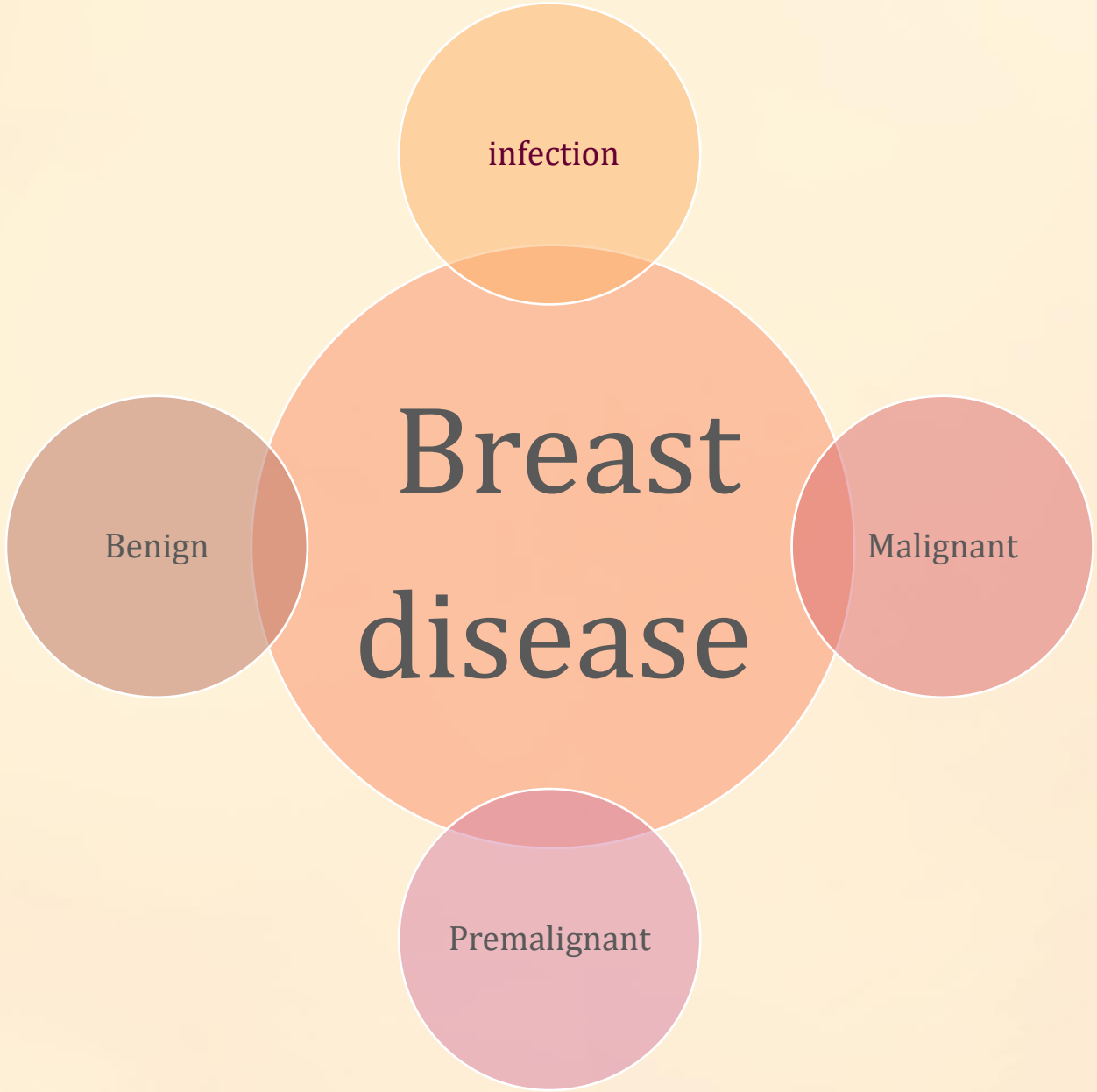
Breast Disease

&

Infertility Trearment

Dr Elham khalaj

General Surgeon


infection
Benign
Breast disease
Malignant
Premalignant

Categorization of Benign Breast Lesions According to the Criteria of Dupont, Page, and Rogers (3)

Nonproliferative

- Cysts
- Papillary apocrine change
- Epithelial-related calcifications
- Mild hyperplasia of the usual type

Proliferative lesions without atypia

- Moderate or florid ductal hyperplasia of the usual type
- Intraductal papilloma
- Sclerosing adenosis
- Fibroadenoma
- Radial scar

Atypical hyperplasia

- Atypical ductal hyperplasia
- Atypical lobular hyperplasia

Cancer risk associated with benign breast disorders and in situ carcinoma of the breast

ABNORMALITY	RELATIVE RISK
Nonproliferative lesions of the breast	No increased risk
Sclerosing adenosis	No increased risk
Intraductal papilloma	No increased risk
Florid hyperplasia	1.5 to 2-fold
Atypical lobular hyperplasia	4-fold
Atypical ductal hyperplasia	4-fold
Ductal involvement by cells of atypical ductal hyperplasia	7-fold
Lobular carcinoma in situ	10-fold
Ductal carcinoma in situ	10-fold

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ELEMENTS OF RISK[k]

Individual does not meet any of the familial risk criteria or tests negative for a genetic predisposition →

Elements that increase risk[l]

- Family history
- Increasing age
- Ethnicity/race[m]
- Lifestyle factors
  - Increased body mass index (BMI)
  - Alcohol consumption
  - Current or prior estrogen and progesterone hormone agent[n]
- Reproductive history
  - Younger age at menarche
  - Nulliparity/Lower parity
  - Older age at first live birth
  - Older age at menopause
- Other
  - History of lobular carcinoma in situ (LCIS); Atypical hyperplasia (ductal and/or lobular)
  - Number of prior breast biopsies
    - ◊ Procedure done with the intent to diagnose cancer; multiple biopsies (needle/excision) of the same lesion are scored as one biopsy.
  - Mammographic breast density (heterogeneously and/or extremely dense breasts)
  - Prior thoracic radiation therapy (RT) <30 y of age

Elements that decrease risk

- Menopause before age 45 y
- Prior risk-reducing agent
- Exercise
- Breastfeeding

→ For breast cancer risk assessment and management, see BRISK-4

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COMPARISON OF PREDICTIVE MODELS OF RISK OF BREAST CANCER AND RISK OF CARRYING PATHOGENIC/LIKELY PATHOGENIC VARIANTS OF BRCA

	Description	Factors Included	Benefits	Limitations
Gail Model	• Individualized breast cancer risk assessment computed based on SEER-specific breast cancer risk data with inclusion of personalized risk factors. • Provides both 5-year and lifetime risk assessment. Five-year risk assessment ≥1.67% used to assess eligibility for a risk-reducing agent.	• Age. • Age at menarche. • Age at first live birth. • Family history (first-degree female relatives with breast cancer only). • Number of previous breast biopsies. • Diagnoses of atypical hyperplasia.	• Validated across multiple studies and cohorts. • Accessible online. • Available to assess eligibility for a risk-reducing agent. • Periodic updates based on changes in breast cancer incidence data. • Accounts for competing risks of mortality other than breast cancer.	• Cannot be used for females <35 years. • Limited use in females of non-European (non-Caucasian) ethnicity. • Considers only a fraction of family history data: ‣ Only includes female first-degree relatives (paternal family history excluded). ‣ Does not include ages of diagnoses of relatives' breast cancers. ‣ Does not include family history of other cancer diagnoses outside breast cancer. ‣ Does not include mantle radiation. • Underestimates risk for development of breast cancer in: ‣ Those with mutations in known breast cancer predisposition genes such as *BRCA1/2* ‣ Those with a strong family history of breast cancer ‣ Those with a family history of ovarian cancer in the maternal or paternal family linage ‣ Non-white females ‣ Those with atypical hyperplasia

COMPARISON OF PREDICTIVE MODELS OF RISK OF BREAST CANCER AND RISK OF CARRYING PATHOGENIC/LIKELY PATHOGENIC VARIANTS OF BRCA

	Description	Factors Included	Benefits	Limitations
Claus[6]	• Table-based risk assessment model based on data from the Cancer and Steroid Hormone Study.	• Family history (first- and second-degree female relatives).	• Allows for incorporation of relatives' ages of diagnoses of breast cancer. • Allows for computation of lifetime breast cancer risk and/or risk calculations at 10-year intervals.	• The population data used to construct this model are now nearly 30 years old and may be outdated for current risk estimation. • Has not been validated outside of the original cohort. • No incorporation of personal breast cancer risk factors (eg, age, reproductive history, history of breast biopsies). • Requires additional calculations to compute 10-year breast cancer risk, thus not amenable to routine use. • Tables are not adaptable for complex family structures and thus cannot be used for all patients. • Excludes family history of male breast cancer, ovarian cancer, and other non-breast cancers in relatives. • Does not consider risk from mantle radiation. • Does not account for competing risks of mortality other than breast cancer.

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COMPARISON OF PREDICTIVE MODELS OF RISK OF BREAST CANCER AND RISK OF CARRYING PATHOGENIC/LIKELY PATHOGENIC VARIANTS OF BRCA

	Description	Factors Included	Benefits	Limitations
International Breast Cancer Intervention Study [IBIS]/ Tyrer-Cuzick (version 8)	• Computerized model based on initial data from the United Kingdom Thames Cancer Registry 2005–2009. • Attribution of risk based on family history data[1] • Provides personalized breast cancer risk assessment based on individual risk factors and family history information. • Both lifetime breast cancer risk (to age 85 in v7+) and 10-year risk estimations are available.	• Age. • Reproductive history (ie, age at menarche, age at first live birth, age at menopause). • Body mass index. • Exogenous hormone exposure (HRT duration). • Family history (comprehensive, see Benefits). • History of breast biopsies and results (including atypical hyperplasia and lobular carcinoma in situ). • Breast density. • Genetic test results (*BRCA1/2* only).	• Can be used in females <35 years. • Accessible online. • Simultaneous computation of risk for *BRCA1/2* pathogenic mutation. • Comprehensive incorporation of family history and overall family structures. Includes: ▸ Affected first-, second-, and third- (first cousins) degree relates ▸ Ovarian cancer diagnoses ▸ Male breast cancer diagnoses ▸ Unaffected relatives. • Periodic updates based on breast cancer incidence data. • Accounts for competing risks of mortality other than breast cancer (have to select option).	• Does not consider risk from mantle radiation. • Overestimates risk for the development of breast cancer in: ▸ Hispanic individuals as this model was validated in primarily Caucasian females in the United Kingdom ▸ Atypical hyperplasia[2-4] ▸ LCIS[5] ▸ Dense breasts

Breast changes during IVF :

Pain

Tenderness

Swelling

IVF Treatment in:

Gene positive

Family history positive

Normal population

IVF

Benign disease

Malignancy

In this population-based sample of women attending mammographic screening, we found that women with a history of infertility had higher absolute dense volume than other women. Among the infertile women, those who had gone through COS had the highest absolute dense volume. This may indicate a potential adverse effect of COS, but could also be due to the underlying infertility. Whether this difference in density may affect their potential breast cancer risk is unknown. Hence, continued monitoring of women undergoing COS is warranted.

Breast Cancer Res. 2016; 18: 36.
Published online 2016 Apr 13. doi: 10.1186/s13058-016-0693-5

Results: Overall, 25 studies, including 617 479 participants, were eligible for inclusion. There was no significant breast-cancer risk association with fertility treatment (compared with general and subfertility reference groups). Summary odds ratio of all included studies was 0.97 (95 per cent c.i. 0.90 to 1.04). Women who received six or more IVF cycles did not have an increased risk of breast cancer. Similarly, there was no excess breast-cancer risk associated with clomiphene, human chorionic gonadotropin, gonadotropin analogues and progesterone when examined individually. Comparably, there was no significant association between fertility treatment and excess breast-cancer risk in patients with more than 10 years' follow-up. Summary odds ratio was 0.97 (95 per cent c.i. 0.85 to 1.12).
Conclusion: This meta-analysis did not find a significant association between fertility treatments and excess breast-cancer risk. Women considering IVF should be informed that it does not appear to increase breast-cancer risk.

Fertility treatment and breast cancer incidence : meta – analysis
Carolyn Cullinane[1,2], Hannah Gillan[1], James Geraghty[1], Denis Evoy[1], Jane Rothwell[1], Damian McCartan[1], Enda W McDermott[1], Ruth S Prichard[1]
BJS Open 2022 Jan 6;6(1):zrab149.
doi: 10.1093/bjsopen/zrab149.

Study	log (odds ratio)	SE	Weight (%)	Odds ratio
Burkman *et al.*[23]	0.1823	0.3537	2.7	1.20 (0.60, 2.40)
Gauthier *et al.*[28]	–0.0305	0.1381	18.0	0.97 (0.74, 1.27)
Guleria *et al.*[29]	–0.1496	0.0841	48.5	0.86 (0.73, 1.02)
Jensen *et al.*[30]	–0.0619	0.129	20.6	0.94 (0.73, 1.21)
van den Belt-Dusebout *et al.*[16]	–0.0408	0.1835	10.2	0.96 (0.67, 1.38)
Total (95% c.i.)			100.0	0.91 (0.81, 1.03)

Heterogeneity: $\chi^2 = 1.40$, 4 d.f., $P = 0.84$; $I^2 = 0\%$
Test for overall effect: $Z = 1.54$, $P = 0.12$

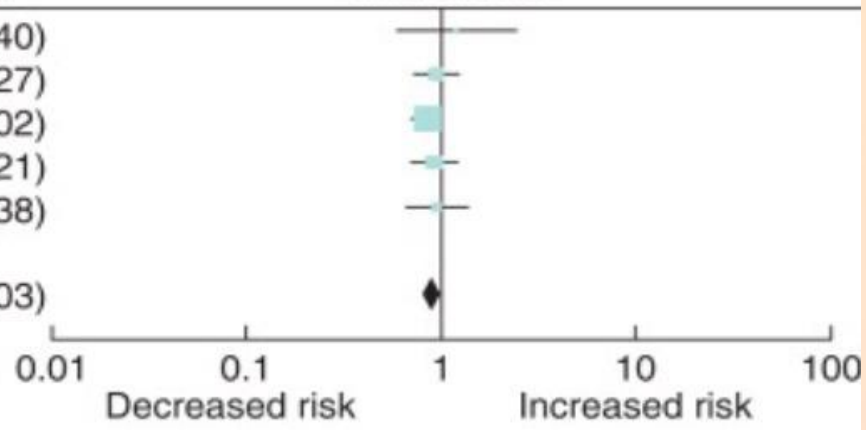

Fig. 3 Forest plot of breast-cancer risk associated with clomiphene

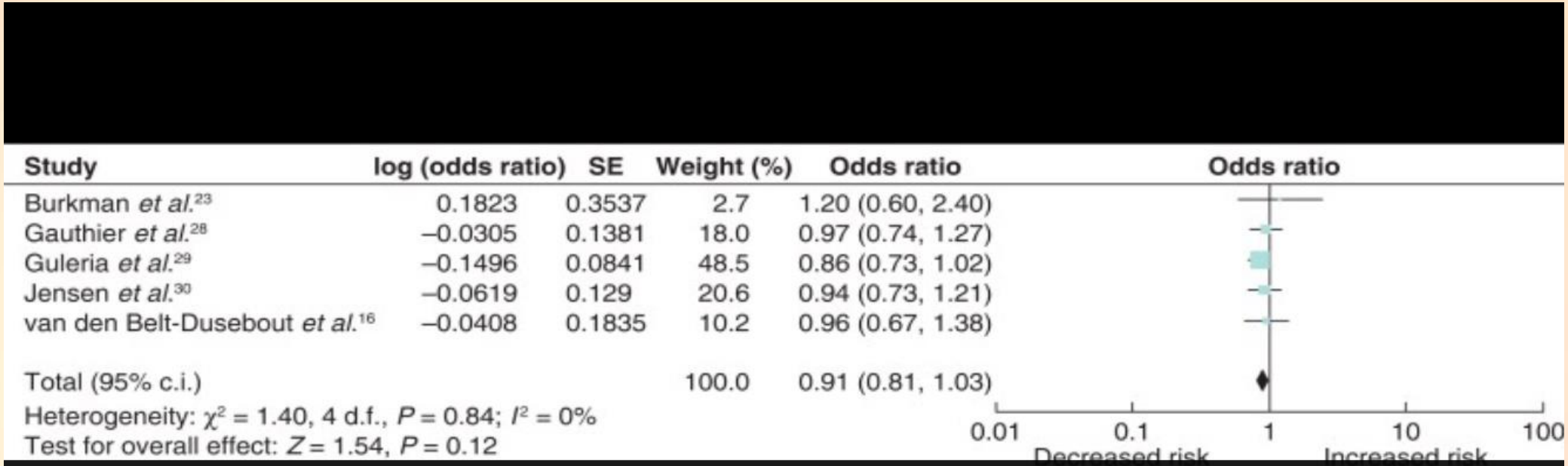

Fig. 4 Forest plot of breast-cancer risk associated with human chorionic gonadotropin

Study	log (odds ratio)	SE	Weight (%)	Odds ratio
Jensen *et al.*[30]	1.2119	0.3785	14.6	3.36 (1.60, 7.06)
van den Belt-Dusebout *et al.*[16]	–0.1985	0.2038	24.1	0.82 (0.55, 1.22)
Brinton *et al.*[22]	–0.2628	0.1054	30.0	0.77 (0.63, 0.95)
Guleria *et al.*[29]	0.1599	0.0734	31.4	1.17 (1.02, 1.35)
Total (95% c.i.)			100.0	1.11 (0.76, 1.61)

Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 21.86$, 3 d.f., $P < 0.001$; $I^2 = 86\%$
Test for overall effect: $Z = 0.52$, $P = 0.61$

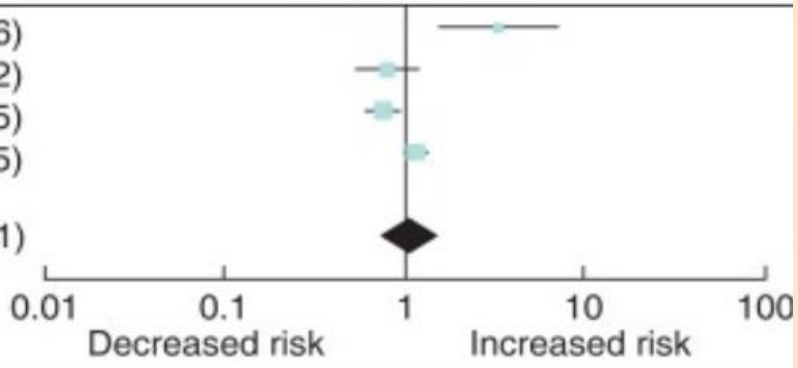

Fig. 5 Forest plot of breast-cancer risk associated with progesterone

Study	log (odds ratio)	SE	Weight (%)	Odds ratio
Brinton *et al.*[22]	0.178	0.2621	2.7	1.19 (0.71, 2.00)
Brukman *et al.*[23]	0.4055	0.2606	2.8	1.50 (0.90, 2.50)
Gauthier *et al.*[28]	−0.0101	0.2147	4.1	0.99 (0.65, 1.51)
Guleria *et al.*[29]	0.01	0.0476	82.7	1.01 (0.92, 1.11)
Jensen *et al.*[30]	0.1823	0.1943	5.0	1.20 (0.82, 1.76)
Orgeas *et al.*[37]	−0.462	0.3299	1.7	0.63 (0.33, 1.20)
Taheripanah *et al.*[38]	0.8109	0.4137	1.1	2.25 (1.00, 5.06)
Total (95% c.i.)			100.0	1.03 (0.95, 1.13)

Heterogeneity: $\chi^2 = 9.00$, 6 d.f., $P = 0.17$; $I^2 = 33\%$
Test for overall effect: $Z = 0.78$, $P = 0.43$

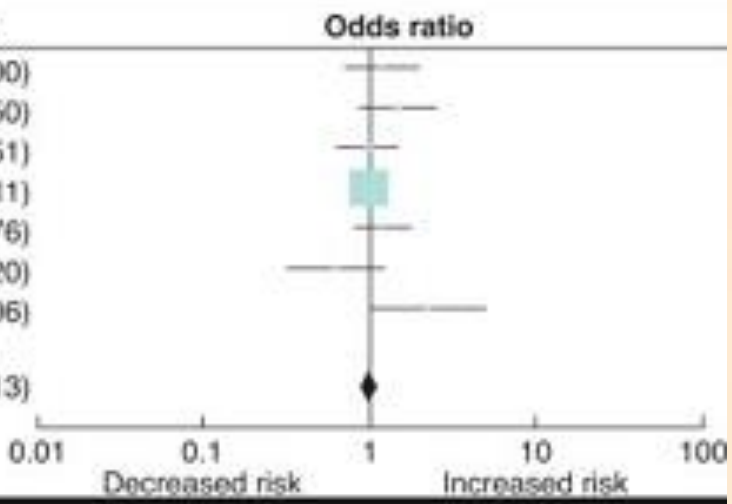

Fig. 6 Forest plot of breast-cancer risk associated with gonadotropins

Study	log (odds ratio)	SE	Weight (%)	Odds ratio
Brinton *et al.*[12]	0.0374	0.1995	16.2	1.04 (0.70, 1.53)
Brinton *et al.*[22]	0.1252	0.1069	24.5	1.13 (0.92, 1.40)
Burkman *et al.*[23]	0.6931	0.7073	2.5	2.00 (0.50, 8.00)
Taheripanah *et al.*[38]	0.5306	0.3245	9.1	1.70 (0.90, 3.21)
van den Belt-Dusebout *et al.*[16]	–0.5978	0.1754	18.2	0.55 (0.39, 0.78)
Williams *et al.*[17]	–0.0101	0.043	29.6	0.99 (0.91, 1.08)
Total (95% c.i.)			100.0	0.99 (0.79, 1.24)

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 16.65$, 5 d.f., $P = 0.005$; $I^2 = 70\%$

Test for overall effect: $Z = 0.08$, $P = 0.94$

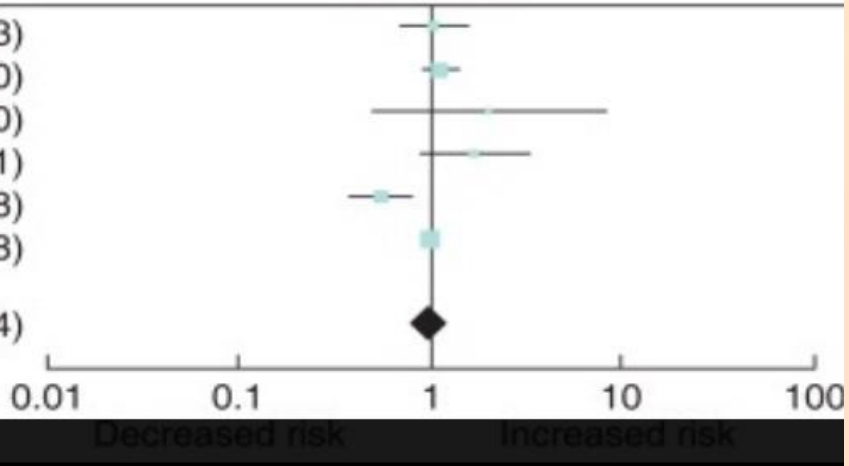

Fig. 7 Forest plot of breast-cancer risk associated with six or more cycles of *in vitro* fertilization

Study	log (odds ratio)	SE	Weight (%)	Odds ratio
Calderon-Margalit *et al.*[24]	0.5172	0.1876	8.4	1.68 (1.16, 2.42)
Guleria *et al.*[29]	–0.086	0.1075	14.0	0.92 (0.74, 1.13)
Katz *et al.*[31]	0.2151	0.0947	15.1	1.24 (1.03, 1.49)
Luke *et al.*[36]	–0.1863	0.0517	18.7	0.83 (0.75, 0.92)
Reigstad *et al.*[18]	0.1851	0.0862	15.8	0.83 (0.70, 0.98)
Tsafrir *et al.*[40]	–0.2744	0.1839	8.6	0.76 (0.53, 1.09)
van den Belt-Dusebout *et al.*[16]	–0.0101	0.0421	19.3	0.99 (0.91, 1.08)
Total (95% c.i.)			100.0	0.97 (0.85, 1.12)

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 28.80$, 6 d.f., $P < 0.001$; $I^2 = 79\%$
Test for overall effect: $Z = 0.37$, $P = 0.71$

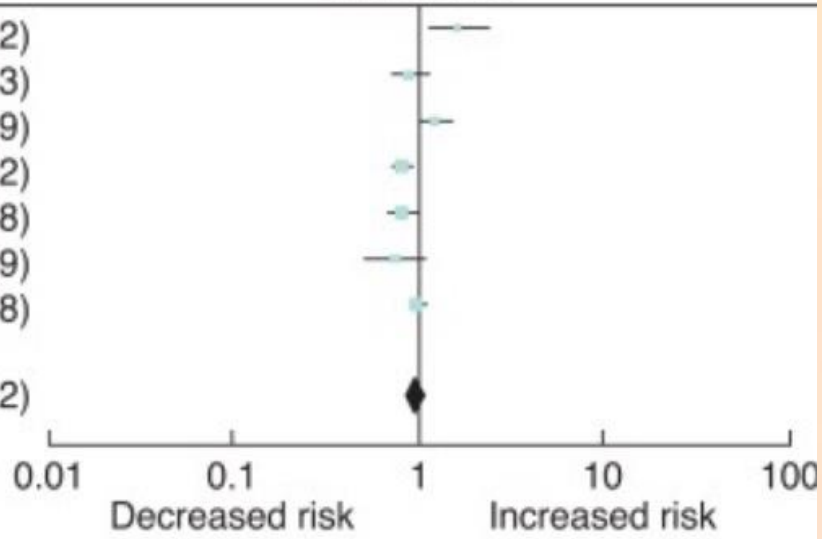

Fig. 8 Forest plot of long-term breast-cancer risk associated with fertility treatment

What Should We Do?