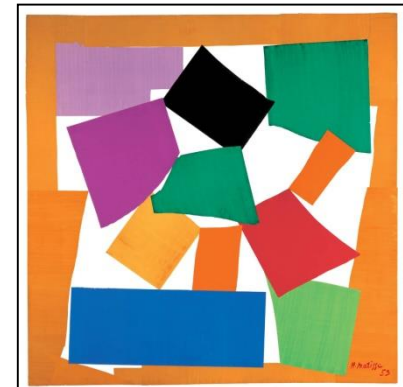
**Endometrial
Cancer**

Cases: 128

Controls: 255

Use of fertility hormones: 7(5.5%) Vs. 10 (3.9%)

Benshushan et al, Eur J Obstet Gynecol Reprod Biol, 2001



Summary of Cohort Studies

Author	Year	Cohort size	RR/SIR	95% CI
Ron	1987	2575	4.8	1.7-10.6
Brinton	1989	2335	0.9	0.4-1.5
Venn	1995	10,358	2.84	1.18-6.81
Modan	1998	2496	4.8	3.0-7.4
Potashnik	1999	1,197	0.68	0.01-3.8
Venn	1999	29,700	1.61	0.92-2.84
Doyle	2002	5,556	0.59	0.1-3.0
Dor	2002	5,026	2.25	0.25-8.11
Brinton	2004	12,193	0.8	0.4-1.5

Summary of Cohort Studies- con't

Author	Year	Cohort size	RR/SIR	95% CI
Althuis	2005	8,401	1.6	1.1-2.1
Calderon-Margalit	2008	14,463	3.3	1.3-8.4
Jensen	2009	54,362	1.10	0.69-1.76
dos Santos Silva	2009	7,355	2.02	1.37-2.87
Yli-Kuha	2012	9,175	2.0	0.37-10.9
Brinton	2013	87, 403	1.25	0.55-2.84
Brinton*	2013	9,832	1.39	0.96-2.01

*for clomiphene

Siristatidis et al, 2012

- **Meta-analysis**
- **9 cohort design**
- **109, 969 women**

RR = 2.04; 95%CI 1.22-3.43
(ref:general population)

RR = 0.45; 95%CI 0.18-1.14
(ref: infertile women)



Zhao et al, 2015

- **Systematic review and Meta-analysis**
- **6 cohort design**

OR = 0.97; 95%CI 0.58-0.1.63
for IVF vs non-IVF



“..no significant increased endometrial cancer incidence rate in patients with IVF.”

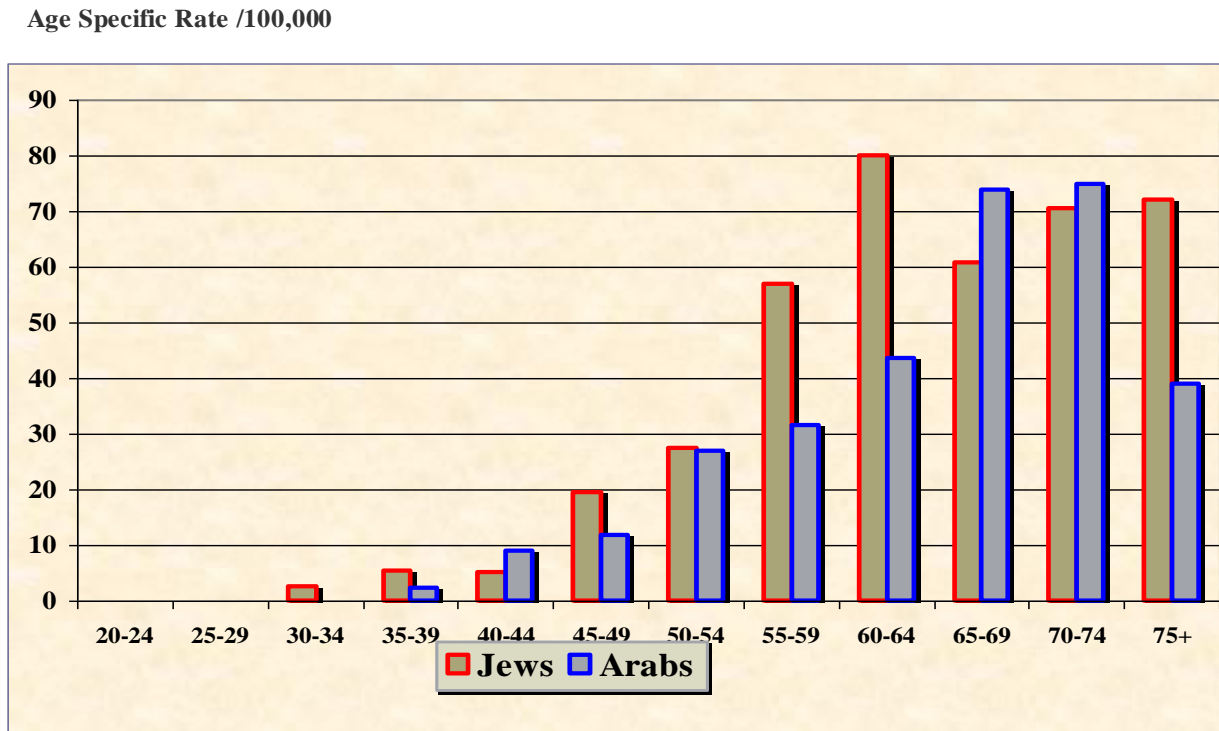


***ARE INFERTILITY TREATMENTS
A POTENTIAL RISK FACTOR
FOR ENDOMETRIAL CANCER ?
PROSPECTIVE OF 30 YEARS OF FOLLOW - UP
Gynecol Endocrinol, 2012***



Endometrial Cancer in Israel by Age

Age Specific Rate / 100,000, 2006



CANCER INCIDENCE IN A COHORT OF INFERTILE WOMEN TREATED BETWEEN 1964-1974

Sheba Medical Center	Ron et al 1987	Modan et al 1998	2003	2009
No of Women	2575	2496	2431	2431
Mean age at first visit	28.7	28.7	28.6	28.6
Women years of follow-up	31,622	56,140	64,762	84,191
Mean years of follow-up	12.3	21.4	26.1	33.8
End of follow-up	31.12.1981	31.12.1991	31.12.1996	31.12.2005
Mean age at the end of follow-up	41.0	50.0	54.7	62.7
Cancer Incidence Observed, Expected (SIR; 95%CI)				
Endometrium	5 4.8; 1.05 1.7-10.6	21, 4.8; 4.3 3.0-7.4	22, 2.6; 8.42 1.6-4.0	30, 1.7; 17.76 1.1-2.4

Observed endometrial cancer cases as compared to expected

Diagnosis of infertility

**Endometrial
Cancer**

	N	Obs.	Exp.	SIR	95%CI
Hormonal	1,340	19	9.38	2.02	1.22-3.16
Non-hormonal	1,061	11	8.37	1.31	0.66-2.35

Observed endometrial cancer cases as compared to expected

Presence of Estrogen and Progesterone

Endometrial Cancer

	N	Obs.	Exp.	SIR	95%CI
Estrogen+ Progesterone-	935	13	6.11	2.13	1.13-3.64
Estrogen+ Progesterone+	671	8	5.31	1.51	0.65-2.97
Estrogen- Progesterone-	129	1	1.11	0.9	0.01-5.01

Observed endometrial cancer cases as compared to expected

Diagnosis of infertility

**Endometrial
Cancer**

	N	Obs.	Exp.	SIR	95% CI
CC+ hMG	238	8	1.6	5.0	2.15-9.85
CC	884	6	5.62	1.07	0.39-2.33
hMG	159	3	1.39	2.16	0.43-6.32
No treatment	1,150	13	9.15	1.42	0.76-2.43

**Endometrial
Cancer**

Poisson model for multivariable analysis

	Hazard Ratio	95%CI
Treated Vs. Untreated	1.1	0.4 - 2.9
Estrogen+ progesterone- Vs. Other	1.4	0.5 - 3.7
Live birth Yes Vs. No	1.4	0.6 - 3.7

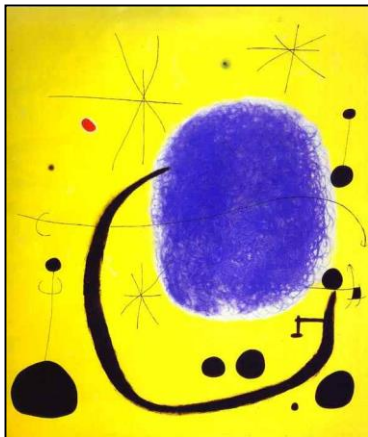
In conclusion

“The risk for endometrial cancer development in infertile women, and especially in women with unopposed estrogen state, is well established.

However, data regarding the possible association to exposure of ovulation-induction drugs to endometrial cancer development is inconclusive.”

Klip et al.

“However, in a society with an increasing age at first birth, even unfavorable results of infertility treatments must be put in prospective and balanced against their benefits”



Cancer Cause and Control 2000;11:319-344

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Thank You for Your Attention!

